



Società Chimica Italiana
Divisione di Chimica
Organica

Atti

del

XXXIX Convegno Nazionale della
Divisione di Chimica Organica

della

Società Chimica Italiana



Torino 8-12 Settembre 2019



UNIVERSITÀ
DEGLI STUDI
DI TORINO



CAMERA DI COMMERCIO
INDUSTRIA ARTIGIANATO E AGRICOLTURA
DI TORINO



UNIVERSITÀ DEL PIEMONTE ORIENTALE



www.cdco2019.unito.it



SCIorganica -



facebook.com/SCIChimicaOrganica/ -



sciorganica – cdco2019@unito.it

INDICE

Comitato Scientifico	pag. 3
Comitato Organizzatore	pag. 4
Benvenuto	pag. 5
Medagli e Premi	pag. 6
Programma	pag. 11
Sessione Poster 1 - Elenco contributi	pag. 25
Sessione Poster 2 - Elenco contributi	pag. 27
Lectures Medaglie	pag. 28
Lectures Premi Senior	pag. 34
Lectures Premi Junior	pag. 39
Keynotes	pag. 44
EurJOC Lecture	pag. 49
ChemPubSoc Lecture	pag. 51
Elsevier Lecture	pag. 53
Lectures Premi Dottorato	pag. 55
Comunicazioni Orali	pag. 59
Comunicazioni Poster – sessione 1 (PC-01 – PC-47)	pag. 167
Comunicazioni Poster – sessione 2 (PC-48 – PC-94)	pag. 214
Elenco dei partecipanti	pag. 262
Elenco degli Sponsors	pag. 273

Comitato Scientifico

Gianluca Farinola

Università degli Studi di Bari

gianluca.farinola@uniba.it

Roberto Ballini

Università degli Studi di Camerino

roberto.ballini@unicam.it

Anna Bernardi

Università degli Studi di Milano

anna.bernardi@unimi.it

Maria Valeria D'Auria

Università degli Studi di Napoli

mariavaleria.dauria@unina.it

Marco Lucarini

Università degli Studi di Bologna

marco.lucarini@unibo.it

Alessandro Mordini

ICCOM – CNR - Firenze

alessandro.mordini@iccom.cnr.it

Andrea Pace

Università degli Studi di Palermo

andrea.pace@unipa.it

Gabriele Razzetti

DiPahrma Francis s.r.l - Milano

gabriele.razzetti@dipharma.com

Claudio Villani

Università degli Studi di Roma "La Sapienza"

claudio.villani@uniroma1.it

Comitato Organizzatore

Cristina Prandi

Università degli Studi di Torino
cristina.prandi@unito.it

Guido Viscardi

Università degli Studi di Torino
guido.viscardi@unito.it

Giovanni Appendino

Università del Piemonte Orientale
giovanni.appendino@uniupo.it

Giancarlo Cravotto

Università degli Studi di Torino
giancarlo.cravotto@unito.it

Alessandro Barge

Università degli Studi di Torino
alessandro.barge@unito.it

Annamaria Deagostino

Università degli Studi di Torino
annamaria.deagostino@unito.it

Pierluigi Quagliotto

Università degli Studi di Torino
pierluigi.quagliotto@unito.it

Lorenzo Tei

Università del Piemonte Orientale
lorenzo.tei@uniupo.it

Margherita Barbero

Università degli Studi di Torino
margherita.barbero@unito.it

Andrea Fin

Università degli Studi di Torino
andrea.fin@unito.it

Marta Da Pian

Università degli Studi di Padova
marta.dapian@unipd.it



*XXXIX Convegno Nazionale della Divisione di
Chimica Organica della Società Chimica Italiana*

Roberto Buscaino

Università degli Studi di Torino

roberto.buscaino@unito.it

Benvenuto

Cari Soci,

benvenuti al **XXXIX Convegno Nazionale della Divisione di Chimica Organica, CDCO Torino 2019**, organizzato dai Colleghi dell'Università di Torino e dell'Università del Piemonte Orientale.

Ci incontreremo dall'8 al 12 settembre 2019 nella capitale piemontese dove saremo ospitati presso la nuova aula magna "Cavallerizza Reale" dell'Università di Torino per le giornate di apertura e di chiusura, mentre nelle giornate centrali le sessioni si svolgeranno nelle vicine strutture di "Torino Incontra", il centro congressi della Camera di Commercio.

Ci prepariamo a trascorrere intense giornate scientifiche, con le conferenze plenarie dei vincitori di medaglie e premi della Divisione di Chimica Organica 2019 e degli speakers invitati, e con numerose comunicazioni orali e poster per aggiornarci sui progressi della ricerca nella Chimica Organica italiana. Anche quest'anno alle attività scientifiche affiancheremo momenti di riflessione sul ruolo sociale ed economico della Chimica Organica nel nostro paese: in collaborazione con la Camera di Commercio di Torino incontreremo chimici organici che lavorano nel tessuto professionale ed industriale della Regione Piemonte ed in tutta Italia; organizzeremo, insieme al Gruppo Interdivisionale di Diffusione della Cultura Chimica, una sessione aperta al pubblico con personalità di richiamo nella divulgazione scientifica; i Soci giovani saranno attivamente coinvolti nella programmazione di eventi e conferenze.

Ci incontreremo poi nell'Assemblea dei Soci, dedicando ampio spazio a discutere delle attività divisionali, ed a pianificare le direzioni future della nostra comunità in seno alla SCI. Non ultimo, condivideremo il piacere dello stare insieme nei momenti sociali, per i quali i Colleghi Organizzatori ci riserveranno ambientazioni molto suggestive nella cornice della loro bellissima città.

Potrete seguire tutti gli aggiornamenti dell'organizzazione su questo sito, facendo pervenire a me, al Consiglio Direttivo ed al Comitato Organizzatore i vostri suggerimenti per il nostro CDCO Torino 2019.

Vi invito a non mancare all'evento più importante della nostra Divisione nel 2019, portando i vostri contributi ai lavori scientifici e le vostre voci alla discussione.

Molti cari saluti



Gianluca Farinola

Presidente della Divisione di Chimica Organica

Medaglie e Premi

Medaglie

Medaglia d'oro **Angelo Mangini:**

Alessandro Casnati – Università di Parma

Per i suoi contributi fondamentali alla chimica dei calixareni, che partendo dalla messa a punto di strategie di funzionalizzazione regio- e stereoselettiva e dallo studio delle proprietà conformazionali di tali piattaforme macrocicliche, hanno portato allo sviluppo razionale di derivati multivalenti con molteplici applicazioni di grande interesse quali la catalisi, il riconoscimento e la veicolazione di principi attivi.

Medaglia d'oro **Adolfo Quilico:**

Marco d'Ischia – Università di Napoli "Federico II"

Per l'originalità, l'ampiezza ed il valore delle sue ricerche sulla chimica ossidativa dei composti fenolici. Tali studi hanno spaziato, con rigore ed eleganza scientifica, dalla sintesi biomimetica, alla definizione dei meccanismi di reazione, fino alla caratterizzazione di polimeri melanici, consentendo una razionalizzazione delle relazioni struttura-proprietà di rilevante importanza per applicazioni biomediche e tecnologiche.

Medaglia d'argento **Giacomo Ciamician:**

Luca Dell'Amico – Università di Padova

Per i brillanti risultati ottenuti nell'ottimizzazione di protocolli sintetici esplorando percorsi innovativi che spaziano dall'organocatalisi polare e fotoorganocatalisi radicalica alla fotocatalisi in reattori microfluidici.

Medaglia **Piero Pino:**

delle Divisioni di Chimica Organica e di Chimica Industriale

Maurizio Benaglia – Università di Milano

Per aver contribuito con creatività e rigore metodologico allo sviluppo di nuovi sistemi organocatalitici, caratterizzati da elevata efficienza e basso impatto ambientale. I suoi studi hanno sviluppato protocolli di grande interesse in ambito industriale utilizzando reagenti supportati e riciclabili e progettando metodiche di sintesi basate su reazioni in flusso continuo. Le ricerche del Prof. Benaglia contribuiscono a colmare lo spazio concettuale e sperimentale tra le metodiche di laboratorio ed i processi di sintesi su larga scala.

Premi alla Ricerca

**Premio alla ricerca “Chimica Organica per l’Ambiente, l’Energia e le Nanoscienze”
(Senior):**

Valeria Conte - Università di Roma Tor Vergata

Per i suoi importanti contributi all'avanzamento degli studi di sistemi di ossi-funzionalizzazione di substrati organici in ambienti prevalentemente acquosi, che mimano i processi biologici puntando allo sviluppo di percorsi sintetici sostenibili.

**Premio alla Ricerca “Chimica Organica per l’Ambiente, l’Energia e le Nanoscienze”
(Junior):**

Giulio Ragazzon - Università di Trieste

Per i suoi contributi allo sviluppo di originali costrutti supramolecolari dinamici ed alla loro implementazione in sistemi catalitici cooperativi ed in nano-assemblati basati sugli acidi nucleici.

Premio alla ricerca “Chimica Organica nei suoi Aspetti Metodologici” (Senior):

Andrea Basso - Università di Genova

Per i suoi contributi rigorosi e creativi allo sviluppo di nuove metodologie fotochimiche e multicomponenti per la generazione di diversità chimica di rilevanza biologica

Premio alla ricerca “Chimica Organica nei suoi Aspetti Metodologici” (Junior):

Damiano Tanini - Università di Firenze

Per il suo contributo allo sviluppo di originali metodi di sintesi e di caratterizzazione chimico-fisica di derivati calcogenati con interessanti e peculiari attività.

Premio alla ricerca “Chimica Organica per le Scienze della Vita” (Senior):

Cristina Nativi - Università di Firenze

Per avere saputo coniugare in modo originale ed innovativo la ricerca di nuovi percorsi di sintesi efficiente e stereoselettiva di molecole di natura saccaridica con lo sviluppo di glicoconiugati e mimetici in ambito biomedico.

Premio alla ricerca “Chimica Organica per le Scienze della Vita” (Junior):

Alberto Dal Corso - Università di Milano

Per i suoi studi sull'incremento dell'affinità di legame tra farmaco e proteina bersaglio e sulla sintesi di composti citotossici coniugati a ligandi selettivi di antigeni tumorali.

Premio alla ricerca “Chimica Organica per lo Sviluppo di Processi e Prodotti nell'Industria” (Senior):

Augusto Canavesi - Teva Active Pharmaceutical Ingredients - TAPI

Per i suoi studi rivolti all'ottimizzazione di processi di produzione di farmaci con particolare riguardo alle strategie sintetiche ed al fenomeno del polimorfismo

Premio alla ricerca “Chimica Organica per lo Sviluppo di Processi e Prodotti nell'Industria” (Junior):

Maria Pia Catalani - Evotec

Per i suoi studi sulla sintesi stereoselettiva di derivati policiclici della piperazina con potenziali attività biologiche.

Premi di Dottorato

Premio Tesi di Dottorato “Chimica Organica per l’Ambiente, l’Energia e le Nanoscienze”:

Gianluigi Albano - Università di Pisa

Per i suoi originali studi sulle proprietà chirottiche di film sottili di oligotiofeni chirali.

Premio Tesi di Dottorato “Chimica Organica nei suoi Aspetti Metodologici”:

Luca Capaldo - Università di Pavia

Per i suoi studi sullo sviluppo di processi sintetici fotocatalizzati ad alta efficienza.

Premio Tesi di Dottorato “Chimica Organica per le Scienze della Vita”:

Chiara Platella - Università di Napoli “Federico II”

Per i risultati ottenuti nella messa a punto di protocolli per l'identificazione di piccole molecole in grado di legare specifiche strutture G-quadruplex.

Programma

Programma Scientifico

Domenica 8 Settembre		
(Presso Aula Magna, Cavallerizza, Università di Torino, via Verdi 9, Torino)		
	14.00-14.30	Saluti, Inizio Lavori e Premiazioni
Sessione Plenaria #1	Chairman: P. Scrimin	
	14.30-15.00	M-01 Medaglia A. Mangini Casnati A. <i>Calixarenes: from Chemical Curiosity and Basic Research to Industrial Implementation</i>
	Chairman: R. Riccio	
	15:00-15:30	M-02 Medaglia Adolfo Quilico d'Ischia M. <i>The Melanin Code: Deciphering Nature's Paradigms for Chemical Functionality</i>
	Chairman: E. Licandro	
	15:30-16:00	PR-S1 Premio: "Chimica Organica nei suoi Aspetti Metodologici" Basso A. <i>Isonitrili al Pesto (Isocyanides in Pesto Sauce)</i>
	16:00-16:30	PR-S2 Premio: "Chimica Organica per le Scienze della Vita" Nativi C. <i>[4+2] Cycloadditions: Vintage Reactions for New Glycan-based Epitopes</i>
16.30-17.00 Coffee Break		
Sessione Plenaria #2	Chairman: F. Sannicolò	
	17:00-17:30	M-03 Medaglia P. Pino Benaglia M. <i>Development of catalytic stereoselective methodologies: sense and sensibility</i>
	Chairman: F. De Angelis	
	17:30-18:00	EurJOC Lecture in ricordo di Cinzia Chiappe Welton T. <i>Ionic Liquid Effects on the Rates of Reactions - A Lecture in Memory of Prof. Cinzia Chiappe</i>
	Chairman: A. Brandi	
	18:00-18:30	KN-01 Laus M. <i>Toward deterministic doping</i>
	18:30-19:00	PR-S3 Premio "Chimica Organica per l'Ambiente, l'Energia e le Nanoscienze" Conte V. <i>V-catalysis in Oxidation Reactions: from Mimesis of HalPO Enzymes to Sustainable Synthesis</i>
	19.30	Buffet di benvenuto. Cortile del Rettorato

Lunedì 9 Settembre - Mattino (Presso Sala Cavour, Centro Congressi Torino Incontra, via Nino Costa 8, Torino)		
Sessione Plenaria #3		Chairman: M. Menicucci
	9.00-9.15	Apertura Lavori
	9.15-11.00	Imprese e Ricerca: storie di connessioni.
11.00-11.30 Coffee Break		
Sessione Plenaria #4		Chairman: M. Menicucci
	11.30-11.45	Il Cluster SPRING per un sistema nazionale che integri ricerca e imprese.
	11.45-13.00	La Chimica si rinnova, Green Chemistry, Nuove Tecnologie ed Open Innovation.

Lunedì 9 Settembre - Pomeriggio (Presso Sala Cavour, Centro Congressi Torino Incontra, via Nino Costa 8, Torino)		
	13.00-15.00	Sessione Poster #1 (Torino Incontra – Foyer)
Sessione #1 (Sala Cavour)	Chairman: M. Taddei	
	15:00-15:30	PR-S4 Premio: "Chimica Organica per lo Sviluppo di Processi e Prodotti nell'Industria" Canavesi A. <i>Challenges and creativity in API process development: facing unexpected impurities formation.</i>
	15:30-15:50	IC-01 Roletto J. <i>Efinaconazole process development and scale up through unconventional use of Grignard reagent</i>
	15:50-16:10	IC-02 Carcone L. <i>Development and Scale-up of a Stereoselective Synthesis to Droxidopa</i>
	16:10-16:30	IC-03 Lombardo A. <i>Pentetrazol: development and industrialization of the manufacturing process</i>
Sessione #2 (Sala Giolitti)	Chairman: G. Oliviero	
	15:00-15:30	PR-J1 Premio: "Chimica Organica nei suoi Aspetti Metodologici" (Junior) Tanini D. <i>Reactivity and synthetic applications of new chalcogen-containing small molecules</i>
	15:30-15:50	OC-01 Esposito A. <i>Synthesis and biological evaluation of novel antimicrobial and antibiofilm agents</i>
	15:50-16:10	OC-02 Clemente F. <i>Stereoselective synthesis of C-2 alkylated trihydroxypiperidines: effect of the chain length and the configuration at C-2 on their activity as Pharmacological Chaperones for Gaucher Disease</i>
	16:10-16:30	OC-03 Teta R. <i>Deciphering the metabolome of marine microbiome through molecular networking</i>
Sessione #3 (Sala Einaudi)	Chairman: O. Bortolini	
	15:00-15:30	PR-J2 Premio: "Chimica Organica per l'Ambiente, l'Energia e le Nanoscienze" (Junior) Ragazzon G. <i>Supramolecular dynamic systems away from equilibrium</i>
	15:30-15:50	OC-04 Da Pian M. <i>A Kinetic and Morphological Study of P3HT Nanowhiskers Formation in the Presence of either PCBM or PCL.</i>
	15:50-16:10	OC-05 Decavoli C. <i>Design of Organic Based Photosensitizer-Catalyst Systems for Photoelectrochemical Solar Fuels</i>
	16:10-16:30	OC-06 Cordaro M. <i>Synthesis of self-assembled BODIPY heterodimer for energy transfer investigations</i>
16.30-17.00 Coffee Break		

Sessione #4 (Sala Cavour)	Chairman: L. Di Bari	
	17:00-17:30	PR-J3 Premio: "Chimica Organica per lo Sviluppo di Processi e Prodotti nell'Industria" (Junior) Catalani M. P. <i>Novel NK1 receptor antagonists</i>
	17:30-17:50	IC-04 De Combarieu E. <i>Investigation of optical purity of natural Cephalotaxine</i>
	17:50-18:10	OC-07 Bandini M. <i>Catalytic manipulations of arenes with light and graphene oxide I</i>
	18:10-18:30	OC-08 Salamone M. <i>Metal-Ion Induced C-H Bond Deactivation in the Hydrogen Atom Transfer Reaction from Diol Substrates to the Cumyloxyl Radical</i>
	18:30-18:50	OC-09 Martin T. <i>Hydrogen Atom Transfer based Aliphatic C-H Bond Functionalization of Cycloalkane Derivatives. Kinetic and Product Studies on the Role of Torsional Effects</i>
	18:50-19:10	OC-10 Galeotti M. <i>Selective aliphatic C-H bond hydroxylation promoted by in situ generated dioxiranes</i>
Sessione #5 (Sala Giolitti)	Chairman: F. Nicotra	
	17:00-17:30	PR-J4 Premio: "Chimica Organica per le Scienze della Vita" (Junior) Dal Corso A. <i>New-generation Self-Immolative Spacers Enable Fast Release of Anticancer Drugs</i>
	17:30-17:50	OC-11 Valgimigli L. <i>The strange case of quinones and hydroperoxyl radicals</i>
	17:50-18:10	OC-12 Doria F. <i>Photoresponsive molecular tools targeting DNA G-quadruplex structures</i>
	18:10-18:30	OC-13 Montesarchio D. <i>The intriguing world of G-quadruplex-based aptamers</i>
	18:30-18:50	OC-14 Sabuzi F. <i>Encapsulation and controlled release of thymol derivatives into lignin microcapsules</i>
	18:50-19:10	OC-15 Roviello G. N. <i>Novel insights on peptide-G4 DNA interaction: a study on the binding behaviour of polyamine peptides on different G4 DNA structures</i>
Sessione #6 (Sala Einaudi)	Chairman: A. Dalla Cort	
	17:00-17:20	OC-16 Poderi C. <i>Novel [2]-Rotaxanes Incorporating a Nitroxide Radical Motif</i>
	17:20-17:40	OC-17 Zinna F. <i>Chiral functionalized fluorescent macrocycles as a scaffold for remarkable chiroptical properties</i>
	17:40-18:00	OC-18 Francesconi O. <i>Development and binding properties of a synthetic receptor for the molecular recognition of caffeine and related xanthines</i>
	18:00-18:20	OC-19 Cringoli M. C. <i>Spike of Sulfur for Photo-Chemistry on Self-assembling Tripeptides</i>
	18:20-18:40	OC-20 Patamia V. <i>Self-Assembled nicotinic acid-based tetrahedral hosts as supramolecular catalysts: synthesis and first applications</i>
	18:40-19:00	OC-21 Di Stefano S. <i>How to Make Autonomous the Motions of a Chemically Fueled Molecular Machine</i>

Martedì 10 Settembre - Mattino (Presso Sala Cavour, Centro Congressi Torino Incontra, via Nino Costa 8, Torino)		
Sessione Plenaria #5 (Sala Cavour)	Chairman: M. Prato	
	9.00-9.30	KN-02 Marchesan S. <i>Entry to peptide Wonderland through the rabbit hole</i>
Sessione #7 (Sala Cavour)	Chairman: A. Dossena	
	09:30-09:50	OC-22 Porcheddu A. <i>Mech@nochemistry: an Appealing Marriage of Innovation and Tradition</i>
	09:50-10:10	OC-23 Guazzelli L. <i>Bio-based ionic liquids: synthesis and applications</i>
	10:10-10:30	OC-24 Chiurchiù E. <i>A new efficient flow chemical synthesis of thiophene-2-carboxylates</i>
Sessione #8 (Sala Giolitti)	Chairman: M. Melucci	
	09:30-09:50	OC-25 Schettini R. <i>Multivalent effect of cyclopeptoid-iminosugar conjugates in glycosidase inhibition</i>
	09:50-10:10	OC-26 Corradini R. <i>PNA- and modified-PNA-based systems: applications to genetic diseases</i>
	10:10-10:30	OC-27 Cardullo N. <i>Synthesis of bisphenol neolignans as bioactive compounds</i>
Sessione #9 (Sala Einaudi)	Chairman: M. Maggini	
	09:30-09:50	OC-28 Russo L. <i>3D Printable biomaterials for tissue models, functionalization strategies</i>
	09:50-10:10	OC-29 Locatelli E. <i>Photoluminescent decoration of iron oxide magnetic nanoparticles for dual-imaging applications</i>
	10:10-10:30	OC-30 Sambri L. <i>Phosphorescent iridium-containing nanomicelles: synthesis, characterization and preliminary applications in nanomedical imaging</i>
10.30-11.00 Coffee Break		
Sala Cavour	11.00-13.00	Assemblea Soci

Martedì 10 Settembre - Pomeriggio (Presso Sala Cavour, Centro Congressi Torino Incontra, via Nino Costa 8, Torino)		
	13.00-15.00	Sessione Poster #2 (Torino Incontra – Foyer)
Sessione #10 (Sala Cavour)	Chairman: E. Beccalli	
	15:00-15:15	PD-01 Premio Dottorato: “Chimica Organica nei suoi Aspetti Metodologici” Capaldo L. <i>The Triangle of Photocatalysis: Different Approaches for Ecosustainable Synthesis</i>
	15:15-15:35	OC-31 Minassi A. <i>Photochemical angular-to-linear switch of the triterpenoid A,B,C ring system: discovery, mechanistic aspects, and biological translation</i>
	15:35-15:55	OC-32 Leggio A. <i>A TiCl₄-based effective protocol for the synthesis of peptides</i>
	15:55-16:15	OC-33 De Luca L. <i>Metal-free Chlorination of Toluenes and Aldehydes Mediated by Visible Light</i>
	16.15-16.35	OC-34 Volpe C. <i>New applications of ester surrogates in organic synthesis</i>
Sessione #11 (Sala Giolitti)	Chairman: M. Da Pian	
	15:00-15:15	<i>Tavola Rotonda</i>
	15:15-15:35	PD-02 Premio Dottorato: “Chimica Organica per le Scienze della Vita” Platella C. <i>Towards DNA-targeting magic bullets: searching for potential conformation-selective G-quadruplex ligands</i>
	15:35-15:55	OC-35 Mancuso A. <i>Structural modifications of glycoamino OPEs: synthesis and properties</i>
	15:55-16:15	OC-36 Finamore C. <i>Synthesis of new oxadiazole derivatives as potent and selective FXR antagonists</i>
	16.15-16.35	OC-37 Bucci R. <i>Enantioselective Syntheses of Morpholino β-Amino Acids for the preparation of different nanomaterials</i>
Sessione #12 (Sala Einaudi)	Chairman: M. Bonchio	
	15:00-15:15	PD-03 Premio Dottorato: “Chimica Organica per l'Ambiente, l'Energia e le Nanoscienze” Albano G. <i>Outstanding chiroptical features in thin films of chiral π-conjugated oligomers: from synthesis to applications</i>
	15:15-15:35	OC-38 D'Anna F. <i>Ionic Liquid Gels: Tunable and Multifaceted Materials</i>
	15:35-15:55	OC-39 Riela S. <i>Clay minerals: a challenge for chemists</i>
	15:55-16:15	OC-40 Giacalone F. <i>Carbon Nanoforms-based Hybrid Catalysts</i>
	16.15-16.35	OC-41 Melucci M. <i>Graphene oxide composites-based filters for tap water purification</i>
16.35-17.00 Coffee Break		

Sessione #13 (Sala Cavour)	Chairman: M. Funicello	
	17:00-17:20	OC-42 Tiecco M. <i>Novel Hydrophobic Deep Eutectic Solvents (DESS) as water-immiscible H-bond-based solvents</i>
	17:20-17:40	OC-43 Benassi A. <i>Light meets click chemistry: development of novel, photoactivable, 2,5-diaryl tetrazoles for labelling nucleic acids</i>
	17:40-18:00	OC-44 Risi C. <i>Hydrogen Borrowing reactions in water medium</i>
	18:00-18:20	OC-45 Ferlin F. <i>Combining Safer Solvents Heterogeneous Catalysis and Flow Technology Toward Sustainable C-H Activation Methodologies</i>
Sessione #14 (Sala Giolitti)		
	18:20-18:40	OC-46 Martina K. <i>Green approach to aerobic alcohol oxidation and transfer hydrogenation of nitro benzene derivatives</i>
	18:40-19:00	OC-47 Valentini F. <i>Highly selective toluene oxidation to benzaldehyde: a sustainable process</i>
	Chairman: A. Liguori	
	17:00-17:20	OC-48 Casertano M. <i>Development and synthesis of simplified analogs of a bioactive natural polyketide</i>
Sessione #15 (Sala Einaudi)	17:20-17:40	OC-49 Cardano F. <i>Spiropyran for light-controlled delivery of Aspirin</i>
	17:40-18:00	OC-50 Forgione R. E. <i>The interplay between NMR spectroscopy and molecular modeling: a powerful tool to investigate protein-glycoconjugate interactions</i>
	18:00-18:20	OC-51 Maranzana, A. <i>Degradation of Ochratoxin A in a wide pH range: experimental and computational study</i>
	18:20-18:40	OC-52 Hawala I. <i>Innovative synthetic approach based on the Native Chemical Ligation for development of new dual PET/OI peptide imaging probes</i>
Sessione #15 (Sala Einaudi)	18:40-19:00	OC-53 Marafon G. <i>α-Amino Aldehydes as Monomers for the Synthesis of Imine-/Amide-based Foldamer Structures</i>
	Chairman: M. Petrini	
	17:00-17:20	OC-54 Cinà V. <i>Modified Carbon Nanoforms Systems for Asymmetric Catalysis</i>
	17:20-17:40	OC-55 Magli S. <i>Multimodal Functionalization of Nanoparticles for b-cells Imaging: new diagnostic tools for pancreatic regenerative therapies</i>
	17:40-18:00	OC-56 Fiammengo R. <i>Site-selective immobilization of leptin on gold nanoparticles</i>
Sessione #15 (Sala Einaudi)		
	18:00-18:20	OC-57 Scala A. <i>Engineered Polylactide-based Nanoparticles as Multifunctional Drug Delivery Systems</i>
	18:20-18:40	OC-58 Sacco M. <i>Azomethine ylides: a powerful tool for Nanodiamonds-based contrast agents and drug delivery systems</i>
	Chairman: G. Reginato	
	18:40-19:00	ChemPubSoc Europe Editor's Lecture Novara F. <i>Current Challenges in Chemistry Publishing</i>

Mercoledì 11 Settembre - Mattino (Presso Sala Cavour, Centro Congressi Torino Incontra, via Nino Costa 8, Torino)		
Sessione Plenaria #6 (Sala Cavour)	Chairman: E. Marcantoni	
	9.00-9.30	KN-03 Pace V. <i>Designing new synthetic concepts for imparting molecular complexity with C-1 sources</i>
Sessione #16 (Sala Cavour)	Chairman: da definire	
	09:30-09:50	OC-59 Brandolese A. <i>N-Heterocyclic Carbene (NHC)-Organocatalyzed kinetic resolution of biologically active Biginelli compounds</i>
	09:50-10:10	OC-60 Rizzo S. <i>High Enantioselection Performances of Inherently Chiral Ionic Liquids with Axial, Helical and Central Stereogenicity</i>
	10:10-10:30	OC-61 Lauro G. <i>DFT/NMR approach for the configuration assignment of groups of diastereoisomers by the combination and comparison of experimental and predicted sets of data</i>
Sessione #17 (Sala Giolitti)	Chairman: V. Costantino	
	09:30-09:50	OC-62 Piccialli V. <i>Synthesis and antitumor activity of polybrominated C15 acetogenin derivatives</i>
	09:50-10:10	OC-63 Zongo L. <i>Folate-Tannin Microcapsules for Oncologic Theragnosis Applications</i>
	10:10-10:30	OC-64 La Ferla B. <i>Sweet and Smart Nanovectors for Live-Cell Drug Delivery and in vivo Bone Targeting</i>
Sessione #18 (Sala Einaudi)	Chairman: A. Goti	
	09:30-09:50	OC-65 Toniolo G. <i>Stable and Water-Dispersible Quantum Dots: Modular Fluorescent Tools for Bioimaging Applications</i>
	09:50-10:10	OC-66 Viglianisi C. <i>Macromolecular and nano-supported antioxidants for practical applications</i>
	10:10-10:30	OC-67 Nitti A. <i>Photopolymerization of Selected Monomers Initiated by Arylazo Sulfones</i>
10.30-11.00 Coffee Break		

Sessione #19 (Sala Cavour)	Chairman: L. Pellacani	
	11:00-11:20	OC-68 Lanzalunga O. <i>N</i> -hydroxyphthalimide: an Efficient Hydrogen Atom Transfer (HAT) Mediator in Hydrocarbon Oxidations Promoted by Nonheme iron(IV)-oxo complexes
	11:20-11:40	OC-69 Navazio F. Efficient Lewis Acid Multicomponent-Promoting System in the Carbon-Nitrogen Bond Formation
	11:40-12:00	OC-70 Cauteruccio S. Non photochemical route to functionalized thiophene-based [7]helicenes
	12:00-12:20	OC-71 Caprioglio D. Iodine-mediated deconstructive annulation of isoprenylchromenes to benzo[<i>c</i>]chromenes. Development of a one-step synthesis of cannabinal (CBN)
	12:20-12:40	OC-72 Menichetti A. Nitroso Diels-Alder chemistry on 1,2-dihydropyridines as a platform to obtain novel anti-diabetic agents
	12:40-13:00	OC-73 Citarella A. Direct and Chemoselective Transfer of the Difluoromethyl (CHF ₂) Unit Into Carbon-Electrophiles under Nucleophilic Regime
Sessione #20 (Sala Giolitti)	Chairman: F. Cardona	
	11:00-11:20	OC-74 Molinaro A. A new biopolymer skeleton formed by a dimer of carbohydrate and aminoacid produced by <i>Rhizobium radiobacter</i> and useful for plant immunity evasion
	11:20-11:40	OC-75 Chini M. G. Application of quantum chemical integrated multistep protocol in the stereochemical determination of natural products
	11:40-12:00	OC-76 Martinelli J. Mn ^{II} -complexation / Al ¹⁸ F-labeling of new AMP-based chelators for applications in Magnetic Resonance Imaging and Positron Emission Tomography
	12:00-12:20	OC-77 Gentile D. Ligand Based Identification of FABP4 Inhibitors: Synthesis and Biological Screening
	12:20-12:40	OC-78 Masi M. Fungal phytotoxins with potential herbicidal activity for <i>Cenchrus ciliaris</i> biocontrol
	12:40-13:00	OC-79 Petricci E. Synthetic approaches to the development of new Antibody-Drug Conjugates charged with unconventional payloads
Sessione #21 (Sala Einaudi)	Chairman: V. Capriati	
	11:00-11:20	OC-80 Rossi S. Technology-driven catalysis: (SLA) 3D-printed devices for organic synthesis
	11:20-11:40	OC-81 Pinna A. Synthesis of new chiral catalysts through multicomponent processes
	11:40-12:00	OC-82 Castagnolo D. Chemo-Enzymatic Cascades for the Synthesis of Heteroaromatic and Sulphur Containing Pharmaceutical Ingredients
	12:00-12:20	OC-83 Zicarelli I. Synthesis of 1,3-oxazinan-2-ones by catalytic incorporation of carbon dioxide into <i>N</i> -alkyl-3-yn-1-amines
	12:20-12:40	OC-84 Filippini G. Highly Performing Iodoperfluoroalkylation of Alkenes Triggered by the Photochemical Activity of Perylene Diimides
	12:40-13:00	OC-85 Zappimbulso N. C–H Bond arylations of 1,2,3-triazoles by reusable Pd/C catalyst in solvent-free condition

Mercoledì 11 Settembre - Pomeriggio (Presso Sala Cavour, Centro Congressi Torino Incontra, via Nino Costa 8, Torino)		
	15.00-15.10	Foto di Gruppo
Sessione #22 (Sala Cavour)	Chairman: A. Evidente	
	15:15-15:35	OC-86 Foschi F. <i>Memory of Chirality Approach to the Synthesis of α-Quaternary Amino Acid Derivatives</i>
	15:35-15:55	OC-87 Massolo E. <i>Tetrachlorosilane mediated direct amidation method</i>
	15:55-16:15	OC-88 Colella M. <i>Straightforward Tactics and Enabling Technologies as useful tools for Fluoroalkylations</i>
	16.15-16.35	OC-89 Lenci E. <i>Diversity-Oriented Synthesis and chemoinformatic analysis of sp^3-rich molecular scaffolds using imine-based multicomponent reactions</i>
Sessione #23 (Sala Giolitti)	Chairman: L. Cipolla	
	15:15-15:35	OC-90 Marzano M. <i>A new symmetric G-rich Oligonucleotides incorporating a 3'-3' inversion of polarity site as an interesting model for ligand binding studies.</i>
	15:35-15:55	OC-91 Falanga A. P. <i>Synthesis and characterization of a PNA probe targeting the Bcl-2 gene promoter: a promising tool in anticancer treatment</i>
	15:55-16:15	OC-92 Leone L. <i>Combined effect of amide protons and second sphere water molecules on the relaxivity of Gd(III)-DO3A-hydroxypropionamide complexes</i>
	16.15-16.35	OC-93 Fioretto L. <i>From microalgae to vaccine adjuvant: immunomodulant activity of sulfavants and its correlation with colloidal self-assembly</i>
Sessione #24 (Sala Einaudi)	Chairman: M. Salamone	
	15:15-15:35	OC-94 Dughera S. <i>Gold Catalysed Coupling Reactions of Arenediazonium o-Benzenedisulfonimides</i>
	15:35-15:55	OC-95 Veltri L. <i>A Palladium Iodide – Catalyzed Oxidative Carbonylation Process for the Synthesis of Functionalized Imidazopyridines</i>
	15:55-16:15	OC-96 Gualandi A. <i>Allylation of Aldehydes by Dual Photoredox and Nickel Catalysis</i>
	16.15-16.35	OC-97 Galloni P. <i>Sustainable Catalytic Bromination of porphyrins</i>
16.40-17.00 Coffee Break		

Sessione Plenaria #7 (Sala Cavour)	Chairman: F. Novara	
	17.00-17.20	Premiazione poster e Flash 1° premio
Sessione #25 (Sala Cavour)	Chairman: R. Noto	
	17.20-17.40	OC-98 Ceccarelli J. <i>Pyridyl and quinolyl methanols: applications in metal-free reductions of aromatic nitro compounds</i>
	17.40-18.00	OC-99 Benzi A. <i>A convenient access to imidazo[1,2-a]pyridines and fluorescent polycycles from nitrodiene building-blocks</i>
	18.00-18.20	OC-100 Maiuolo L. <i>Base Mediated 1,3-Dipolar Cycloaddition of Azides with Substituted Enaminones for Regioselective Synthesis of Trisubstituted 1,2,3-Triazoles</i>
	18.20-18.40	OC-101 Giofrè S. <i>Divergent reactivity of N-allyl-2-aminophenols in domino reactions exploiting hypervalent iodine(III) reagents</i>
	18.40-19.00	OC-102 Romeo R. <i>Synthesis of 1,2,3-Triazole/MWCNT Conjugates for Environmental Application</i>
(Sala Giolitti)	17.20-19.00	Riunione Gruppo Interdivisionale Biotecnologie
Sessione #26 (Sala Einaudi)	Chairman: S. Menichetti	
	17.20-17.40	OC-103 Cerveri A. <i>Phosphine-catalyzed stereoselective dearomatization of 3-NO₂-indoles with allenates</i>
	17.40-18.0	OC-104 Pomelli C. S. <i>Dicationic Ionic Liquids: Synthesis, Characterization and catalytic Properties</i>
	18.00-18.20	OC-105 Dessì A. <i>Photocatalytic hydrogen production by means of Pt/brookite TiO₂ sensitized with dithienosilole-based organic dyes</i>
	18.20-18.40	OC-106 Matassini C. <i>Copper-free methodologies for the multimerization of bioactive iminosugars</i>
	18.40-19.00	OC-107 Moran Plata M. J. <i>Non-conventional technologies for copper heterogeneous catalysts production and its applications in organic synthesis</i>
20.30 - Cena Sociale: Sala dei Re – Museo Egizio		

Giovedì 12 Settembre (Presso Aula Magna, Cavallerizza, Università di Torino, via Verdi 9, Torino)		
Sessione Plenaria #8	Chairman: A. Abbotto	
	9.00-9.30	M-04 Medaglia G. Ciamician Dell'Amico L. <i>The Ciamician Up-To-Date Lesson to a Ciamician Medalist. Organo-, Stereoselective-, and Photocatalysis in Sustainable Organic Synthesis.</i>
	Chairman: L. Triggiani – M. Da Pian	
	9:30-10.00	Elsevier Lecture Rodriguez del Rio C. <i>Finding novel lead compounds in pesticide discovery inspired by pharmaceutical research</i>
	10.00-10:15	Premio Reaxys
	Chairman: D. Misiti	
	10:15-10:45	KN-04 Cevasco G. <i>I primi 150 anni della Tavola Periodica degli Elementi Chimici: tra Chimica, Storia e Letteratura</i>
10.45-11.15 Coffee Break		
Sessione Plenaria #8	Chairman: S. Tortorella, - E. Lenci	
	11.15-11.20	Apertura evento
	11:20-11:40	Redazione FRidA <i>Tu la conosci FRidA? Una piattaforma web, un laboratorio di comunicazione, tutta la ricerca di UniTO</i>
	11.40-12.10	Garlaschelli L. <i>Chimica e Misteri</i>
	12.10-12.40	Malvaldi M. <i>L'acqua di Babele, ovvero come non fare un esperimento</i>
	12.40-12.45	Chiusura evento
	12.45-13.00	Conclusione Lavori

Lunedì 9 Settembre 2019: Prima sessione Poster – h 13.00-15.00.

Autore Presentatore	Titolo	Codice
T. Tedeschi	Study of Milk Proteins' Digestibility: Characterization of the Peptide Fraction Released and Potential Impact on Allergenicity	PC-01
C. Coppola	Design of novel organic hole transport materials for perovskite solar cells	PC-02
S. Tallarico	Alternative Chemocatalytic Methods for Selective Conversion of Cellulose into Lactic Acid	PC-03
S. Nejrotti	Natural deep eutectic solvents as an efficient and versatile catalytic system for the Nazarov cyclization	PC-04
A. Rinaldi	Synthesis of Indenes by Tandem Gold(I)-Catalyzed Propargyl Claisen Rearrangement/Hydroarylation Reaction	PC-05
R. Mancuso	PdI2-Catalyzed Carbonylative Approach to Benzothiophene Derivatives from (2-Alkynyl)(methylthio)benzenes	PC-06
C. Rizzo	Hybrid ionogels as potential antioxidant agents	PC-07
F. Billeci	Gluconic acid for eco-friendly Ionic Liquids: chemical and biological investigations.	PC-08
S. Marullo	Conversion of carbohydrates into 5-HMF in Deep Eutectic Solvents under mild reaction conditions	PC-09
M. Massaro	Zinc oxide nanoparticles supported on halloysite nanotubes for environmental remediation	PC-10
E. Azzi	Visible-Light-Driven Synthesis of Tetrahydropyridazines from γ - δ Unsaturated N-Tosylhydrazones	PC-11
E. Mezzina	Synthesis and EPR investigation of a new stable diradical macrocycle	PC-12
T. Laurita	Regio- and diastereoselective organo-zinc promoted arylation of trans 2,3-diaryloxiranes by arylboronic acids: stereoselective access to trans 2,3-diphenyl-2,3-dihydrobenzofuran.	PC-13
P. La Manna	Green and Mild Friedel-Crafts Benzoylation of Arenes and Heteroarenes Under On Water Conditions	PC-14
R. D'Orsi	From HIV protease inhibitors to anticancer agents: diversity-oriented synthesis of new compounds with double biological activity	PC-15
A. Campofelice	New Molecules as Translational Readthrough Promoters of Nonsense Mutations: Rescuing the CFTR Protein	PC-16
F. Buonsenso	A novel procedure for rapid and accurate quantification of amino functionalities bonded to solid porous matrices	PC-17
C. Capacchione	Synthesis of new Water Reducer Plasticizers for concrete, gypsum and clay	PC-18
L. Menduti	Boron-functionalized benzodithiophenes	PC-19
M. Novello	New Synthesis of 4-Iodothienopyranone Derivatives by Iodocyclization Reaction	PC-20
M. Cirillo	Development of new beta-lactam-based integrin ligands: Synthesis and Applications	PC-21
A. Massi	Enantioselective Desymmetrization of 1,4-Dihydropyridines by Oxidative NHC-Catalysis	PC-22
C. Bellomo	Functionalization of the BODIPY core with styryl carboranes: synthesis, characterization and photophysical properties.	PC-23
M. Blangetti	Chemoselective Addition of Highly Polar Organolithium Reagents to Carboxamides in Deep Eutectic Solvents (DESS) Under Air: Novel Opportunities for the Synthesis of Ketones in Unconventional Solvents	PC-24
P. Russo	A New Synthesis Of 2-(imidazo[1,2-a]pyridin-3-yl)acetamides By Palladium-Catalyzed Oxidative Aminocarbonylation Of (N-Prop-2-yn-1-yl)pyridin-2-amines	PC-25

S. Ghinato	An Unusually Divergent Reactivity of Basic Organolithium Compounds in Protic Unconventional Media: Novel Opportunities for the Synthetic Elaboration of Aryl Carboxyamides in Deep Eutectic Solvents	PC-26
S. De Vita	Cl.O.E.: An automated workflow to simplify the early steps of Structure-Based Inverse Virtual Screening	PC-27
A. Gelain	Unravelling the interactions between an antiproliferative 1,2,5-oxadiazole derivative and STAT3	PC-28
F. Franco	One-pot synthesis of α -trifluoromethylthiolated carboxylic acid derivatives	PC-29
F. Migliorini	Synthesis and development of linker for bioconjugation of Smo inhibitors	PC-30
D. Gentili	Synthesis of substituted 1,2-dihydropyridines by cerium(III) catalyzed amine-aldehyde polycondensation	PC-31
C. Del Plato	Resorc[4]arene-based site directed immobilization of antibodies for immunosensors development	PC-32
L. Forti	The marine worm <i>Hermodice carunculata</i> is a promising biocatalyst for aldol reactions	PC-33
L. Zongo	Chemical Derivatisation of Tannins for Functional Materials	PC-34
L. Zongo	Stability Profiles of Lignin Microcapsules	PC-35
G. Pastore	Bio-based renewable polymeric materials from research to industrial point of view	PC-36
G. Lupidi	Novel Synthetic Analogues of Climacostol as Potent Anticancer Nature-Inspired Small Molecules	PC-37
G. Marsico	Synthesis of the fungal metabolites radicinin and its natural precursor deoxyradicinin: potential bioherbicides for invasive species control	PC-38
G. Marsico	Enantioselective Carbolithiation-Trapping Reaction of 1-Aryl-1-Alkenyl Carbamates	PC-39
P. Musci	Intriguing role of iodine on the stability and reactivity of dihalomethylithium carbenoids	PC-40
M. Barbero	Diastereoselective synthesis of axially chiral styrenes	PC-41
G. Biagiotti	GLYCOG Lab 4.0, the sweet nanofiller: a tangible case of transfer of technology (TOT)	PC-42
L. Leone	Accelerating water exchange in GdIII-DO3A-acetophenone derivatives by favouring the dissociative mechanism through hydrogen bonding	PC-43
J. Martinelli	MnEDTA-based multimeric contrast agents based on G0 and G2 PAMAM dendrimers	PC-44
E. Colarusso	Targeting mPGES-1 by a combinatorial approach: identification of 2-aminobenzothiazoles as scaffold for new PGE2 modulator in human cancer cells	PC-45
S. Baldino	Unprecedented use of a deep eutectic solvent as hydrogen source for Ru(II)-catalyzed transfer hydrogenation of carbonyl compounds under mild conditions	PC-46
A. D'Amato	Quinoline cyclic tripeptoids as novel DNA bis-intercalating agents	PC-47

Martedì 10 Settembre 2019 Seconda Sessione Poster - h 13.00-15.00

Autore Presentatore	Titolo	Codice
S. Terracciano	Modulation of biological target selectivity through an appropriate scaffold decoration	PC-48
M. Potenza	A multistep computational protocol towards the identification of 2-amino-1,3,4-thiadiazole-based molecules as novel mPGES-1 inhibitors	PC-49
F. Cardona	Synthesis of bifunctional inhibitors to address type 2 diabetes by dual enzyme targeting	PC-50
P. Quagliotto	Micellar Assisted Synthesis of Chalcones as Intermediates for Bipyridines	PC-51
M.M.H. Desoky	Synthesis and characterization of polymers as HTMs for perovskite solar cells	PC-52
M.M.H. Desoky	Synthesis of a donor-acceptor polymer for perovskite solar cells	PC-53
M. Gastaldi	Azodyes based polymers for 3D printing	PC-54
G. Viscardi	Squaraine dyes: interaction with bovine serum albumin to investigate supramolecular adducts with aggregation-induced emission (AIE) properties	PC-55
V. Patamia	Sigma-1 Receptors: Computational Model to Predict the Agonist/Antagonist Effect	PC-56
C. Carlucci	Flow technology for the preparation of Active Pharmaceutical Ingredients	PC-57
G. Siani	Zwitterionic Natural Deep Eutectic Solvents as green alternative for the CO ₂ capture	PC-58
R. Di Lecce	Bioactive metabolites produced by the fungal pathogens <i>Diplodia fraxini</i> and <i>Hymenoscyphus fraxineus</i> isolated from infected <i>Fraxinus</i> spp. trees	PC-59
M. Masi	Natural products as stimulants and inhibitors of parasitic seed germination and radical growth	PC-60
A. Zarrelli	New degradation products of Irbesartan: Analysis and identification from a simulated chlorinated disinfection treatment [1]	PC-61
D. Tanini	Sulfur, Selenium, and some silicon: A new access to disulfides and mixed chalcogenides with GPx-like activity	PC-62
G. Di Fabio	New Phosphate-Linked Tyrosol Dimers: Synthesis, antioxidant activity, metal chelating capacity and effect on A β aggregation ¹	PC-63
G. Di Fabio	A general synthetic strategy and preliminary investigations of pro-drug Silibinin conjugates	PC-64
D. Franchi	Structural modification of pyridine-containing ligands: customize optical and electrochemical properties of Cu complexes	PC-65
E. Licandro	Luminescent rhenium(III)-peptide nucleic acids conjugates for microRNA targeting	PC-66
V. Pelliccioli	Synthesis and characterization of chiral bis-benzo[1,2-b:4,3-b']dithiophenes	PC-67
M. Vagnoni	Lipase catalyzed oxidation in sugar-derived Natural Deep Eutectic Solvents	PC-68
S. Menichetti	Synthesis of heterohelicenes through the Povarov reaction	PC-69
G. Forti	Sustainable and Water-Soluble Non-Fullerene Acceptors for Bulk Heterojunction Solar Cells	PC-70
F. Formaggio	Influence of flat and helical peptide spacers on the redox properties of two covalently bound, ferrocenyl moieties	PC-71
O. Yildirim	Squaraine-Based Porous Organic Polymers Containing Trigonal Linkers	PC-72
V. Marsicano	Coinage-metal catalyzed functionalizations of propargylic amine derivatives	PC-73

O. Celaj	Spectroscopic elucidation and antimicrobial screening of myrtogalloyl glycosides from <i>Myrtus communis</i>	PC-74
K. Fidecka	Collagen capped halloysite nanotubes as multifunctional drug carriers	PC-75
A. Pagano	Visible-Light Promoted Dearomatizing Spirocyclizations of Ynone-Tethered Indoles	PC-76
F. Trapani	Plasticizers from Natural Resources	PC-77
F. Pollastro	Synthesis of Pre-cannabinoid Terpenyl esters, an Unexplored Class of Native Phytocannabinoids	PC-78
D. Mattoteia	Molecular Editing of Cannabichromene (CBC)	PC-79
V. Algieri	Synthesis of Nucleobase-Containing 1,2,3-Triazoles with Potential Biological Activity through Metal Catalyzed Azide-Alkyne 1,3-Dipolar Cycloaddition	PC-80
A. Fontana	Preparation and characterization of graphene oxide foils for applications in the biomedical field	PC-81
A. Menichetti	Developing new ways to introduce the boron atom in organic molecules by ring-opening reactions	PC-82
R. Stefania	Synthesis of fluorinated curcumin-based molecules for detecting amyloid plaques by ¹⁹ F-MRI	PC-83
M. S. Christodoulou	Ruthenium-catalyzed ring transformation of 4,4-disubstituted isoxazolin-5-ones to different heterocyclic systems	PC-84
S. V. Giofrè	N,N-bis-Triazol-Sulphenamides: A New Family of Halogen Free Flame Retardants	PC-85
M. C. Ligi	Decoration of carbon nanotubes for the combined therapy of cancer	PC-86
V. Raglione	Synthesis of new amphiphilic Zn-Salophen complexes derivatized by bile acids	PC-87
J. Mateos	Naphtochromenones as Cross-Border Light Photoredox Catalysts	PC-88
A. Vega Peñaloza	Microfluidic Dearomatisation of Indoles by a Light-Driven [2+2] Paternò-Büchi Process	PC-89
G. Bertuzzi	Higher order cycloadditions: from a stereoselective rediscovery to a computational fascination	PC-90
M. De Angelis	Stereocontrolled synthesis of pyrrolidine iminosugars' lipophilic derivatives	PC-91
L. Primitivo	Synthesis of new 1,2-diaminic ligand for the asymmetric Henry reaction	PC-92
A. Vasco Corti	Catalytic Asymmetric Oxidative γ -Coupling of α,β -unsaturated Aldehydes with Air as the Terminal Oxidant	PC-93
P. Capurro	Synthesis of α -Amido Silyl Enol Ethers via Silylative Ketene 3-Component Reactions: Synthetic Applications in Organic and Natural Products Synthesis	PC-94

Lectures Medaglie

Calixarenes: from Chemical Curiosity and Basic Research to Industrial Implementation

A. Casnati

Department of Chemistry, Life Science and Environmental Sustainability,
Parco Area delle Scienze 17/a, 43124 Parma
e-mail: casnati@unipr.it

Although the story of the cyclic oligomers obtained by basic condensation of p-alkylphenols and formaldehyde traces back in the early 1940s, it was at the end of the 1970s that the potentiality of these macrocycles in supramolecular chemistry was apparent thanks to the work of C. D. Gutsche, who developed their selective syntheses, and of R. Ungaro and A. Pochini at Parma University that definitely demonstrated their cyclic structure by X-ray crystallography.¹ Since then, their synthesis and functionalization were deeply studied worldwide and calixarenes became extremely popular platforms giving rise to a burst in basic research publications for these macrocycles.² Starting from the early 1990s, we have proposed a series of calixarene-based receptors for spherical metal ions, especially caesium and potassium, anions and ion-pairs which, in some cases, still remain among the most selective ligands for these ions known so far. More recently,³ we moved our interests towards the targeting of biologically relevant species thus obtaining derivatives possessing antimicrobial activity, able to inhibiting the adhesion of lectins on cell surface or to selectively bind specific amino acid residues on proteins. Multivalency, moreover, was properly exploited to implement a series of calixarene-based delivery systems able to bind and transfect nucleic acids (NAs) into cells with efficiency even better than that observed for commercially available formulations. Calixarenes also exhibited to be proper scaffolds for the design of multifunctional catalysts for the cleavage of carboxylic or phosphoric esters. Mechanistic studies disclosed a high level of cooperation between catalytic units especially in the enhancement of the rates of cleavage of NA models, di- or oligonucleotides.

Altogether, these studies highlight that calixarenes are special scaffolds for the development of highly efficient receptors, functional materials, catalysts and ligands for bio(macro)molecules, exploiting different tools typical of supramolecular chemistry such as preorganization and cooperativity of ligating/catalytic sites, multivalent effects and self-assembly. Their lipophilic backbone can be, moreover, exploited to give rise to peculiar amphiphilic structures extremely useful for applications in (bio)nanotechnology, separation science and formulation chemistry. Two special industrial implementations of studied calixarenes will be also discussed in radioactive waste treatment³ and lubricant additive formulation.⁴

References:

- [1] G. D. Andreetti, R. Ungaro, A. Pochini, *J. Chem. Soc., Chem. Commun.* **1979**, 1005-1007.
- [2] A. Casnati, *Chem. Commun.* **2013**, 49, 6827-6830.
- [3] M. Giuliani, I. Morbioli, F. Sansone, A. Casnati, *Chem. Commun.* **2015**, 51, 14140-14159.
- [4] M. Notari, A. Roselli, A. Casnati, F. Sansone, A. Burlini, *PCT Int. Appl. (2017)*, WO 2017025900 A1 20170216.

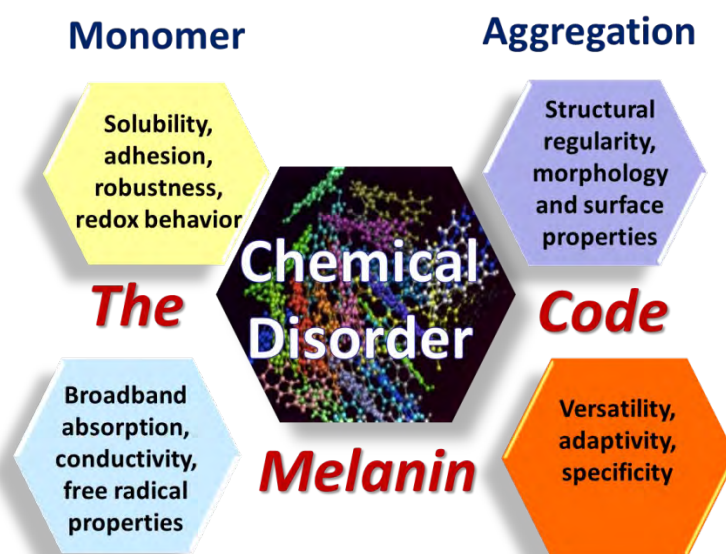
The *Melanin* Code: Deciphering Nature's Paradigms for Chemical Functionality

M. d'Ischia

Department of Chemical Sciences, University of Naples Federico II, Via Cinthia 80126 Naples Italy
dischia@unina.it

Melanins are a class of black-to-reddish brown functional pigments derived biogenetically from the oxidative polymerization of tyrosine and other phenolic precursors. Found widespread in nature, from man and mammals to birds, cephalopods, plants and microorganisms, melanins provide a paradigm system for translating biological concepts into innovative biomedical and technological solutions. This is due to the highly disordered and heterogenous nature of these polymeric pigments, which share unique physicochemical properties, including high insolubility, a semiconductor behavior, efficient light-dissipation capacity, a permanent free radical character and an amorphous supramolecular architecture. Although melanins are believed to play a broad range of biological roles, from photoprotection to antioxidant defense, metal and toxin binding and radioprotection, the evolving scenario of theories and observations still suffers from the lack of a complete frame of structure-property-function relationships that could be translated into innovative applications in biomedicine and materials science.

Aim of this presentation is to critically discuss Nature's counterintuitive logic of selecting a single class of insoluble and structurally disordered polymers (the melanins) to implement multipurpose multifunctional systems for diverse biological roles. Following a brief survey of recent advances, a possible rationale is proposed, which is referred to as "**The Melanin Code**". **Chemical disorder**, which is both **monomer-** and **aggregation-**dependent, is the key to unveil this "Code". It provides an ingenious means of generating and combining unique opto-electronic and paramagnetic properties, via intrinsically and extrinsically controlled π -electron delocalization, with versatility, adaptivity and site-specificity to ensure dynamic responses in different biological contexts.



M-03

Development of catalytic stereoselective methodologies: sense and sensibility

M. Benaglia

Dipartimento di Chimica, Università degli Studi di Milano, Via Golgi, 19, 20133 Milano
maurizio.benaglia@unimi.it

Organic synthesis has traditionally been performed in batch that means in round-bottomed flasks, test tubes or closed vessels; however, continuous flow processes have gained lately much attention from synthetic organic chemists. Application of these systems for the preparation of fine chemicals, such as natural products or active pharmaceutical ingredients (APIs) is becoming very popular. Although pharma industry still relies on multipurpose batch or semi-batch reactors, it is evident that interest is arising towards continuous flow manufacturing of APIs.¹

Aim of the presentation will be to highlight some of the stereoselective catalytic methodologies developed by our group, with a special focus on the very recent advances concerning the continuous flow multistep synthesis of chiral organic molecules.

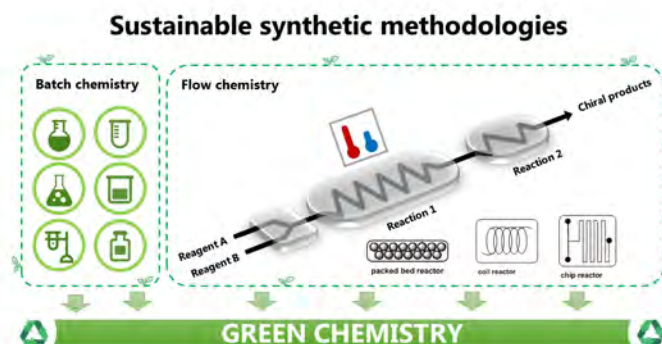


Figure 1: technology-driven organic synthesis

Organocatalytic stereoselective transformations using catalytic reactors will be presented; both packed-bed and monolithic reactors, either made by silica and/or organic polymers, have been successfully used in reactions promoted by immobilized enantiopure amines. Furthermore, the use of different chiral metal-free catalysts in micro- and mesofluidic devices, to perform technology-assisted stereoselective transformations will be also discussed, including reactions of nitroacrylates and metal-free catalytic synthesis of biologically active chiral amines.²

Catalytic reactions in (micro)-mesoreactors will be compared with stereoselective catalytic in-flow reactions in 3D-printed reactors.³ The fabrication of *ad hoc* designed reactors and other devices, to perform different organic reactions, may give new impulse to the use of enabling technologies in the synthesis of complex (chiral) molecules.

References:

- [1] R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, 20, 2-25.
- [2] S. Rossi, A. Puglisi, L. Raimondi, M. Benaglia, *ChemCatChem* **2018**, 10, 2717-2733.
- [3] S. Rossi, D. Brenna, R. Porta, A. Puglisi, M. Benaglia, *Angew. Chem. Int. Ed.* **2017**, 56, 4290-4294;

The Ciamician Up-To-Date Lesson to a Ciamician Medalist. Organo-, Stereoselective-, and Photocatalysis in Sustainable Organic Synthesis.

L. Dell'Amico

Department of Chemical Sciences, University of Padova, Via Marzolo 1, 35131 Padova, Italy
luca.dellamico@unipd.it

Sustainability has nowadays become not only a priority but a way-of-life we all must adopt. Since the past centuries, the utilisation of renewables for the generation of new substances or for energy production has been recognised as one of the main needs of our society. This was limpidly highlighted by Giacomo Ciamician back in 1912.¹ He recognised the renewables, such as light and CO₂, as indispensable ingredients towards a modern chemical synthesis.

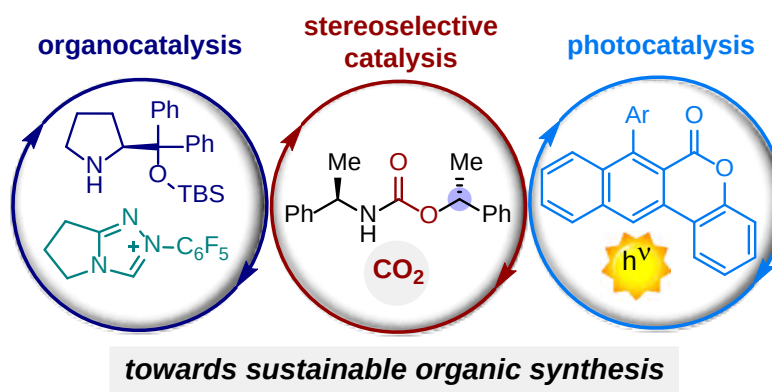


Figure 1: development and application of diverse types of catalysis towards sustainable organic synthesis.

About a hundred year later, also the research I performed has always – sometimes unconsciously – been guided by the principles of sustainable synthesis (Figure 1). Starting from the use of small organic molecules as organocatalysts,² to the catalytic stereoselective construction of complex molecular architectures using CO₂,³ through the use of light as key reagent⁴ to the progress of innovative reaction pathways.⁵

The lecture will focus on the key features of the different types of catalysis (organo-, stereo-, and photocatalysis), highlighting my personal contributions to the fields. Finally, perspectives towards the sustainability aspects will be discussed.

References:

- [1] G. Ciamician, *Science* **1912**, 36, 385-412.
- [2] a) L. Dell'Amico, Ł. Albrecht, T. Naicker, P. H. Poulsen, K. A. Jørgensen *J. Am. Chem. Soc.* **2013**, 135, 8063-8070. b) L. Dell'Amico, G. Rassu, V. Zambrano, A. Sartori, C. Curti, L. Battistini, G. Pelosi, G. Casiraghi, F. Zanardi, *J. Am. Chem. Soc.* **2014**, 136, 11107-11116.
- [3] J. Mateos, A. Cherubini, T. Carofiglio, M. Bonchio, N. Marino, X. Companyó, L. Dell'Amico, *Chem. Comm.* **2018**, 54, 6820-6823.
- [4] L. Dell'Amico, A. Vega-Penaloza, S. Cuadros, P. Melchiorre, *Angew. Chem. Int. Ed.* **2016**, 55, 3313-3317.
- [5] J. Mateos, F. Rigodanza, A. Vega-Penaloza, A. Sartorel, M. Natali, X. Companyó, M. Bonchio, L. Dell'Amico, **2019**, just submitted manuscript.

Lectures Premi Senior

Isonitrili al Pesto (*Isocyanides in Pesto Sauce*)

A. Basso

Università degli Studi di Genova, Dipartimento di Chimica e Chimica Industriale, Via Dodecaneso 31,
Genova
andrea.basso@unige.it



Searching for a common thread able to connect the research topics investigated in recent years in Genova, isocyanides¹ are indeed a constant presence (and fragrance!). We have employed them not only as building blocks in classic multicomponent reactions, such as the Passerini and Ugi ones, but also:

- as building blocks in the development of novel multicomponent reactions^{2,3}
- as activators of arylacetic acids to generate ketenes, further elaborated to captodative olefins⁴
- as dipolarophiles in cycloaddition reactions to assemble complex tetrazole compounds⁵
- as nitrogen source in the synthesis of combinatorial libraries of polycyclic (spiro)compounds⁶
- as fluorescent probes during *in cellulo* activation of prodrugs

This communication will be a journey through the multiple applications of this extremely versatile class of compounds, with main focus on the most recent results and on the combination of isocyanide chemistry with photoinduced and photocatalyzed processes.

References:

- [1] M. Giustiniano, A. Basso, V. Mercalli, A. Massarotti, E. Novellino, G. C. Tron, J. P. Zhu, *Chem. Soc. Rev.* **2017**, 46, 1295-1357.
- [2] A. Basso, L. Banfi, S. Garbarino, R. Riva, *Angew. Chem. Int. Ed.* **2013**, 52, 2096-2099.
- [3] F. Ibba, P. Capurro, S. Garbarino, M. Anselmo, L. Moni, A. Basso, *Org. Lett.* **2018**, 20, 1098-1101.
- [4] A. Basso, L. Banfi, A. Galatini, G. Guanti, F. Rastrelli, R. Riva, *Org. Lett.* **2009**, 11, 4068-4071.
- [5] P. Capurro, L. Moni, A. Galatini, C. Mang, A. Basso, *Molecules* **2018**, 23, 2758.
- [6] L. Moni, F. De Moliner, S. Garbarino, J. Saupe, C. Mang, A. Basso, *Front. Chem.* **2018**, 6, 668.

[4+2] Cycloadditions: Vintage Reactions for New Glycan-based Epitopes

C. Nativi

Department of Chemistry "Ugo Schiff", University of Florence; via della Lastruccia, 13 Sesto Fiorentino (FI)
Italy
cristina.nativi@unifi.it

Inverse electron-demand [4+2] cycloadditions involving glycals as electron rich dienophiles and α,α' -dioxothiones as electron poor dienes, are powerful reactions to afford glycosides chemo-, regio- and stereoselectively.¹ Relying on these versatile reactions, diastereomerically pure O-glycosides have been prepared and employed as starting material to obtain oligosaccharides, glycopeptides and glycoproteins. Among recent applications, the synthesis of a fucose mimetic (**1**) and of two saccharidic antigen mimetics (the mimetic of the melanoma antigen GM3 lactone, **2** and the mimetic of the mucin antigen Tn, **3**) have been developed (Figure 1).^{2,3}

Thanks to their structure versatility, these three mimetics have been used to decorate multivalent constructs, including nanoparticles,^{4,5} nano fibers,⁶ a cyclopeptidic (RAFT) scaffold⁷ as well as proteins. In particular, the synthesis, the multivalent presentation and biological assays run with a structurally constrained Tn antigen mimetic will be presented.

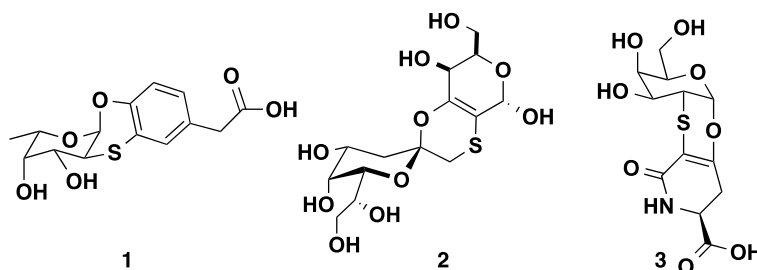


Figure 1: Structure of the fucose mimetic, **1**, of the GM3 lactone saccharide mimetic, **2** and of the MUC1 TnThr antigen mimetic **3**.

References:

- [1] C. Capozzi, A. Dios, R. W. Franck, A. Geer, C. Marzabadi, S. Menichetti, C. Nativi, M. Tamarez, *Angew. Chem.* **1996**, *108*, 805-807.
- [2] A. Arcangeli, G. Toma, L. Contiero, O. Crociani, L. Legnani, C. Lunghi, E. Nesti, G. Moneti, B. Richichi, C. Nativi, *Bioconj. Chem.* **2010**, *21*, 1432-1438.
- [3] J. Jimenez-Barbero, E. Dragoni, C. Venturi, F. Nannucci, A. Arda, M. Fontanella, S. Andre, F. J. Canada, H.-J. Gabius, C. Nativi, *Chemistry Eur. J.* **2009**, *15*, 10423-10431.
- [4] M. Manuelli, S. Fallarini, G. Lombardi, C. Sangregorio, C. Nativi, B. Richichi, *Nanoscale* **2014**, *6*, 7643-7655.
- [5] R. Gracia, M. Marradi, G. Salerno, R. Pérez-Nicado, A. Pérez-San Vicente, D. Dupin, J. Rodriguez, I. Loinaz, F. Chiodo, C. Nativi, *ACS Macro Lett.* **2018**, *7*, 196-200.
- [6] G. Gunay, M. Sardan Ekiz, X. Ferhati, B. Richichi, C. Nativi, A. B. Tekinay, M. O. Guler, *ACS Appl. Mater. Interfaces* **2017**, *9*, 16035-16042.
- [7] B. Richichi, B. Thomas, M. Fiore, R. Bosco, H. Qureshi, C. Nativi, O. Renaudet, L. BenMohamed, *Angew. Chemie Int. Ed.* **2014**, *53*, 11917-11920.

V-catalysis in Oxidation Reactions: from Mimesis of HalPO Enzymes to Sustainable Synthesis

V. Conte

Tor Vergata, Università di Roma, Dipartimento di Scienze e Tecnologie Chimiche,
via della Ricerca Scientifica, snc. 00133 Roma, Italy
valeria.conte@uniroma2.it

In the course of the years, elucidation of the mechanistic details of vanadium based oxidative catalytic systems has been the focus of the research in my group, performing *inter alia* kinetic, NMR, electrochemical and spectroscopic experiments, as well as theoretical calculations.¹ These studies allowed to establish correlation between the nature of the ligands bound to vanadium centre and catalytic activity in benchmark oxidations.

Meanwhile,² in our labs we developed a mild and efficient system for metal (V and Mo) catalyzed oxybromination of alkenes inspired by the activity of haloperoxidases enzymes. In particular we used a two-phase system where a brominating intermediate is formed in water from the metal catalyst, H₂O₂ and bromide ion. The peroxometal complex then oxidize the substrate dissolved in the organic phase. Yields and selectivities obtained, together with replacement of Br₂ with Br⁻, provide a procedure of significant synthetic interest. Indeed, excellent results were obtained with different substrates: aromatics, alkenes and alkynes. To render our system even more interesting from the sustainable point of view, we have improved it by substituting molecular chlorinated solvents with ILs, testing both hydrophilic and lipophilic ones. Also with such modification, first-class results in terms of reaction rates and selectivities have been obtained with alkenes and alkynes.^{1,2} More recently, we applied our procedure to the bromination of toluene and similar molecules;^{3,4} the reaction proceeds under very mild conditions, and nicely the substrates can be used as solvent, thus further improving the sustainability of the process.

Possible industrial applications of such procedure in the functionalization of natural products⁵ will be presented.

References:

- [1] a) V. Conte, A. Coletti, A.; Floris, B.; Licini, G.; Zonta C. *Coord. Chem. Rev.* **2011**, 255, 2165-2177. b) Conte, V.; Coletti, A.; Mba, M.; Zonta, C.; Licini G. *Coord. Chem. Rev.* **2011**, 255, 2345-2357.
- [2] a) F. Sabuzi, G. Pomarico, B. Floris, F. Valentini, P. Galloni, V. Conte, *Coord. Chem. Rev.* **2019**, 385, 100-136; b) B. Floris, F. Sabuzi, A. Coletti, V. Conte, *Cat. Today* **2017**, 285, 49–56; b) V. Conte, B. Floris, *Inorg. Chim. Acta* **2010**, 363, 1935-1946.
- [3] P. Galloni, M. Mancini, B. Floris, V. Conte, *Dalton Trans.* **2013**, 42, 11963-11970.
- [4] a) A. Coletti, P. Galloni, A. Sartorel, V. Conte, B. Floris, *Catal. Today* **2012**, 192, 44-55. b) B. Floris, F. Sabuzi, P. Galloni, V. Conte, *Catalysts* **2017**, 7, 261.
- [5] a) F. Sabuzi, E. Churakova, P. Galloni, R. Wever, F. Hollmann, B. Floris, V. Conte, *Eur. J. Inorg. Chem.* **2015**, 3519-3525; b) P. Galloni, V. Conte, F. Sabuzi, L. Migliore, M. C. Thaller, G. Matteucci, WO-2018/046584 A1, PCT/EP2017/072435.

PR-S4

**Challenges and creativity in API process development:
facing unexpected impurities formation.**A. Canavesi, P. Paravidino*Teva/Tapi, Sicor S.r.l.; via Terrazzano 77, Rho (MI)
Augusto.Canavesi@sicor.it*

Control of impurities is one of the major aspects in API development. A deep chemical knowledge of impurities formation mechanism is always very useful for setting a good control strategy for each and every possible impurity. Case studies are discussed for unexpected impurities formation: the origin of the impurities and the theoretical formation mechanisms are explored and analyzed in order to set the appropriate control strategy during process development.

Lectures Premi Junior

Reactivity and synthetic applications of new chalcogen-containing small molecules

D. Tanini

Department of Chemistry "Ugo Schiff" University of Florence, Via della Lastruccia 3-13, I-50019, Sesto Fiorentino, Firenze, Italy
E-mail: damiano.tanini@unifi.it

Organochalcogen compounds are valuable intermediates in organic synthesis and have additional applications in biology, medicinal chemistry, materials science, and catalysis. Sulfur- and selenium-containing small molecules and enzymes have been demonstrated to play a key role in a wide range of biological functions and biochemical mechanisms.¹ Recently, the synthesis and the use of organotellurium compounds have also faced a strong development, due to their unique properties and reactivity. Furthermore, over the past years a high number of selenium- and tellurium-containing catalytic antioxidants have been proposed as synthetic mimics of glutathione peroxidase (GPx).¹ In this context, the development of novel methodologies to access chalcogen-containing organic small molecules is highly sought after.

Our long standing interest in the study of the reactivity of silyl chalcogenides led us to disclose silicon mediated routes for the synthesis of new variously functionalized S-, Se-, and Te-containing derivatives.² Such procedures have been applied to the synthesis of novel cyclic and open chain derivatives, useful in organic synthesis, biology, and medicinal chemistry. In this communication, the reactivity of novel chalcogen-containing reagents, as well as their application to the synthesis and the evaluation of the antioxidant activity of novel GPx-like catalysts will be discussed. The modulation of chalcogen-bonding interactions as an effective strategy to enhance the catalytic antioxidant properties of functionalized selenides and tellurides will also be described.^{2,3}

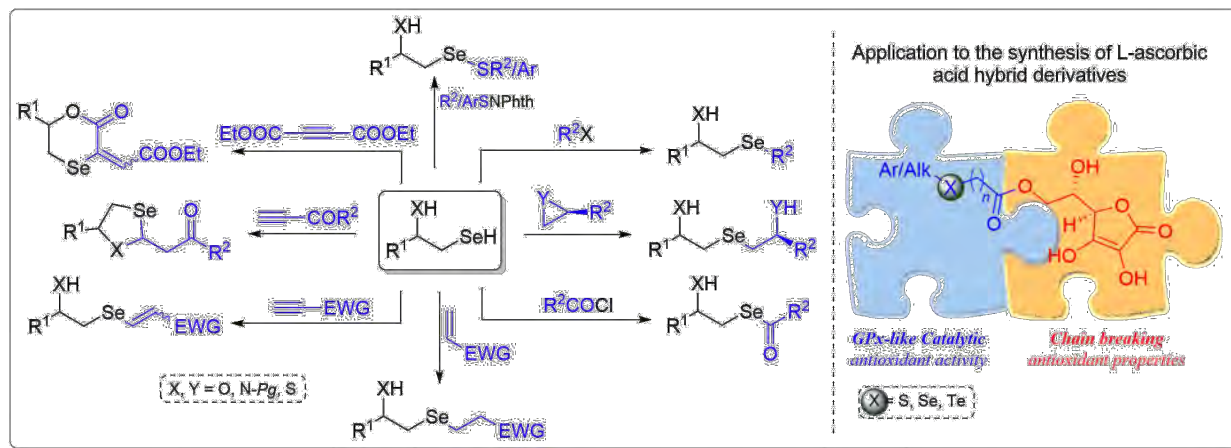


Figure 1: Examples of reactivity and synthetic applications of chalcogen-containing small molecules

References:

- [1] V. K. Jain, K. I. Priyadarsini, *Organoselenium Compounds in Biology and Medicine: Synthesis, Biological and Therapeutic Treatments*, Royal Society of Chemistry, London, **2018**.
- [2] (a) D. Tanini, A. Capperucci, et al. *Adv. Synth. Catal.*, **2018**, 360, 3367–3375; (b) D. Tanini, A. Capperucci, et al. *Adv. Synth. Catal.*, **2019**, 361, 2337–2346.
- [3] (a) D. Tanini, A. Capperucci, et al. *New J. Chem.*, **2018**, 42, 6077–6083; (b) D. Tanini, C. Viglianisi, A. Capperucci, S. Menichetti, et al., *Catalysts*, **2019**, 9, 333; (c) D. Tanini, A. Capperucci, et al. *Chem. Commun.*, **2019**, 55, 5705–5708.

Supramolecular dynamic systems away from equilibrium

G. Ragazzon,^a L. J. Prins^b

^a Department of Chemical and Pharmaceutical Sciences, University of Trieste, via L. Giorgeri 1, 34127 Trieste, Italy

^b Department of Chemical Sciences, University of Padova, via Marzolo 1, 35122 Padova, Italy
gragazzon@units.it

Weak interactions underlie recognition events at the nanoscale. In most cases, these interactions have been studied in static systems, mostly at equilibrium. However, supramolecular chemistry is transitioning to the study of dynamic systems, that exist and operate away from equilibrium while dissipating energy.¹ Such a new domain might open new opportunities for both material and biological science. Ultimately, Life is a nonequilibrium phenomenon.

We approached this innovative domain merging our previous experiences in molecular machines and self-assembly,² as well as exploiting the opportunities offered by DNA nanotechnology.³ In particular, we have rationalized current experimental approaches to nonequilibrium self-assembly, disclosing general underlying principles for driven (endergonic) self-assembly.⁴ It emerged that energy consumption is not a sufficient requirement for driving chemical reactions away from equilibrium. Cooperative catalysis instead is a useful prerequisite to obtain high-energy assemblies (figure 1, left). For this reason, the substrate-induced self-assembly of cooperative catalysts has been investigated, engineering the formation of catalytic vesicles in which a transesterification reaction occurs at the surface, owing to a Zn²⁺ mediated cooperative mechanism (figure 1, right).⁵

An overview of the work performed in this area will be presented.

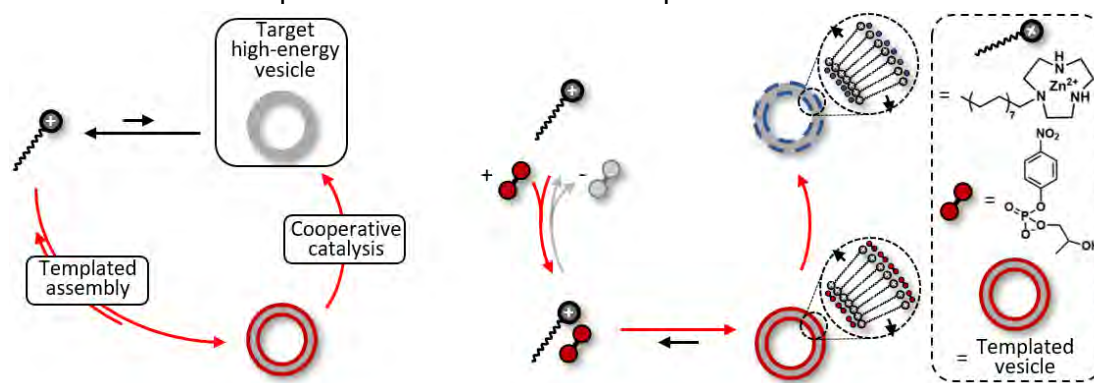


Figure 1: Reaction schemes for driven self-assembly; left: a minimal strategy to obtain a high-energy assembly; right: steps implemented in a studied artificial system.

References:

- [1] E. Mattia, S. Otto, *Nat. Nanotechnol.* **2015**, *10*, 111-119.
- [2] G. Ragazzon, M. Baroncini, S. Silvi, M. Venturi, A. Credi, *Nat. Nanotechnol.* **2015**, *10*, 70-75; (b) S. Maiti, I. Fortunati, C. Ferrante, P. Scrimin, L. J. Prins, *Nat. Chem.* **2016**, *8*, 725-731.
- [3] a) E. Del Grosso, A. Amodio, G. Ragazzon, L. J. Prins, F. Ricci, *Angew. Chem. Int. Ed.* **2018**, *57*, 10489-10493; b) E. Del Grosso, G. Ragazzon, L. J. Prins, F. Ricci, *Angew. Chem. Int. Ed.* **2019**, *58*, 5582-5586.
- [4] G. Ragazzon, L. J. Prins, *Nat. Nanotechnol.* **2018**, *13*, 882-889.
- [5] P. Solís Muñana, G. Ragazzon, J. Dupont, C. Z.-J. Ren, J. L.-Y. Chen, L. J. Prins, *Angew. Chem. Int. Ed.* **2018**, *57*, 16469-16474.

Novel NK₁ receptor antagonists

M. P. Catalani,^a R. Di Fabio, A. Pozzan,^a H. Bladh,^b J. Felding,^b M. D. Sorensen^b

^a Aptuit, an Evotec Company, Via A. Fleming 4, 37135 Verona (Italy).

^b LEO Pharma, A/S Industriparken, 55DK-2750, Ballerup (Denmark)
maria.catalani@aptuit.com

NK₁ receptor¹ (G- protein – coupled - receptor) research has been pursued aggressively over the last two decades by several pharmaceutical companies, in an effort to develop drugs that might be useful in a wide range of pathological affections: inflammatory conditions, migraine, emesis, schizophrenia, depression, anxiety, tinnitus, hearing loss, bronchoconstriction and regulation of gastrointestinal effects. Chemically diverse non-peptide NK₁ receptor antagonists have been identified since the discovery of CP-96,345 by Pfizer in 1991². In 2003 a NK₁ receptor antagonist (Aprepitant)³ was approved and launched onto the market for the prevention of chemotherapy – induced nausea and vomiting (CINV).

New NK₁ receptor antagonists, incorporating a bicyclic core, with potential activity in the treatment of inflammatory skin diseases, have been identified and synthesized.

The bicyclic core, containing the piperazine ring (Figure 1), has been obtained through a diastereoselective approach.

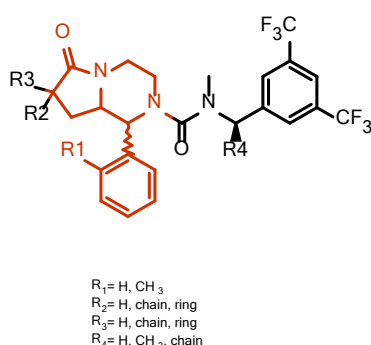


Figure 1

The synthesis involved two crucial cyclization steps: a first step mediated by [bis (trifluoroacetoxy)iodo]benzene (PIFA)⁵ and a second condensation step that gave as product only the **ANTI**-derivative.

References:

- [1] R. Patacchini, C. A. Maggi, *Eur. J. Pharmacol.* **2001**, 429, 13-21.
- [2] R. M. Snider, J. W. Constantine, J. A. Lowe, K. P. Longo, W. S. Lebel, H. A. Woody, S. E. Drozda, M. C. Desai, F. J. Vinik, R. W. Spencer, *Science* **1991**; 251, 435-437.
- [3] Poli-Bigelli S. et al. *Cancer* **2003**; 97, 3090-3098.
- [4] M. D. Sorensen, R. Di Fabio, A., Pozzan, M. P. Catalani, H. Bladh, J. Felding, *PCT Int. Appl.* (2013), WO 2013124286.
- [5] a) I. Tellitu, S. Serna, M. T. Herrero, I. Morero, E. Dominguez, R. SanMartin, *J.Org.Chem.* **2007**, 72, 1526-1529; b) L. M. Pardo, I. Tellitu, E. A. Domingues, *Synthesis*, **2010**, 6, 971-978.

New-generation Self-Immolative Spacers Enable Fast Release of Anticancer Drugs

A. Dal Corso

Università Degli Studi Di Milano, Dipartimento di Chimica, via Golgi 19 - 20133 Milan, Italy
alberto.dalcorso@unimi.it

The covalent conjugation of anticancer drugs to small ligands, capable of selective binding to tumor-overexpressed receptors, has been proposed as a suitable strategy to overcome important pharmacokinetic limitations of large monoclonal antibodies.¹ The so-called small molecule-drug conjugates are often designed to release the anticancer agent in the presence of tumor-associated enzymes, which cleave a specific chemical bond (i.e. the linker) between the drug and the ligand.² In particular, a spacer between the linker and the drug is fundamental to lower the steric hindrance around the substrate and to allow an efficient enzymatic action. These spacers, often referred to as “self-immolative units”, are designed to undergo spontaneous degradation upon linker cleavage, thus releasing the free drug in its active form. To ensure therapeutic efficacy, the design of self-immolative spacers must take into account different aspects, such as synthetic accessibility, the anchoring point on the anticancer drug and plasma stability. Moreover, high drug release rates may be fundamental, as long half-lives of the inactive prodrug may lead to suboptimal therapeutic efficacy and toxicity to healthy tissues.

In this work, different diamine spacers were synthesized and conjugated to anticancer drugs at OH groups, through the formation of hydrolytically-stable carbamate bonds. The cyclization rates of the prodrugs' amine moieties onto the carbamate bonds were measured, resulting in the formation of a cyclic urea and the release of the free drug (Figure 1).

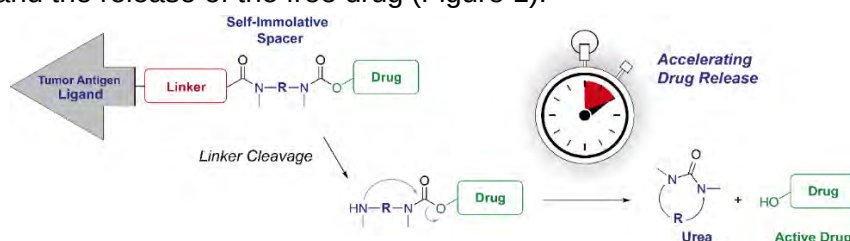


Figure 1: Mechanism of action of cyclization-based self-immolative spacers installed on a linker-drug module in a small molecule-drug conjugate. The rate-limiting step of the drug release process is highlighted, consisting in the intramolecular nucleophilic attack of the amine moiety to the carbonyl.

Structurally modified self-immolative units were found to influence significantly the drug release rates, being in some cases much more efficient than benchmark spacers. The evaluation of the impact of the accelerated drug release mechanism on the therapeutic effects is in progress. Besides holding promises on the development of new generation prodrugs, the structural basis for producing efficient self-immolative spacers may find important applications in analytical chemistry and material sciences.³

References:

- [1] S. Cazzamalli, A. Dal Corso, F. Widmayer, D. Neri, *J. Am. Chem. Soc.* **2018**, *140*, 1617-1621.
- [2] a) A. Dal Corso, M. Caruso, L. Belvisi, D. Arosio, U. Piarulli, C. Albanese, F. Gasparri, A. Marsiglio, F. Sola, S. Troiani, B. Valsasina, L. Pignataro, D. Donati, C. Gennari, *Chem. Eur. J.* **2015**, *21* 6921-6929; b) A. Raposo Moreira Dias, A. Pina, A. Dean, H.-G. Lerchen, M. Caruso, F. Gasparri, I. Fraietta, S. Troiani, D. Arosio, L. Belvisi, L. Pignataro, A. Dal Corso, C. Gennari *Chem. Eur. J.* **2019**, *25*, 1696-1700.
- [3] A. Alouane, R. Labruère, T. Le Saux, F. Schmidt, L. Jullien, *Angew. Chem. Int. Ed.* **2015**, *54*, 7492-7509.

KEYNOTES

Toward Deterministic Doping

M. Laus

*Dipartimento di Scienze e Innovazione Tecnologica (DISIT), Università del Piemonte Orientale "A. Avogadro", Viale T. Michel 11, 115121 Alessandria, Italy
michele.laus@uniupo.it*

Atomic scale devices represent the cutting edge of Si technology¹. Control over concentration and exact positioning of impurity atoms in semiconductor structures is the key to support device scaling down to atomic scale. On the other side, scaling down of microelectronic devices posed several challenges in terms of short-channel-effect control and leakage current issues determining the development of non-planar architectures as multigate FETs such as FinFETs (Fin shaped Field Effect Transistors), thus in turn requiring a conformal doping technology. Ion implantation, the standard industrial technique for doping, is highly effective in modulating the concentration of non-isoelectronic impurities in semiconductors but it is mono-directional in nature and consequently not suitable for advanced device architectures. In addition, it lacks adequate control over the dopant atom positioning, being even destructive to the crystal structure. Conversely, solid- and gas-phase source diffusion processes, still representing alternative doping technologies, do not allow precise control over the dopant dose and atom positioning.

A novel conceptual approach was recently introduced² by our group by developing functional polymers, featuring controlled molar mass and narrow molar mass distribution, terminated by a dopant containing moiety. This polymeric architecture allows the chemistry of grafting reaction to be kept constant whereas tuning of the number of polymeric molecules linked to the substrate is achieved simply by changing the molar mass of the polymer. Pushing the self-limited "grafting to" reaction to the corresponding pseudo-plateau thickness values of two times the gyration radius of the grafted macromolecule allows to obtain a very high degree of reproducibility in the dopant dose amount. The amount of dopant atoms deposited on the substrate was found to decrease from 8×10^{13} to 2×10^{12} atoms/cm² as the molar mass of the polymeric carrier increases from 2.3 kg/mol to 25 kg/mol. In addition, the nature of the end groups was found able to outperform the dopant dose control. Moreover, the proposed approach was demonstrated to significantly reduced carbon contamination with respect to conventional approaches, thus increasing the activation rate of the P atoms incorporated into the Si substrate. These results suggest the possibility to integrate this technology into the conventional process flow of semiconductor device fabrication.

References:

- [1] B. Weber, S. Mahapatra, T. F. Watson and M. Y. Simmons, *Nano Lett.* **2012**, *12*, 4001-4006.
- [2] M. Perego, G. Seguin, E. Arduca, A. Nomellini, K. Sparnacci, D. Antonioli, V. Gianotti and M. Laus, *ACS Nano* **2018**, *12*, 178-186.

Entry to peptide Wonderland through the rabbit hole

A. M. Garcia,^a D. Iglesias,^a E. Parisi,^a K. E. Styan,^b L. J. Waddington,^b C. Deganutti,^a R. De Zorzi,^a
M. Grassi,^c M. Melchionna,^a A. V. Vargiu,^d S. Marchesan^a

^aUniversity of Trieste, Chem. Pharm. Sc. Dept., Via Giorgieri 1, 34127 Trieste, Italy

^bCSIRO Manufacturing, Clayton VIC3168, Australia

^cUniversity of Trieste, Eng. and Architecture Dept., 34127 Trieste, Italy

^dUniversity of Cagliari, Physics Dept., 09042 Monserrato (CA), Italy

smarchesan@units.it www.marchesanlab.com [@MarchesanLab](https://twitter.com/MarchesanLab)

Nature's preference for homochirality (e.g., L-peptides, D-carbohydrates) has animated our investigations, as we question it with heterochiral D,L-peptides. We took inspiration from Alice, who steps through the mirror into Wonderland, whereby everyday life elements are combined in fantastic ways.¹ Similarly, we discovered new self-assembly scenarios by using L-amino acids in combination with their mirror-image D-enantiomers at selected positions in short, D,L-peptide sequences. The use of small peptide libraries with variations in amino acid sequence or stereoconfiguration is leading to the emergence of self-assembly rules to obtain nanostructures or nanostructured hydrogels.^{2,3} We monitored the divergent path of homochiral and heterochiral tripeptides through self-assembly from the molecular, to the nano-, micro- and macroscopic scale. In this manner, we could link back the final material properties with fine structural variations of the building blocks.³

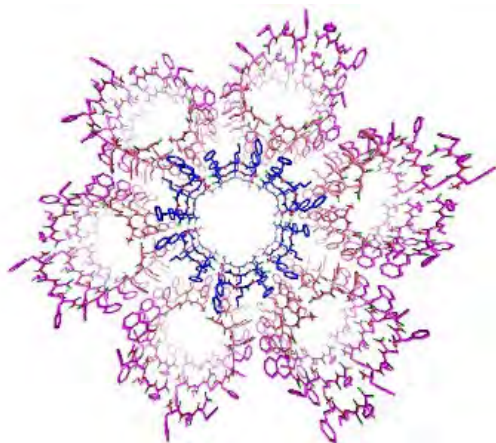


Fig. 1: XRD structure of D,L-tripeptide reveals 2 nm-wide water channels.³

As Alice enters Wonderland through the rabbit hole,⁴ we can follow the self-assembly into supramolecular water channels of D,L-tripeptides (**Fig. 1**) that form nanostructured hydrogels, while their L-stereoisomers do not. Present studies are focussing on a more diverse library with various functional groups. Applications go from biomaterials^{3,5} to supramolecular catalysis⁶ and embedding of other components, such as carbon nanostructures⁷ or metal-organic cages for selective chemical separation.⁸ An attractive feature of these systems is the ability to have a function that can be switched on/off with assembly/disassembly, as well as biodegradability.

References:

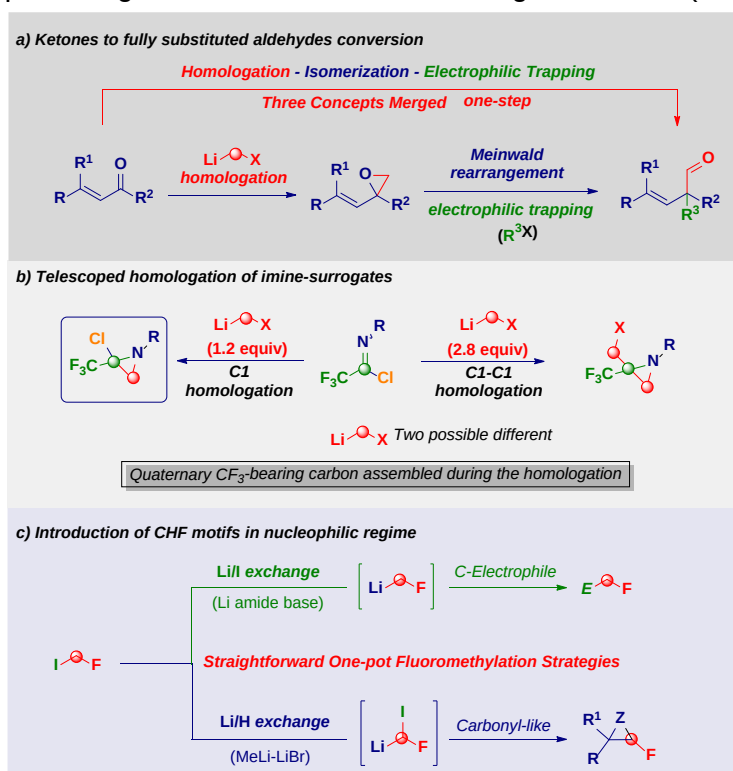
- [1] L. Carroll, J. Tenniel. "Through the Looking-Glass, and What Alice Found There" Macmillan, London, **1871**.
- [2] S. Marchesan, K. E. Styan, C. D. Easton, L. Waddington, A. V. Vargiu, *J. Mater. Chem. B* **2015**, 3, 8123-8132.
- [3] A. M. Garcia, D. Iglesias, E. Parisi, K. E. Styan, L. J. Waddington, C. Deganutti, R. De Zorzi, M. Grassi, M. Melchionna, A. V. Vargiu, S. Marchesan, *Chem* **2018**, 4, 1862-1876.
- [4] L. Carroll, "Alice's Adventures in Wonderland" Macmillan, London, **1865**.
- [5] A. V. Vargiu, D. Iglesias, K. E. Styan, L. J. Waddington, C. D. Easton, S. Marchesan, *Chem. Commun.* **2016**, 52, 5912-5915.
- [6] A. M. Garcia, M. Kurbasic, S. Kralj, M. Melchionna, S. Marchesan, *Chem. Commun.* **2017**, 53, 8110-8113.
- [7] D. Iglesias, M. Melle-Franco, M. Kurbasic, M. Melchionna, M. Abrami, M. Grassi, M. Prato, S. Marchesan, *ACS Nano* **2018**, 12, 5530-5538.
- [8] M. Kieffer, A. M. Garcia, C. J. E. Haynes, S. Kralj, D. Iglesias, J. Nitschke, S. Marchesan, *Angew. Chem. Int. Ed.* **2019**, in press, doi: 10.1002/ange.201900429.

Designing New Synthetic Concepts for Imparting Molecular Complexity with C-1 Sources

V. Pace^a

Department of Pharmaceutical Chemistry, University of Vienna, Althanstrasse 14, 1090 Vienna (Austria).
e-mail: vittorio.pace@univie.ac.at; web: drugsynthesis.univie.ac.at

The direct transfer of a reactive nucleophilic CH_2X unit into an existing linkage enables the formal introduction of the moiety with the precisely defined degree of functionalization.¹ Upon the fine tuning of the reaction conditions governing the transformation, the initial homologation event can serve as the manifold for triggering unusual rearrangement sequences leading to complex architectures through a unique synthetic operation. The direct – full chemoselective – conversion of a ketone into the homologated all-carbon quaternary aldehyde (via a)² and, the telescoped homologation of imine-surrogates to quaternary aziridines (via b)³ will illustrate these unprecedented concepts. Additionally, the one-step mono-fluoromethylation of carbon electrophiles with extremely labile fluoromethyl lithium reagents will provide a novel entry to valuable fluorinated building-blocks without the needing of using protecting elements for fluoro-containing carbanions (via c).⁴



References

- [1] For an overview, see: (a) L. Castoldi, S. Monticelli, R. Senatore, L. Ielo, V. Pace *Chem. Commun.* **2018**, 54, 6692-6704. (b) R. Senatore, L. Castoldi, L. Ielo, W. Holzer, V. Pace *Org. Lett.* **2018**, 20, 2685-2688.
- [2] V. Pace, L. Castoldi, E. Mazzeo, M. Rui, T. Langer, W. Holzer *Angew. Chem. Int. Ed.* **2017**, 56, 12677-12682.
- [3] L. Ielo, S. Touqeer, A. Roller, T. Langer, W. Holzer, V. Pace, *Angew. Chem. Int. Ed.* **2019**, 58, 2479-2484.
- [4] (a) G. Parisi, M. Colella, S. Monticelli, G. Romanazzi, W. Holzer, W.; T. Langer, L. Degennaro, V. Pace, R. Luisi *J. Am. Chem. Soc.* **2017**, 139, 13648-13651. (b) S. Monticelli, M. Colella, V. Pillari, A. Tota, T. Langer, W. Holzer, L. Degennaro, R. Luisi, V. Pace *Org. Lett.* **2019**, 21, 584-588.

I primi 150 anni della Tavola Periodica degli Elementi Chimici: tra Chimica, Storia e Letteratura

Giorgio Cevasco

*Vicepresidente SCI, Viale Liegi, 48c - Roma
giorgio.cevasco@unige.it*

L'UNESCO ha proclamato l'anno 2019 Anno Internazionale della Tabella Periodica degli Elementi per celebrare i 150 anni dalla pubblicazione della tabella dello scienziato russo Dmitri Mendeleev che è alla base di quella che oggi tutti conoscono. Gli elementi, come mattoncini elementari, costituiscono il nostro mondo, noi stessi e tutto ciò che ci circonda, visibile od invisibile e da ciò deriva la straordinaria importanza, scientifica e non solo, della Tabella Periodica.

Lo stesso Mendeleev riconobbe pubblicamente che alla base della sua tavola periodica c'era in larga misura il lavoro di uno scienziato italiano, Stanislao Cannizzaro, che negli anni 1855-1861, quando era professore di chimica all'Università di Genova, mise a punto un metodo per determinare con precisione il peso atomico degli elementi. Cannizzaro in realtà non fu solo un chimico. Partecipò ai moti siciliani del 1848, fuggì in Francia, tornò poi in Italia (partecipò alla seconda spedizione di Garibaldi del 1860) e infine divenne vicepresidente del Senato realizzando importanti riforme nell'ambito dell'istruzione e della salute pubblica.

Ma nel 2019 ricorrono altri importanti anniversari ed uno di questi è il centenario della nascita di Primo Levi che fu chimico e scrittore, vittima e lucido testimone della tragedia della Shoah, i cui libri più importanti e noti a livello internazionale sono certamente "Se questo è un uomo", un resoconto scientifico della tragedia dei lager, e "Il Sistema Periodico" una serie di affascinanti racconti dedicati appunto agli elementi e dunque è evidente lo strettissimo legame che unisce questi due anniversari.

Nel racconto intitolato Ferro del Sistema Periodico Levi scrive: "...il Sistema Periodico di Mendeleev, era una poesia, più alta e più solenne di tutte le poesie digerite in liceo: a pensarci bene, aveva perfino le rime!"

E allora immaginiamo la Tabella Periodica come una tastiera perché come dice Levi: "... non è detto che il mestiere di cucire insieme lunghe molecole presumibilmente utili al prossimo, non insegni nulla sul modo di cucire insieme parole ed idee."

Ancora una volta ci rendiamo così conto che non esiste differenza tra la cultura umanistica e quella scientifica in quanto esse coesistono in una sola!

EurJOC Lecture

Ionic Liquid Effects on the Rates of Reactions

A Lecture in Memory of Prof. Cinzia Chiappe

T. Welton

Department of Chemistry, Imperial College London, White City Campus,
80 Wood Lane, London, UK
t.welton@imperial.ac.uk

Since the introduction of air and water stable salts that are liquid at room temperature, there has been an explosion of interest in the application of these as solvents for chemicals synthesis and processing. Much of this interest has been centered on the possibility that the ionic media provided by these solvents offer a different kind of chemical environment to molecular solvents perhaps leading to novel behaviors that cannot be achieved with molecular solvents.

Using a combination of detailed kinetic investigations of both Diels-Alder and S_N2 reactions in a range of ionic liquids and measurements of the spectra of probe compounds, we have identified how ion-solute interactions in ionic liquids can be used to change the reactivity of solutes.

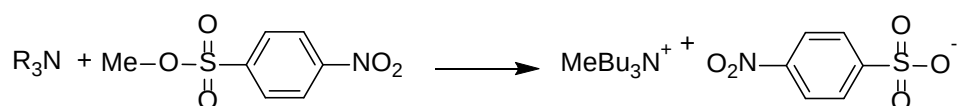


Figure 1: S_N2 reactions of neutral nucleophiles with neutral substrates are accelerated in ionic liquids.

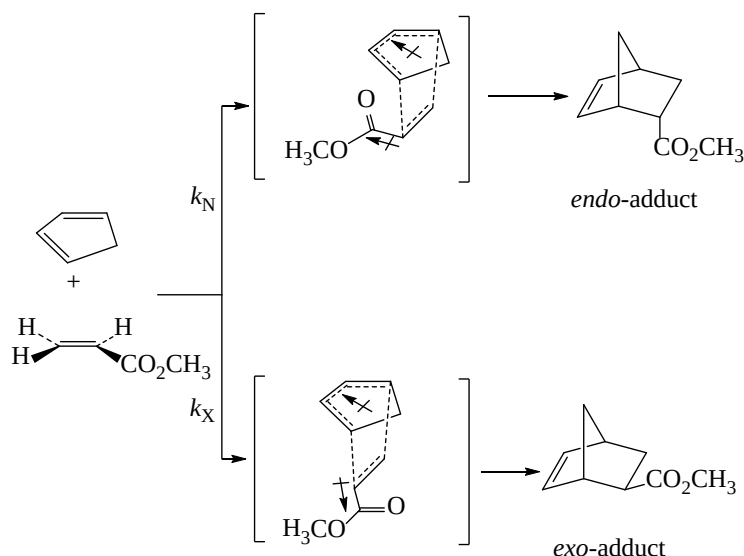


Figure 2: Selectivity of Diels-Alder reaction towards endo- and exo- adducts.

ChemPubSoc Lecture

ChemPubSoc Lecture

Current Challenges in Chemistry Publishing

F. R. Novara^a

^aSenior Associate Editor, *Chemistry - A European Journal*,
Deputy Editor, *ChemistryOpen*, Wiley-VCH, Boschstrasse 12 Weinheim (Germany)
frnovara@wiley.com

Scholarly publishing is crucial to the advancement of chemistry and has a fundamental role in connecting scientists and providing them with a platform to share their findings with the appropriate audience. In this contribution, current developments and trends within chemistry publishing will be addressed and questions and concerns will be answered. Topics to be covered include open science and open access, good publication practices, and future trends.



Figure 1: Two journals owned by ChemPubSoc Europe.

References:

- [1] H. Ross, *Chem. Eur. J.* **2019**, 25, 6-10.

Elsevier Lecture

Elsevier Lecture

Finding novel lead compounds in pesticide discovery inspired by pharmaceutical researchF. van den Borek,^a M. Shkrob,^a A. Kumar,^a A. Yuriev,^a C. Rodriguez del Rio^a^aElsevier B.V. Radarweg 29, Amsterdam, Netherlands
c.rodriguezdelrio@elsevier.com

The use of high throughput (HTP) methodologies for supporting discovery and development of new agrochemical products opens up new opportunities to test many new compounds potentially acting on biological targets in various organisms. Finding new lead compounds which might act as a new pesticide can sometimes be a lengthy process; we present a method which can provide lead compounds by using the breadth of information available from pharmaceutical research. This talk will give an overview of the chemical and biological informatics methods and data used to map compounds active against biological targets in parasites in humans to fungal targets. The talk will also explore how information solution workflow enabling tools such as Reaxys and AI and Machine Learning techniques recently developed for pharmaceutical research projects can augment these developments. Thereby demonstrating how findings from pharmaceutical research can be transferred to crop protection research.

Lectures Premi di Dottorato

The Triangle of Photocatalysis: Different Approaches for Ecosustainable Synthesis

L. Capaldo, M. Fagnoni, D. Ravelli

Department of Chemistry, University of Pavia, viale Taramelli 12, Pavia
luca.capaldo@unipv.it

Over the past decades, photochemical synthesis, i.e. organic synthesis that uses light as source of energy to break and forge bonds, has vehemently re-emerged as an ecosustainable methodology in organic chemistry. A natural speed up in this direction was represented by the emergence of photocatalysis: in these reactions, a purposely added molecule (photocatalyst, PC) is responsible for the conversion of light energy into chemical energy for the activation of a substrate in a highly predictable and selective way. This activation can occur via three different mechanisms: Single-Electron Transfer (SET), Hydrogen-Atom Transfer (HAT) or Energy Transfer (EnT), as shown in Figure 1. In my Ph.D. thesis I decided to explore the potentialities of each approach for the generation of highly reactive intermediates under extremely mild conditions and for the ensuing development of novel ecosustainable synthetic protocols. One case for each activation manifold will be presented.

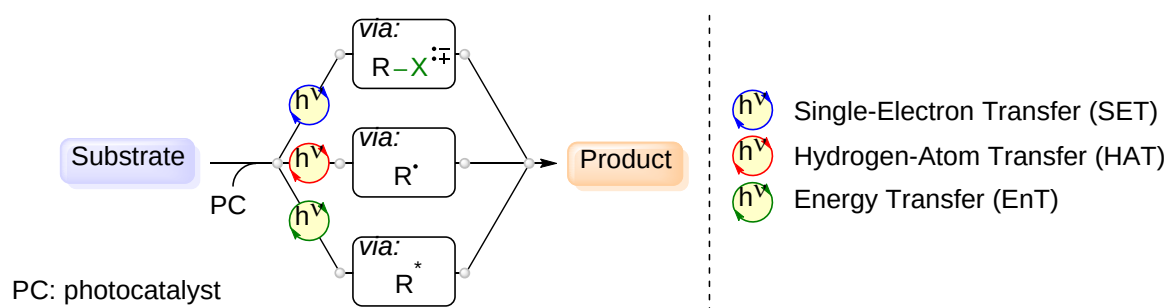


Figure 1: Different activation manifolds in organic photocatalysis.

Generally speaking, one of the most remarkable goals achieved is the generation of fleeting intermediates such as benzyl¹ and acyl radicals² via SET and aliphatic radicals via HAT³. Moreover, detailed investigations on novel classes of photocatalysts able to promote the C-H to C-C bond conversion under visible-light are reported.⁴ Finally, interesting results on the use of transition metal complexes as photosensitizer via EnT for the synthesis of cyclobutanes via [2+2] photocycloadditions are included.⁵

References:

- [1] L. Capaldo, L. Buzzetti, D. Merli, M. Fagnoni, D. Ravelli, *J. Org. Chem.* **2016**, *81*, 7102-7109.
- [2] L. Capaldo, R. Riccardi, D. Ravelli, M. Fagnoni, *ACS Catal.* **2018**, *8*, 304-309.
- [3] L. Capaldo, M. Fagnoni, D. Ravelli, *Chem. Eur. J.* **2017**, *23*, 6527-6530.
- [4] L. Capaldo, D. Merli, M. Fagnoni, D. Ravelli, *ACS Catal.* **2019**, *9*, 3054-3058.
- [5] manuscript in preparation

Towards DNA-targeting magic bullets: searching for potential conformation-selective G-quadruplex ligands

C. Platella,^a D. Musumeci,^a A. Arciello,^a F. Doria,^b M. Freccero,^b
A. Biroccio,^c A. Randazzo,^d J. Amato,^d B. Pagano,^d D. Montesarchio^a

^aDepartment of Chemical Sciences, University of Naples Federico II, via Cintia 21, 80126 Naples, Italy

^bDepartment of Chemistry, University of Pavia, Viale Taramelli 12, 27100 Pavia, Italy

^cOncogenomic and Epigenetic Unit, IRCCS - Regina Elena National Cancer Institute, 00144 Rome, Italy

^dDepartment of Pharmacy, University of Naples Federico II, via D. Montesano 49, 80131 Naples, Italy
chiara.platella@unina.it

In the search for effective and minimally toxic anticancer therapies, G-quadruplex (G4) structures emerged as appealing targets for their crucial roles in human telomeres and oncogene promoters.¹ G4s are non-canonical nucleic acid secondary structures exhibiting marked structural polymorphism.^{1,2} To achieve an optimal recognition selectivity, thus reducing drug toxicity, a major challenge is the identification of ligands which are not only structure-selective, *i.e.* able to discriminate G4 vs. duplex DNA, but also conformation-selective, *i.e.* able to specifically recognize different G4 conformations. Thus, considerable efforts are currently devoted to the design of molecules able to selectively target conformationally different G4s and discriminate duplex DNA. To be effective, the huge impulse to synthesize libraries of potential conformation-selective ligands has to be coupled with fast and reliable High Throughput Screening assays.

In this context, during my PhD I developed: i) a method for the on-line synthesis of glass support-bound, fully deprotected secondary structure-forming oligonucleotides,³ and ii) an affinity chromatography-based assay, named G-quadruplex on Controlled Pore Glass (G4-CPG), for the screening of libraries of putative conformation-selective G4 ligands.⁴

After full optimization of the G4-CPG assay, two different libraries of putative G4 selective ligands, based either on a furobenzoxazine naphthoquinone⁵ or a naphthalene diimide⁶ scaffold, were designed, synthesized and evaluated. The strongest and most selective ligands, selected by the G4-CPG assay, were further investigated in their binding to G4 structures having different conformations by several biophysical techniques, as well as subjected to *in vitro* biological assays.

In this presentation, I will describe the novel developed G4-CPG method based on our newly designed CPG support that allowed us selecting promising candidate drugs for *in vivo* studies, endowed with strong activity against cancer cells (IC₅₀ in the low nM range) and very good selectivity in killing cancer cells vs. normal cells.

References:

- [1] R. Hänsel-Hertsch, M. Di Antonio, S. Balasubramanian, *Nat. Rev. Mol. Cell Biol.* **2017**, *18*, 279-284.
- [2] C. Platella, C. Riccardi, D. Montesarchio, G. N. Roveillo, D. Musumeci, *Biochim. Biophys. Acta. - Gen. Subj.* **2017**, *1861*, 1429-1447.
- [3] C. Platella, D. Musumeci, J. Amato, A. Randazzo, B. Pagano, D. Montesarchio, European Patent Application EP3378556 (A1), **2018**.
- [4] C. Platella, D. Musumeci, A. Arciello, F. Doria, M. Freccero, A. Randazzo, J. Amato, B. Pagano, D. Montesarchio, *Anal. Chim. Acta* **2018**, *1030*, 133-141.
- [5] J. Amato, C. Platella, S. Iachettini, P. Zizza, D. Musumeci, A. Pagano, E. Novellino, A. Biroccio, A. Randazzo, B. Pagano, D. Montesarchio, *Eur. J. Med. Chem.* **2019**, *163*, 295-306.
- [6] Manuscript in preparation.

Outstanding chiroptical features in thin films of chiral π -conjugated oligomers: from synthesis to applications

G. Albano,^a L. A. Aronica,^a L. Di Bari^a

^a Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via G. Moruzzi 13, 56124 Pisa, Italy
e-mail: gianluigi.albano@dcc.i.unipi.it

In the last years, chirality has gained an increasing interest in the fields of metamaterials and organic optoelectronics as an important parameter for controlling supramolecular arrangement of π -conjugated systems at different hierarchy levels, opening the way to highly innovative technological applications.^[1] Most of these devices are based on the different interaction of the active layer with left- and right-handed circularly polarized light, therefore a current research goal is to obtain thin films of organic π -conjugated systems displaying significant chiroptical properties in absorption (*i.e.* electronic circular dichroism, ECD) or in emission (*i.e.* circularly polarized luminescence, CPL).

In the present work we developed a family of novel chiral π -conjugated oligomers functionalized with inexpensive alkyl chiral groups from natural sources, studying their ECD and CPL features in thin films. Although in general we found a manifold of situations, revealing the central role of different local supramolecular structures (strictly related to chemical structure, deposition technique and post-deposition operations), in some cases we discovered outstanding chiroptical features.

Concerning the ECD properties, for some of them we found the very uncommon property of ECD signal inversion upon sample flipping (**Figure 1a**).^[2] due to the interference between linear dichroism and linear birefringence (called LDLB effect), it could be exploited for the realization of new devices, able to discriminate the direction of sample illumination. For the CPL properties, in general quite large dissymmetry factors g_{lum} values (in the order of 10^{-2}) on a wide wavelengths range were obtained, despite their structural differences. Encouraged by promising results, we investigated their possible application in circularly polarized organic light-emitting diode (CP-OLED) devices: a *multilayer* device based on a 9*H*-carbazole-oligothiophene as active layer was developed (**Figure 1b**), representing to the best of our knowledge the first example of CP-OLEDs based on chiral oligothiophenes.

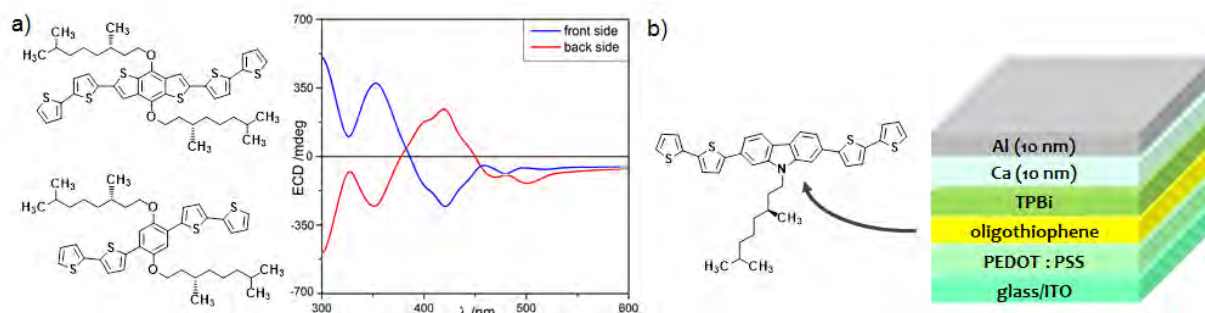


Figure 1: a) ECD spectrum inversion by sample flipping due to LDLB effect in thin films of our compounds; b) architecture of the *multilayer* CP-OLED based on 9*H*-carbazole-oligothiophene developed in this work.

References:

- [1] J. R. Brandt, F. Salerno, M. J. Fuchter, *Nat. Rev. Chem.* **2017**, *1*, 0045.
[2] a) G. Albano, M. Lissia, G. Pescitelli, L. A. Aronica, L. Di Bari, *Mater. Chem. Front.* **2017**, *1*, 2047-2056; b) G. Albano, F. Salerno, L. Portus, W. Porzio, L. A. Aronica, L. Di Bari, *ChemNanoMat* **2018**, *4*, 1059-1070.

Contributi Orali

Synthesis and biological evaluation of novel antimicrobial and antibiofilm agents

A. Esposito,^a E. De Gregorio,^b M. De Fenza,^a L. Rocco,^b D. D'Alonzo,^a A. Guaragna^a

^aDept. of Chemical Sciences, University of Napoli Federico II, via Cintia, 80126 Napoli, Italy

^bDept. of Molecular Medicine and Medical Biotechnologies, University of Napoli Federico II,
Via S. Pansini, 80131 Napoli, Italy
anna.esposito5@unina.it

Bacterial infections represent a serious threat in the public health due to the emergence of antibiotic-resistant pathogens resulting from the wide use and abuse of antimicrobial agents.¹ In addition, bacteria ability to form biofilms increases the difficulties to eradicate the pathogens leading to chronic and resistant infections. Therefore, development of novel candidates active against bacteria in planktonic state, as well as growing in biofilm, represents an important issue. In this context, our interest in the development of novel small molecules endowed with biological activity led us to identify two class of compounds, *N*-alkyl-L-iminosugars and corticosteroid derivatives (**Figure 1**) as novel potential antibacterial and antibiofilm agents. Despite the interesting biological properties for both of these classes of compounds,² to the best of our knowledge, only few data are reported on their action on bacterial infections. Regarding *N*-alkyl-L-iminosugars, a recent study aimed to explore their inflammatory potential in Cystic Fibrosis lung disease, suggested a possible role as molecules able to control microbial infection. In our lab a *de novo* synthesis has been tuned up to gain access to the iminosugar core,² along with a scalable procedure for the alkyl chains assembly (**Figure 1a**). On the other hand, our attention has been attracted by a series of steroid derivatives whose synthesis has been realized starting from the commercially available tetraene acetate (3TR) (**Figure 1b**).

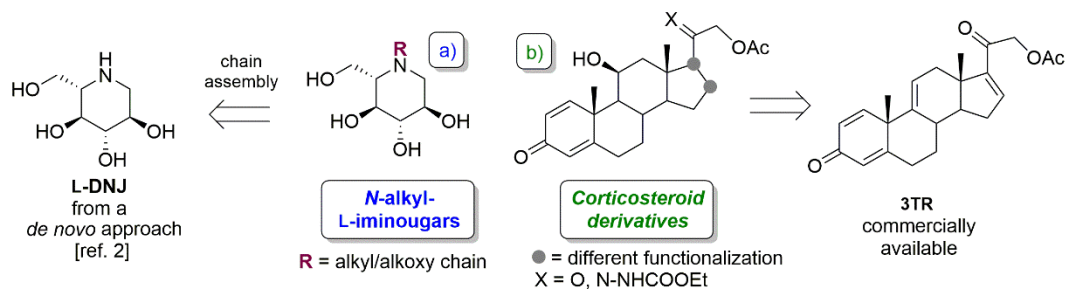


Figure 1: Synthesis of *N*-alkyl-L-iminosugars (a) and of corticosteroid derivatives (b).

Both classes of compounds were subjected to preliminary biological assays showing interesting antimicrobial activity against both Gram-positive (*S. aureus*) and Gram negative (*P. aeruginosa* and *S. maltophilia*), as well as a good ability to prevent biofilm formation and, in some cases, to disperse pre-established existing biofilms. These first data prompted us to explore the therapeutic potential of these compounds, also by studying their behaviour when used in combination or jointed to form a single molecular system.

References:

- [1] L. Cantas, S. Q. A. Shah, L. M. Cavaco, C. M. Manaia, F. Walsh, *Front. Microbiol.*, **2013**, *4*, 1-14.
- [2] D. D'Alonzo, M. De Fenza, C. Porto, R. Iacono, M. Huebecker, B. Cobucci-Ponzano, D. Priestman, F. Platt, G. Parenti, M. Moracci, G. Palumbo, A. Guaragna, *J. Med. Chem.*, **2017**, *60*, 9462-9469.

Stereoselective synthesis of C-2 alkylated trihydroxypiperidines: effect of the chain length and the configuration at C-2 on their activity as Pharmacological Chaperones for Gaucher Disease

F. Clemente,^a C. Matassini,^a A. Goti,^a F. Cardona^a

^a Dipartimento di Chimica "Ugo Schiff", University of Florence, Via della Lastruccia 3-13, 50019 Sesto Fiorentino, Italy
e-mail: francesca.clemente@unifi.it

A synthetic strategy based on the addition of Grignard reagents onto nitron **1**, derived from aldehyde **2**, followed by intramolecular reductive amination, provides access to C-2 alkylated trihydroxypiperidines bearing different alkyl chains (octyl, nonyl, undecyl, dodecyl and tridecyl). Lewis acid addition during the Grignard reaction allowed access to both epimers at the newly created stereocentre, providing the target trihydroxypiperidines with both configuration at C-2. The overall synthesis was achieved in 8 steps from low cost D-mannose and provided the final compounds in 35-45% overall yield.^{1,2} With this approach, a small library of new iminosugars of biological interest was accessed as potential Pharmacological Chaperones (PCs). PCs are small molecules that bind and stabilize enzymes, rescuing the enzymatic activity of misfolded or deficient enzymes when they are used at sub-inhibitory concentration.³ In particular, it is of great interest the search for PCs able to improve the cellular folding and trafficking defects associated with Gaucher disease (GD), the most common autosomal recessive lysosomal storage disorder. GD is caused by point mutations in the gene encoding for acid- β -glucosidase (β -GCase), the enzyme responsible for glucosylceramide metabolism into glucose and ceramide. The effect of the chain length and the configuration at C-2 on GCase inhibition, in extracts from human leukocytes homogenate isolated from healthy donors and on chaperoning activity, in human fibroblasts derived from Gaucher patients bearing the N370 and L444P mutation, will be presented. Furthermore, the selectivity towards other human glycosidases was determined on these molecules together with their cytotoxicity and mechanism of action.²

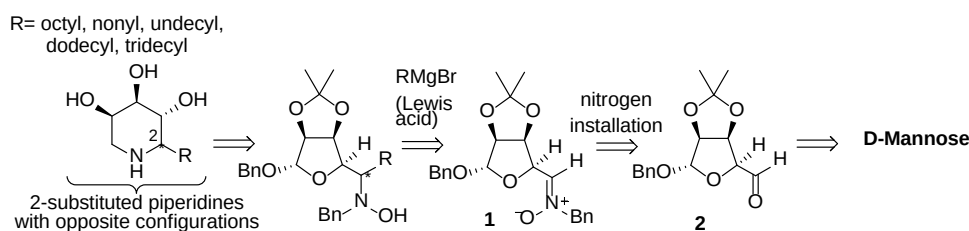


Figure 1: Retrosynthetic strategies to access 2-substituted piperidines.

Acknowledgements: Fondazione Cassa di Risparmio di Pistoia e Pescia (Bando Giovani@Ricerca scientifica 2017).

References:

- [1] S. Mirabella, G. Fibbi, C. Matassini, C. Faggi, A. Goti, F. Cardona, *Org. Biomol. Chem.*, **2017**, 5, 9121-9126.
- [2] F. Clemente, C. Matassini, A. Goti, A. Morrone, P. Paoli, F. Cardona, *ACS Med. Chem. Lett.* **2019**, DOI: 10.1021/acsmchemlett.8b00602
- [3] E. M. Sánchez-Fernández, J. M. García-Fernández, C. Ortiz Mellet, *Chem. Commun.* **2016**, 52, 5497-5515.

Deciphering the metabolome of marine microbiome through molecular networking

R. Teta,^a G. Esposito,^a G. Della Sala,^b V. Costantino,^a A. Mangoni^a

^aDipartimento di Farmacia, Università degli Studi di Napoli Federico II, via Domenico Montesano 49, 80131 Napoli, Italy

^bLaboratory of Pre-clinical and Translational Research, IRCCS-CROB, Referral Cancer Center of Basilicata, Via Padre Pio 1, 85028 Rionero in Vulture, Italy.
Email: roberta.teta@unina.it

Marine environment provides an unrivaled degree of biodiversity that is paralleled with biochemical and chemical diversity, making it a cornucopia for the discovery of new chemical entities of potential clinical efficacy. Our research is focused on the study of the chemistry of natural products from marine organisms (sponges) and microorganisms (sponge symbionts, cyanobacteria) that are extremely prolific in new bioactive natural products.

In this context, we have explored the use of molecular networking,¹ a recently-developed method for automated LC-MS data analysis and mining,^{2,3} to discover novel lead compounds for anticancer, antibiotic and anti-inflammatory drug design.⁴

In our most recent studies, in the Caribbean sponges *Smenospongia aurea* and *Smenospongia conulosa* we have found a series of chlorinated mixed-biogenesis NRPS/PKS compounds, namely smenamides⁵ and smenothiazoles⁶ from *S. aurea* and conulothiazoles⁷ from *S. conulosa*, showing a potent cytotoxic activity at the nanomolar level. The bloom-forming cyanobacteria *Trichodesmium* sp. have been recently shown to produce some of the chlorinated peptides/polyketides previously isolated from the marine sponge *S. aurea*.⁸ A comparative analysis of the organic extracts of *S. aurea* and *Trichodesmium* sp. was performed combining high-resolution LC-MS/MS and molecular networking, showing that both *S. aurea* and *Trichodesmium* sp. contain a wide range of such chlorinated compounds, many of which are present in both organisms. Following this integrated approach, new antiproliferative chlorinated polyketides, smenolactones A-D, were isolated from *S. aurea*, and two new conulothiazole analogues, isoconulothiazole B and conulothiazole C were isolated from *Trichodesmium* sp., and their structures elucidated. These findings confirmed molecular networking as a powerful tool in the discovery and development of new drug leads.

References:

- [1] R. Teta, G. Della Sala, E. Glukhov, L. Gerwick, W. H. Gerwick, A. Mangoni, V. Costantino, *Environ. Sci. Technol.* **2015**, 49, 14301-14310. DOI:10.1021/acs.est.5b04415
- [2] G. Esposito, R. Teta, R. Marrone, C. De Sterlich, M. Casazza, A. Anastasio, M. Lega, V. Costantino, *Chemosphere* **2019**, 225, 342-351.
- [3] S. Costantini, E. Guerriero, R. Teta, F. Capone, A. Caso, A. Sorice, G. Romano, A. Ianora, N. Ruocco, A. Budillon, V. Costantino, M. Costantini, *Int. J. Mol. Sci.* **2017**, 18, 2112.
- [4] R. Teta, V. T. Marteinsson, A. Longeon, A. M. Klonowski, R. Groben, M.-L. Bourguet-Kondracki, V. Costantino, A. Mangoni, *J. Nat. Prod.* **2017**, 80, 2530-2535.
- [5] R. Teta, E. Irollo, G. Della Sala, G. Pirozzi, A. Mangoni, V. Costantino, *Mar. Drugs* **2013**, 11, 4451-4463.
- [6] G. Esposito, R. Teta, R. Miceli, L. S. Ceccarelli, G. D. Sala, R. Camerlingo, E. Irollo, A. Mangoni, G. Pirozzi, V. Costantino, *Mar. Drugs* **2015**, 13, 444-459.
- [7] G. Esposito, G. Della Sala, R. Teta, A. Caso, M.-L. Bourguet-Kondracki, J.R. Pawlik, A. Mangoni, V. Costantino, *Eur. J. Org. Chem.* **2016**, 2871-2875.
- [8] C. W. Via, E. Glukhov, S. Costa, P. V. Zimba, P. D. R. Moeller, W. H. Gerwick and M. J. Bertin, *Front. Chem.*, **2018**, 6, 1-9.

A Kinetic and Morphological Study of P3HT Nanowhiskers Formation in the Presence of either PCBM or PCL.

M. Da Pian,^a M. Maggini,^a G. J. Vancso,^b V. Causin,^a E. M. Benetti^{b,c}

^a Dipartimento di Scienze Chimiche, Università degli Studi di Padova, via Marzolo 1, 35131 Padova, Italy.

^b Mesa+ Institute for Nanotechnology, University of Twente, 7500 AE Enschede, The Netherlands.

^c Department of Materials, ETH Zürich, Vladimir-Prelog-Weg 1-5/10, CH-8093 Zurich, Switzerland
E-mail: marta.dapian@unipd.it

Poly-3-(hexyl thiophene) (P3HT) is currently the benchmark semiconducting polymer for organic photovoltaics. Its physical, electrical, photophysical properties are strongly dependent on its morphology in the solid state. However, several issues remain unclear, regarding the forces that drive the assembly/crystallization of P3HT to form fibrillar nanocrystals (NCs) in marginal solvent conditions (anisole)^{1,2}.

This work reports the results of a systematic study on the aggregation/crystallization behavior of P3HT to NCs under different solution conditions and in the presence of different relative contents of either PCBM³ or poly(ϵ -caprolactone) PCL.⁴ PCBM and PCL confined the aggregation/crystallization process of P3HT NCs allowing the formation of extended crystallites, on the other hand at high concentrations in solution it hindered the formation of NCs slowing down their assembly. The results obtained in this work offer a promising perspective for the obtainment of functional all-polymeric NCs.

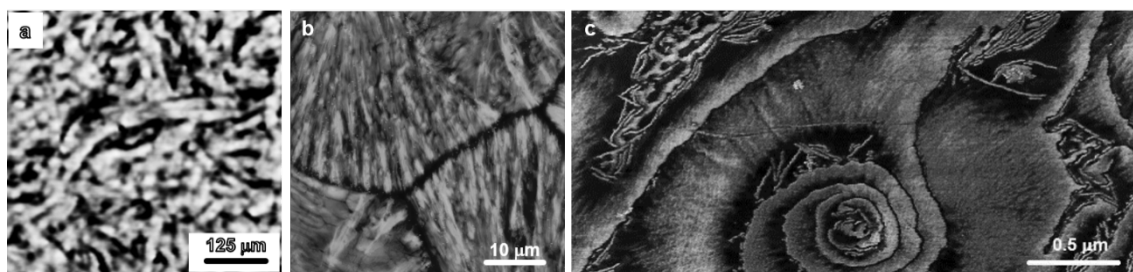


Figure 1: AFM phase micrograph of P3HT NCs mixture obtained from a) P3HT:PCBM 1:1, b) and c) P3HT:PCL 160:1 relative concentrations (w/w).

References:

- [1] E.M. Benetti, V. Causin and M. Maggini, *Adv. Mater.*, **2012**, 24, 5636-5641.
- [2] S. Sun, T. Salim, L.H. Wong, Y.L. Foo, F. Boeya and Y.M. Lam, *J. Mater. Chem.* **2011**, 21, 377–386.
- [3] M. Da Pian, M. Maggini, G.J. Vancso, V. Causin, E.M. Benetti, *Eur. Polym. J.*, **2018**, 109, 222-228.
- [4] M. Da Pian, M. Maggini, G.J. Vancso, V. Causin, E.M. Benetti, *Eur. Polym. J.*, **2019**, 114, 144-150.

Design of Organic Based Photosensitizer-Catalyst Systems for Photoelectrochemical Solar Fuels

C. Decavoli, C. L. Boldrini, N. Manfredi, A. Abboto

Department of Materials Science and Solar Energy Research Center MIB-SOLAR,
University of Milano-Bicocca, and INSTM Milano-Bicocca Research Unit
Via Cozzi 55, 20126 Milano, Italy
c.decavoli@campus.unimib.it

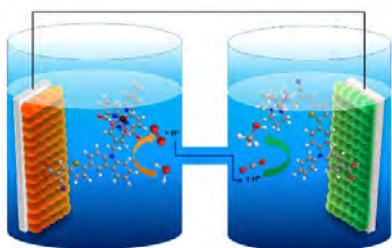


Figure 1: Scheme of a DS-PEC.

Photoelectrochemical cells (PEC) are the new frontier for the conversion of water and solar radiation into oxygen and hydrogen with zero carbon footprint. Two electrodes, soaked into two different half-cells and connected by an external circuit, compose the cell. The electrodes are p-type and n-type semiconductors (SC), both dye-sensitized (e.g by organic molecules) to enhance light harvesting. In the media either a water oxidation catalyst and a hydrogen evolution catalyst are solubilized to oxidize water and

to reduce protons. The goal of a dye-sensitized PEC (DS-PEC) is to mimic the nature, achieving an artificial leaf able to produce solar fuels like hydrogen and/or hydrocarbons from the reduction of water or carbon dioxide (**Figure 1**). The organic dye is the strategic center of the device and, upon irradiation, generates the electron/hole couple. Organic dyes have been playing an emerging role in photocatalysis and in DS-PEC due to their easy synthesis, low cost, and abundance of precursors.¹

This work focuses on the design and the synthesis of new types of organic push-pull dyes that can be connected to the corresponding catalysts exploiting various types of photosensitizer-catalyst interactions (**Figure 2**). The first series of dyes will exploit the host-guest properties of calix[4]arene moiety to direct the catalytic process. In the second series, the sensitizer is covalently linked to a carbon based π -framework to exploit π - π interactions with

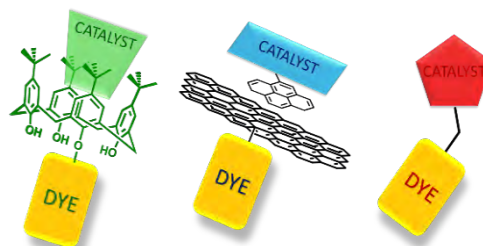


Figure 2: Investigated molecular designs.

the catalyst.² Finally, in order to reach the most ambitious goal achieving an integrated artificial photosystem, catalyst and sensitizer are directly covalently linked. The type of interaction between catalyst and dye is important for the efficiency of the device because can control the charge transfer and define the arrangement on the SC surface that can reduce charge recombination reactions.

References:

- [1] a) B. Cecconi, N. Manfredi, T. Montini, P. Fornasiero, A. Abboto, *Eur. J. Org. Chem.* **2016**, 81, 5194-5215; b) B. Cecconi, N. Manfredi, R. Ruffo, T. Montini, I. Romero-Ocana, P. Fornasiero, A. Abboto, *ChemSusChem* **2015**, 8, 4216-4228; c) N. Manfredi, B. Cecconi, V. Calabrese, A. Minotti, F. Peri, R. Ruffo, M. Monai, I. Romero-Ocana, T. Montini, P. Fornasiero, A. Abboto, *Chem. Commun.* **2016**, 52, 6977-6980; d) N. Manfredi, M. Monai, T. Montini, M. Salamone, R. Ruffo, P. Fornasiero, A. Abboto, *Sustainable Energy Fuels* **2017**, 1, 694-698; e) N. Manfredi, C. L. Boldrini, A. Abboto, *ChemElectroChem* **2018**, 5, 2395-2402; f) N. Manfredi, M. Monai, T. Montini, F. Peri, F. De Angelis, P. Fornasiero, A. Abboto, *ACS Energy Letters* **2017**, 3, 85-91.
[2] T. Gatti, N. Manfredi, C. Boldrini, F. Lamberti, A. Abboto, E. Menna, *Carbon* **2017**, 115, 746-753.

Synthesis of self-assembled BODIPY heterodimer for energy transfer investigations

M. Cordaro,^a M. Trapani,^b E. Collini,^c L. Monsù Scolaro,^a M. A. Castriciano^b

^a Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche ed Ambientali, Università di Messina, V.le F. Stagno d'Alcontres 31, Messina

^b Istituto per lo Studio dei Materiali Nanostrutturati (CNR-ISMN) c/o Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche ed Ambientali, V.le F. Stagno D'Alcontres 31, Messina

^c Dipartimento di Scienze Chimiche, Università di Padova, via Marzolo 1, Padova
mcordaro@unime.it

The crucial step in the conversion of solar to chemical energy in photosynthesis takes place in the reaction center, where the absorbed excitation energy is converted into a stable charge-separated state by ultrafast electron transfer events. However, the fundamental mechanisms responsible for efficiency of these processes are still largely unknown. The development of 2D spectroscopic techniques has shown that coherent transfer of electronic wave-packets is an essential step.¹ These findings are raising questions also about the role of quantum coherence in artificial devices, but only few papers have been devoted to the investigation of not-biological complexes.² One of the key challenges for the future will be to learn how to construct artificial molecular materials enabling the harvesting of sunlight exploiting quantum effects. Here we will report the synthesis and experimental investigations on an innovative Bodipy-type multichromophoric self-assembled system (Figure 1). The synthetic strategies for Bodipy building blocks linked to peripheral complementary triple hydrogen bonding moieties, will be presented.

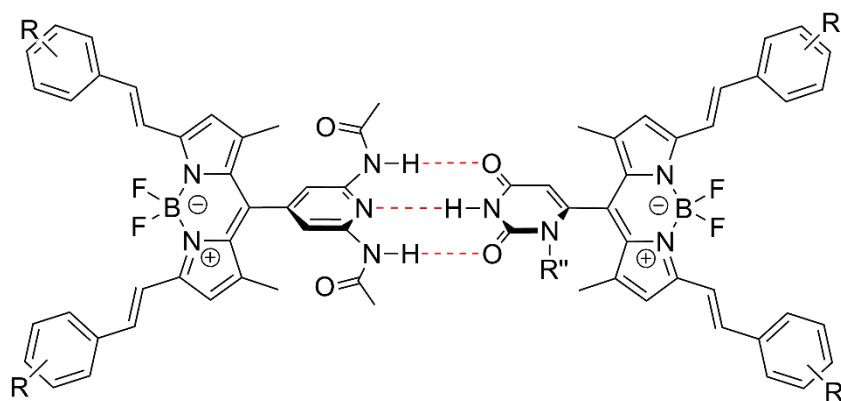


Figure 1: Heterodimer of DAPA-BODIPY and Orotic-BODIPY

The spectroscopic characterization of the heterodimer and preliminary studies of electron transfer by 2D technique, will be also shown.

References:

- [1] (a) E. Collini, G. D. Scholes *Science* **2009**, 323, 369-373. (b) E. Collini, C. Y. Wong, K. E. Wilk, P. M. G. Curmi, P. Brumer, G. D. Scholes *Nature* **2010**, 463, 644-647.
- [2] C. A. Rozzi, S. M. Falke, N. Spallanzani, A. Rubio, E. Molinari, D. Brida, M. Maiuri, G. Cerullo, H. Schramm, J. Christoffers, C. Lienau *Nature Comm.* **2013**, 4, 1602.

Catalytic Manipulations of Arenes with Light and Graphene Oxide

L. Lombardi,^a A. Parodi,^a S. Battaglioli,^a R. Pedrazzini,^a M. Bandini^a

^aDipartimento di Chimica “G. Ciamician”, Alma Mater Studiorum – Università di Bologna
Via Selmi 2, 40126 Bologna
marco.bandini@unibo.it

Aromatic motifs are contained in countless number of organic species with applications spanning from pharma to molecular machines. The current trends in synthetic methodologies dealing with aromatic systems can be organized in three major areas: synthesis of the ring, site-selective functionalization of the arene periphery and dearomatization protocols. Catalysis represent the ultimate strategy for all these fields.¹

Over the past decade our group has been engaged in this intriguing field by means of metal (Au, Ni) and metal-free (Brønsted acid, phosphine) catalysis, generating a wide portfolio of chemical diversity within 2D- and 3D-heterocyclic realms.

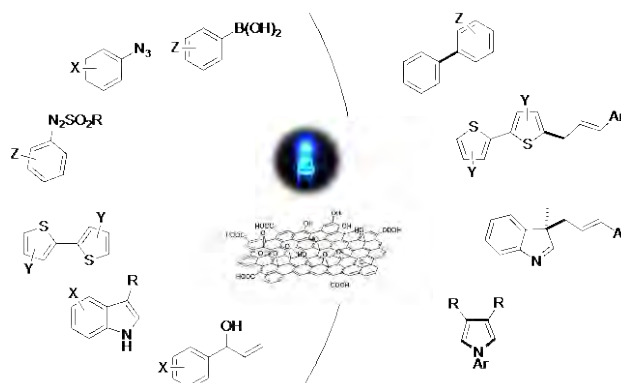


Figure 1: Visible-light photoredox and carbo-catalytic tools in arene chemistry.

In the present communication, our latest findings in the synthesis as well as functionalization of hetero-aromatic compounds via visible-light photoredox processes^{2a,b} and carbo-catalytic tools will be presented (Figure 1).^{2c,d}

References:

- [1] *Arene Chemistry: Reaction Mechanisms and Methods for Aromatic Compounds*, Ed. J. Mortier, Wiley, **2015**.
[2] a) C. Sauer, Y. Liu, A. De Nisi, S. Protti, M. Fagnoni, M. Bandini, *ChemCatChem*. **2017**, 9, 4456-4459; b) Y. Liu, A. Parodi, S. Battaglioli, S. Protti, M. Bandini, *unpublished*; c) L. Favaretto, J. An, M. Sambo, A. De Nisi, C. Bettini, M. Melucci, A. Kovtun, A. Liscio, V. Palermo, A. Bottoni, F. Zerbetto, M. Calvaresi, M. Bandini, *Org. Lett.* **2018**, 20, 3705-3709; d) L. Lombardi, M. Bandini, *unpublished*.

Metal-Ion Induced C–H Bond Deactivation in the Hydrogen Atom Transfer Reaction from Diol Substrates to the Cumyloxyl Radical

T. Martin, M. Salamone and M. Bietti

*Dipartimento di Scienze e Tecnologie Chimiche, Università "Tor Vergata",
Via della Ricerca Scientifica, 1 I-00133 Rome, Italy
michela.salamone@uniroma2.it*

Aliphatic C–H bond functionalization procedures based on hydrogen atom transfer (HAT) to radical and radical-like species are attracting considerable interest in view of the possibilities they offer to introduce a variety of functional groups and to promote highly selective transformations.¹⁻³

Within this framework, medium effects have recently emerged as a powerful tool that has been successfully employed to control reactivity and site-selectivity in an increasing number of synthetically useful examples.⁴

From a mechanistic point of view, recent studies in our group have provided a quantitative evaluation of the effect of Lewis acid-base interactions on HAT from aliphatic C–H bonds to the electrophilic cumyloxyl radical ($\text{PhC}(\text{CH}_3)_2\text{O}^\bullet$, $\text{CumO}^\bullet$). In acetonitrile solution, deactivating effects have been observed following alkali or alkaline earth metal ion addition for HAT from the α -C–H bonds of a series of basic substrates such as amines, amides and ethers, with the magnitude of these effects that has been shown to depend on the nature of the metal ion and on the substrate Lewis basicity.^{4,5}

The study has been extended to the reactions of $\text{CumO}^\bullet$ with acyclic and cyclic alkanols and alkanediols. The results of a detailed time-resolved kinetic study in acetonitrile solution on the effect of alkali and alkaline earth metal ion salts on these latter reactions as a function of the nature of the metal ion and the substrate structure, and the possible implications in terms of synthetically useful C–H bond functionalization procedures will be discussed.

References:

- [1] M. C. White, J. Zhao, *J. Am. Chem. Soc.* **2018**, *140*, 13988-14009.
- [2] D. Ravelli, M. Fagnoni, T. Fukuyama, T. Nishikawa, I. Ryu, *ACS Catal.* **2018**, *8*, 701-713.
- [3] M. Milan, M. Salamone, M. Costas, M. Bietti, *Acc. Chem. Res.* **2018**, *51*, 1984-1995.
- [4] M. Bietti, *Angew. Chem. Int. Ed.* **2018**, *57*, 16618-16637.
- [5] M. Salamone, M. Bietti, *Acc. Chem. Res.* **2015**, *48*, 2895-2903.

Hydrogen Atom Transfer based Aliphatic C–H Bond Functionalization of Cycloalkane Derivatives. Kinetic and Product Studies on the Role of Torsional Effects

T. Martin, M. Galeotti, A. Palone, M. Salamone, M. Bietti

Dipartimento di Scienze e Tecnologie Chimiche, Università degli Studi di Roma "Tor Vergata",
Via della Ricerca Scientifica, 1 00133 Rome, Italy
teo.martin@uniroma2.it

The direct functionalization of aliphatic C–H bonds is currently one of the main goals of modern synthetic organic chemistry, because these reactions can offer advantages both in terms of decreased waste generation and reaction step economy.¹ Methodologies based on Hydrogen Atom Transfer (HAT) to radical and radical-like species have proven to be successful in pursuing this challenging goal.²

The factors that govern reactivity and selectivity in HAT reactions from aliphatic C–H bonds have been discussed in detail.^{1a,3,4} A major role is generally played by the C–H bond dissociation energy (BDE), but other factors can also play a relevant role. Among them, we can enlist electronic, stereoelectronic, and medium effects. Torsional effects have also been shown to play an important role in the reactions of cyclohexane derivatives with HAT reagents,^{5,6} where in particular tertiary equatorial C–H bond activation and tertiary axial C–H bond deactivation has been observed.

In view of these findings, and in order to provide a quantitative evaluation of the role of torsional effects on HAT from the C–H bonds of cycloalkane derivatives, we have carried out detailed time resolved kinetic study on the reactions of an extended series of monosubstituted and disubstituted cycloalkanes with a prototypical HAT reagent such as the cumyloxyl radical ($\text{PhC}(\text{CH}_3)_2\text{O}^\bullet$, $\text{CumO}^\bullet$). These studies have been accompanied by product studies on the reactions of the same substrates with $\text{CumO}^\bullet$ and with *in situ* generated dioxiranes. The results thus obtained will be presented.

References:

- [1] a) T. Newhouse, P. S. Baran, *Angew. Chem. Int. Ed.* **2011**, 50, 3362-3374; b) R. R. Karimov, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2018**, 57, 4234-4241.
- [2] See for example: a) L. K. G. Ackerman, J. I. Martinez Alvarado, A. G. Doyle, *J. Am. Chem. Soc.*, **2018**, 140, 14059-14063; b) D. Ravelli, M. Fagnoni, T. Fukuyama, T. Nishikawa, I. Ryu, *ACS Catal.*, **2018**, 8, 701-713.
- [3] M. C. White, J. Zhao, *J. Am. Chem. Soc.* **2018**, 140, 13988-14009.
- [4] M. Salamone, M. Bietti, *Acc. Chem. Res.* **2015**, 48, 2895-2903.
- [5] a) K. Chen, A. Eschenmoser, P. S. Baran, *Angew. Chem. Int. Ed.* **2009**, 48, 9705-9708; b) L. Zou, R. S. Paton, A. Eschenmoser, T. Newhouse, P. S. Baran, K. N. Houk, *J. Org. Chem.* **2013**, 78, 4037-4048.
- [6] M. Salamone, V. B. Ortega, M. Bietti, *J. Org. Chem.* **2015**, 80, 4710-4715.

Selective aliphatic C–H bond hydroxylation promoted by *in situ* generated dioxiranes

I. Coletti, M. Galeotti, A. Palone, M. Salamone, M. Bietti

Dipartimento di Scienze e Tecnologie Chimiche, Università “Tor Vergata”, Via della Ricerca Scientifica, 1, I-00133 Rome, Italy
marco.galeotti@uniroma2.it

The selective oxidation of nonactivated aliphatic C–H bonds represents one of the most challenging reactions in modern organic synthesis.¹ Among the methodologies that have been developed for this purpose, procedures based on hydrogen atom transfer (HAT) from aliphatic C–H bonds have aroused great interest. Within this framework, dioxiranes have been shown to promote the hydroxylation of these bonds² and a mechanism that proceeds through initial HAT followed by fast OH-rebound has been recently proposed.³ In this context, a recent article by Hilinski and coworkers has described the development of a new method for *in situ* dioxirane generation that has been then applied to aliphatic C–H bond oxidations.⁴ Taking the results of this study as the starting point, in order to obtain information on the effect of dioxirane structure on the oxidation reaction we have carried out a detailed mechanistic investigation, taking adamantane as the reference substrate and employing a wide range of ketones as precursors of the dioxiranes. The optimized conditions have been then extended to the oxidation of a variety of hydrocarbons. The results thus obtained will be discussed.

References:

- [1] M. C. White, J. Zhao, *J. Am. Chem. Soc.* **2018**, *140* (43), 13988-14009.
- [2] R. Curci, L. D'Accolti, C. Fusco, *Acc. Chem. Res.* **2006**, *39*, 1-9.
- [3] Z. Yang, P. Yu, K. N. Houk, *J. Am. Chem. Soc.* **2016**, *138*, 4237- 4242.
- [4] W.G. Shuler, S. L. Johnson; M. K. Hilinski, *Org. Lett.* **2017**, *19*, 4790- 4793.

The strange case of quinones and hydroperoxyl radicals

R. Amorati,^a A. Baschieri,^a Y. Guo,^a J. Cedrowski,^b G. Litwinienko,^b L. Valgimigli^a

^aUniversity of Bologna, Department of Chemistry "G. Ciamician", Via S. Giacomo 11, 40126 Bologna

^bUniversity of Warsaw, Faculty of Chemistry, Pasteura 1, 02-093 Warsaw

luca.valgimigli@unibo.it

Hydroperoxyl radicals ($\text{HOO}\cdot$), along with alkylperoxyl radicals ($\text{ROO}\cdot$) are the main chain-carrying oxidizing species in organic systems and in biology. On the other hand, catechols and hydroquinones are among the most important antioxidants both in nature and among synthetic compounds. While catechols (e.g. 1H_2) efficiently trap 2 peroxyl radicals being oxidized to the corresponding quinones (**1**), hydroquinones (e.g. 2H_2) have lower efficiency due to competing pro-oxidant behaviour based on the formation of $\text{HOO}\cdot$ by reaction of their semiquinone radical ($2\text{H}\cdot$) with O_2 .¹ Quinones (*ortho* or *para*), instead, have no known antioxidant activity, being unable to trap peroxyl radicals. We have recently shown that, paradoxically, $\text{HOO}\cdot$ could have co-operative antioxidant effect upon interaction with species like nitroxyl radicals, affording antioxidant systems of unmatched efficiency based on a catalytic redox cycle.² It was also shown that $\text{HOO}\cdot$ can act as reducing agent toward phenoxyl radicals.³ Here we will show how this chemistry can be called into action to afford extremely effective antioxidant systems based on the interplay of quinones and semiquinones with hydroperoxyl radicals, as summarized in Figure 1.

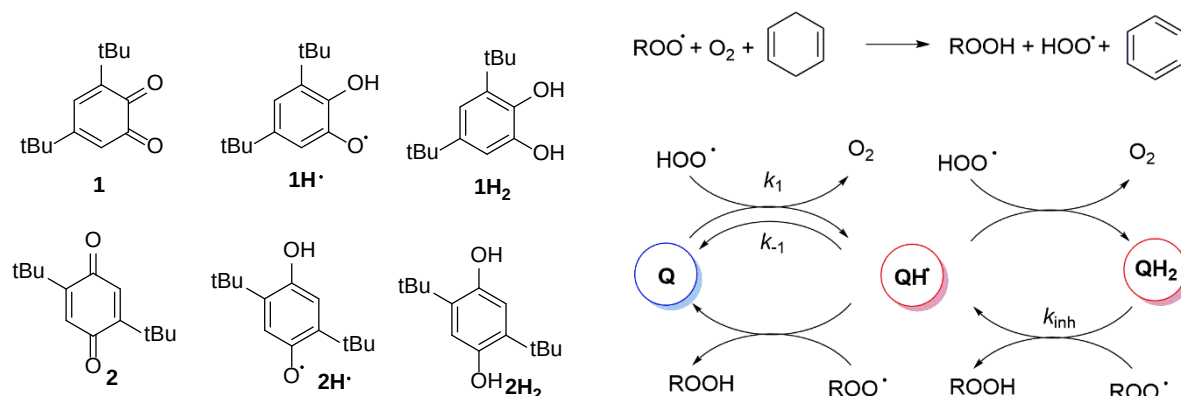


Figure 1: Key reactions explaining the antioxidant activity of quinones mediated by $\text{HOO}\cdot$, **Q** = **1** or **2**.

The picture arising from this study eventually clarifies the controversial antioxidant behaviour of quinones and hydroquinones, both in nature and in man-made materials and sets the basis for the rational use of this fascinating chemistry.

References:

- [1] L. Valgimigli, R. Amorati, M. G. Fumo, G. A. DiLabio, G. F. Pedulli, K. U. Ingold, D. A. Pratt, *J. Org. Chem.* **2008**, *73*, 1830-1841.
- [2] A. Baschieri, L. Valgimigli, S. Gabbanini, G. A. DiLabio, E. Romero-Montalvo, R. Amorati, *J. Am. Chem. Soc.* **2018**, *140*, 10354-10362.
- [3] J. Cedrowski, G. Litwinienko, A. Baschieri, R. Amorati, *Chem. Eur. J.* **2016**, *22*, 16441-16445.

Photoresponsive molecular tools targeting DNA G-quadruplex structures

F. Doria,^a V. Pirota,^a M. Freccero^a

^a Department of Chemistry, University of Pavia, V.le Taramelli 10, 27100 Pavia, Italy;
filippo.doria@unipv.it

In the last few years a nucleic acid secondary structures known as G quadruplex (G4) have been extensively investigated for their critical role in the regulation of biological processes. G4s are non-canonical supramolecular structures formed by guanine-rich oligonucleotides. Four Gs bind via Hoogsteen-type hydrogen bonds base-pairing to yield G-quartets, which in turn stack on top of each other to form the G4. In the human genome and in prokaryotes, have been found G4- forming sequences at the telomeres and in proximity of transcription starting sites, within regulatory elements (e.g., promoters, untranslated regions, rDNA). Recently, the presence of G4s in viruses and their involvement in virus key steps has also been provided. All these experimental evidences have been validated G4s as therapeutic (e.g., anticancer, antiviral) targets suitable for chemical intervention. New methodologies for selectively sensing G4 formation, both in vitro and in vivo, are therefore urgently needed. Optical light-up probes are perfectly suited for such applications, allowing fast, simple, and ultrasensitive detection of biomolecules. For this purpose our group developed different selective G4 ligand starting from Naphthalenediimide core (NDI).

NDIs are very versatile molecules for the design of new molecular systems; their optoelectronic properties can be effectively tuned by substituents on the aromatic core, thus giving origin to absorption and emission in the red spectroscopic window, which makes them appealing for fluorescence imaging and photodynamic therapy (PDT). In addition, their well-known binding properties toward G-quadruplex (G4), make the NDIs the best candidates for a selective G4 fluorescence sensing¹⁻⁷.

References:

- [1] F. Doria, I. Manet, V. Grande, S. Monti, M. Freccero. *J Org Chem.* **2013**, 78, 8065-8073.
- [2] F. Doria, A. Oppi, F. Manoli, S. Botti, N. Kandoth, V. Grande, I. Manet, M. Freccero. *Chem. Comm.* **2015**, 51, 9105-9108.
- [3] M. Zuffo, F. Doria, V. Spalluto, S. Ladame, M. Freccero. *Chem. Eur. J.*, **2015**, 21, 17596-17600.
- [4] R. Perrone, F. Doria, E. Butovskaya, I. Frasson, S. Botti, M. Scalabrin, S. Lago, V. Grande, M. Nadai, M. Freccero, S. N. Richter. *J. Med. Chem.*, **2015**, 58, 9639-9652.
- [5] F. Doria, M. Nadai, M. Zuffo, R. Perrone, M. Freccero, S. N. Richter. *Chem. Comm.*, **2017**, 52, 2268-2271.
- [6] M. Zuffo, F. Doria, S. Botti, G. Bergamaschi, M. Freccero. *Biochim. Biophys. Acta*, **2017**, 1861, 1303-1311.
- [7] M. Zuffo, A. Guédin, E. D. Leriche, F. Doria, V. Pirota, V. Gabelica, J.-L. Mergny, M. Freccero. *Nucleic Acid Res.*, **2018**, 24(19), e115.

The intriguing world of G-quadruplex-based aptamers

D. Musumeci, F. Moccia, C. Platella, C. Riccardi, D. Montesarchio*

Department of Chemical Sciences, University of Napoli Federico II, via Cintia, 21, Napoli
daniela.montesarchio@unina.it

Among the known aptamers, many are guanine-rich oligomers. The relatively high abundance of guanine-rich aptamers identified by SELEX, coupled with their ability to recognize very different targets, is not surprising.¹⁻³ In fact, guanine-rich oligonucleotides share a distinctive ability to fold into stable but also extremely different G-quadruplex (G4) structures, which are non-canonical nucleic acid conformations stabilized by guanine tetrads, i.e. cyclic planar arrangements of four guanines linked through Hoogsteen-type hydrogen bonds. Stacking of two or more guanine tetrads generates the G4 motif, further stabilized by cations complexed in the central cavity of the G4.⁴ The apparently rigid G4 structure is indeed rather plastic and can fit into a variety of nucleic acid architectures. Thus, even very similar DNA sequences can exhibit an extraordinarily wide structural variability, and therefore provide precious and versatile scaffolds to evolve highly specific aptamers, accounting for very different biological effects.

In this frame, we are currently investigating several G4-forming aptamers, specifically targeting inflammation- and cancer-related proteins. Our recent results concerning aptamers selectively recognizing two peculiar systems, i.e. the proteins VEGF and IgM, widely recognized biomarkers of different cancer forms, will be here presented as case studies. For these proteins, we studied brand new G4-based aptamers (IgM),⁵ or provided conspicuous new knowledge on known G4-based aptamers (VEGF).⁶

The conformational behaviour of these aptamers, analysed by multiple biophysical methods, proved to dramatically depend on their solution environments. In pseudo-physiological buffers mimicking extra- or intracellular media, the studied aptamers proved to be highly polymorphic, folding into stable, unimolecular G-quadruplex structures in K⁺-rich solutions. In all cases, their functional conformations have been identified and characterized.

These findings demonstrate the key role of G-quadruplex folding in the molecular recognition and efficient binding of both anti-mIgM and anti-VEGF aptamers, providing a precious rational basis for the design of effective aptamer-based biosensors potentially useful for the detection of cancer-relevant biomarkers.

References:

- [1] J. Zhou, J. Rossi, *Nat. Rev. Drug Discov.* **2017**, *16*, 181-202.
- [2] C. Platella, C. Riccardi, D. Montesarchio, G. N. Roviello, D. Musumeci, *Biochim. Biophys. Acta - Gen. Subj.* **2017**, *1861*, 1429-1447.
- [3] D. Musumeci, C. Platella, C. Riccardi, F. Moccia, D. Montesarchio, *Cancers* **2017**, *9*, 1-43.
- [4] D. Rhodes, H. J. Lipps, *Nucleic Acids Res.* **2015**, *43*, 8627-8637.
- [5] F. Moccia, C. Platella, D. Musumeci, S. Batool, H. Zumrut, J. Bradshaw, P. Mallikaratchy, D. Montesarchio, *Int J Biol Macromol.* **2019**, doi: 10.1016/j.ijbiomac.2019.04.141.
- [6] F. Moccia, C. Riccardi et al., manuscript under revision.

Encapsulation and controlled release of thymol derivatives into lignin microcapsules

F. Sabuzi,^a C. Piombino,^a H. Lange,^a L. Zongo,^a P. Galloni,^a C. Crestini,^{a,b} V. Conte^a

^a Department of Chemical Science and Technologies, University of Rome Tor Vergata,
Via della Ricerca Scientifica, 00133-Rome

^b Department of Molecular Sciences and Nanosystems, University Ca' Foscari,
Via Torino 155, 30172-Venezia
federica.sabuzi@uniroma2.it

Thymol and the corresponding brominated derivatives constitute important biological active molecules as antibacterial, antioxidant, antifungal and antiparasitic agents.^{1,2} However, their use as preservatives in food industry or in packaging materials is often limited because of their pronounced fragrance, their poor solubility in water and their high volatility. Among the others, active molecules encapsulation represents a successful strategy to overcome such limitations.

In this communication, preliminary results related to the encapsulation of different thymol derivatives into biocompatible lignin-microcapsules will be presented. As a matter of fact, the adoption of an encapsulating material possessing relevant antibacterial and antioxidant activity as well as high biocompatibility -such as lignin-^{3,4} allows the easy development of new materials that are suitable for the application in several industrial fields. To this purpose, lignin microcapsules containing thymol, 4-bromothymol, 2,4-dibromothymol and the corresponding methoxy derivatives have been efficiently prepared through ultrasonication (Fig. 1). Studies of encapsulation efficiency, morphology and release will be presented.

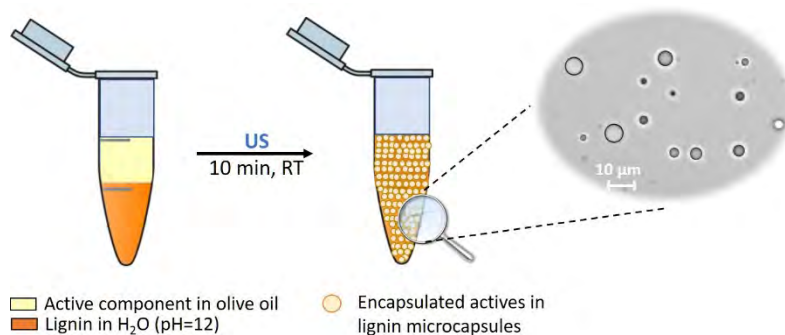


Figure 1: Encapsulation process of the active components in lignin microcapsules. In the zoom: microscope images of lignin microcapsules.

Acknowledgments:

Authors thank University of Rome Tor Vergata "SUSCARE project" for financial support.

References:

- [1] F. Sabuzi, E. Churakova, P. Galloni, R. Wever, F. Hollmann, B. Floris, V. Conte, *Eur. J. Inorg. Chem.* **2015**, 3519-3525.
- [2] P. Galloni, V. Conte, F. Sabuzi, L. Migliore, M. C. Thaller, G. Matteucci, WO2018/046584 A1 (International Patent).
- [3] M. R. Tortora, F. Cavalieri, P. Mosesso, F. Ciaffardini, F. Melone, C. Crestini, *Biomacromolecules* **2014**, 15, 1634-1643.
- [4] E. D. Bartzoka, H. Lange, K. Tiehl, C. Crestini, *ACS Sustainable Chem. Eng.* **2016**, 4, 5194–5203.

Novel insights on peptide-G4 DNA interaction: a study on the binding behaviour of polyamine peptides on different G4 DNA structures

G. N. Roviello,^a N. Borbone,^b D. Marasco^b, A. P. Falanga^b, M. Marzano^b and G. Oliviero^c

^aInstitute of Biostructures and Bioimaging -CNR 1, Via Mezzocannone 16 - 80134, Naples

^b Department of Pharmacy University of Naples Federico II, Via Domenico Montesano 49 - 80131, Naples

^cDepartment of Molecular Medicine and Medical Biotechnologies

University of Napoli Federico II, Via Sergio Pansini 5 - 80131, Naples

giovini@unina.it

Guanine-rich sequences are found in DNAs able to fold into intramolecular G-quadruplex structures, which may play a relevant role in a number of biological processes and disease related mechanisms¹. Thus, the discovery and the characterization of new supramolecular G4 assemblies represent a very interesting challenge². Apart cations, such as potassium or sodium, also molecules such as polyamines and triethylene tetraamine contribute to the stability of G4 structures to which they bind provoking noteworthy biological effects, including telomerase inhibition.^{3,4}

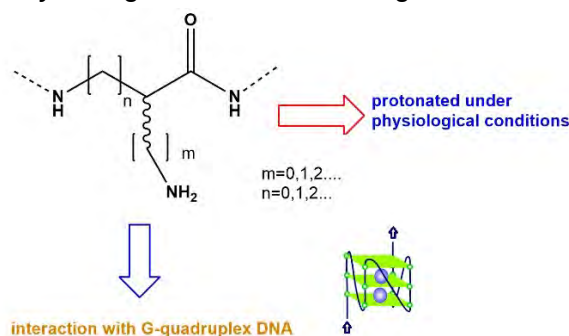


Figure 1: Schematic representation of the repeating unit of a generic diamino acid-based peptide to be studied in G4-DNA targeting

In this study we investigate the potential as G4 binders of artificial polyamine peptides, unnatural peptides based on the oligomerization of diamino acids, synthesized by solid phase synthesis and fully characterized. The effects on different models of G4-DNAs, including the parallel topology-forming c-myc and tel₂₂ in a hybrid mixed parallel/antiparallel topology, are discussed on the light of CD, UV and fluorescence binding evidences that seem to indicate polyamine peptides, positively charged under physiological conditions, as G4 binders able to induce specific structural modifications in the different G4 topologies.

References:

- [1] T. Simonsson, *Biol. Chem.* **2001**, 382, 621-628.
- [2] M. Marzano, A. Falanga, S. D'Errico, B. Pinto, G. N. Roviello, G. Piccialli, G. Oliviero, N. Borbone, *Molecules* **2019**, 24, 654-663.
- [3] N. Kumar, R. Basundra, S. Maiti, *Nucleic Acids Res.* **2009**, 37, 3321-3331.
- [4] F. Yin, J. Liu, X. Peng, *Bioorg. Med. Chem. Lett.* **2003**, 22, 3923-3926.

Novel [2]-Rotaxanes Incorporating a Nitroxide Radical Motif

C. Poderi,^a P. Franchi,^a L. Gualandi,^a E. Mezzina,^{*a} and M. Lucarini^{*a}

^aDepartment of Chemistry "Giacomo Ciamician", University of Bologna, Via S. Giacomo 11, 40126 Bologna, Italy.

E-mail: cecilia.poderi2@unibo.it

Dialkyl nitroxide radicals ($R_2N-O\bullet$) are an important example of open-shell molecules largely employed in many fields of chemistry and related sciences.¹ If compared to related diamagnetic functional groups, the use of nitroxides in molecular-level assembly processes remains, however, basically unexplored. This is somewhat surprising given their desirable intrinsic properties: nitroxides possess one of the largest dipole moments known for any functional-group type (close to 3 D), making them potentially useful for control of molecular orientation. In particular the N-O $\bullet$ motif is a good hydrogen and halogen-bond acceptor,² and offers a simple reversible route to diamagnetic oxammonium species via one-electron electrochemical oxidation.¹ On this basis, we investigated the possibility to prepare the first examples of nitroxide-containing bistable rotaxanes in which the N-O $\bullet$ motif would act not only as EPR probe for the shuttling process, but can be also directly involved in the recognition process both in its radical state³ or in its diamagnetic oxidized form. In the reported [2]rotaxanes, the wheel is a 2,5-dimethyl-2,5-diphenylpyrrolidine-N-oxyl radical bound to a crown ether fragment at the *meta* positions of both aromatic rings (**1**, Figure 1). Two different interlocked molecules were investigated: in one case the thread contained 4,4'-bipyridinium (BPY²⁺) and dialkylammonium (NH₂⁺) stations (**2**) while in the other, the BPY²⁺ unit was replaced by a triazole fragment (**3**). Shuttling of the paramagnetic ring along the threads was induced by applying both acid-base or electrochemical inputs and was monitored by using different spectroscopic techniques, including EPR. It will be shown that the ability to switch between different states in these rotaxanes, using electrochemical power-source or by pH variation, highlights the possibility of creating elaborated molecular architectures, capable of progressively complex functions.

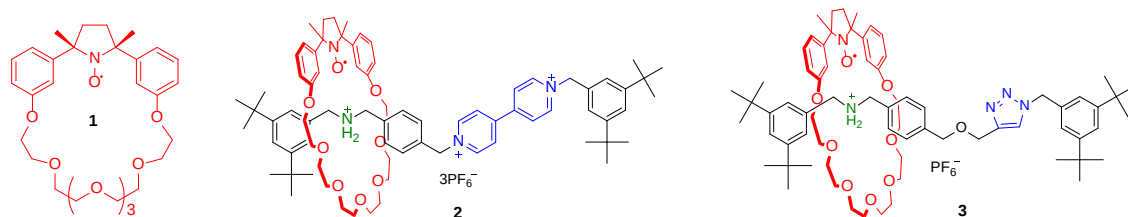


Figure 1: Structures of macrocycle **1** and rotaxanes **2-3**.

References:

- [1] G. I. Likhtenshtein, J. Yamauchi, S. Nakatsuji, S. Smirnov, R. Tamura, *Nitroxides: Applications in Chemistry, Biomedicine and Materials Science*, Wiley-VCH, Weinheim, **2008**, Vol. 47, pp. 9596-9597.
- [2] L. Gualandi, E. Mezzina, P. Franchi, M. Lucarini, *Chem. Eur. J.* **2016**, 22, 16017-16021.
- [3] V. Bleve, P. Franchi, E. Konstanteli, L. Gualandi, S. M. Goldup, E. Mezzina, M. Lucarini, *Chem. Eur. J.* **2018**, 24, 1198-1203.

Chiral functionalized fluorescent macrocycles as a scaffold for remarkable chiroptical properties

F. Zinna,^a A. Homberg,^b E. Brun,^b S. Voci,^c L. Arrico,^a N. Sojic,^c J. Lacour,^b L. Di Bari,^a

^a Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Moruzzi 13, 56124 Pisa, Italy.

^b Department of Organic Chemistry, University of Geneva, Quai E. Ansermet 30, 1211 Geneva 4, Switzerland.

^c Univ. Bordeaux, Bordeaux INP, CNRS, Institut des Sciences Moléculaires, UMR 5255
16 avenue Pey-Berland, 33607 Pessac, France.
francesco.zinna@unipi.it

We investigated a series of chiral macrocycles, di-functionalized with various fluorescent moieties. These compounds display strong intramolecular excimer fluorescence and allied highly circularly polarized luminescence (CPL) with a circular polarization degree in the upper range of the ones reported for non-aggregated chiral molecules (g_{lum} up to $1.7 \cdot 10^{-2}$). Upon interaction with alkaline and alkaline earth cations (Na^+ , Ba^{2+}), the systems undergo deep conformational rearrangements which can result in a complete quenching of the excimer fluorescence and CPL (on/off), while the ECD profile is strongly modified, with some bands showing a sign inversion (+/-).¹

Upon reversible decomplexation excimer fluorescence and the original ECD and CPL spectra are almost perfectly recovered. Such effect can be observed over several complexation/decomplexation cycles.¹

In this way, rare examples of completely reversible switching of both +/- ECD and on/off CPL were attained.

Moreover, taking advantage of such molecular scaffold, we obtained the first example of circularly polarized electrochemiluminescence stemming from an organic molecule.²

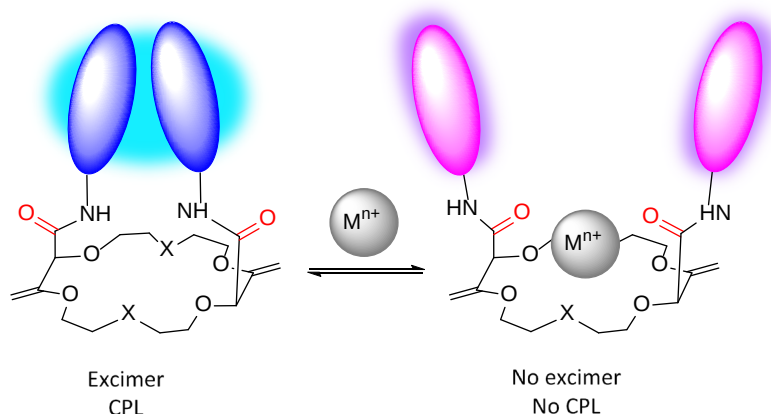


Figure 1: (Chiro)optical response upon cation binding by functionalized macrocycles.

References:

- [1] A. Homberg, E. Brun, F. Zinna, S. Pascal, M. Górecki, L. Monnier, C. Besnard, G. Pescitelli, L. Di Bari, J. Lacour, *Chem. Sci.* **2018**, 9(35), 7043 – 7052.
- [2] F. Zinna, S. Voci, L. Arrico, E. Brun, A. Homberg, L. Bouffier, T. Funaioli, J. Lacour, N. Sojic, L. Di Bari, *Angew. Chem. Int. Ed.* **2019**, accepted manuscript, DOI: 10.1002/ange.201901303.

Development and binding properties of a synthetic receptor for the molecular recognition of caffeine and related xanthines

O. Francesconi,^a A. Ienco,^a M. Dolce,^a C. Nativi,^a S. Roelens^a

^a Department of Chemistry and INSTM, University of Florence, Polo Scientifico e Tecnologico, 50019 Sesto Fiorentino, Florence (Italy)
oscar.francesconi@unifi.it

Caffeine and related xanthines, are among the most widely used psychoactive substances in the world, since they are consumed with traditional drinks, such as tea and coffee, but also with commercial energy drinks and with different kind of analgesics.¹ Xanthines have various pharmacological activities,² such as central nervous system stimulation, in addition to diuretic, anti-tussive and anti-bronchospastic properties. Furthermore, a protective role of caffeine seems to be involved in neurovegetative diseases, such as Parkinson's, Alzheimer's and ischemia.

Because biological functions of caffeine and of its main metabolites, theophylline and theobromine, are mediated by specific molecular recognition receptors, the study of their recognition is fundamental to understand their role in biological systems. The use of artificial receptors, possessing a very simplified structure and accessibility is essential for mimicking the function of the biological counterpart and for defining the structural and functional requirements that determine binding ability and selectivity. In this context, the realization of water-soluble synthetic receptors with high affinity and selectivity remains a goal pursued with much interest.

In recent years, in our research group, a family of synthetic receptors designed for carbohydrate recognition have been successfully developed.³ The architecture of these receptors consists of aromatic platforms bridged by aminocarbazole units and endowed with hydrosolubilizing groups, an architecture that seems structurally and functionally appropriate to recognize xanthines as well. On the basis of receptors developed up to now, the synthesis of a new structure has been carried out and recognition ability towards xanthines of particular interest has been evaluated.

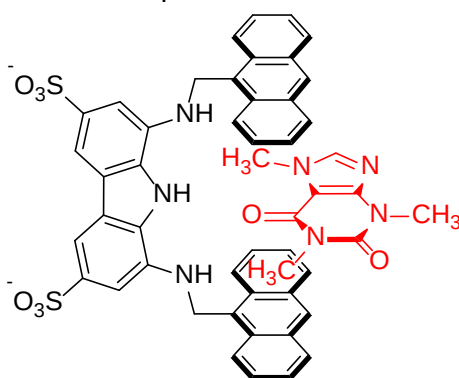


Figure 1: Schematic representation of receptor-caffeine complex.

References:

- [1] B. A. Weinberg, B. K. Bealer *The world of caffeine: The science and culture of the world's most popular drug*; Routledge: New York, N. Y. **2001**, pp. 235-265
- [2] H. Milon, R. Guidoux, J. A. Antonioli, *Physiological effects of coffee and its components*; In: *Coffee: Physiology*; R. J. Clarke,; R. Macrae, (Eds.), Elsevier: Amsterdam, **2003**, Vol. 3, pp. 81-122.
- [3] O. Francesconi, M. Martinucci, L. Badii, C. Nativi, S. Roelens, *Chem. Eur. J.*, **2018**, 24, 6828-6836.

Spike of Sulfur for Photo-Chemistry on Self-assembling Tripeptides

M.C. Cringoli,^a D. Iglesias,^a S. Kralj,^b and S. Marchesan^a

^a Dept. of Chem. and Pharm. Sci., University of Trieste, Via L. Giorgieri,1, Trieste, Italy, 34127.

^b Dept. for Materials Synthesis, K8, Jožef Stefan Institute, Jamova 39, Ljubljana, Slovenia, 1000.
mariacristina.cringoli@phd.units.it

Tripeptides are attractive minimalistic bioactive motifs and low-cost building blocks for supramolecular hydrogels.¹ Amongst the various design approaches, combination of D- and L-amino acids is proving successful for hydrophobic sequences.^{2,3} The identification of new motifs containing cysteine or methionine could be interesting for added properties, such as the possibility to undergo redox cycles, metal coordination, or sulfur-based reversible chemistry to develop dynamic functional materials.

We report on a series of self-assembling D,L-tripeptides containing either methionine or cysteine to give dynamic materials that can undergo reversible cycles of assembly. The supramolecular behaviour of these materials is characterized by circular dichroism, single-crystal XRD, FT-IR, Thioflavin T fluorescence, and TEM.

The possibility to control the supramolecular behaviour by means of a photo-switch is an attractive strategy to obtain new smart materials, useful for technological and medical applications. Popular photo-switches are reversible and often based on *cis-trans* isomerization. However, for specific applications, such as cargo delivery or final disposal of the functional material, irreversible photo-switches could be desirable.

The observation that an alanine-containing tripeptide is not able to self-assemble into a hydrogel, while its cysteine containing analogue does, suggests that a cysteine-to-alanine conversion, through a photo-induced desulfurization, could be a good strategy to disassemble a supramolecular nanostructured hydrogel in an irreversible manner. In literature, several reactions of desulfurization are reported in the context of native chemical ligation, but they typically require harsher reaction conditions or bring to the formation of several side products. Photo-activated desulfurization of cysteine in water is reported and applied to D,L-tripeptides that self-assemble into hydrogels, to convert them into analogues that do not gel. In this way, irreversible disassembly can be spatially-resolved by using a photo-mask (Fig. 1).

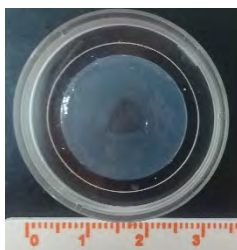


Figure 1: Photograph of a hydrogel irradiated with UV light using a triangle-shaped mask.

References:

- [1] P. Ung, D. A. Winkler, *J. Med. Chem.* **2011**, *54*, 1111-1125.
- [2] a) A.M. Garcia, D. Iglesias, E. Parisi, K. E. Styan, L.J. Waddington, C. Deganutti, R. D. Zorzi, M. Grassi, M. Melchionna, A. V. Vargiu, S. Marchesan, *Chem* **2018**, *4*, 1862-1876; b) A. M. Garcia, M. Kurbasic, S. Kralj, M. Melchionna, S. Marchesan, *Chem. Commun.* **2017**, *53*, 8110-8113.
- [3] A. V. Vargiu, D. Iglesias, K. E. Styan, L. J. Waddington, C. D. Easton, S. Marchesan, *Chem. Commun.* **2016**, *52*, 5912-5915.

Self-Assembled nicotinic acid-based tetrahedral hosts as supramolecular catalysts: synthesis and first applications

G. Floresta,^a D. Gentile,^a V. Patamia,^a A. Rescifina^a

^aDipartimento di Scienze del Farmaco, Università di Catania, Viale Andrea Doria 6, 95125 - Catania, Italy
giuseppe.floresta@unict.it

The field of supramolecular chemistry has its foundation in mimic the nature catalysts, in which microenvironments promote reactions with remarkable rate acceleration, substrate specificity, and product selectivity.^{1,2} Drawing inspiration from early studies, self-assembled supramolecular hosts continue to capture a significant amount of interest toward their development as catalysts for increasingly complex transformations.³

This communication describes our recent developments in the application of new nicotinic acid-based tetrahedral hosts as catalysts for organic transformations. The monomer for the tetrahedral complex was synthesized by simple amide coupling reactions, and the tetrahedral catalyst was then self-assembled in the presence of gallium(III) (Figure 1). The formation of the tetrahedral structure was confirmed by NMR and MS analyses. The catalytic capabilities of the novel nicotinic acid-based tetrahedral host have been firstly studied by different uninvestigated examples of reaction. 1,3-dipolar cycloaddition and reductive amination are here reported. The mechanism of the reaction and the inclusion of reagents and products in the supramolecular catalyst have been studied and rationalized by NMR spectroscopy experiments and molecular modeling calculations.

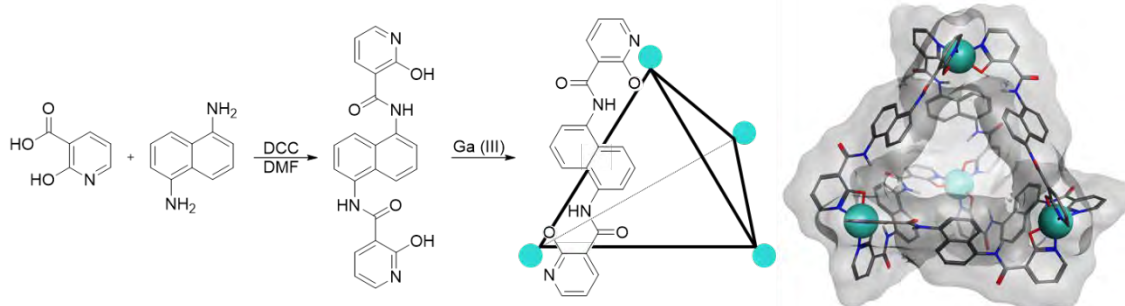


Figure 1: Synthesis and schematic representation of the nicotinic acid-based tetrahedral hosts.

References:

- [1] G. Floresta, C. Talotta, C. Gaeta, M. De Rosa, U. Chiacchio, P. Neri, A. Rescifina, *J. Org. Chem.* **2017**, 82, 4631-4639.
- [2] P. La Manna, C. Talotta, G. Floresta, M. De Rosa, A. Soriente, A. Rescifina, C. Gaeta, Placido Neri, *Angew Chem. Int. Ed.* **2018**, 57, 5423-5428.
- [3] C. M. Hong, R. G. Bergman, K. N. Raymond, F. D. Toste, *Acc. Chem. Res.* **2018**, 51, 2447-2455.

How to Make Autonomous the Motions of a Chemically Fueled Molecular Machine

C. Biagini, G. Capocasa, V. Cataldi, D. Del Giudice, L. Mandolini, S. Di Stefano

*Dipartimento di Chimica, Università di Roma "La Sapienza", and Istituto CNR per i Sistemi Biologici (ISB-CNR), Sezione Meccanismi di Reazione, P.le A. Moro 5, 00185 Roma
stefano.distefano@uniroma1.it*

In recent years, molecular machines (switches and motors) have been one of the hottest topic in chemical science. Applications of the principles and concepts developed in this field to future nanosciences and nanotechnologies are so promising that the related advantages for mankind are nowadays hardly imaginable.

Our main contribution to molecular machines is the use of the decarboxylation reaction of activated carboxylic acids as a source of energy for molecular motions. In particular, back and forth motions of an acid-base operated molecular machine (a switch) were demonstrated to occur on addition of such fuel acids with no need of subsequent addition of any counter-stimulus.^{1,2,3} Our system was of inspiration to Leigh and co-workers who used the decarboxylation reaction of trichloroacetic acid as source of energy for the unidirectional operation of rotary and linear molecular motors.⁴ However, a main drawback related to the use of our acids lied in the impossibility to use an excess fuel with respect to the molecular machine, which posed severe limitations to an "autonomous" operation of the machine itself.

In this communication we report that the use of a pre-fuel allows to overcome the above drawback. Indeed, we found that the slow and continuous transformation of the pre-fuel into the acid fuel triggers the back and forth motions of machine.⁵ Importantly, the chemical reaction that transforms the pre-fuel into the fuel and the cyclic motions of the switch turned out to be matched in such a way that excess of acid (fuel) with respect to the switch (machine) is never present in solution. As a consequence, the machine does not require a reloading after each cycle, but repeatedly switches back and forth as long as fuel is present. This system represents the first example of a chemically fueled molecular machine that autonomously carries out a number of motion cycles with no need of supply of material or radiant energy during the operation.

References:

- [1] J. A. Berrocal, C. Biagini, L. Mandolini, S. Di Stefano, *Angew. Chem. Int. Ed.* **2016**, 55, 6997-7001.
- [2] C. Biagini, S. Albano, R. Caruso, L. Mandolini, J. A. Berrocal, S. Di Stefano, *Chem. Sci.* **2018**, 9, 181-188.
- [3] C. Biagini, F. Di Pietri, L. Mandolini, O. Lanzalunga, S. Di Stefano, *Chem. Eur. J.* **2018**, 24, 10122-10127.
- [4] S. Erbas-Cakmak, S. D. P. Fielden, U. Karaca, D. A. Leigh, C. T. McTernan, D. J. Tetlow, M. R. Wilson, *Science* **2017**, 358, 340-343.
- [5] C. Biagini, G. Capocasa, V. Cataldi, D. Del Giudice, L. Mandolini, S. Di Stefano, submitted.

Mech@nochemistry: an Appealing Marriage of Innovation and Tradition

A. Porcheddu,^a E. Colacino,^b F. Delogu^c

^a Dipartimento di Scienze Chimiche e Geologiche, Università degli Studi di Cagliari, Cittadella Universitaria, SS 554 bivio per Sestu, 09042 Monserrato Cagliari (Italy)

^b Université de Montpellier & Institut Charles Gerhardt de Montpellier (ICGM), UMR5253 CNRS – UM – ENSCM, 8 Rue de l'Ecole Normale, 34296 Montpellier, Cedex 5, France.

^c Dipartimento di Ingegneria Meccanica, Chimica e dei Materiali, Università degli Studi di Cagliari, via Marengo 2, 09123 Cagliari, (Italy);
porcheddu@unica.it

In the not too distant past, the design of a synthetic process was mainly focused on maximizing yields by neglecting all aspects related to safety and environmental impact. For this reason, in public opinion chemistry, pollution and disaster sound the same way. Nowadays, it is possible to improve a chemical process by using very advanced technologies switching from conventional heating to photochemistry. Unfortunately, solvents are still today the primary source of pollution and represent the most significant portion of chemical waste in an organic transformation. Toxic solvents can be replaced with greener one, but in the end, the problem remains unresolved. The most sustainable solvent is the solvent that is not used. Mechanochemical reactions, conducted by milling, grinding, or shearing, are rapidly emerging as an attractive, clean, energy- and materials-efficient alternative to conventional solution-based synthesis and are considered to be promising candidates in solvent-free synthesis. In this scenario, “*mechanical energy*” represents an alternative mean to activate chemical processes, which have not been widely explored yet. Moreover, the *mechanochemical activation* of organic synthesis allows overcoming some of the issues of classical synthesis in solution, enables the design of unexplored synthetic strategies, thus expanding the scope of chemical reactions to insoluble starting materials (Scheme 1). In this communication, the potential of “*Mechanochemistry*” applied to some significant reactions recently developed in our laboratories, and some of the related challenges will be discussed in detail.¹⁻³

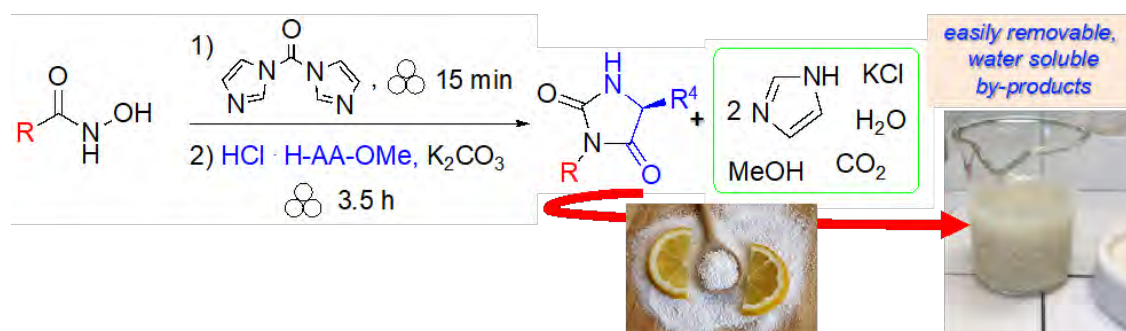


Figure 1: An eco-compatible synthesis of 3,5-disubstituted hydantoins by CDI-mediated “*mechanochemical Lossen transposition*”.

References:

- [1] E. Colacino, A. Porcheddu, C. Charnay, F. Delogu, *React. Chem. Eng.* **2019**, DOI: 10.1039/C9RE00069K.
- [2] A. Porcheddu, F. Delogu, L. De Luca, E. Colacino, *ACS Sustainable Chem. Eng.* **2019**, 7, (under revision).
- [3] E. Colacino, A. Porcheddu, I. Halasz, C. Charnay, F. Delogu, R. Guerra and J. Fullenwarth, *Green Chem.*, **2018**, 20, 2973-2977.

Bio-based ionic liquids: synthesis and applications

C. Chiappe,^a L. Guazzelli,^a C.S. Pomelli,^a F. D'Andrea,^a A. Mezzetta,^a S. Becherini,^a

^aDipartimento di Farmacia, Università di Pisa, Via Bonanno 33, 56126 Pisa
lorenzo.guazzelli@unipi.it

Ionic liquids (ILs) are salts composed by an organic cation and either an organic or an inorganic anion, which are in the liquid state at temperatures below 100 °C. ILs are characterized by unique physico-chemical properties such as high thermal stability, low combustibility, negligible vapor pressure, and favorable solvating properties for a range of polar and non-polar compounds.

Since the beginning of the century, ILs attracted growing interest and found use in a wide range of applications which span for instance from alternative reaction media for organic reactions, to materials science and biological science.

During the last ten years, questions related to the real green character and even sustainability of ILs have been posed. Therefore, a recent trend in the ILs field is to select more carefully the constituting ions looking with increasing interest to natural and bio-based options¹. Replacement of petrol-derived ions with natural or bio-based ones, could represent a way to address both issues by reducing ILs toxicity and enhancing their biodegradability.



Figure 1: preparation of bio-based ionic liquids and potential applications.

Here we present our results in the preparation of ILs and protic ILs comprised of ions with natural origins (eg fatty acids, terpenoids, levulinic acid)²⁻⁴.

Characterization of the obtained ILs as well as potential fields of applications explored thus far will be presented (Figure 1).

References:

- [1] J. Hulsbosch, D. E. De Vos, K. Binnemans, R. Ameloot, *ACS Sustainable Chem. Eng.* **2016**, *4*, 2917-2931.
- [2] A. Mezzetta, L. Guazzelli, M. Seggiani, C. S. Pomelli, M. Puccini, C. Chiappe, *Green Chem.* **2017**, *19*, 3103-3111.
- [3] M. Longhi, S. Arnaboldi, E. Husanu, S. Grecchi, I.F. Buzzi, R. Cirilli, S. Rizzo, C. Chiappe, P. R. Mussini, L. Guazzelli, *Electrochim. Acta* **2019**, *298*, 194–209.
- [4] S. Becherini, A. Mezzetta, C. Chiappe, L. Guazzelli, *New J. Chem.* **2019**, *43*, 4554-4561.

A new efficient flow chemical synthesis of thiophene-2-carboxylates

E. Chiurchiù,^a Y. Patehebieke,^a S. Gabrielli,^a R. Ballini,^a A. Palmieri^a

^aUniversity of Camerino, Via Sant'Agostino 1, 62032 Camerino, Italy
elena.chiurchiu@unicam.it

Thiophenes, especially 2-carboxylate derivatives **4**, are key building blocks for synthesizing biologically active compounds used for the treatment of cancer, neurological, inflammatory and fibrotic diseases.^{1,2,3} Synthetic methods for their preparation reported in literature^{4,5,6} show significant drawbacks such as the use of expensive metal catalysts, harsh reaction conditions or restricted substrates generality.

Following our studies related to the reactivity of β -nitroacrylates,^{7,8,9,10} we propose a new efficient, fast and general procedure to prepare the title compounds in good to excellent overall yields. The method is based on the reaction between β -nitroacrylates of type **1** and thioacetic acid using a continuous flow system. The three step synthesis involves: (i) promoter-free conjugate addition of thioacetic acid to the β -nitroacrylates (intermediate **2**); (ii) base-induced nitrous acid elimination (intermediate **3**) and (iii) acid-promoted cyclization-aromatization. The use of solid supported reagents avoids any intermediate purification and leads to the target compounds in a one-pot procedure that is applicable to a wide variety of β -nitroacrylates.

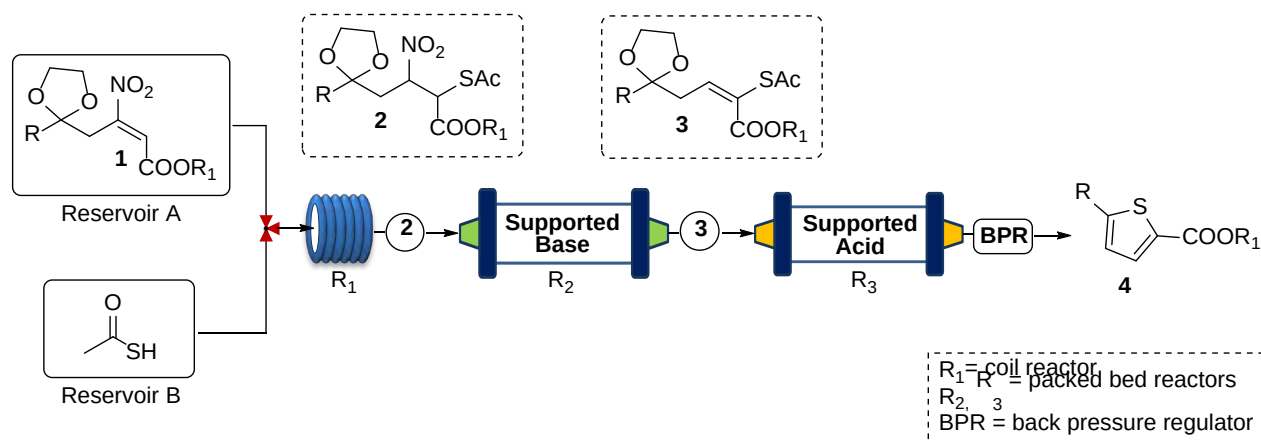


Figure 1: Continuous flow apparatus for the synthesis of 2-carboxythiophenes.

References:

- [1] M. Brindisi *et al*, *Tetrahedron*, **2016**, 57, 920- 923.
- [2] F. Del Bello *et al.*, *Bioorg. Med. Chem.*, **2015**, 23, 5725-5733.
- [3] P. Segupta *et al.*, *Eur. J. Med. Chem.*, **2011**, 46, 5549-5555.
- [4] G. Ulrich, S. Goeb, E. De Nicola, P. Retailleau, R. Ziessel, *J. Org. Chem.*, **2011**, 76, 4489- 4505.
- [5] J. Marchal, J. Bodiguel, I. Fort, P. Caubere, *J. Org. Chem.*, **1995**, 60, 8336- 8340.
- [6] Y. Ju, D. Miao, R. Yu, S. Koo, *Org. Biomol. Chem.*, **2015**, 13, 2588- 2599.
- [7] R. Ballini, S. Gabrielli, A. Palmieri, *Synlett*, **2009**, 6, 965- 967.
- [8] A. Pamieri, S. Gabrielli, M. Parlapiano, R. Ballini, *RSC Adv.*, **2015**, 5, 4210-4213.
- [9] A. Palmieri, S. Gabrielli, D. Lanari, L. Vaccaro, R. Ballini, *Adv. Synth. Catal.*, **2011**, 353, 1425-1428.
- [10] S. Gabrielli, E. Chiurchiù, A. Palmieri, *Adv. Synth. Catal.*, **2019**, 361, 630-653.

Multivalent effect of cyclopeptoid-iminosugar conjugates in glycosidase inhibition

R. Schettini,^a F. De Riccardis,^a Y. Liang,^b A. Bodlenner,^b P. Compain,^b I. Izzo^a

^a Department of Chemistry and Biology "A. Zambelli", University of Salerno, Fisciano 84084, Italy

^b Laboratoire d'Innovation Moléculaire et Applications (LIMA), Univ. de Strasbourg | UHA | CNRS (UMR 7042), ECPM, 25 Rue Becquerel, 67000 Strasbourg, France
rschettini@unisa.it

An attractive class of carbohydrate mimics, known as inhibitors of glycosidases, are the iminosugars, which are emerging drugs for an impressive variety of diseases¹ such as viral infections, diabetes, cancer, lysosomal storage disorders, cystic fibrosis.² Multivalent effect can be a powerful tool to improve the therapeutic potential of enzyme inhibitors, increasing binding potencies.² The first evidence of a significant multivalent effect in glycosidase inhibition was reported for a fullerene-based iminosugar cluster, which displayed a strong binding enhancement to α -mannosidase.³ In 2014, the first examples of iminosugar clusters, based on cyclic peptoid core were reported.⁴ In few years, a series of cyclic peptoid-based iminosugar conjugates has been evaluated and in 2016 the largest binding enhancement ever reported before was observed for 36-valent cyclic peptoid-based inhibitor, against Jack bean α -mannosidase.⁵ More recently, the first high resolution crystal structure of Jack bean α -mannosidase in presence of the cyclic peptoid-based inhibitor has been reported (figure 1).⁶ In order to rationally design more efficient multivalent inhibitors the synthesis of new cyclic peptoidic cores containing different number and position of propargylic side chains has been realized. Design, synthesis and biological activities will be discussed.

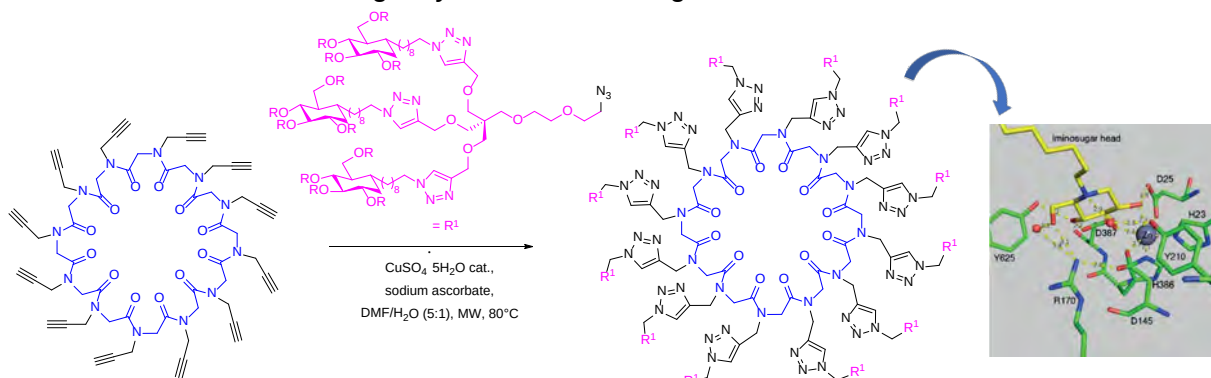


Figure 1: Cyclic peptoid-based iminosugar clusters.

References:

- [1] Iminosugars: From Synthesis to Therapeutic Applications, ed. P. Compain and O. R. Martin, Wiley VCH, New York, 2007.
- [2] M. Bols, O' L. López, F. Ortega-Caballero, *Comprehensive Glycoscience*, 2007, 816-884.
- [3] P. Compain, C. Decroocq, J. Iehl, M. Holler, D. Hazelard, T. MenaBarrag_n, C. Ortiz Mellet, J.-F. Nierengarten *Angew. Chem. Int. Ed.* **2010**, 49, 5753 - 5756.
- [4] M. L. Lepage, A. Meli, A. Bodlenner, C. Tarnus, F. De Riccardis, I. Izzo, P. Compain, *Beilstein J. Org. Chem.*, **2014**, 10, 1406- 1412.
- [5] M. L. Lepage, J. P. Schneider, A. Bodlenner, A. Meli, F. De Riccardis, M. Schmitt, C. Tarnus, N.-T. Nguyen-Huynh, Y.-N. Francois, E. Leize-Wagner, C. Birck, A. Cousido-Siah, A. Mitschler, A. Podjarny, I. Izzo, P. Compain, *Chem. Eur. J.*, **2016**, 22, 5151-5155.
- [6] E. Howard, A. Cousido-Siah, M. L. Lepage, J. P. Schneider, A. Bodlenner, A. Mitschler, A. Meli, I. Izzo, H. Ariel Alvarez, A. Podjarny, P. Compain *Angew. Chem. Int. Ed.* **2018**, 57, 8002-8006.

PNA- and modified-PNA-based systems: applications to genetic diseases

S. Volpi,^a A. Finotti,^b M. Neri,^a A. Rozzi,^a S. Korom,^a L.C. Cosenza,^b J. Gasparello,^b E. Fabbri,^b
R. Gambari,^b R. Corradini^a

Scienze 17/A Parma, Italy. ^b Dipartimento di Scienze della vita e Biotecnologie, Università di Ferrara, Via
Fossato di Mortara 74, 44121 Ferrara, Italy
roberto.corradini@unipr.it

The development of Peptide Nucleic Acids (PNAs) and their analogs allows to produce very important tools for personalised therapies (Figure 1).¹ We have approached the design of new PNA structures using rational tools, such as molecular dynamics and metadynamics analysis;² synthetic modular strategies, have been developed enabling to rationally create PNAs with improved cellular uptake, biostability and recognition properties,³ and the use of nanocarriers has created new possibilities for PNA cellular delivery.⁴ Recently our group has designed PNAs and modified PNAs able to regulate gene expression as potential treatments for presently intractable genetic diseases.⁵ In these applications, PNA can be designed in order to: a) target microRNA, short RNAs which down-regulate protein production through RNA binding and activation of the RISC silencing complex; b) target defective DNA by strand invasion, which has been shown by P. Glazer and co-workers to enhance the homologous recombination process, thus allowing efficient gene editing.⁶

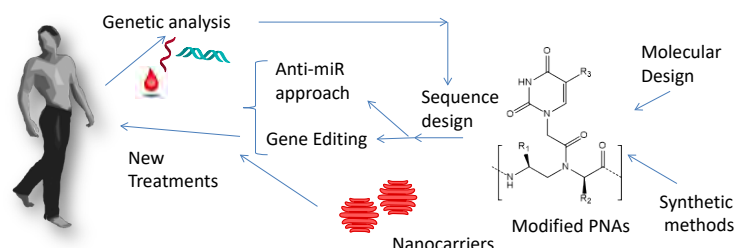


Figure 1: PNA-based personalized medicine for genetic diseases.

The design and synthesis of new PNAs for these applications will be described, and illustrated by examples of our recent work on the PNA-based treatment of cystic fibrosis (CF) by modulation of the Cystic Fibrosis conductance Transmembrane Regulator (CFTR) functionality by anti-miR PNAs. In this approach several key proteins, such as partially inactive CFTR or auxiliary proteins enabling the correct CFTR folding could be up-regulated.

Perspectives in the use of PNA-based systems and their conjugates with nanostructures for gene-editing will also be discussed. New strategies for co-delivery of different PNAs, and of PNAs and other therapeutic components (small drugs, RNA and DNA) using nanocarriers will be presented.

References:

- [1] A. Manicardi, R. Gambari, L. de Cola, R. Corradini, *Methods Mol. Biol.* **2018**, *1811*, 49-63.
- [2] M. D. Verona, V. Verdolino, F. Palazzesi, R. Corradini, *Sci. Rep.* **2017**, *7*, 42799.
- [3] A. Manicardi, A. Bertucci, A. Rozzi, R. Corradini, *Org. Lett.* **2016**, *18*, 5452-5455.
- [4] A. Bertucci, S. Silvestrini, R. Corradini, L. De Cola, *Methods Mol Biol.* **2018**, *1811*, 65-77.
- [5] E. Fabbri, A. Tamanini, T. Jakova, J. Gasparello, A. Manicardi, R. Corradini, G. Sabbioni, A. Finotti, M. Borgatti, I. Lampronti, S. Munari, M. C. Dehecchi, G. Cabrini, R. Gambari, *Molecules*, **2018**, *23*, 71.
- [6] A. S. Ricciardi, E. Quijano, R. Putman, W. M. Saltzman, P. M. Glazer, *Molecules* **2018**, *23*, 632-647.

Synthesis of bisphenol neolignans as bioactive compounds

N. Cardullo,^a V. Muccilli,^a C. Tringali^a

^aDipartimento di Scienze Chimiche, Università degli Studi di Catania, V.le A. Doria n. 6, Catania
ncardullo@unict.it

Lignans and related compounds (neolignans, oxyneolignans, and mixed lignans) represent a large family of natural products, showing an interesting variety of structures and biological activities.

In recent years, two simple dimeric neolignans, namely the bisphenols magnolol and honokiol, have gained growing attention for their multiple biological activities. Both are natural products originally isolated from the bark of *Magnolia* spp., used in Japanese and Chinese traditional medicine for various diseases such as gastrointestinal disorders, anxiety, allergy, inflammation and others.

The biological properties of the two neolignans have been the subject of many studies, and a non-exhaustive list includes antitumor, antiangiogenic, anti-inflammatory, antimicrobial, antiviral, antioxidant and neuroprotective effects.¹ These properties prompted a number of research groups to synthesize magnolol and honokiol analogues as potential bioactive molecules.

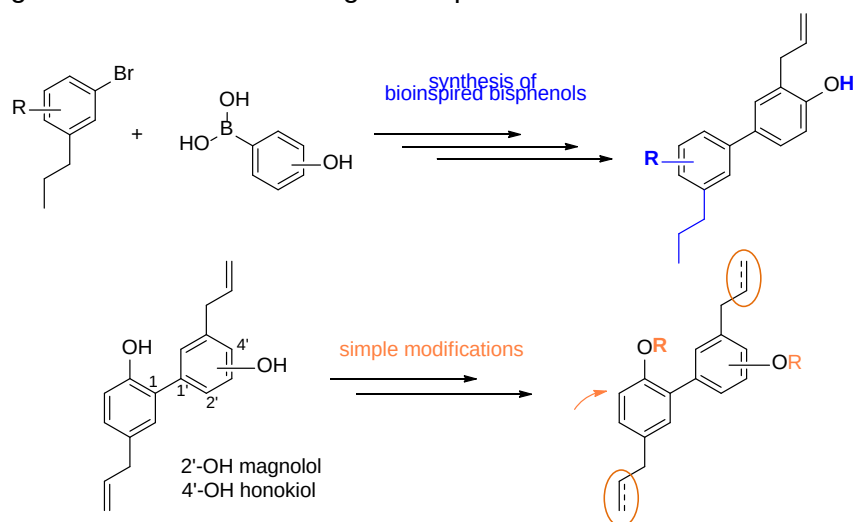


Figure 1: Schematic representation of the synthesis of bisphenol neolignans

The main objective of the present work is to obtain bisphenol neolignans inspired by honokiol and magnolol through Suzuki-Miyaura coupling or simple modifications of natural leads. The new compounds will be subjected to several biological evaluations, including the study of antiproliferative and hypoglycemic activity.

References:

[1] J.-L. Shen, K.-M. Man, P. H. Huang, W.-C. Chen, D.-C. Chen, Y.-W. Cheng, P.-L. Liu, M.-C. Chou, Y.-H. Chen. *Molecules* **2010**, *15*, 6452-6465.

3D Printable biomaterials for tissue models, functionalization strategies

L. Russo,^a S. Sampaolesi,^a S. Magli,^a L. Rabacchin,^a G. Risi,^{b,c} S. Bertini,^b C. Cosentino,^b F. Nicotra^a

^aUniversity of Milano-Bicocca, Department of Biotechnology and Biosciences. P.zza della Scienza 2, Milan

^dRonzoni Institute for Chemical and Biochemical Research, via G. Colombo 81, Milan, Italy

^cDepartment of Chemistry, University of Pavia, viale Taramelli 12, Pavia, Italy

e-mail of submitter: laura.russo@unimib.it

In the last decades, the development of regenerative medicine was in charge of the design of biomaterials because of their capability to mimic the complex Extracellular Matrix (ECM) microenvironment. To develop new biomaterials able to mimic mechanical, morphological and biochemical role of ECM, natural and synthetic polymers can be synthesized and modified in order to control the properties of final hybrid biomaterial. The 3D bioprinting technology represents today a transformative approach to generate customizable living scaffolds. The design of new synthetic strategies aimed to obtain new nano- and 3D bioprintable materials (bioinks) biologically inspired, has high impact in different biomedical fields, from nanomedicine, to tissue engineering and cell biology studies [1,2]. Taking inspiration from ECM role in cell-cell and cell-ECM interactions, different functionalized hybrid biomaterials are needed.

We will present our results in the functionalization of biomaterial with complementary functional groups for chemoselective ligation, and the subsequent crosslinking, in order to generate bioinks for 3D-bioprinting with different architectures.

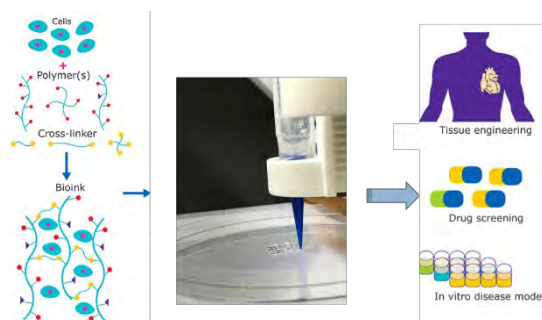


Figure 1: Bioinks and 3D bioprinting

Acknowledgments: Ministero della Salute, RICERCA FINALIZZATA 2016 RF-2016-02362946 (1/3/2018-28/2/2021) Theoryenhancing Projects. Title: Dissecting the link between pulmonary stromal changes and lung cancer progression for biomarkers discovery and therapeutic intervention

References:

- [1] S. Sampaolesi, F. Nicotra, L. Russo. *Future Medicinal Chemistry*, **2019**, 11, 43-60.
- [2] I. Donderwinkel, J.C.M. van Hest, N.R. Cameron. *Polym. Chem.*, **2017**, 8, 4451-4471.

Photoluminescent decoration of iron oxide magnetic nanoparticles for dual-imaging applications

A. Palumbo Piccionello^a, L. Menichetti^b, P. Armanetti^b, A. Flori^b, I. Monaco^c, M. Maturi^c, A. Pace^a, E. Locatelli^c.

^a *Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche. STEBICEF, Università degli Studi di Palermo, Viale delle Scienze Ed. 17, 90128 Palermo, Italy*

^b *CNR Institute of Clinical Physiology, Via Moruzzi, 1, 56124 Pisa, Italy*

^c *Department of Industrial Chemistry BToso Montanari[^], Viale Risorgimento 4, 40136 Bologna, Italy
e-mail: erica.locatelli2@unibo.it*

The design of multifunctional nanosystems for dual- imaging applications has been largely investigated in order to improve cancer diagnosis and treatment by creating a synergism of different imaging techniques.¹ In this light a fluorescent magnetic nanoparticle has been synthesized from a nitrobenzofurazan (NBD)-labeled dopamine (DA) capping agent. The selective functionalization of dopamine with the photoluminescent moiety was achieved through a one-pot protection-functionalization-deprotection sequence leading to the DA-NBD derivative. Capping of iron oxide nanoparticles with DA-NBD and further embodiment into PLGA-b-PEG polymeric nanocarriers² produced an “onion-like” nanoparticle with latent photoluminescent properties. Indeed, disassembling of the polymeric layer fully restored the fluorescence of the capping agent. The controllable photoluminescence of the obtained multilayered magnetic nanoparticles encourages their use as multimaging systems for both optical imaging and magnetic resonance.

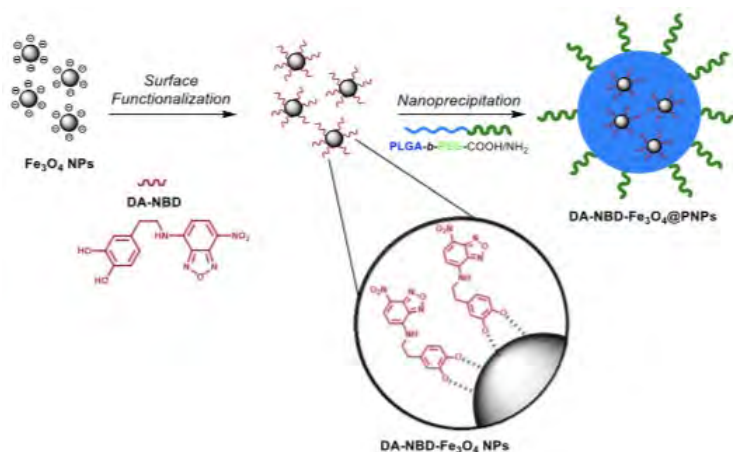


Figure 1: schematic representation of the nanosystem preparation.

References:

- [1] M. Baker, *Nature*, **2010**, 463(7283), 977–980.
- [2] E. Locatelli, M. Comes Franchini. *J. Nanopart Res.*, **2012**, 14(12), 1316-1333.

Phosphorescent iridium-containing nanomicelles: synthesis, characterization and preliminary applications in nanomedical imaging

M. Maturi,^a E. Locatelli,^a A. Baschieri,^b M. Comes Franchini,^a L. Sambri,^a

^aDepartment of Industrial Chemistry "Toso Montanari", UNIBO, Viale Risorgimento 4, Bologna, Italy

^bDepartment of Chemistry "G. Ciamician", UNIBO, Via Selmi 2, 40126 Bologna, Italy
letizia.sambri@unibo.it

Nanoparticle technology represents a great promise for drug delivery applications in nanomedicine due to its beneficial properties such as better encapsulation, bioavailability, controlled release, and a lower toxic effect. The opportunity to ingrate an imaging/diagnostic approach can produce important results due to the fast advance of imaging techniques, and the opportunity to map biochemical pathways in vivo at an unprecedented level.¹

Among various imaging techniques, optical imaging has emerged as an easy, non-ionizing and flexible imaging modality. Recently, the use of phosphorescent transition metal complexes, such as cyclometalated Ir(III)-complexes, as intra- cellular sensors and bioimaging reagents has received great attention. This is by virtue of some of their unique properties, such as large Stokes' shifts, high quantum yields, long-lived phosphorescence, high photostability, and cell permeability, making them ideal candidates for bioimaging agents.

From a synthetic point of view, a straightforward approach is to conjugate the "diagnostic luminescent tag" onto the surface of the nano- systems used for drug delivery. We report here, our recent studies^{4,5} about the potential of nanoscale phosphorescent iridium-containing micelles as a novel platform for the design of luminescent hybrid nano- particles with high contrast for optical imaging and nanomedicine applications (Figure 1).

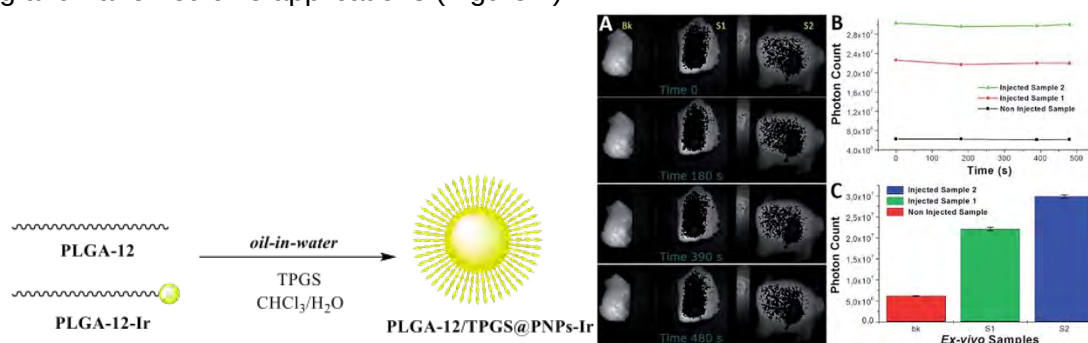


Figure 1: Schematic representation of luminescent nanoparticles

References:

- [1] T. Ramasamy, J. O. Kim et al., *J. Controlled Release*, **2017**, 258, 226-253.
- [2] P. Padmanabhan, A. Kumar, S. Kumar, R. K. Chaudhary, B. Gulyás, *Acta biomater.*, **2016**, 41, 1-16.
- [3] K. K.-W. Lo. *Acc. Chem. Res.* 2015, 48, 2985-2995.
- [4] M. Naddaka, E. Locatelli, D. Colecchia, L. Sambri, I. Monaco, A. Baschieri, F. Sasdelli, M. Chiariello, E. Matteucci, P. Zani, M. Comes Franchini, *RSC Adv.*, **2015**, 5, 1091-1099.
- [5] I. Monaco, M. Maturi, E. Matteucci, E. Locatelli, A. Baschieri, P. Zani, P. Armanetti, L. Menichetti, L. Sambri, M. Comes Franchini, *RSC Adv.*, **2018**, 8, 34162-34167.

Photochemical angular-to-linear switch of the triterpenoid A,B,C ring system: discovery, mechanistic aspects, and biological translation

C. Ingallina^a F. Rogati,^b D. Caprioglio,^b L. Mannina,^a A. Minassi^b

^aDipartimento di Chimica e Tecnologie del Farmaco, Piazzale Aldo Moro 5, Roma

^bDipartimento di Scienze del Farmaco, L.go Donegani 2/3, Novara
alberto.minassi@uniupo.it

Remodeling the carbon skeleton of natural compounds represents a powerful tool in organic chemistry to rapidly generate new natural-like libraries to study different biological processes.¹ Bond breaking and structure rearrangements are dominant features in the photoreactivity of 4,4-dialkyl-2-cyclohexenones that irradiated undergo to the lumiketone rearrangement giving bicyclo [3.1.0] hexenones as well demonstrated in Δ^4 -cholesten-3-one (**1**).²

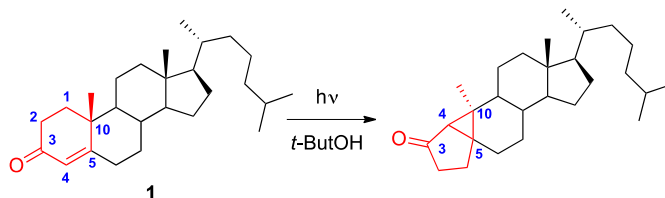


Figure 1: Lumiketone rearrangement of Δ^4 -cholesten-3-one.

Pentacyclic triterpenic acids (PCTTAs) are a class of isoprenoids targeting different macromolecular endpoints, facing a “*biological renaissance*” after the discovery of two pre-clinical potent derivatives: the anti-viral bevirimat and the antioxidant inflammation modulator bardoxolone methyl. Compared to steroids, they have long been considered as “*chemical pariahs*” remaining ignored by the greats of chemistry and with their chemical space largely untouched. In search of new ideas to fertilize the field, we have focused our attention on the photoreactivity of the Δ^1 -3-enones of easily available PCTTAs (**2**), that under irradiation gave a complete rearrangement of the A/B rings leading a new class of *iso*-PCTTA-3-enones (**3**).

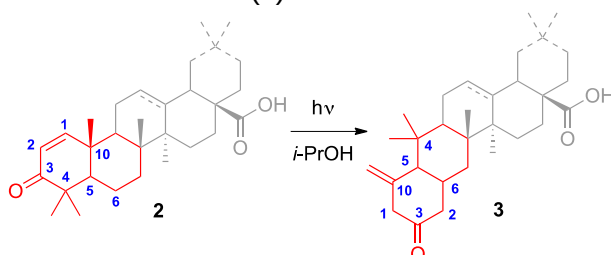


Figure 2: Lumiketone rearrangement of Δ^1 -PCTTA-3-enones.

The mechanism of this remarkable rearrangement along with the scope, the limitations and the biological translation will be discussed.

References:

- [1] R. W. Huigens III, K. C. Morrison, R. W. Hicklin, T. A. Flood Jr, M. F. Richter and P. J. Hergenrother, *Nat. Chem.* **2013**, 5, 195-202
- [2] W. W. Kwie, B. A. Shoulders, P. D. Gardner, *J. Am. Chem. Soc.* **1962**, 84, 2268-2269.

A TiCl_4 -based effective protocol for the synthesis of peptides

A. Leggio, E. L. Belsito, A. Comandè, M. Greco, A. Liguori

Dipartimento di Farmacia e Scienze della Salute e della Nutrizione,
Università della Calabria, Edificio Polifunzionale, I-87036 Arcavacata di Rende, Italy.
antonella.leggio@unical.it

The synthesis of peptides constitutes a major application of amide bond formation chemistry. The most commonly used methods for amidation involve the activation of carboxylic function through its conversion into acyl chloride, anhydride or activated ester or through the use of a coupling agent.¹⁻³

Having recently developed a method for general amidation using TiCl_4 ,⁴ we investigated the applicability of this approach in the synthesis of peptide systems. The synthesis of a selection of dipeptides by using TiCl_4 as coupling agent was designed.

Dipeptide systems were synthesized easily and in high yields through a TiCl_4 -assisted condensation reaction between *N*-protected amino acids and amino acid methyl esters in pyridine that acts both as solvent and base.

The reaction was applied successfully to amino acids protected on the α -amino function with different protecting groups. The adopted experimental conditions allowed preserving not only the α -amino protecting groups but also the side chain protecting groups.

Instead, the pyridine-free treatment of dipeptides protected by acid-labile groups with TiCl_4 provided the corresponding dipeptides deprotected on the amino function that were also employed for obtaining tripeptide systems by using the TiCl_4 /pyridine reagent system.

Furthermore, the preservation of the stereochemical integrity at the amino acid chiral centres has been verified.

References:

- [1] A. Leggio, E. L. Belsito, G. De Luca, M. L. Di Gioia, V. Leotta, E. Romio, C. Siciliano, A. Liguori, *RSC Adv.* **2016**, 6, 34468-34475.
- [2] J. R. Dunetz, J. Magano, G. A. Weisenburger, *Org. Process Res. Dev.* **2016**, 20, 140-177.
- [3] E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, 38, 606-631.
- [4] A. Leggio, J. Bagalà, E. L. Belsito, A. Comandè, M. Greco, A. Liguori, *Chem. Cent. J.* **2017**, 11, 1-12.

Metal-free Chlorination of Toluenes and Aldehydes Mediated by Visible Light

S. Gaspa,^a L. De Luca^a

^aDipartimento di Chimica e Farmacia, Università degli Studi di Sassari, Via Vienna 2, Sassari
ldeluca@uniss.it

One of the most interesting research themes in modern organic synthesis is the development of new methodologies induced by visible light.¹ Photosynthesis can be described as the conversion of sunlight into chemical energy effectively employed to carry out chemical reactions, allowing the development of sustainable and efficient procedures. Solar energy is a promising tool as the green energy source because it is a reliable, renewable and valuable source of energy. For these reasons, a reaction that occurs by means of solar radiation is an ideal goal. Many photochemical reactions require complexes of heavy or rare metals such Ru and Ir, so a photoreaction that arises without any metal catalyst represents a great aim. In this context we have developed efficient metal-free, mediated by both sunlight and artificial visible light, procedures. By these methodologies was possible to chlorinate substituted toluenes to corresponding benzyl chloride² (Figure 1, path a) and aldehydes to corresponding acyl chloride, which were then converted, in one pot fashion, to esters, carboxylic anhydrides and amides³ (Figure 1, path b).

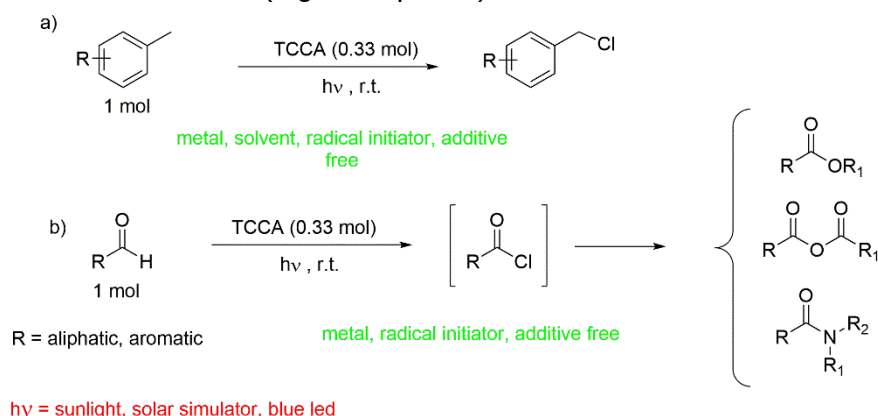


Figure 1: Chlorination of toluenes and aldehydes.

The methodologies have shown to have a big versatility and applicability on differently substituted toluenes and both aliphatic and aromatic aldehydes. The stoichiometric ratio of the reactants is optimal and the use of visible light as source of energy is very appealing from an ecological point of view. A key advantage of this process is that avoids the use of expensive and toxic transition metals-based catalysts. The reactions can be driven using different visible light sources, such as blue led, solar simulator and, more importantly, the sun. The procedures are operationally simple and the starting reagents as well as the visible light sources are inexpensive and readily accessible.

Acknowledgements: Regione Autonoma della Sardegna (CRP 72, "Capitale Umano ad Alta Qualificazione, 2015_L.R. 7/8/07, no. 7") and (RASSR81788, "INVITO A PRESENTARE PROGETTI DI RICERCA DI BASE -Annualità 2017")

References:

- [1] (a) Q. Liu and L.-Z. Wu, National Science Review 2017, 4, 359-380; (b) L. Marzo, S. K. Pagire, O. Reiser and B. König, Angew. Chem. Int. Ed. 2018, 57, 10034-10072; Angew. Chem., 2018, 130, 10188-10228.
- [2] S. Gaspa, A. Valentoni, G. Mulas, A. Porcheddu and L. De Luca, ChemistrySelect 2018, 3, 7991-7995.
- [3] Manuscript in preparation.

New applications of ester surrogates in organic synthesis

C. Volpe, S. Meninno, A. Lattanzi

Dipartimento di Chimica e Biologia, Università di Salerno, Via Giovanni Paolo II,
Fisciano, Italy
cvolpe@unisa.it

Masked esters/amides are scaffolds with great potential in organic synthesis.¹ Ester surrogates of proper acidity can be converted into enolates which react with opportune electrophiles. In the presence of cyclic azomethine ylides a [3+2] cycloaddition occurs thanks to the leaving group ability of corresponding heterocycle. We developed a convenient methodology to obtain bicyclic pyrazolidinones by using readily available reagents and working under mild reaction conditions.² Moreover, we worked out a facile synthesis of α -iminoesters derivatives by reacting nitrosobenzenes with masked esters. This scaffold is very useful, since subsequent reactions allow the elaboration to important intermediates frequently applied in organic synthesis.³

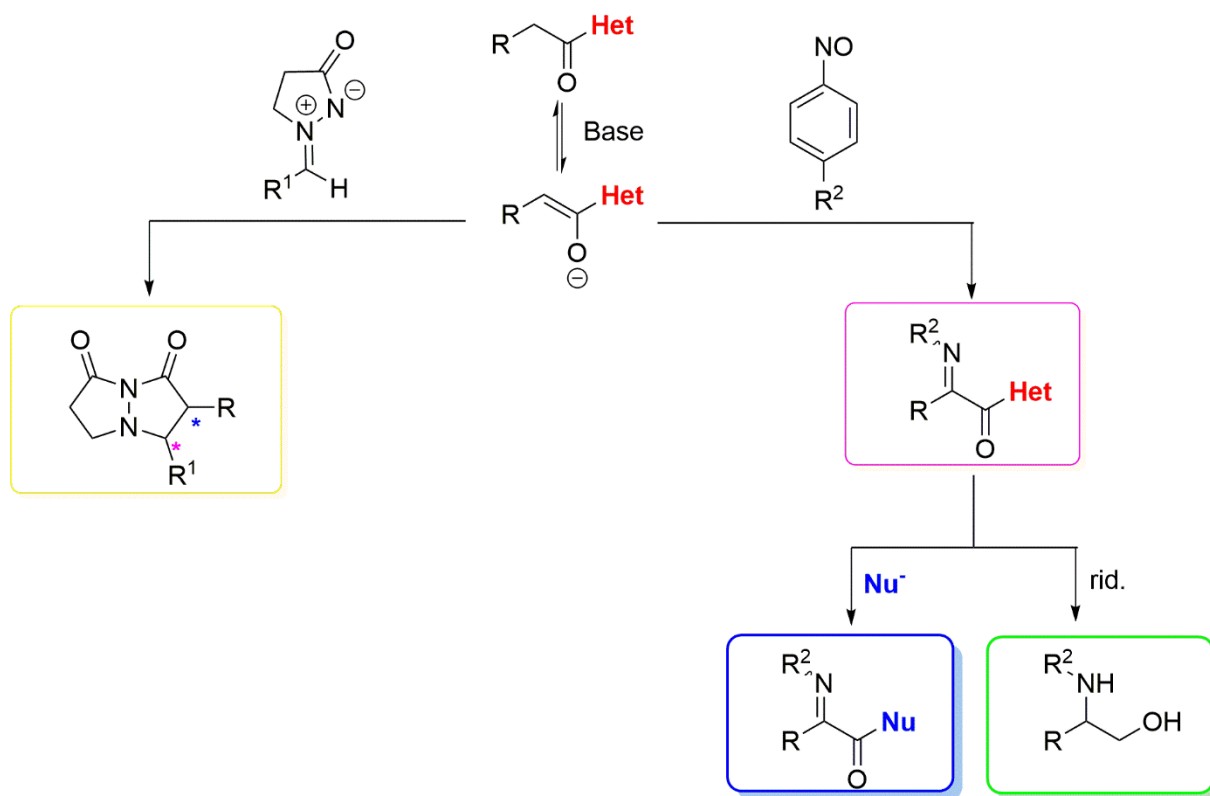


Figure 1: General scheme for the use of masked esters/amides.

References:

- [1] D. Monge, H. Jiang, Y. Alvarez-Casao, *Chem. Eur. J.* **2015**, *21*, 4494-4504.
- [2] C. Volpe, S. Meninno, A. Capobianco, G. Vigliotta, A. Lattanzi, *Adv. Synth. Catal.* **2019**, *361*, 1018-1022.
- [3] Unpublished results.

Structural modifications of glycoamino OPEs: synthesis and properties

A. Mancuso, P. Bonaccorsi, A. Barattucci.

Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche ed Ambientali (ChiBioFarAm),
Università di Messina, Viale F. Stagno d'Alcontres 31, 98166, vill. S. Agata - Messina
mancusoaurora@gmail.com

The synthesis of sugar-decorated molecular systems represents a significant tool in biotechnological, pharmaceutical and medical fields. In fact, conjugation with carbohydrates provides a guidance mechanism for sick cells, enabling drugs to arrive there with precision and act properly without (or with minimum) side effects.¹

In the last years, the introduction of glucose moieties as chain terminations of Oligo(phenylene-ethynylene)s (OPEs) gave to this class of compounds one of the first applications in the bioimaging field. In fact, the joint presence of the hydrophilic sugar moieties, the hydrophobic conjugated system and the dimethylamino (**Figure 1**) group allows the permeation to the cellular membrane, showing their potential uses as cellular dyes.² Otherwise, their production of singlet oxygen opened the way in their use as Photosensitizers in superficial Photodynamic Therapy (PDT).³

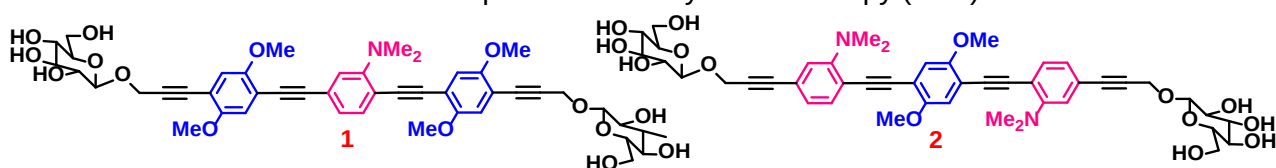


Figure 1

On the basis of these results, in order to explore the possibility to improve their use in this kind of medical procedures, the aim of our research has lately been to modify the structure of glycoamino-OPEs. First of all, the nitrogen quaternarization has been realized; as result, the presence of the new positive charges, joint with the peculiar structural features of compounds **1** and **2**, such as the biologically relevant sugar moieties and the flat aromatic cores, makes these luminescent dyes soluble in aqueous media and able to strongly interact with DNA.⁴

Moreover, the introduction of sugar terminations different from glucose (galactose, mannose, maltose) has been realized; among them, the functionalization with the disaccharide maltose has improved the water solubility of these compounds. Biological studies on the new systems are now ongoing. Finally, new strategies for the elongation and desymmetrization of the chain are underway, giving us the opportunity to extend their use in different fields: the anchoring of our biocompatible systems to upconverting lanthanide nanoparticles is one of these aims.

References:

- [1] "Carbohydrates and Drug Design", Anatole A. Klyosov *ACS Symposium Series*, Vol. 1102, Chapter 1, pp 3-22.
- [2] A. Barattucci, E. Deni, P. Bonaccorsi, M. G. Ceraolo, T. Papalia, A. Santoro, M. T. Sciortino, F. Puntoriero, *J. Org. Chem.* **2014**, 79, 5113-5120.
- [3] E. Deni, A. Zamarrón, P. Bonaccorsi, M. C. Carreño, Á. Juarraz, F. Puntoriero, M.T. Sciortino, M. Ribagorda, A. Barattucci, *Eur. J. Med. Chem.* **2016**, 111, 58-71.
- [4] A. Mancuso, A. Barattucci, P. Bonaccorsi, A. Giannetto, G. La Ganga, G.; M. Musarra-Pizzo, T. M. G. Salerno, A. Santoro, M. T. Sciortino, F. Puntoriero, M. L. Di Pietro, *Chem. Eur. J.*, **2018**, 24, 16972-16976.

Synthesis of new oxadiazole derivatives as potent and selective FXR antagonists

C. Festa,^a C. Finamore,^a S. Marchianò,^b F. S. Di Leva,^a A. Carino,^b M. C. Monti,^d F. del Gaudio,^d
S. Ceccacci,^d V. Limongelli,^{a,c} A. Zampella,^a S. Fiorucci^b and S. De Marino^{a*}

^aDepartment of Pharmacy, University of Naples "Federico II", Via D. Montesano 49, 80131 Naples, Italy.

^bDepartment of Surgery and Biomedical Sciences, Nuova Facoltà di Medicina, Perugia, Italy.

^cUniversità della Svizzera Italiana (USI), Faculty of Biomedical Sciences, Institute of Computational Science
Center for Computational Medicine in Cardiology, Via G. Buffi 13, CH-6900 Lugano, Switzerland.

^dDepartment of Pharmacy, University of Salerno, Via Giovanni Paolo II, 132, 84084, Fisciano, Salerno, Italy.
claudia.finamore@unina.it

Farnesoid X Receptor (FXR) is a member of the nuclear receptor super-family and is highly expressed in liver, intestine, kidney, and adrenals. This receptor is involved in bile acid homeostasis¹ and governs lipid and glucose metabolism in the liver.² For all these reasons, FXR represents a promising pharmacological target in the management of metabolic disorders. In the last few years, several FXR agonists, belonging to steroidal and non-steroidal scaffolds, have been identified as potential leads for the treatment of metabolic disorders, with some of them progressed in advanced clinical trials for the treatment of patients with primary biliary cirrhosis (PBC) and non-alcoholic steatohepatitis (NASH). However, recently, has been discovered that the FXR gene ablation protects from liver injury caused by bile duct ligation (BDL), moving the attention towards the FXR antagonism in the treatment of obstructive cholestasis. As in the case of the agonists, the speculation around both steroidal and non-steroidal scaffolds led to the identification of several FXR antagonists. In order to discover novel non-steroidal FXR antagonists, we started from a recent work of Flesch *et al.*³ where is showed that the structural fragmentation of GW4064,⁴ a highly potent and selective non-steroidal FXR agonist, can lead to the shift of the receptor modulation from the agonism to the antagonism.

In particular, the replacement of the isoxazole ring in GW4064 with a 3,5-disubstituted oxadiazole led to compounds with different activity profiles, from agonism, partial agonism to antagonism. This is the case of compound **1**, a highly simplified GW4064 derivative, endowed with an antagonistic profile toward FXR. Therefore, we have decided to manipulate further the oxadiazole scaffold, modifying both substituents at C-3 and C-5, developing a small library of derivatives some of which characterized by a potent FXR antagonistic activity and promising pharmacokinetic properties.

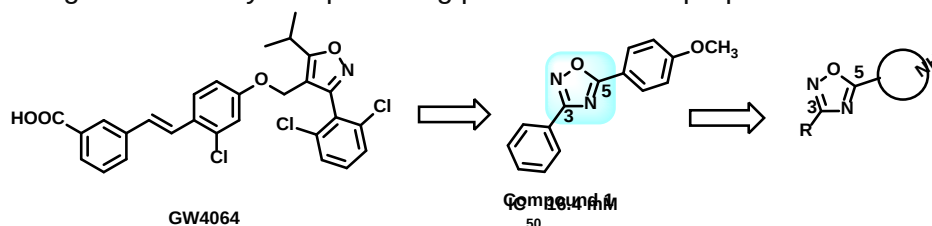


Figure 1. Fragmentation pathway on GW4064 in the identification of FXR antagonist

References:

- [1] B. M. Forman, E. Goode, J. Chen, A. E. Oro, D. J. Bradley, T. Perlmann, D. J. n, L. T. Burka, T. McMorris, W. W. Lamph, R. M. Evans, C. Weinberger, *Cell* **1995**, *81*, 687-693.
- [2] M. Makishima, A. Y. Okamoto, J. J. Repa, H. Tu, R. M. Learned, A. Luk, M. V. Hull, K. D. Lustig, D. J. Mangelsdorf, B. Shan, *Science* **1999**, *284*, 1362-1365.
- [3] D. Flesch, M. Gabler, A. Lill, R. Carrasco Gomez, R. Steri, G. Schneider, H. Stark, M. Schubert-Zsilavecz, D. Merk, *Bioorg Med. Chem.* **2015**, *23*, 3490-3498.
- [4] C. Gege, O. Kinzel, C. Steeneck, A. Schulz, C. Kremoser, *Curr. Top. Med. Chem.* **2014**, *14*(19), 2143-2158.

Enantioselective Syntheses of Morpholino β -Amino Acids for the preparation of different nanomaterials

R. Bucci,^a F. Vaghi,^a E. Erba, M. Reches,^b S. Pellegrino,^a M. L. Gelmi^a

^aDISFARM, Università degli Studi di Milano, Sezione Chimica Generale e Organica "A. Marchesini", Via Venezian 21, 20133 Milan

^b Institute of Chemistry, The Hebrew University of Jerusalem, Jerusalem 91904, Israel
raffaella.bucci@unimi.it

Molecular self-assembly is a powerful approach for the building of novel supramolecular architectures and it is ubiquitous in natural world. In billions of years of evolution, Nature has produced a basic set of 'Molecular Lego', such as 20 amino acids, few nucleotides, lipid molecules and sugars as well as naturally modified building blocks apt to self-organize, thanks to weak and noncovalent bonds¹. Nowadays, one of the most challenging efforts of scientist is to reproduce these organized architectures in laboratory for disparate applications, from biomedicine to electrochemistry and catalysis².

Here we reported the enantioselective syntheses of differently functionalized constrained morpholino β -amino acids (AAs). As β -AAs, they could confer a high stability in proteolytic environment and the presence of the oxygen on the ring, as H-bond acceptor, leads to conformational stabilization.

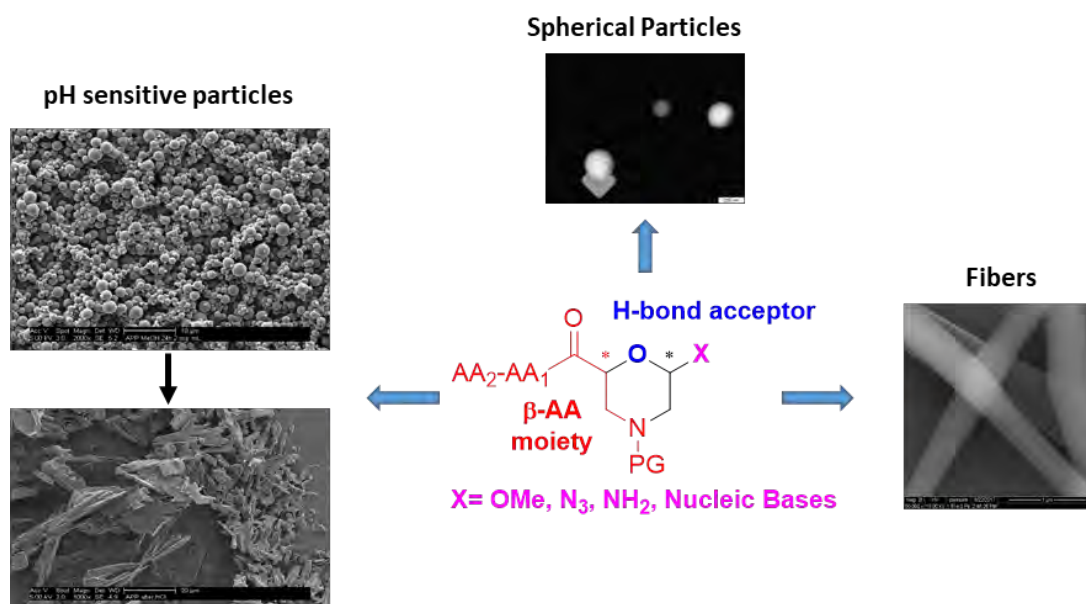


Figure 1: Nanomaterials obtained from ultra-short peptides containing β -Morpholino Amino Acids.

These new β -AAs have been inserted in ultra-short peptides. We found that, depending on the stereochemistry, the substitutions on C-2 and C-6, the protecting group on the N-terminus, they are able to form different type of nanomaterials. All these obtained nanostructures were characterized by DLS, TEM, SEM, FT-IR and NMR techniques.

References:

- [1] S. Zhang, *Nature Biotechnol.* **2003**, 21, 1171-1178.
- [2] W. Yao, Y. Yan, L. Xue, C. Zhang, G. Li, Q. Zheng, Y.S. Zhao, H. Jiang, J. Yao, *Angew. Chem.* **2013**, 125, 8875-8879.

Ionic Liquid Gels: Tunable and Multifaceted Materials

F. D'Anna

Dipartimento STEBICEF-Sezione di Chimica, Viale delle Scienze Ed. 17, 90128 Palermo
francesca.danna@unipa.it

Materials based on ionic liquids retain properties of solvent components, like low vapor pressure, high thermal stability and structure tunability. The latter allows changing properties of materials by making small variations in the cation or anion structure, opening the way to a plethora of different applications.

In this context, ionic liquid gels can represent a challenge especially if they are obtained from gelation of ionic liquid binary mixtures or of organic salts in ionic liquids.

In the framework of our interest in studying ionic liquids properties and applications, in the last few years, we have addressed our attention to the obtainment of ionic liquid gels.¹ We have deeply investigated their properties and analyzed the possible applications, preparing systems used for environmental preservation² or remediation,³ as well as to avoid deterioration of materials.⁴

In this communication, a brief overview of results collected in the last few years will be presented.



Figure 1: Applications of Ionic Liquid Gels.

References:

- [1] F. D'Anna, C. Rizzo; P. Vitale; G. Lazzara; R. Noto *Soft Matter* **2014**, 10, 9281-9292.
- [2] F. Billeci; F. D'Anna; H. Q. N. Gunaratne; N. V. Plechkova, K. R. Seddon *Green Chem.* **2018**, 20, 4260-4276.
- [3] C. Rizzo, F. Arcudi, L. Dordevic; N. Tz. Dintcheva; R. Noto; F. D'Anna; M. Prato *ACS Nano* **2018**, 12, 1296-1305.
- [4] C. Rizzo, S. Marullo; P. R. Campodonico; I. Pibiri; N. Tz. Dintcheva; R. Noto; D. Millan; F. D'Anna *ACS Sustainable Chem. Eng.* **2018**, 6, 12453-12462.

Clay minerals: a challenge for chemists

S. Riela,^a G. Cavallaro,^b C. G. Colletti,^a G. Lazzara,^b M. Massaro,^a S. Milioto,^b F. Parisi,^b R. Noto^a

^a *Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche (STEBICEF), University of Palermo, Viale delle Scienze, Ed. 17, 90128 Palermo*

^b *Dipartimento di Fisica e Chimica (DiFC), University of Palermo, Viale delle Scienze, Ed. 17, 90128 Palermo*
serena.riela@unipa.it

Halloysite nanotube, an aluminosilicate of the kaolin group, is an emerging nanomaterial which possesses peculiar chemical characteristics. By means of suitable modifications, such as supramolecular functionalization or covalent modifications, it is possible to obtain novel nanomaterials with tunable properties for several applications.^{1,2} In this context the covalent grafting of suitable organic moieties on the external surface or in the halloysite lumen has been exploited to improve the loading and release of several biologically active molecules. The resulting hybrid nanomaterials have been applied as drug carrier and delivery systems, as fillers for hydrogels, in tissue regeneration and in the gene delivery field.³ Furthermore the loading and release of specific molecules have been also investigated for environmental purposes.

References:

- [1] M. Massaro, G. Cavallaro, C. G. Colletti, G. Lazzara, S. Milioto, R. Noto, S. Riela *J. Mater. Chem. B* **2018**, 6, 3415-3433.
- [2] M. Massaro, C. G. Colletti, G. Lazzara, S. Milioto, R. Noto, S. Riela *J. Mater. Chem. A* **2017**, 5, 13276-13293.
- [3] M. Massaro, C. G. Colletti, G. Lazzara, S. Riela *J. Funct. Biomater.* **2018**, 9(4), 58.

Carbon Nanoforms-based Hybrid Catalysts

F. Giacalone,^a M. Gruttadauria,^a V. Campisciano,^a C. Calabrese^a

^aDepartment of Biological, Chemical and Pharmaceutical Sciences and Technologies, University of Palermo,
Viale delle Scienze, Ed. 17, Palermo
francesco.giacalone@unipa.it

Carbon nanoforms such as fullerene, nanotubes, graphene, nanohorns etc. are emerging as useful scaffolds in the preparation of last generation nanostructured catalysts,¹ due to a series of features comprising high chemical inertness under many conditions, thermal stability and mechanical resistance along with a lightness that other conventional materials cannot match. Moreover, in several cases, the use of these nanomaterials as support structures offers better performances than conventional supports.² On the other hand, CNFs are nanoobjects with well-defined structure and dimensions often displaying sharp size distribution, which allow for a homogeneous dispersion of the functionalities and active sites all over their surface, allowing obtaining reproducible hybrids with reproducible properties.

In the last recent years, our research group has investigated the use of different nanocarbons as platforms for anchoring catalytic moieties directly or for covalently linking dendrimers and polymers for the stabilization of palladium nanoparticles (Figure 1).

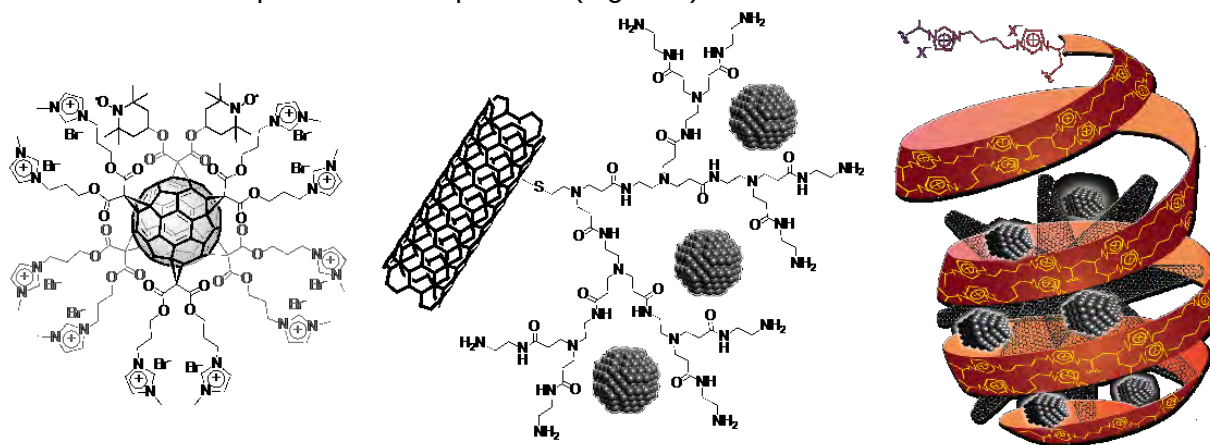


Figure 1: Examples of nanocarbon-based hybrid catalysts.

In such a way, the resulting hybrids have been successfully employed as recyclable materials in organocatalysis³ as well as in organometallic catalysis⁴ showing in some case synergistic effect or enhanced performances compared to other supported catalysts.

References:

- [1] V. Campisciano, M. Gruttadauria, F. Giacalone, *ChemCatChem* **2019**, *11*, 90-133.
- [2] P. Serp, J. L. Figueiredo, *Carbon Materials for Catalysis*, Wiley-VCH, Hoboken, New Jersey, **2009**.
- [3] a) H. A. Beejapur, V. Campisciano, F. Giacalone, M. Gruttadauria, *Adv. Synth. Catal.* **2015**, *357*, 51-58; b) C. Calabrese, L. F. Liotta, E. Carbonell, F. Giacalone, M. Gruttadauria, C. Aprile, *ChemSusChem* **2017**, *10*, 1202-1209.
- [4] a) F. Giacalone, V. Campisciano, C. Calabrese, V. La Parola, Z. Syrgiannis, M. Prato, M. Gruttadauria, *ACS Nano* **2016**, *10*, 4627-4636; b) F. Giacalone, V. Campisciano, C. Calabrese, V. La Parola, L. F. Liotta, C. Aprile, M. Gruttadauria, *J. Mater. Chem. A* **2016**, *4*, 17193-17206.

Graphene oxide composites-based filters for tap water purification

M. Zambianchi,^a M.L. Navacchia,^a A. Kovtun,^a M. Gazzano,^a L. Bocchi,^b V. Palermo,^{a,c} M. Melucci^a

^a Consiglio Nazionale delle Ricerche- Istituto per la Sintesi Organica e la Fotoreattività (CNR-ISOF), via Piero Gobetti 101, 40129 Bologna, Italy.

^b Medica spa, Via degli Artigiani, 7, 41036 Medolla MO

^c Industrial and Materials Science, Chalmers University of Technology, 41258 Göteborg, Sweden
manuela.melucci@isof.cnr.it

Much of our tap water comes from rivers, streams, lakes and groundwater. These water resources are increasingly contaminated by discharges of chemicals from industries and urban areas, most of them not fully removed by basic water treatment. Traces of prescription medications, antimicrobial chemicals, pesticides, cosmetics, with suspicious or even proved toxic effects have been found in several EU water bodies, this calling for the development of new efficient, low cost and sustainable purification technologies. In the last years, due to their outstanding adsorption properties, high processability and versatile chemical modification options, graphene-based materials have emerged as the most promising nanomaterials for advanced water treatment technologies.

Here, we report the preparation of new polysulfone-graphene oxide composites (PSGO) specifically designed for the simultaneous filtration and adsorption of organic contaminants of emerging concern from tap water.¹ Stable fixation of GO and chemically modified GO on commercial PS membranes (Medisulfone[®]) is achieved by thermal activation under mild conditions.² The unique combination of numerous adsorption sites and interlayer enabled filtration provided by GO with the porosity of the PS scaffolds, significantly enhances the removal performances of several selected contaminants, including drugs, from tap water with respect to PS-only and to activated carbon (the industrial standard). Working mechanism, regeneration and GO release have been also investigated. The proposed approach is also exploited to revalue and reuse scraps of the industrial production of PS membranes ($\approx 10\%$ of the total year production, $\approx 1,5$ tons).³

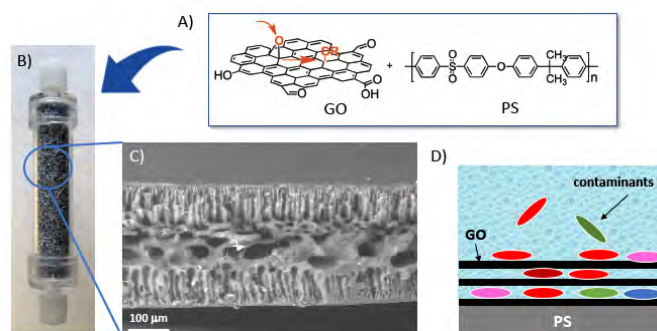


Figure 1: a) composition of the active materials, b) representative PSGO filter, c) structure of a PSGO composite membrane, d) working mechanism of a PSGO membrane.

References:

- [1] M. Zambianchi, M. Durso, A. Liscio, E. Treossi, C. Bettini, M. L. Capobianco, A. Aluigi, A. Kovtun, G. Ruani, F. Corticelli, M. Brucalè, V. Palermo, M. L. Navacchia and M. Melucci, *Chem. Eng. J.*, **2017**, 326, 130-140.
- [2] M. Melucci, V. Palermo, M. Zambianchi, A. Liscio, A. Kovtun, E. Treossi, M.L. Navacchia, L. Bocchi Medica spa-CNR joint Patent application IT 102018000010402 and submitted manuscript.
- [3] M. Zambianchi, A. Aluigi, M. L. Capobianco, F. Corticelli, I. Elmi, S. Zampolli, F. Stante, L. Bocchi, F. Belosi, M. L. Navacchia and M. Melucci, *Advanced Sustainable Systems*, **2017**, 1, 1700019.

Novel Hydrophobic Deep Eutectic Solvents (DESSs) as water-immiscible H-bond-based solvents

M. Tiecco,^a F. Cappellini,^a F. Nicoletti,^a T. Del Giacco,^a P. Di Profio,^b R. Germani^a

^aDept. Chemistry, Biology and Biotechnology, University of Perugia, via Elce di Sotto 8, Perugia

^bDept. of Pharmacy, University of Chieti, via dei Vestini 31, Chieti
matteotiecco@gmail.com

Deep Eutectic Solvents (DESSs) are a class of liquids formed by H-bond interactions between two species: a hydrogen bond donor (HBD) compound and a hydrogen bond acceptor (HBA) compound. The intra- and inter-molecular H-bonds between the two species lead to a difficult regular crystal lattice formation, therefore to a liquid phase.¹

DESSs represent a novel class of green liquids for many reasons: they can be obtained from natural source molecules (NADESSs: NATural Deep Eutectic Solvents); they have low or absent vapour pressure; they are showing low toxicity; they can be easily recycled and reused; their synthesis does not involve any use of solvents because they are obtained by simply mixing and heating the two solid compounds. In addition to their ecological advantages, DESSs have many practical advantages that promote their use in many topics such as: their active role in many chemical reactions (i.e. acid catalyst; reactants or reagents); their chiral organocatalytic properties in the case they are formed by chiral molecules,² the possibility of “out of the hood” procedures and so on.

Even if they are formed by H-bonds, their behaviour with water is peculiar and it depends on the chemical structures used as HBD or HBA and on their concentration: they can be dissolved in it, they can form clusters of HBD-HBA aggregates, they can be separated from it.³

In this work, we present the realization and the characterization of the properties of novel hydrophobic DESSs.⁴ We chose a set of water-miscible and -immiscible HBA and HBD molecules; this permitted us to define the role of the components for the proper development of H-bond-based mixtures that can result water-separable. We performed the characterization of the properties of these liquids (density, eutectic profiles), the water separation ranges and the phases contamination via Karl Fischer titration and with ¹H-NMR spectroscopy. Finally, we successfully performed the extraction of polluting phenol compounds and a dye from water with efficiencies >90-95%. Further experiments at pH = 2 and at pH = 9 showed these mixtures as well-separable and excellent extracting liquids even in these conditions.

The novel hydrophobic Deep Eutectic Solvents are promising tools as hydrophobic extraction agents and as hydrophobic green reaction media.

References:

- [1] C.F. Araujo, J.A.P. Coutinho, M.M. Nolasco, S.F. Parker, P.J.A. Ribeiro-Claro, S. Rudić, P.D. Vaz, *Phys. Chem. Chem. Phys.* **2017**, 19(27), 17998-18009.
- [2] T. Palomba, G. Ciancaleoni, T. Del Giacco, R. Germani, F. Ianni, M. Tiecco, *J. Mol. Liq.* **2018**, 262, 285-294.
- [3] C. Ma, A. Laaksonen, C. Liu, X. Lu, X. Ji, *Chem. Soc. Rev.* **2018**, 47(23), 8685-8720.
- [4] M. Tiecco, F. Cappellini, F. Nicoletti, T. Del Giacco, R. Germani, P. Di Profio, *J. Mol. Liq.* **2019**, 281, 423-430.

Light meets click chemistry: development of novel, photoactivable, 2,5-diaryl tetrazoles for labelling nucleic acids

A. Benassi,^a G. Preda,^a A. Tosello Gardini,^a F. Doria,^a M. Freccero^a

^aUniversity of Pavia, Viale Taramelli 10, Pavia
alessandra.benassi01@universitadipavia.it

Click chemistry represents a useful method to create covalent bonds among two reagents, with high yields, fast reaction kinetic and under mild conditions. During the last years, this powerful strategy has been extensively employed in bioorthogonal ligation for labelling biological molecules (proteins, DNA, RNA), in order to monitor and understand the mechanism of many physiological processes ¹.

Although targeting nucleic acids has become fundamental, currently just few click reactions are reported for this kind of application, such as azide-alkyne cycloaddition (CuAAC) and inverse-electron demand Diels-Alder (IEDDA)².

However, these approaches present some limitations: azide-alkyne cycloaddition requires copper as a catalyst, which is not very compatible with systems and fluorescent probes must be used to observe product formation, so in order to overcome these drawbacks, we decided to employ a new strategy: recently, Lin and co-workers reported the use of a 2,5-diaryl tetrazole as photoactivable moiety for bioorthogonal ligation on proteins³. This compound, under irradiation, generate a 1,3-nitrile imine dipole (NI), an intermediate able to react with different types of dipolarophiles, to generate a fluorescent pyrazoline. Despite these promising properties, when this reaction is performed in physiological environment, many byproducts are formed and this represents a relevant impediment for previously described applications.

Here, we reported the synthesis of a library of 2,5-diaryl tetrazoles, properly functionalized in order to investigate how substituents can modulate NI generation and reactivity, in particular in aqueous solution.

In our preliminary studies, for each compound, we measured quantum yield of NI generation at 310 nm. Furthermore, photoreactivity was explored by irradiation of substrates in presence of various dipolarophiles and products distribution has been analyzed, in order to identify the best candidates for labeling of biomolecules.

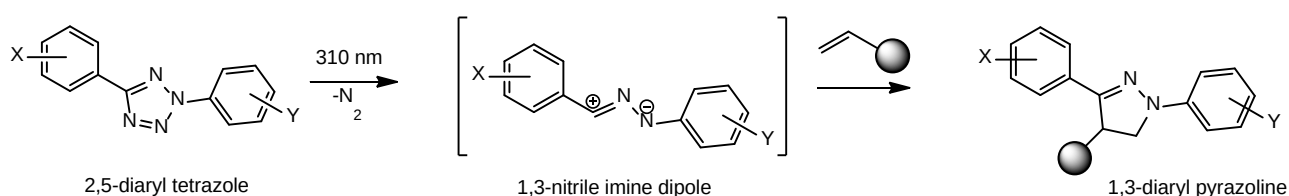


Figure 1: Photogeneration of 1,3-nitrile imine dipole.

References:

- [1] M. Gehring and S. A. Laufer, *Angew. Chem. Int. Ed.* **2017**, 56, 15504-15505.
- [2] U. Rieder and N. W. Luedtke, *Angew. Chem. Int. Ed.* **2014**, 53, 9168-9172.
- [3] P. An, T. M. Lewandowski, T. G. Erbay, P. Liu and Q. Lin, *J. Am. Chem. Soc.* **2018**, 140, 4860-4868.

Hydrogen Borrowing reactions in water medium

C. Risi, E. Petricci, E. Cini, F. Rosati, M. Taddei

Dipartimento di Biotecnologie, Chimica e Farmacia, Università degli Studi di Siena, Via A. Moro 2, 53100, Siena, Italy

e-mail: risi@student.unisi.it

Hydrogen Borrowing (HB)¹ is very useful reaction to access amines and other molecules in a sustainable way in terms of redox and atom economy. The reaction mechanism basically involves the dehydrogenation of an alcohol to form the corresponding aldehyde, which reacts with a nucleophile such as an amine to generate an imine. In the same catalytic cycle, the hydrogen produced during the alcohol oxidation is involved in the further hydrogenation of the imine giving the alkylated amine as the reaction product. In spite of the excellent results in terms of efficacy and selectivity obtained with this methodology on different substrates, the high temperatures,² the use of not environmentally friendly solvents (i.e. toluene)³ in the presence of noble metals based catalysts still represent important issues.⁴ In order to find more sustainable conditions and to extend the reaction scope, we decide to investigate the possibility to carry out the HB reaction in water, in the presence of surfactants. The micellar environment worked well with standard Ru catalysts and, once the reaction conditions have been optimized, different secondary and tertiary amines have been obtained in good yields. An intramolecular HB cyclisation has been also successfully explored. The use of micelles has been extended as well to other reactions based on hydrogen transfer processes.



Scheme 1: Hydrogen borrowing using metal catalysts in H₂O.

References:

- [1] Corma, A.; Navas, J.; Sabater, M. J. *Chem. Rev.* **2018**, *118*, 1410-459.
- [2] Jumde, V. R.; Gonsalvi, L.; Guerriero, A.; Peruzzini, M.; Taddei, M. *Eur. J. Org. Chem.* **2015**, 1829-1833.
- [3] Cini, E.; Petricci, E.; Truglio, G. I.; Vecchio, M.; Taddei, M. *RSC Adv.* **2016**, *6*, 31386-31390.
- [4] Taddei, M.; Mura, M. G.; Rajamaeki, S.; De Luca, L.; Porcheddu, A. *Adv. Synth. Catal.* **2013**, *355*, 3002-3013.

Combining Safer Solvents Heterogeneous Catalysis and Flow Technology Toward Sustainable C-H Activation Methodologies

F. Ferlin,^a L. Vaccaro^a

^aGreen S.O.C., Dipartimento di Chimica, Biologia e Biotecnologie, Università degli Studi di Perugia I-06123
Perugia: <http://www.dccb.unipg.it/greensoc>
e-mail: ferlin.francesco@gmail.com

In recent years C–H activation has proven to be a powerful synthetic tool for the direct and selective construction of C–C bonds.¹ Generally, metal-catalyzed C–H bond cleavage relies on the use of a homogeneous metal catalyst and it is often performed in petrol-based toxic organic solvents.^{2b-c} Both aspects render the available methodologies for C–H activation/functionalization limited from the sustainability point of view.

In this communication, we report our results on the definition of novel protocols for C–H functionalization reactions based on the combined use of heterogeneous catalysts, safer biomass-derived reaction media and customized flow reactors. Our protocols have been specifically developed to feature advantages in terms of safety, waste minimization and minimal catalyst leaching in order to minimize purification procedures and preserve the catalyst stability and longevity.

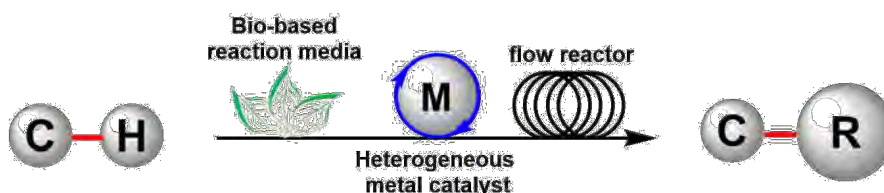


Figure 1: Our approach to sustainable C–H functionalization technology.

This contribution is part of our research program dedicated to the definition of environmentally and chemically-efficient procedures for C–H functionalization² in order to access highly valuable materials while minimizing waste production.³

References:

- [1] (a) P. Gandeepan, L. Ackermann, *Chem*, **2018**, *4*, 199-222; (b) J. He, M. Wasa, K. S. L. Chan, Q. Shao, J.-Q. Yu, *Chem. Rev.* **2017**, *117*, 8754-8786.
- [2] (a) S. Santoro, F. Ferlin, L. Ackermann, L. Vaccaro, *Chem. Soc. Rev.*, **2019**, doi: 10.1039/C8CS00211H; (b) S. Santoro, F. Ferlin, L. Luciani, L. Ackermann, L. Vaccaro, *Green Chem.*, **2017**, *19*, 1601-1612; (c) S. Santoro, S. I. Kozhushkov, L. Ackermann, L. Vaccaro, *Green Chem.*, **2016**, *18*, 3471-3493.
- [3] (a) F. Ferlin, L. Luciani, S. Santoro, A. Marrocchi, D. Lanari, A. Bechtoldt, L. Ackermann, L. Vaccaro, *Green Chem.*, **2018**, *20*, 2888-2893; (b) F. Ferlin, S. Santoro, L. Ackermann, L. Vaccaro, *Green Chem.*, **2017**, *19*, 2510-2514; (c) D. Rasina, K.-Q. Arianna, S. Ziarelli, S. Warratz, H. Cao, S. Santoro, L. Ackermann, L. Vaccaro, *Green Chem.* **2016**, *18*, 5025-5030. (d) X. Tian, F. Yang, D. Rasina, M. Bauer, S. Warratz, F. Ferlin, L. Vaccaro, L. Ackermann, *Chem. Commun.*, **2016**, *52*, 9777-9780.

Green approach to aerobic alcohol oxidation and transfer hydrogenation of nitro benzene derivatives

K. Martina, M. J. Moran, G. Cravotto

Department of Drug Science and Technology, University of Turin, Via Pietro Giuria 9, 10125, Turin
katia.martina@unito.it

Selective oxidation and reduction are fundamental organic transformations of critical importance to produce value-added products from simple organic molecules. The use of green reagents and the study of efficient procedures under mild conditions with cost-effective and environmentally friendly characters provide the reduction of cost and of environmentally hazardous by-products. Catalytic aerobic oxidation and transfer hydrogenation have recently become the center of research in organic synthesis and these synthetic methods enabled breakthroughs in product synthesis, materials science, and bioorganic chemistry.

The so called “enabling technologies” such as microwave, ultrasound, ball mill besides an efficient heat and mass transfer, may generate high energy micro-environments that strongly enhance reactivity and reaction rate. Herein we report the development of convenient and efficient strategies in the field of Pd catalysed aerobic oxidation of alcohol to methyl ester under MW irradiation.¹ In the search of new procedures, mechanochemical activation was exploited to efficiently reduce nitro benzene and alkyl/aryl azide in a stainless steel jars without catalyst addition. Copper nanoparticles were also used in glycerol for efficiently reducing nitro benzene in a tunable way.

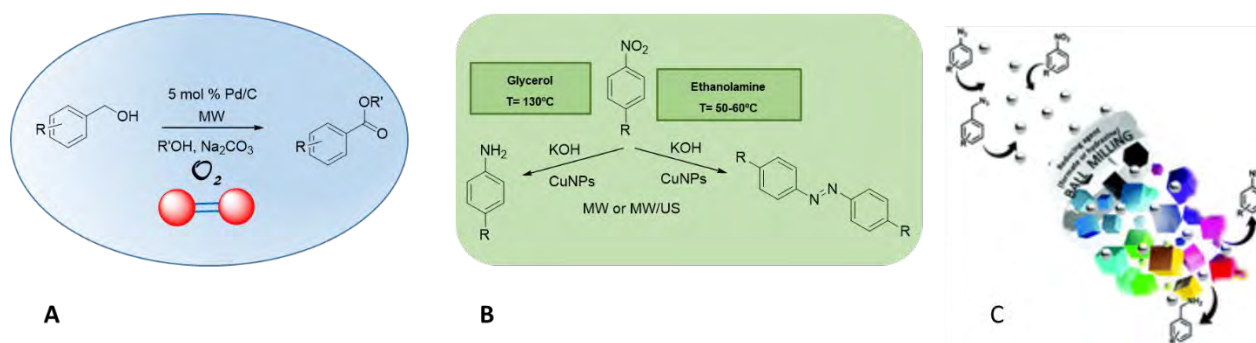


Figure 1: Schematic representation of A) MW promoted aerobic oxidation of benzylic alcohols B) tunable reduction of nitro benzenes with CuNPs, C) mechanochemically promoted nitro benzene and alkyl/aryl azide reduction.

References:

- [1] M. Caporaso, G. Cravotto, S. Georgakopoulos, G. Heropoulos, K. Martina, S. Tagliapietra *Beilstein J. Org. Chem.* **2014**, *10*, 1454-1461.
- [2] K. Martina, F. Baricco, S. Tagliapietra, M. J. Moran, G. Cravotto, P. Cintas *New J. Chem.* **2018**, *42*, 18881-18888

Highly selective toluene oxidation to benzaldehyde: a sustainable process

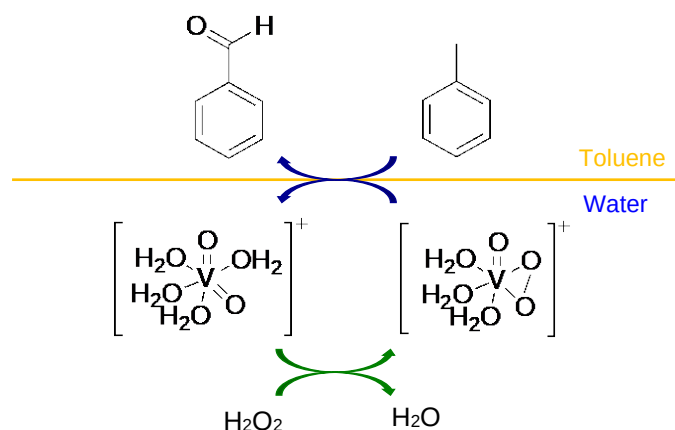
F. Valentini,^a F. Sabuzi,^a G. Pomarico,^a P. Galloni,^a V. Conte^a

^a Department of Chemical Science and Technologies, University of Rome Tor Vergata, via della ricerca scientifica, snc, 00133, Rome
f.valentini@scienze.uniroma2.it

Selective toluene oxidation to benzaldehyde is one of the most challenging oxidation reactions because oxidation products such as benzyl alcohol or benzoic acid are produced in large quantity. Benzaldehyde is an important chemical intermediate in the manufacture of pesticides, pharmaceuticals, perfumes and food industry.¹ Traditionally benzaldehyde has been produced from chlorination of toluene on benzylic position followed by hydrolysis.² This process is not environmental friendly due to very harsh condition required and hazardous waste produced. Moreover, benzaldehyde obtained is not suitable for usage in pharmaceuticals and food application because of chlorinating contaminants. In the last years several attempts using homogenous catalysis have been done in order to obtain benzaldehyde from toluene in high selectivity and yield possibly with an environmental friendly process, but the results are still unsatisfactory mostly in terms of selectivity.³

In our previous work,⁴ we found that monoperoxo V(V) species are able to perform oxidative bromination of toluene in the presence of hydrogen peroxide and a bromine source at acidic pH, one of the by products of the reaction being benzaldehyde.

In this contribution highly selective toluene oxidation to benzaldehyde using cheap and environmental friendly starting materials as ammonium vanadate, hydrogen peroxide and an inorganic salt with a sustainable process will be presented.



Scheme 1: Vanadium based system for toluene oxidation

References:

- [1] D. Datta Mal, S. Khilari, D. Pradhan, *Green Chem.* **2018**, *20*, 2279-2289.
- [2] W. Partenheimer, *Catal. Today* **1995**, *23*, 69-158.
- [3] H. Xia, Z. Liu, Y. Xu J. Zuo, Z. Qin, *Catal. Commun.* **2016**, *86*, 72-76.
- [4] P. Galloni, M. Mancini, B. Floris, V. Conte, *Dalton Trans.* **2013**, *42*, 11963-11970.

Development and synthesis of simplified analogs of a bioactive natural polyketide

M. Casertano, A. Aiello, C. Imperatore, P. Luciano, M. Menna

Department of Pharmacy, University of Naples "Federico II", Via D. Montesano, 49, 80131, Naples, Italy
marcello.casertano@unina.it

Natural compounds are characterized by a considerable structural diversity that remain a key inspirational factor in the search for new therapeutic agents. In the marine environment, one of the largest and most interesting family of complex natural products is represented by polyketides.¹ These compounds are generally produced by specific enzymatic systems of microorganisms, bacteria and/or fungi, associated to marine invertebrates finding a wide range of pharmaceutical applications.² Marine polyketides are often built by polyhydroxy and polyoxy substituents in their structure with respect to sulphate and phosphate groups that are more rarely present.³

In this view, the recent isolation of the phosphoeleganin (**Figure 1**), a novel phosphorylated polyketide from the Mediterranean ascidian, *Sydnium elegans*,^{4,5} characterized by a significant inhibitory activity against the human protein tyrosine phosphatase 1B (PTP1B), encouraged the development of several simplified analogs of the natural metabolite.

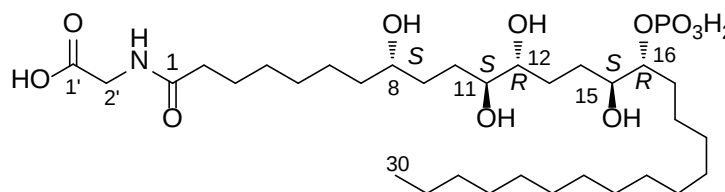


Figure 1: Structure of phosphoeleganin.

This research was aimed by the possibility to synthesize diastereoisomeric model compounds as profitable instrument to assign the absolute configuration of complex, acyclic and polysubstituted molecules. In addition, the synthesis and the pharmacological evaluation of these phosphorylated polyols represent the starting point to understand the essential structural requirements for the activity against PTP1B. In this communication, it's reported the synthetic protocol based on the combination of organic stereoselective reactions and chiral derivatization allowing to obtain a small chemical library of phosphorylated products.

References:

- [1] L. Katz, *Chem. Rev.* **1997**, 97, 2557-2575.
- [2] S. Fushimi, S. Nishikawa, A. Shimazu, H. Seto, *J. Antibiot.* **1989**, 49, 1019-1025.
- [3] A. E. Fagerholm, D. Habrant, A. M. P. Koskinen, *Mar. Drugs* **2010**, 8, 122-172.
- [4] C. Imperatore, P. Luciano, A. Aiello, R. Vitalone, C. Irace, R. Santamaria, J. Li, Y. Guo, M. Menna, *J. Nat. Prod.* **2016**, 79, 1144-1148.
- [5] P. Luciano, C. Imperatore, M. Senese, A. Aiello, M. Casertano, Y. Guo, M. Menna, *J. Nat. Prod.* **2017**, 80, 2118-2123.

Spiroprans for light-controlled delivery of Aspirin

F. Cardano,^{a,b} E. Del Canto,^c S. Giordani,^{*a,d}

^a Istituto Italiano di Tecnologia (IIT), Nano Carbon Materials, via Livorno 60, 10144 Turin.

^b University of Genoa, Department of Chemistry and Industrial Chemistry, via Dodecaneso 31, 16146 Genoa.

^c Trinity College Dublin, School of Chemistry, College Green, Dublin 2.

^d Dublin City University, School of Chemical Sciences, Glasnevin, Dublin 9.

^{*}on leave from University of Torino, Department of Chemistry, via Giuria 7, 10125, Turin

silvia.giordani@dcu.ie

The study and development of new stimuli responsive nano-devices is an appealing research field^{1,2}. In the nano-medicine realm, the possibility to create new smart platforms, for the selective delivery of active agents, using simple and bio-compatible external stimuli such as visible light is a promising field of investigation. For this purpose, we have designed and synthesised a smart platform based on a photo-switchable spiropyran (SP) taking advantage of its well-known capabilities to coordinate metal ions and form stable merocyanine (ME)-metal complexes^{3,4,5}. We have selected Zinc(II) for its intrinsic properties and for its essentiality in the human being and Aspirin as the biologically active compound. We have planned the study of a ternary Visible light regulated system (figure 1) for the delivery of two active agents at the same time. The system has been investigated through spectroscopic techniques to define its features and its ON/OFF switching properties. Our results show the formation of the ternary system ME:Zn:ASA in solution and its Visible light photo-controlled properties paving the way for its use in the assembly of new devices for medicinal chemistry purposes.

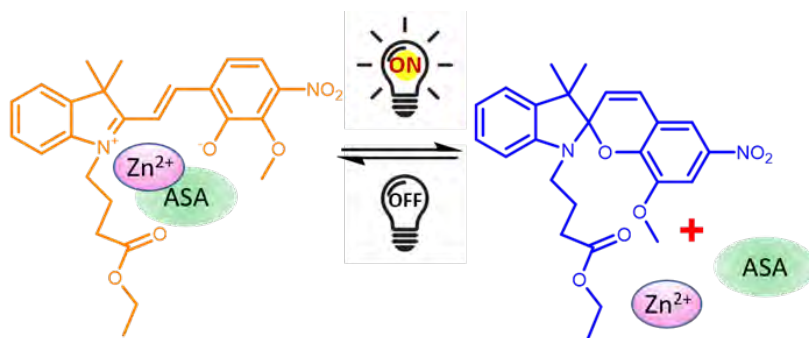


Figure 1: Schematic representation of the proposed drug-delivery system.

References:

- [1] S. Mura, J. Nicolas, P. Couvreur, *Nat. Mater.* **2013**, 12, 991-1003.
- [2] M. Natali, S. Giordani, *Chem. Soc. Rev.* **2012**, 41, 4010-4029.
- [3] M. Natali, L. Soldi, S. Giordani, *Tetrahedron* **2010**, 66, 7612-7617.
- [4] M. Natali, S. Giordani, *Org. Biomol. Chem.* **2012**, 10, 1162-1171.
- [5] M. Baldrighi, G. Locatelli, J. Desper, C. B. Aakeroy, S. Giordani, *Chem. Eur. J.* **2016**, 22, 13976-13984.

The interplay between NMR spectroscopy and molecular modeling: a powerful tool to investigate protein-glycoconjugate interactions.

R. E. Forgione,^a C. Di Carluccio,^a R. Marchetti,^a A. Molinaro,^a A. Silipo^a

^a Dipartimento di Scienze Chimiche, Università degli Studi di Napoli Federico II, Strada Comunale Cinthia, 4, 80126 Napoli, Italy.
rosaester.forgione@unina.it

Protein-carbohydrates interactions set the basis of molecular recognition processes, indeed, they are involved in events like cell-cell interactions, signal transduction, inflammation, viral entry, and host bacteria recognition, thereby participating in disease, defense and symbiosis^{1,2}. Understanding the roles that complex carbohydrate such as glycans plays in the aforementioned biological events offers opportunities for developing therapeutic strategies for the treatment of various diseases³.

However, comprehending the dynamic of protein- glycoconjugates interactions represents a major challenge due to extreme structural complexity and variability of both mammalian and bacterial glycans, as well as the multivalent nature of their interactions with proteins^{4,5}. The present work applies magnetic resonance (NMR) techniques to dissect the binding events occurring between sialylated glycans and their receptors, mainly through a ligand-based approach⁶. Furthermore, computational methods are implemented to provide a complete picture of protein- glycoconjugate binding mechanisms. With the raised awareness that the presentation of a glycan epitope can affect its recognition by proteins³, the aim of the work is to rigorously define the bioactive conformation and binding epitope of the selected ligand for a deeper comprehension and modulation of biological processes closely related to biomedicine applications⁷.

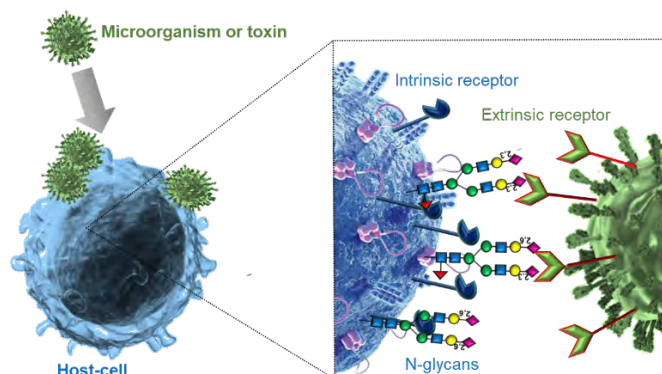


Figure 1: Molecular recognition of sialylated glycans by intrinsic and extrinsic receptors. Sia's can act as marker of self in the immune system, as such residues are absent in most microbes. On the other hand, host Sias are frequently exploited as attachment sites by pathogens including protozoa, viruses, bacteria, and toxins.

References

- [1] R. L. Schnaar, *J. Allergy Clin. Immunol.*, **2015**, 135, 609-615.
- [2] G. A. Rabinovich, D. O. Croci, *Immunity*, **2012**, 36, 322-335.
- [3] T. Johannssen, B. Lepenies, *Trends Biotechnol.*, **2017**, 35, 334-346.
- [4] R. D. T. Cummings, *Mol. Biosyst.*, **2009**, 5, 1087-1104.
- [5] L. E. Comstock, D. L. Kasper, *Cell* **2006**, 126, 847-850.
- [6] R. Marchetti, S. Perez, A. Arda, A. Imberty, J. Jimenez-Barbero, A. Silipo, A. Molinaro, *ChemistryOpen* **2016**, 5, 274-296.
- [7] S. Sattin, A. Bernardi, *Carbohydr. Chem.*, **2015**, 41, 1-25.

Degradation of Ochratoxin A in a wide pH range: experimental and computational study

I. Cagnasso,^{a,b} G. Tonachini,^c S. Berto,^c A. Giacomino,^d L. Mandrile,^a A. Maranzana,^c F. Durbiano^a

^aMetrology for Quality of Life Division, Istituto Nazionale di Ricerca Metrologica, strada delle Cacce 91, Torino, Italy;

^bDepartment of Electronics and Telecommunications, Politecnico di Torino, corso Duca degli Abruzzi 24, Torino, Italy;

^cChemistry Department, Università di Torino, via Giuria 7, Torino, Italy; ^dDrug Science and Technology Department, Università di Torino, via Giuria 9, Torino, Italy; andrea.maranzana@unito.it

Ochratoxin A (OTA) is a potent toxin that is able to cause negative effects on animal and human health: it can affect a large variety of alimentary commodities such as cereals, wine, spices and animal feed.¹⁻² OTA is considered one of the most important dietary risk factor, and a possible carcinogen to humans.³ The behaviour of OTA in aqueous solutions in a pH range from 1.0 to 12.5 was studied by two independent spectroscopic techniques (UV-Vis absorption spectrophotometry and fluorescence spectroscopy) and Density Functional Theory (DFT) calculations. ω B97XD functional with Pople's 6-311++G(d,p) basis set were used in the DFT optimizations. Excitation energies were calculated by Time Dependent-DFT calculations. OTA shows three levels of proton dissociation in the pH range from 1.0 to 8.0 and under alkaline conditions, it displays degradation processes. Some of the reaction products were revealed at pH higher than 12, such as OTA with hydrolyzed lactone ring and ochratoxin alpha ($OT\alpha$) with hydrolyzed ring. The product of lactone ring opening and $OT\alpha$ are less toxic than the protonated forms of OTA.

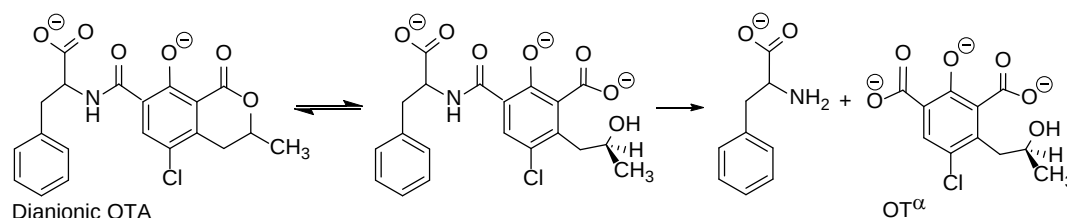


Figure 1: Ochratoxin A degradation steps.

However, the reversibility studies showed that the species obtained upon re-acidification depend on those initially present under alkaline conditions, that can differ depending on pH and storage time. Dianionic and trianionic forms of OTA at pH 12.5 in fresh solution return to the neutral form of OTA when the acidic conditions are quickly restored, representing again a hazard to humans. Conversely, $OT\alpha$ with the hydrolyzed ring does not return to the neutral OTA, but only to the neutral $OT\alpha$. Irreversible fragmentation can be completed only after a very long time (more than one week) in strongly basic solutions. These conditions are necessary to achieve an effective OTA inactivation. The theoretical study suggests a reaction pathway that matches experimental data and facilitates their interpretation. Also, the computed absorption maxima of the intermediates along the suggested pathway resulted consistent with experiments.

References:

- [1] H. J. Lee, D. Ryu, *J. Agric. Food Chem.*, **2017**, 65, 7034-7051.
- [2] S. Z. Iqbal, Z. Mehmood, M. R. Asi, M. Shahid, M. Sehar, N. Malik, *J. Food Saf.*, **2018**, 38, e12462.
- [3] IARC Monographs (International Agency for Research on Cancer), **1993**, 56, 489-521

Innovative synthetic approach based on the Native Chemical Ligation for development of new dual PET/OI peptide imaging probes

I. Hawala,^a L. De Rosa,^b S. Aime,^a L. D. D'Andrea^c

^a Dipartimento di Biotecnologie Molecolari e Scienze per la salute, Centro di Imaging Molecolare, Università degli Studi di Torino, Via Nizza 52, 10126, Torino (TO), Italy

^b Istituto di Biostrutture e Bioimmagini, CNR, Via Mezzocannone 16, 80134 Napoli (NA), Italy

^c Istituto di Biostrutture e Bioimmagini, CNR, Via Nizza 52, 10126 Torino (TO), Italy
ivan.hawala@unito.it

Dual Optical/PET peptide imaging probes are considered as efficient tools for disease diagnosis and/or monitoring. Their preparation is still a challenging task due to the complicated synthetic protocols requiring fully-protected peptide segments (in solution) or the use of orthogonal protection groups (solid phase) to achieve the dual site-specific labelling. An advantageous strategy for peptide site-specific modification of unprotected peptide in solution, overcoming most of the above mentioned limitations, relies on the use of native chemical ligation (NCL).¹

Targeting peptide AE105 (reported antagonist of uPAR) was synthesized using a solid phase peptide synthesis approach and functionalized with a cysteine to allow the condensation with AAZTA-C4-COOH, pre-activated as thioester with 2-Mercaptoethanesulfonic acid sodium salt (MESNA). After the reaction between the free thiol of the cysteine and the AAZTA thioester derivative, a rearrangement gives a stable amide bond between the N-terminus of the same cysteine and the carboxylic group of the arm of AAZTA-C4-COOH. The transposition of the chemical bond on the amine, made the thiol accessible to the subsequent reaction with a maleimide pre-activated fluorophore (i.e. cy 5.5). With this approach, it was possible to use the same thiol group of the peptide cysteine residue to achieve two chemoselective reactions in sequence, reducing significantly the formation of side products. The desired product (Figure 1) was afforded from preparative HPLC with a chemical purity over 95%. Final complexation with ^{nat}Ga was performed at pH 4, in order to evaluate the labelling efficiency with the metal and to demonstrate, by *in vitro* binding evaluations monitored by Flow Cytometry, that all the above modifications on the native peptide structure, did not affect the affinity for the uPAR receptor. Herein we developed a standard synthetic strategy to easily obtain a targeting molecule functionalized with a fluorophore to be employed in optical imaging applications and a cage, to allow the complexation with PETs radionuclides.

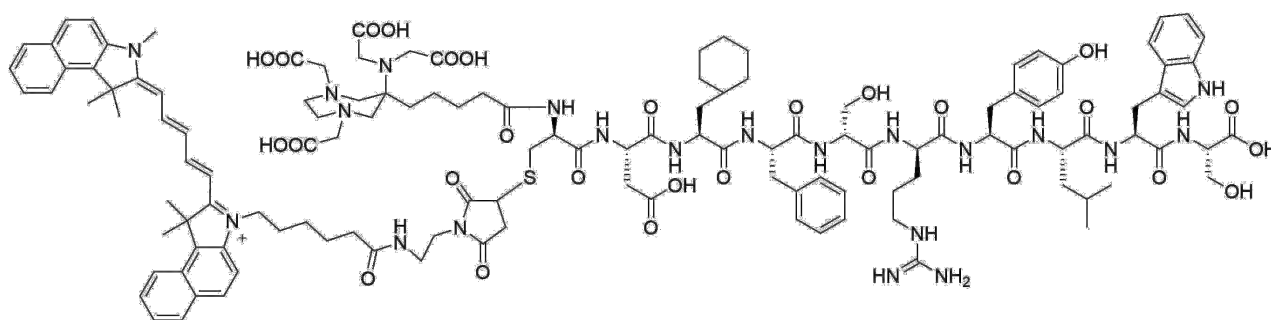


Figure 1: Chemical structure of AAZTA-C4-CO-Cys(Cy 5.5)-AE105

References:

- [1] L. De Rosa, A. L. Contajarena, A. Romanelli, L. Regan, L. D. D'Andrea, *Org. Biomol. Chem.* **2012**, *10*, 273-280.

α -Amino Aldehydes as Monomers for the Synthesis of Imine-/Amide-based Foldamer Structures

G. Marafon,^a C. Toniolo,^a M. Crisma,^b A. Moretto^a

^aDepartment of Chemical Science, University of Padova, 35131 Padova, Italy

^bInstitute of Biomolecular Chemistry, Padova Unit, CNR, 35131 Padova, Italy
giulia.marafon@phd.unipd.it

Schiff bases (imines) are condensation products of primary amines with carbonyl compounds.¹ Natural and non-natural α -amino acids can be easily chemically converted into their α -amino aldehyde derivatives.² Surprisingly, despite of their potential interest, incorporation of these non-natural α -amino acid derivatives into peptide sequences has not been investigated so far.

We found that self-polymerization of different types of α -amino aldehydes provides formation of stable conjugated polymers, which display different colors and enhanced fluorescent properties depending on their length. In our strategy, a Boc-protected α -amino aldehyde was treated with trifluoroacetic acid (TFA) in dichloromethane to remove the Boc group. Subsequently, the resulting free amino group was able to react (in methanol solution) with the aldehyde function of another unit forming an imine bond. Repeating this reaction, leads to formation of different all-imide, linear and cyclic, polymeric structures. During polymerization, solutions of N α -deprotected amino aldehydes rapidly change their color. This phenomenon was accompanied by the occurrence of fluorescence emission which indicated formation of extensive π - π backbone conjugation generated by the tautomeric equilibrium between the imine/enamine forms. Moreover, we found that in their polymerization short peptides based on Boc-Xxx-Aib-H (Xxx, chiral α -amino acid; Aib-H, α -aminoisobutyric aldehyde), when made to react as mentioned above, underwent repetition of the H-Xxx-Aib-H unit into a well-defined, chiral foldamer structure, where peptide bonds alternate with imine bonds (Figure 1, where Xxx is Val).

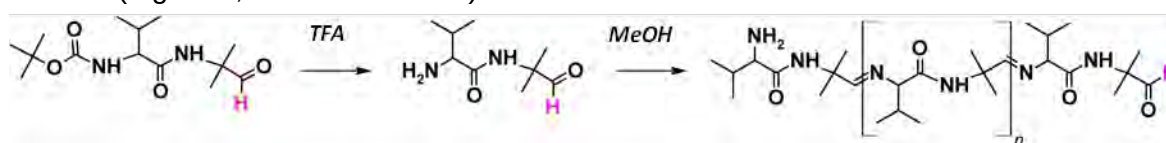


Figure 1: foldamers composed by alternation of amide/imide groups.

Finally, imine/amide polymer chains were analyzed in terms of H-Xxx-Aib-H release by virtue of the imine bond cleavage that we found to be prone to hydrolysis under mild conditions (37°C at pH 7.2). In particular, the polymer structure was, slowly and quantitatively, hydrolysed in 48 hours. These polymeric systems may represent an interesting platform in the pharmaceutical field for the time-controlled release, under nearly physiological conditions, of small-peptide drugs “masked” in large polymeric matrix.

References:

- [1] T. T. Tidwell, *Angew. Chem. Int. Ed.* **2008**, 47, 1016-1020.
- [2] S. Nahm, S. M. Weinreb, *Tetrahedron Lett.*, **1981**, 22, 3815-3818.

Modified Carbon Nanoforms Systems for Asymmetric Catalysis

V. Cinà,^{a,b} M. Guagliardo,^a L. Fusaro,^b M. Gruttadauria,^a C. Aprile,^b F. Giacalone^a

^a Department of Biological, Chemical and Pharmaceutical Sciences and Technologies, University of Palermo, Italy

^b Unit of Nanomaterial Chemistry (CNano), University of Namur (UNamur), Belgium
valerio.cina@unipa.it

In the last years the chemistry of carbon nanoform (CNFs) attracted attention in the field of catalysis, especially in the preparation of last generation nanostructured catalysts. Here are reported synthesis and catalytic applications of chemically modified nanocarbons such as C₆₀, carbon nanohorns and nanotubes. The well-developed chemistry for CNFs functionalization allows operating multiple additions on their structures, and this can be exploited for sensibly increasing catalyst loading or for adding different functionalities.¹ In this way, it is possible to explore synergistic or detrimental effects due to the close proximity of catalytic moieties. In addition, the peculiar solubility profile of CNFs-derivatives may be used for recovering a homogeneous catalyst by simple precipitation.

Herein CNFs were functionalized with a series of chiral bisoxazoline (BOX) ligands, widely used in asymmetric catalysis.² In the case of C₆₀-adducts, these were functionalized in order to obtain mono- and hexakis-adducts as well as monoadducts endowed with ten 1,2-dimethylimidazolium moieties in order to get hybrid with a different solubility profile (Figure 1a). All the CNFs-BOX systems were employed, along with copper(II) salts as catalysts in asymmetric Henry and Diels-Alder reactions (Figure 1b). Furthermore, their ease separation from the reaction mixture allow for a facile reuse in multiple cycles.

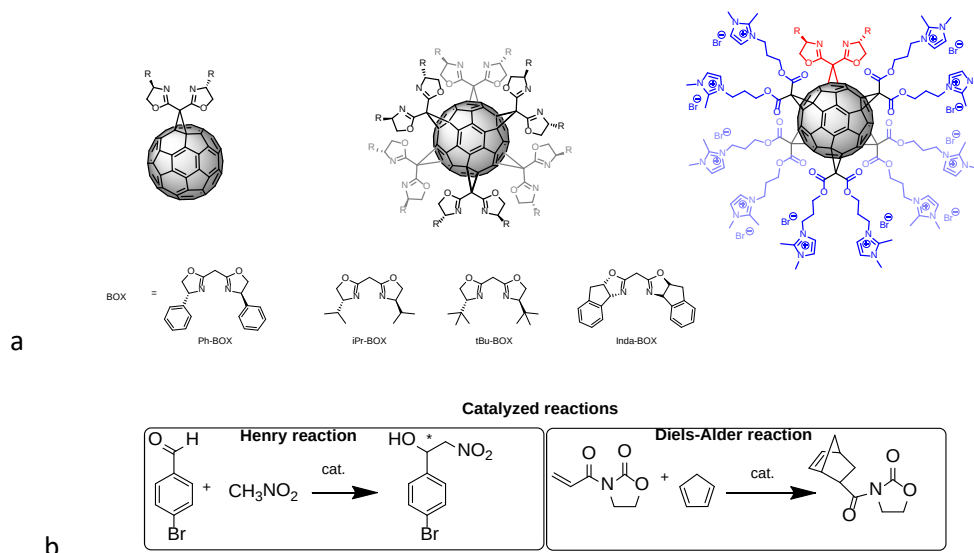


Figure 1 a) Fullerene and BOX based catalysts. b) Asymmetric Henry and Diels-Alder reactions.

References:

- [1] a) V. Campisciano, M. Gruttadauria, F. Giacalone, *ChemCatChem* **2019**, *11*, 90-133. b) D. S. Su, S. Perathoner, G. Centi, *Chem. Rev.* **2013**, *113*, 5782-5816.
[2] a) D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, *J. Am. Chem. Soc.* **1991**, *113*, 726-728; b) R. E. Lowenthal, A. Abiko, S.; Masamune, *Tetrahedron Lett.* **1990**, *31*, 6005-6008.

Multimodal Functionalization of Nanoparticles for β -cells Imaging: new diagnostic tools for pancreatic regenerative therapies

S. Magli,^a L. Russo,^a L. Rabbachin,^a E. Prépost,^b K. Kerekes,^b Z. Körhegyi,^b M. Bodnar,^b F. Nicotra^a

^aUniversity of Milano-Bicocca, Department of Biotechnology and Biosciences. P.zza della Scienza 2, Milan

^bBBS Nanotechnology, Böszörményi út 212, Debrecen 4032, Hungary

s.magli1@campus.unimib.it

In the context of the H2020 project iNanoBIT, a new medical device able to produce insulin for diabetic patients will be experimented. The device, once implanted, undergoes vascularization. It will be filled with transgenic porcine beta-cells that produce insulin. The vascularization allows insulin to exit and nutrients to get into the device. The viability of the porcine pancreatic cell however must be monitored to program the substitution. For this purpose we generated nano-diagnostics with multiple functionalization, able to interact with a ligand of living beta cells and suitable for two different diagnostic protocols applicable on patients. Specifically, we selected peptide exendin-4 as ligand of the GLP1 receptor overexpressed at the surface of living beta-cells, 99-Tc for SPECT and/or 64-Cu for PET, and IRDye® 800CW a new optoacoustic diagnostic protocol (MSOT). The multifunctional nano-diagnostics have been generated on FDA approved nanoparticles, obtained by aggregation of cationic and anionic biopolymers, chitosan and polyglutamic acid. We developed synthetic strategies to decorate chitosan and polyglutamic acid with functional groups suitable for chemoselective ligation of: i) exendin-4, ii) DOTA as chelator of 99-TC and 64-Cu, iii) IRDye® 800CW.

In order to perform the chemoselective ligation, exendin-4, DOTA and IRDye® 800CW were functionalised with the complementary chemoselective group. The obtained multifunctionalised nano-diagnostics were characterized for their capacity to interact with pancreatic beta-cell and are under evaluation for the diagnostic potential.

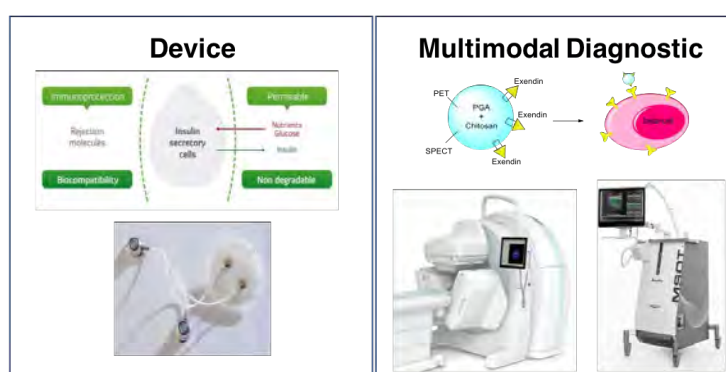


Figure 1: BioArtificial Pancreas Device and Multimodal NPs

Acknowledgments: this project is funded by H2020-NMBP-15-2017- GA-760986 — iNanoBIT (1.10.2017-30.9.2022) Integration of Nano- and Biotechnology for beta-cell and islet Transplantation. <http://inanobit.eu/>

Site-selective immobilization of leptin on gold nanoparticles

R. Fiammengo,^a V. Mangini,^a V. Maggi,^{a,b}

^aCenter for Biomolecular Nanotechnologies@UniLe, Istituto Italiano di Tecnologia (IIT), Via Barsanti, 73010 Arnesano, Lecce; ^bDepartment of Engineering for Innovation, University of Salento, Via per Monteroni Km 1, 73100, Lecce, Italy
roberto.fiammengo@iit.it

The immobilization of proteins on nanoparticles has a significant impact on the ultimate performances of the nanoconstructs.¹ Choosing correctly the most suitable conjugation strategy can be determinant to direct the interaction between protein-functionalized nanoparticles and biological systems, to achieve more effective diagnostic tools and eventually to improve the targeting efficiency of drug formulations based on nanoparticles.

Leptin is a non-glycosylated pleiotropic cytokine of 16 kDa that plays a key role in body energy homeostasis and is involved in cell differentiation and proliferation, immunity, and tumorigenesis.² Leptin is primarily produced by adipocytes, but carries out its biological action on many peripheral cell types, including on neurons after crossing the blood-brain barrier (BBB) through an active transport mechanism.³ We propose that immobilization of leptin on nanoparticles may facilitate the understanding of some aspect of leptin biological activity, including receptor binding and transport across the BBB. This latter aspect is of special relevance in the context of targeted brain delivery.

In this contribution, we describe the site-selective immobilization of full length leptin on PEGylated AuNPs following a disulfide rebridging strategy.⁴ We show that these nanoparticles target the leptin receptor in vitro significantly better than control AuNPs obtained via a more commonly employed, random immobilization strategy. Furthermore, leptin signaling via phosphorylation of the signal transducer and activator of transcription 3 (STAT3) is retained only when leptin is immobilized site-selectively on the AuNPs.

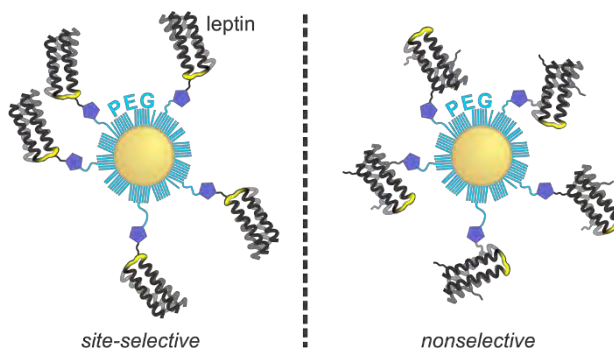


Figure 1: Site-selective vs. nonselective immobilization of leptin on PEGylated AuNPs.

References:

- [1] C. D. Spicer, C. Jumeaux, B. Gupta, M. M. Stevens, *Chem. Soc. Rev.* **2018**, 47, 3574-3620.
- [2] a) Y. Zhang, S. Chua Jr, *Compr. Physiol.* **2018**, 8, 351-369; b) W. W. Pan, M. G. Myers Jr, *Nat. Rev. Neurosci.* **2018**, 19, 95-105.
- [3] D. Gonzalez-Carter, A. E. Goode, R. Fiammengo, I. E. Dunlop, D. T. Dexter, A. E. Porter, *J. Neuroendocrinol.* **2016**, 28, doi: 10.1111/jne.12392.
- [4] S. L. Kuan, T. Wang, T. Weil, *Chem. Eur. J.* **2016**, 22, 17112-17129.

Engineered Polylactide-based Nanoparticles as Multifunctional Drug Delivery Systems

A. Scala,^a A. Piperno,^a Serena M. Torcasio,^a P. G. Mineo,^b O. Coulembier^c

^aUniversity of Messina, Dept. of Chemical, Biological, Pharmaceutical and Environmental Sciences, V.le F. Stagno D'Alcontres 31, I-98166 Messina (Italy)

^b University of Catania, Dept. of Chemical Sciences, V.le A. Doria, I-95125 Catania (Italy)

^cUniversity of Mons, Center of Innovation and Research in Materials and Polymers (CIRMAP), Laboratory of Polymeric and Composite Materials, Place du Parc 23, 7000 Mons (Belgium)
ascale@unime.it

In the last few years, engineered polymeric nanoparticles with tailor-made functionalizations have attracted increasing interest for drug delivery and tissue engineering applications.¹

PolyLactic Acid (PLA) is frequently used for nanoparticles fabrication due to its biodegradability, biocompatibility and properties tunability by chemical modification.²

Herein, different synthetic strategies for the grafting of acetylene groups on PLA backbone will be discussed, leading to alkyne-grafted PLA derivatives, useful building blocks for click chemistry exploitations (Figure 1).³ The reactions of “clickable” PLA derivatives with azide-functionalized compounds, such as polyethylene glycol (PEG), azide-fluor 545, folic acid and integrin-targeting RGD peptide, have been investigated to access a variety of functionalized polymers by Cu(I)-catalyzed cycloaddition reaction (CuAAC). Finally, different formulation strategies have been used to produce multifunctional PLA nanoparticles armed with targeting agent and fluorescent probes for biomedical applications.

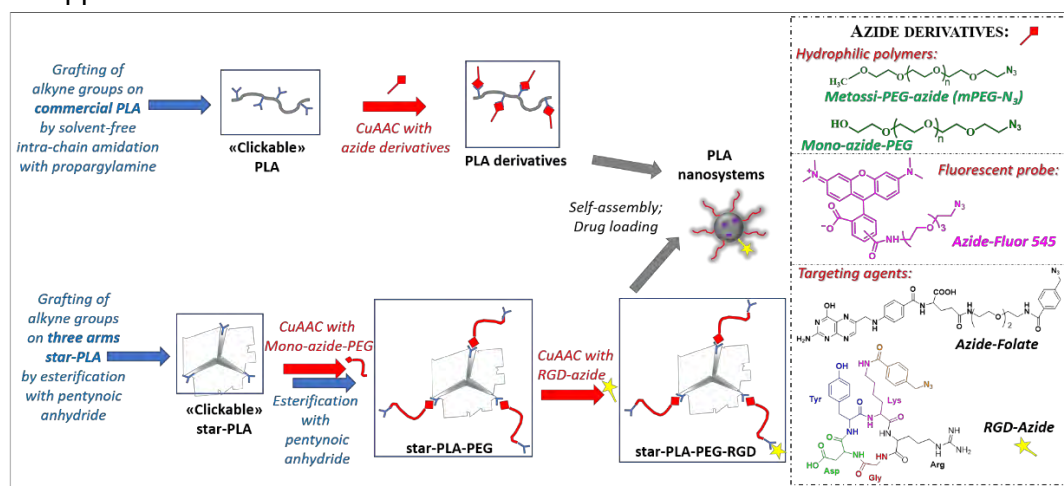


Figure 1: Overview of our recent exploitation of *click chemistry* for PLA functionalization.

References:

- [1] V. Beer, K. Koynov, W. Steffen, K. Landfester, A. Musyanovych, *Macromol. Chem. Phys.* **2015**, 216, 1774-1781
- [2] R. Ghasemi, M. Abdollahi, E. E. Zadeh, K. Khodabakhshi, A. Badeli, H. Bagheri, S. Hosseinkhani, *Sci. Rep.* **2018**, 8, 9854.
- [3] A. Scala, A. Piperno, S. M. Torcasio, A. Nicosia, P. G. Mineo, G. Grassi, *Eur. Polymer J.* **2018**, 109, 341-346.

Azomethine ylides: a powerful tool for Nanodiamonds-based contrast agents and drug delivery systems

M. Sacco,^{a,b} P. Aprà,^c F. Picollo,^c S. Tagliapietra,^a A. Binello,^a A. Barge^a

^aDipartimento di Scienza e Tecnologia del Farmaco, Via P. Giuria 9, Torino

^bIstituto Italiano di Tecnologia - Center for Neuroscience and Cognitive Systems,
Corso Bettini 31, Rovereto

^cDipartimento di Fisica, Via P. Giuria 1, Torino
mirko.sacco@unito.it

Specific and uniform surface functionalization of carbon nanomaterials is an intriguing topic. In recent years the research is focusing on Nanodiamonds (NDs), a promising nanometric scale carbon allotrope useful for technology (lubricants, abrasive materials...) and biomedicine (drug delivery, biosensors, imaging...) applications. Despite of inertness of its diamond-like core, NDs surface is reactive and it can be modified by covalent attachment of functional moieties. Whereas the linkage of oxygen, halogen or sulphur atoms is relatively simple to achieve, the covalent conjugation of nitrogen, with high yield, is a growing challenge¹. Amino groups are suitable for further functional moieties grafting, in order to link biomedical relevant molecules, such as antibodies, drugs or contrast agents. The already known procedures^{2,3} provide surface functionalization by formation of pyrrolidine or tetrahydroindolizine rings.

In this work we modify NDs surface with amino groups, by means of 1,3-dipolar cycloaddition via aminoacids-generated azomethine ylides (Figure 1). The 1,3-dipoles irreversibly react with the partially graphitized surface, giving N-grafted nanomaterials, with the aim to obtain Nanodiamonds-based contrast agents (CA) and drug delivery systems (DDS).

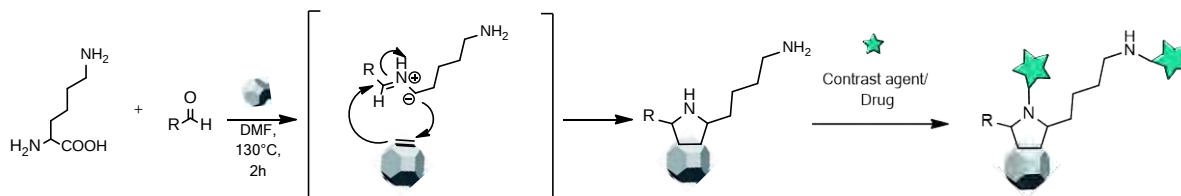


Figure 1: Synthesis of Nanodiamonds-based CA and DDS, by mean of prior surface amination via a *in situ* aminoacid-formed azomethine ylide.

The surface functionalization was characterized by zeta potential, FTIR and thermogravimetric analyses.

The irreversibility of the process, which allows to carry out more than one functionalization step, together with the easiness of reaction preparation and the wide reagents choice, make 1,3-dipolar cycloadditions via aminoacids-generated azomethine ylides an interesting and flexible route for nanodiamonds surface N-grafting, in a non-destructive manner.

References:

- [1] H. Tinwala, S. Wairkar, *Mater. Sci. Eng. C* **2019**, 97, 913-931.
- [2] D. Lang, A. Krueger, *Diam. Relat. Mater.* **2017**, 79, 102-107.
- [3] D. Lang, A. Krueger, *Diam. Relat. Mater.* **2011**, 20, 101-104.

N-Heterocyclic Carbene (NHC)-Organocatalyzed kinetic resolution of biologically active Biginelli compounds

A. Brandolese,^a D. Ragno,^a G. Di Carmine,^a L. Preti,^a S. Buoso,^a G. Botti,^a O. Bortolini,^a A. Massi^a

^aDepartment of Chemical and Pharmaceutical Sciences, University of Ferrara, via L-Borsari 46, 44121 Ferrara, Italy.
arianna.brandolese@unife.it

Dihydropyrimidones (DHPMs), well known as Biginelli products, can be simply synthesized through an efficient multicomponent reaction using highly accessible aldehydes, active methylene compounds and (thio)ureas in acidic medium.¹ In recent years, DHPMs have attracted considerable attention, thanks to their several biological and pharmaceutical applications. Optically active DHPMs represent challenging synthetic targets accessible through direct asymmetric synthesis or chemical resolution processes.² Kinetic resolution constitutes a useful method in asymmetric synthesis representing one of the most widely used industrial procedure for the preparation of chiral compounds.

In the present work, optically enriched DHPMs have been synthesized through N-heterocyclic carbene catalysed kinetic resolution of racemic Biginelli compounds.³

The aim of this study was to carry out a stereoselective N-3 acylation of racemic DHPMs. The reaction promoted by chiral N-heterocyclic carbene catalyst (NHC) in oxidative conditions leads to optically active N-acylated products and enantioenriched unreacted DHPMs (Figure 1). Reaction conditions were optimized to reach satisfactory level of conversion (up to 45%) and stereoselectivity (up to 80:15 er).

To the best of our knowledge, this work represents the first example of kinetic resolution of amides and in the future could be extended to other biological and pharmaceutical interesting amide compounds.

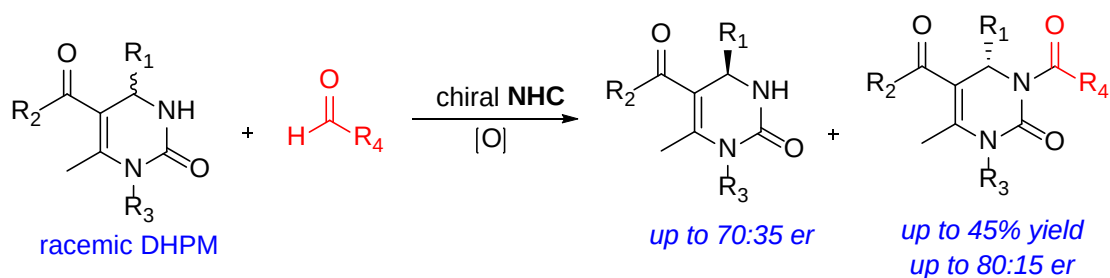


Figure 1: Kinetic resolution of DHPMs promoted by NHC in oxidative conditions.

References:

- [1] H. Nagarajaiah, A. Mukhopadhyay, J. N. Moorthy, *Tetrahedron Lett.* **2016**, 57, 5135-5149.
- [2] Z. Wang, D. Pan, T. Li, Z. Jin, *Chem. Asian J.* **2018**, 13, 2149-2163.
- [3] M. M. Heravi, R. Moradi, L. Mohammadkhani, B. Moradi, *Mol. Diversity* **2018**, 22, 751-767.

High Enantioselection Performances of Inherently Chiral Ionic Liquids with Axial, Helical and Central Stereogenicity

S. Rizzo,^a P. R. Mussini,^b S. Arnaboldi,^b M. Longhi,^b F. Fontana,^c R. Cirilli,^d A. Forni,^a L. Guazzelli^e

^aCNR, Inst. of Molecular Science and Technologies, Via Golgi 19, 20133 Milan, Italy

^bUniversity of Milan, Dept. of Chemistry, Via Golgi 19, 20133 Milan, Italy

^cUniversity of Bergamo, Dept. of Engineering and Applied Science, V.le Marconi 5, 24044 Dalmine, Italy

^dNat. Inst. of Health, Nat. Cent. for Control and Evaluation of Medicines, V.le Regina Elena 299, 00161 Rome, Italy

^eUniversity of Pisa, Dept. of Pharmacy, Via Bonanno 33, 56126 Pisa, Italy

simona.rizzo@istm.cnr.it

We define as "inherently chiral" functional materials the compounds in which the stereogenic scaffold responsible for chirality and the molecular group responsible for their specific properties coincide.^{1,2} This structural combination results in outstanding enantioselection properties, much higher than those exhibited by compounds in which stereogenic unit and functional group are independent moieties. The validity of this concept was proved in the design of high symmetry (D_n) macrocyclic oligo-thiophenes in which chirality results from a tailored torsion of regio-regular thiophene sequences. They were employed as highly stereoselective electrode surfaces.²

Here we report the results of the application of the inherent chirality concept to Chiral Ionic Liquids (CILs). We checked first the effects produced by a stereogenic axis and then extended the research to Inherently Chiral Ionic Liquids (ICILs) based on helices and stereocenters.

In our project the ICILs based on a stereogenic axis are characterized by suitably substituted 3,3'-bipyridinium (**1**) or 1,1'-bibenzimidazolium (**2**) atropisomeric scaffolds.¹ Considering that pyridinium and imidazolium groups are classical IL functionalities, and that a pair of them are involved in the hindered rotation around the interanular bond, responsible for chirality, it is evident that the attribute of ICILs to these compounds is correct. Aza- and di-aza-hexahelicenium cations (**3**) also fulfill the requirements to be defined as ICILs, since the pyridinium unit is essential part of the helical scaffold. As for ICILs based on stereogenic centers, we have planned the alkylation of configurationally stable phosphanes (**4**) like DIPAMP. (Figure 1).

Synthesis and characterization of all new ICILs and electrochemical enantiodifferentiation performances of the antipodes of several chiral probes are discussed in comparison with the behavior of CILs designed according to classical strategies (**5**).³

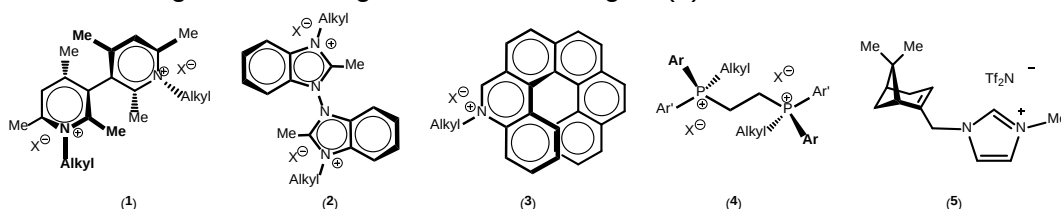


Figure 1: Prototypes of inherently chiral organic salts characterized by stereogenic axis (**1,2**), helix (**3**) and stereocenter (**4**), and example of a new traditionally designed CIL (**5**).

References:

- [1] S. Rizzo, S. Arnaboldi, V. Mihali, R. Cirilli, A. Forni, A. Gennaro, A. A. Isse, M. Pierini, P. R. Mussini, F. Sannicolò, *Angew. Chem. Int. Ed.* **2017**, 56, 2079-2082.
- [2] F. Sannicolò, S. Arnaboldi, T. Benincori, R. Cirilli, L. Dunsch, W. Kutner, G. Longhi, P. R. Mussini, M. Panigati, M. Pierini, S. Rizzo, *Angew. Chem. Int. Ed.*, **2014**, 53, 2623-2627.
- [3] M. Longhi, S. Arnaboldi, E. Husanu, S. Grecchi, I. F. Buzzzi, R. Cirilli, S. Rizzo, C. Chiappe, P. R. Mussini, L. Guazzelli, *Electrochim. Acta* **2019**, 298, 194-209.

DFT/NMR approach for the configuration assignment of groups of diastereoisomers by the combination and comparison of experimental and predicted sets of data

G. Lauro,^a D. S. Reddy,^{b,c} G. Bifulco^a

^aDepartment of Pharmacy, University of Salerno, Via Giovanni Paolo II 132, Fisciano (SA) 84084, Italy.

^bOrganic Chemistry Division, CSIR-National Chemical Laboratory, Dr Homi Bhabha Road, Pune, 411008, India.

^cAcademy of Scientific and Innovative Research (AcSIR), New Delhi, 110 025, India
glauro@unisa.it

DFT/NMR approaches have been widely used for the configuration assignments of organic compounds generally comparing one cluster of experimentally determined data (e.g. $^{13}\text{C}/^1\text{H}$ chemical shifts) with those predicted for all the possible theoretical diastereoisomeric species.^{1,2} However, more than one set of experimental data, each related to a specific diastereoisomer (e.g. pairs, triads, tetrads etc.), may occur in some specific cases. Accordingly, the accurate configurational assignment of each species can be obtained combining the experimental/computed data in different ways.³

We here introduce a novel straightforward methodology based on the simultaneous analysis, combination, and comparison of all the available sets of experimental/calculated $^{13}\text{C}/^1\text{H}$ chemical shifts for the configuration assignment of groups of diastereoisomers. This method relies on mathematical manipulations on both the experimental and predicted data, avoiding errors arising from the calibration procedures and, as a consequence, strongly reducing systematic errors. Also, we noticed a remarkable benefit in simultaneously accounting and comparing all the experimental/calculated chemical shifts: specifically, aligned values drive the results towards the correct assignment and, accordingly, disarranged data aid in excluding incorrect stereoisomers.

As a proof of concept, we have applied this methodology on a tetrad of synthesized cladospirin diastereoisomers (cladologs),⁴ showing the identification of the correct correspondences between experimental/calculated sets of data.

References:

- [1] G. Bifulco, P. Dambruoso, L. Gomez-Paloma, R. Riccio, *Chem. Rev.* **2007**, *107*, 3744-3779.
- [2] A. Cerulli, G. Lauro, M. Masullo, V. Cantone, B. Olas, B. Kontek, F. Nazzaro, G. Bifulco, S. Piacente, *J. Nat Prod.* **2017**, *80*, 1703-1713.
- [3] S. G. Smith, J. M. Goodman, *J. Org. Chem.* **2009**, *74*, 4597-4607.
- [4] P. Das, P. Babbar, N. Malhotra, M. Sharma, G. R. Jachak, R. G. Gonnade, D. Shanmugam, K. Harlos, M. Yogavel, A. Sharma, D. S. Reddy, *J. Med. Chem.* **2018**, *61*, 5664-5678.

Synthesis and antitumor activity of polybrominated C₁₅ acetogenin derivatives.

V. Piccialli,^a D. Capasso,^b S. di Gaetano^c

^a Department of Chemical Sciences, University of Naples Federico II, via Cintia 4, 80126 Naples, Italy.

^b Department of Pharmacy, University of Naples Federico II, via Mezzocannone 16, 80134, Naples, Italy.

^c Institute of Biostructure and Bioimaging, CNR, via Mezzocannone 16, 80134, Naples, Italy
vinpicci@unina.it

C₁₅ acetogenins are typical metabolites from red algae belonging to the genus *Laurencia*. They are usually halogenated substances including one or more cyclic ethers with different ring sizes and an enyne or a bromoallene terminal group.¹

In 1990 we isolated a new member of this class of substances from the encrusting sponge *Mycale rotalis*² (**1**, Figure 1). This finding was rather unusual and was explained by hypothesizing that the sponge could preferentially grow on a *Laurencia* species engulfing it entirely.

Our group is currently actively involved in the search of new antitumor lead substances either of synthetic or natural origin. In this context, the effect of compound **1** on the proliferation of human tumor cells such as melanoma (A375), adenocarcinoma (HeLa), breast cancer (MCF-7) and human normal dermal fibroblasts (HDF), was tested. It showed a good activity on HeLa and A375 cell lines as well as pro-apoptotic ability. Based on this result a number of variously functionalised and degraded derivatives of **1** (Figure 1) were prepared and tested. The chemistry developed, and the preliminary biological results obtained will be presented in this communication.

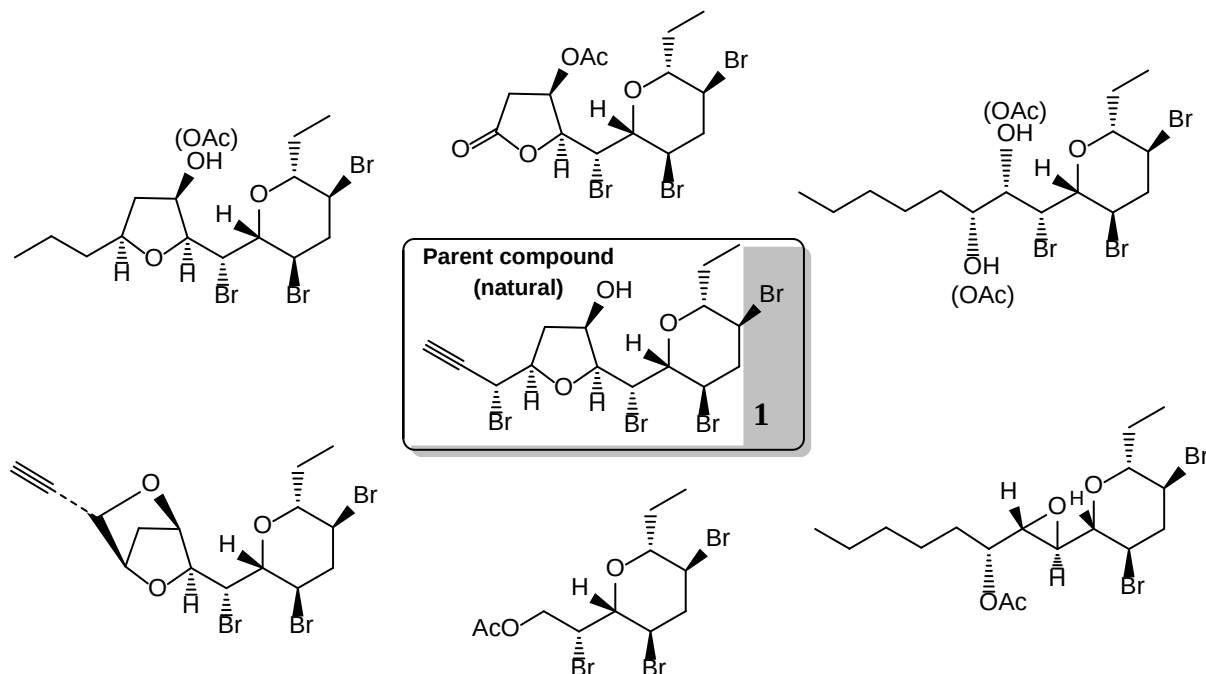


Figure 1: Polybrominated C₁₅ acetogenin derivatives.

References:

- [1] T. Wanke, A. C. Philippus, G. A. Zattel, L. F. Oliveira Vieira, C. Lhullier, M. Falkenberg, *Rev. Bras. Farmacogn.* **2015**, 25, 569-587.
- [2] F. Giordano, L. Mayol, G. Notaro, V. Piccialli, D. Sica, *J. Chem. Soc., Chem. Commun.* **1990**, 1559-1961.

Folate-Tannin Microcapsules for Oncologic Theragnosis Applications

L. Zongo,^a H. Lange,^{a,b} C. Crestini^{a,c}

^a University of Rome 'Tor Vergata', Department of Chemical Sciences and Technologies
Via della Ricerca Scientifica, 00133 Rome, Italy

^b University of Naples 'Federico II', Department of Pharmacy
Via Domenico Montesano 49, 80131 Naples, Italy

^c University of Venice Ca' Foscari, Department of Molecular Sciences and Nanosystems
Via Torino 155, 30170 Venice Mestre, Italy

luc.zongo@uniroma2.it

Cell surface receptors for folic acid are generally overexpressed in human cancer. In several studies folate has been used as a targeting moiety of various anti-cancer agents to avoid their non-specific attacks on normal tissues as well as to increase their cellular uptake within target cells.¹ Tannins possess several relevant biological activities such as antioxidant and anti-inflammatory properties, anti-mutagenic and anti-carcinogenic activities, prevention and delay of cardiovascular diseases, increase in lifespan and retarded the onset of age-related markers. Such activities are due to their specific chemical and physical properties as significant chelating and stacking capacity.² In addition, the polyphenolic character of tannins displays further functionalisation possibilities.

Tannins thus represent a very versatile class of compounds with respect to the use of both as substrate of functionalisation³ and as shell material in the generation of microcapsules for pharmaceutical and biomedical applications.^{4,5} Consequently, the folate functionalized tannins represent one of the most plausible ideal candidates for the development of a new class of microcapsules for oncologic theragnosis.

In the present study these unique combinations of interesting properties of tannins were exploited in the synthesis of folate-tannin moieties, which have been used as shell material for the generation of gadolinium reinforced folate-tannin microcapsules containing 5-fluorouracil for cancer therapy and diagnosis purpose.⁶

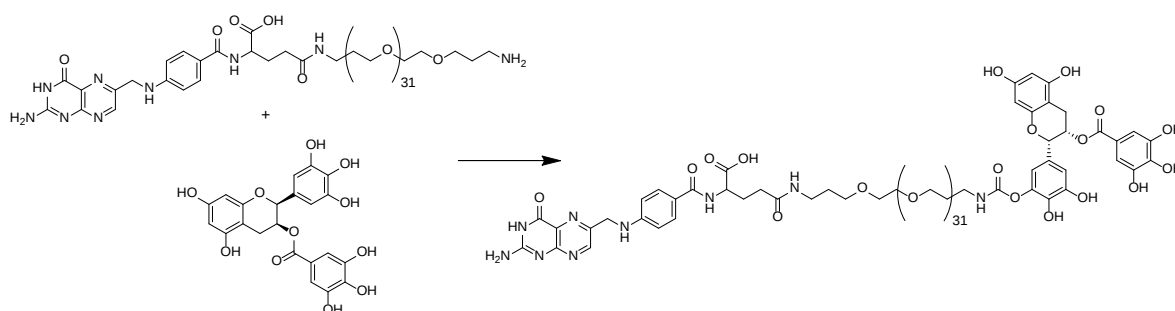


Figure 1: Folate-tannin synthesis using PEG-ylated folic acid and epigallocatechin gallate.

References:

- [1] A. Gabizon, A. T. Horowitz, D. Goren, D. Tzemach, F. Mandelbaum-Shavit, M. M. Qazen, S. Zalipsky, *Bioconjug. Chem.* **1999**, *10*, 289-298.
- [2] K. Khanbabaee, T. van Ree. *Nat. Prod. Rep.* **2001**, *18*, 641-649.
- [3] L. Zongo, L. Zhen, H. Lange, C. Crestini, *manuscript in preparation*.
- [4] E. D. Bartzoka, H. Lange, P. Mosesso, C. Crestini, *Green Chem.* **2017**, *19*, 5074-5091.
- [5] E. D. Bartzoka, H. Lange, G. Poce, C. Crestini, *ChemSusChem* **2018**, *11*, 3975-3991.
- [6] L. Zongo, C. Crestini, H. Lange, *manuscript in preparation*.

Sweet and Smart Nanovectors for Live-Cell Drug Delivery and *in vivo* Bone Targeting

B. La Ferla,^a A. Palmioli,^a L. Zoia,^b P. Bigini,^c A. Maeda,^d P. Allavena^d

^aUniversity of Milano-Bicocca, Dep. of Biotechnology and Bioscience, Piazza della Scienza 2, I-20126, Milan

^bUniversity of Milano-Bicocca, Dep. of Earth and Environmental Science, Piazza della Scienza 1, I-20126 Milan

^cIRCCS-Istituto di Ricerche Farmacologiche "Mario Negri", via La Masa 19, 20156 Milan

^dDepartment of Immunology and Inflammation, IRCCS-Humanitas Clinical and Research Center, 20089 Rozzano, Milan

e-mail barbara.laferla@unimib.it

Surface functionalized nanoparticles (NPs) are gaining great importance in the biomedical field due to the emerging role of nanomedicine. Nanotechnology is orienteering towards the development of nano-medical devices as drug delivery and diagnostic systems with improved properties and reduced side effects if compared to traditional medicine. The presence of a specific molecular entity (ligand) on the NPs' surface, can target the nanodevice to specific tissue; this can be used for direct tumor targeting, exploiting its overexpression of specific receptor recognized by specific ligands, or can allow to reach biological districts, such as bones, for which drugs usually show a very low tropism. In this context, we have realised two different types nanoparticles where sugar moieties play different crucial roles.

The first type is a sugar decorated polymeric NP loaded with cytotoxic drugs, designed to engulf immune cells and use them as Live-Cell Drug Delivery systems.^{1,2} As polymer we selected poly(lactic-co-glycolic acid) (PLGA), and for the surface decoration we used different sugars and sugar-dendrimers, that exploit specific receptors on cell surface. In this context we adopted a chemoselective method applied on a free sugar, that can be extended to the conjugation of any sugar/oligosaccharide moiety bearing a reducing end.³

The second type consist in Cellulose-Nano-Crystals (CNCs). We differently functionalised the surface of these NPs with Ca⁺⁺ chelating moieties (sulfates, pyrophosphonates and carboxylates) to address bone tropism. On these NPs we carried out a careful evaluation of the biodistribution, accumulation and clearance in filter organs of CNCs in mice, using fluorescent labelled CNCs detectable by *in vivo* Optical Imaging^{2,4}.

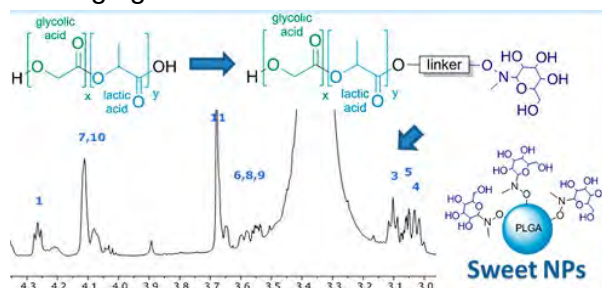


Figure 1: Derivatization and characterization of PLGA-sugar derivatives.

References:

- [1] A. Maeda, R. Avigni, B. La Ferla, F. Torres Andon, P. Allavena **2018** Keystone Symposia Conference: Cancer Immunotherapy March 23 - March 27, 2018, Montreal, Canada.
- [2] Manuscript in preparation
- [3] A Palmioli, B. La Ferla *Org. Lett.* **2018**, 20(12), 3509-3512.
- [4] L. Colombo, L. Zoia, M. B. Violatto, S. Previdi, L. Talamini, L. Sitia, F. Nicotra, M. Orlandi, M. Salmona, P. Bigini, B. La Ferla. *Biomacromolecules* **2015**, 16, 2862-2871.

Stable and Water-Dispersible Quantum Dots: Modular Fluorescent Tools for Bioimaging Applications

G.Toniolo,^a G. Salerno,^a B.Richichi^a

^a Department of Chemistry 'Ugo Schiff', University of Florence, Via della Lastruccia 13, 50019 Sesto F.no, FI, Italy.
gianluca.toniolo@unifi.it

Quantum dots (QDs) are luminescent semiconductor nanomaterials displaying a wide range of unique electro-optical properties.^{1,2} The decoration of QDs with synthetic organic molecules is fundamental since it gives these nanoparticles excellent stability in aqueous media, which is the basis to rely on for any biological applications.³ Also, by taking advantage of the functional groups of the organic layer, further functionalization of the QDs opens up a virtually-unlimited range of bio-related opportunities. In other words, water-dispersible QDs are extremely versatile and can be used as stable and efficient probes for bioimaging, diagnostic and drug delivery combining the optical/electrochemical properties with the biological function of a chosen biomolecule.



Figure 1: a) Schematic representation of conjugated QDs; b) DHLA-EDADA coated CdSe/ZnS QDs water dispersion under white and UV light.

The presentation will give an overview on the enormous potential of water-stable QDs by reviewing the most impactful papers in the field, along with the most recent results of our group. The attention will be focused on the applications and advantages of water-dispersible QDs, such as bio-imaging, where the QDs serve as imaging tag while the attached molecule may serve as a targeting agent. Also, the conjugation of QDs with biomolecules will be taken into consideration. Such conjugates can be used as probes toward specific biological mechanisms in immunoassays and live-cell imaging as well as in a variety of other fluorescence-based detection assays, which could give the opportunity to explore further certain biological functions.

References:

- [1] R. E. Galian and M. de la Guardia, *TrAC, Trends Anal. Chem.*, **2009**, 28(3), 279-291.
- [2] I. L. Mendiz, H. T. Uyeda, E. R. Goldman and H. Mattoussi, *Nat. Mater.*, **2005**, 6, 435-446.
- [3] G. Salerno, S. Scarano, M. Mamusa, M. Consumi, S. Giuntini, A. Macagnano, S. Nativi, M. Fragai, M. Minunni, D. Berti, A. Magnani, C. Nativi and B. Richichi, *Nanoscale* **2018**, 10, 19720-19732.

Macromolecular and nano-supported antioxidants for practical applications

C. Viglianisi,^a S. Menichetti,^a R. Amorati,^b P. Stagnaro,^c S. Losio^d

^aDepartment of Chemistry 'U. Schiff', University of Florence, Via Della Lastruccia 3-13, 50019 Sesto Fiorentino, Italy.

^bDepartment of Chemistry 'Ciamician', University of Bologna, Via San Giacomo 11, 40126 Bologna, Italy.

^cCNR-ISMAL, Via De Marini 6, 16149 Genova, Italy

^dCNR-ISMAL, Via Alfonso Corti 12, 20133 Milano, Italy

caterina.viglianisi@unifi.it

All organic materials exposed to air will degrade over time as function of chemical structure, use and storage. In addition, the products of certain degradation processes pose a potential safety risk if present at high levels. Polyolefins and ethereal solvents, two very common classes of organic materials, require special handling and storage considerations, and the addition of stabilizers to inhibit or retard thermo- and/or photo-oxidative degradation. Several additives are low molecular weight polar compounds, such as hindered phenols and amines, which however are structurally different from the apolar polyolefinic matrices. This causes poor compatibility with stabilizer and physical loss by migration.

To overcome these drawbacks, we proposed different families of macromolecular additives¹ consisting in ethylene- and propylene-based copolymers containing tuned amounts of suitable olefinic comonomers bearing a stabilizing functionality (Figure 1). On the other hand, additives used in ether solvents must be removed before use with time, cost and safety concerns. In this communication we report also the synthesis of novel graphite-coated magnetic cobalt nanoparticles² decorated with hindered phenolic antioxidant for easily removable nanoantioxidants capable of preventing the autoxidation of organic solvents such as THF (Figure 1).

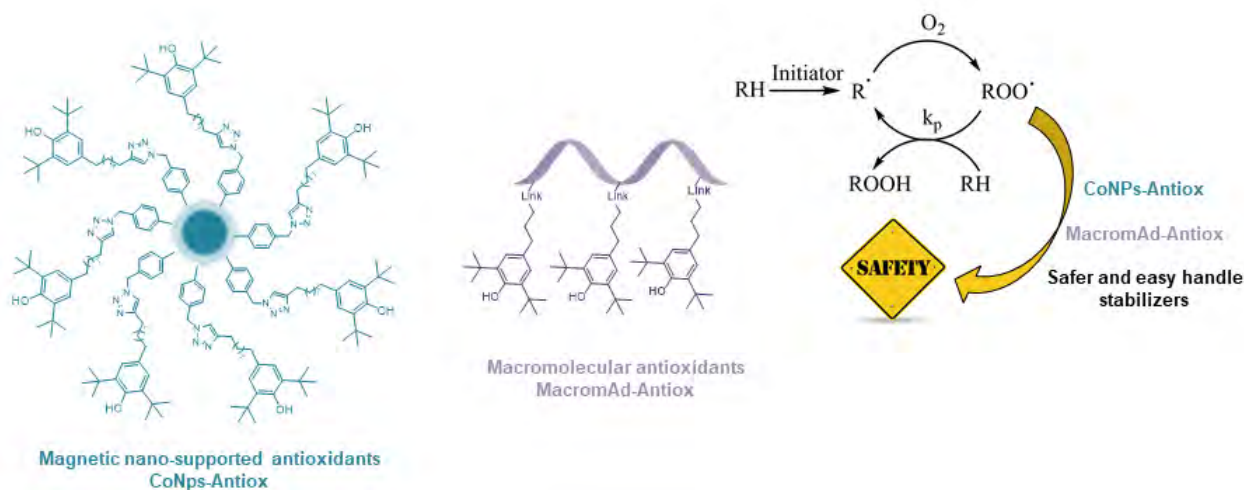


Figure 1: Nano-supported and macromolecular antioxidants.

References:

- [1] S. Losio, I. Tritto, L. Boggioni, G. Mancini, G. Luciano, L. Tofani, C. Viglianisi, S. Menichetti, M. C. Sacchi, P. Stagnaro, *Polymer. Degrad. Stab.*, **2017**, *144*, 167-175, and references therein.
- [2] C. Viglianisi, V. Di Pilla, S. Menichetti, V. M. Rotello, G. Candiani, C. Malloggi, R. Amorati, *Chem. Eur. J.*, **2014**, *20*, 6857-6860.

Photopolymerization of Selected Monomers Initiated by Arylazo Sulfones

A. Nitti,^{a,b} F. Batteux,^a S. Protti,^a M. Fagnoni,^a D. Pasini^{a,b}

^a Department of Chemistry, University of Pavia, Viale Taramelli 10, 27110 Pavia, Italy

^b INSTM Research Unit, University of Pavia, Viale Taramelli 10, 27110 Pavia, Italy
andrea.nitti01@universitadipavia.it

Photopolymerization offer several advantages over classical thermal polymerizations such as rapidity of execution, solvent-free conditions and reduced emission of volatile organic compounds as the consequence of the mild reaction conditions. Photoinitiators are essential for the photopolymerization because their light-induced dissociation lead to the formation of radical, cationic or anionic intermediates responsible for initiating the polymerization. Photopolymerizations have been traditionally developed for 2D printing technological applications such as photolithography,¹ and they are currently experiencing a resurgence of interest for applications in the fields of stereolithographic 3D and 4D printing.² The possibility to photogenerate different intermediates in the same material with good spatial and temporal control of the process, has been recently addressed in multimaterial, 2D and 3D printing applications.³ There is therefore a demand for dually-activatable photoinitiators, in order to address more precisely the multimaterial printing.

Arylazo sulfones are compounds studied as radical initiators in thermal polymerizations during '60 and '70, and recently arylazo sulfones, as thermally stable derivatives of aryl diazonium salts, were studied as arylating agents for the photoinduced metal-free direct arylation of (hetero)aryls.⁴ They can, according to the irradiation wavelength, produce radicalic or cationic species. We describe the use of arylazo sulfones as new class of photoinitiators for the radical and cationic polymerization of several vinyl monomers. Their efficiency, in terms of polymerization yields, dispersity and degree of polymerization, will be presented in relation to different class of monomers used.

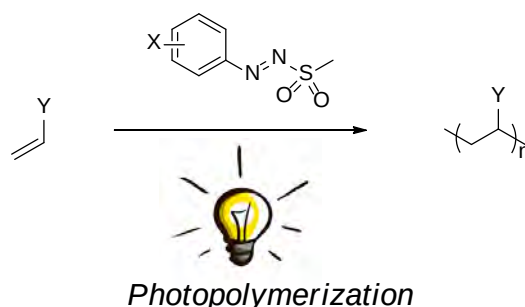


Figure 1: Photopolymerization of selected monomers using arylazo sulfones as initiators.

References:

- [1] D. Pasini, E. Low, J. M. J. Fréchet *Adv. Mater.* **2000**, *12*, 347-351.
- [2] (a) B. E. Kelly, I. Bhattacharya, H. Heidari, M. Shusteff, C. M. Spadaccini, H. K. Taylor *Science* **2019**, *363*, 1075-1079. (b) M. Wei, Y. Gao, X. Li, M. J. Serpe, *Polym. Chem.* **2017**, *8*, 127-143.
- [3] N. D. Dolinski, Z. A. Page, E. B. Callaway, F. Eisenreich, R. V. Garcia, R. Chavez, D. P. Bothman, S. Hecht, F. W. Zok, C. J. Hawker *Adv. Mater.* **2018**, 1800364
- [4] (a) S. Crespi, S. Protti, M. Fagnoni *J. Org. Chem.* **2016**, *81*, 9612-9619. (b) C. Sauer, Y. Liu, A. De Nisi, S. Protti, M. Fagnoni, M. Bandini *ChemCatChem* **2017**, *9*, 4456-4459.

***N*-hydroxyphthalimide: an Efficient Hydrogen Atom Transfer (HAT) Mediator in Hydrocarbon Oxidations Promoted by Nonheme iron(IV)-oxo complexes**

A. Barbieri, O. Lanzalunga, A. Lapi, S. Di Stefano

*Dipartimento di Chimica and Istituto CNR per i Sistemi Biologici (ISB-CNR), Sezione Meccanismi di Reazione, Università di Roma "La Sapienza", P.le A. Moro, 5, 00185 Rome, Italy
osvaldo.lanzalunga@uniroma1.it*

Oxidation processes mediated by *N*-hydroxyphthalimide (NHPI) have attracted a special attention in recent years. For example NHPI is an efficient mediator in the aerobic oxidation of organic compounds promoted by laccase, a multicopper oxidase active in wood delignification.¹ After oxidation by the Cu(II) form of the enzyme, the oxidized mediator phthalimide-*N*-oxyl radical (PINO) diffuse into the woody fibres and oxidize the lignin polymer with a hydrogen atom transfer (HAT) process regenerating the mediator. NHPI plays also an important role as redox mediator under electrochemical conditions. PINO can be easily generated at the electrode surface after electron removal from NHPI enabling a wide range of electrosynthetic organic transformations.²

We have recently discovered that NHPI is an efficient mediator in the oxidations of hydrocarbons promoted by nonheme-iron(IV) oxo complexes, biomimetic models of the active species formed in nonheme-iron oxygenases.³ Kinetic studies of the reaction of hydrocarbons (triphenylmethane, cumene, ethylbenzene, toluene and cyclohexane) with the nonheme iron(IV)-oxo complex, [(N4Py)Fe^{IV}(O)]²⁺ showed a faster decay of the oxidant in the presence of NHPI. The increase of reactivity is associated to the oxidation of the mediator to PINO (Figure 1, step a) which efficiently abstracts hydrogen atom from the substrates regenerating the mediator NHPI (Figure 1, step b).

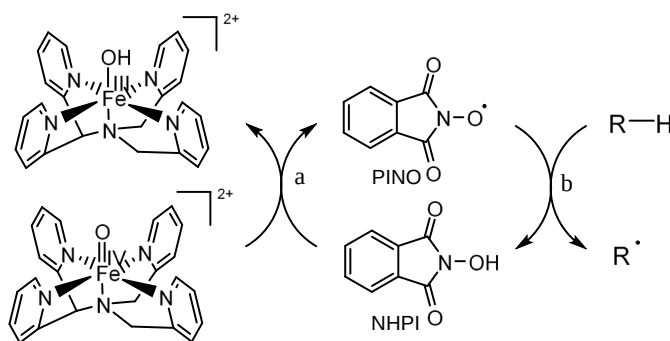


Figure 1: NHPI mediated oxidation of organic compounds promoted by [(N4Py)Fe^{IV}(O)]²⁺

The mediation effect of NHPI in the oxidations promoted by [(N4Py)Fe^{IV}(O)]²⁺ is confirmed by the results of product analysis of the oxidation of triphenylmethane, ethylbenzene and toluene showing that significant higher product yields are observed in the presence of the NHPI mediator.

References:

- [1] C. Galli, P. Gentili, O. Lanzalunga, *Angew. Chem. Int. Ed.* **2008**, *47*, 4790-4796.
- [2] J. E. Nutting, M. Rafiee, S. S. Stahl, *Chem. Rev.* **2018**, *118*, 4834-4885.
- [3] W. Nam, Y.-M. Lee, S. Fukuzumi, *Acc. Chem. Res.* **2014**, *47*, 1146-1154.

Efficient Lewis Acid Multicomponent-Promoting System in the Carbon-Nitrogen Bond Formation

F. Navazio,^a C. Cimorelli,^a D. Gentili,^a G. Lupidi,^a E. Marcantoni,^a F. V. Rossi^a

^a University of Camerino, School of Science and Technology, Chemistry Division,
Via S. Agostino 1, 62032, Camerino (Italy)
e-mail: federica.navazio@unicam.it

The Lewis acid promoters, widely used for carbon-nitrogen bond formation are an active area of research in organic chemistry. They play an important role in such reactions, and thus they find wide application in the synthesis of polysubstituted nitrogen-containing heterocycles.¹ The function of many biologically active molecules requires the presence of carbon-nitrogen bonds in strategic positions and chemical synthesis allows to synthesize natural products more efficiently than biosynthetic pathways. For this reason the efficiency in the preparation of carbon-nitrogen bonds has an environmental impact.

Recent studies by us and by others have shown that a multicomponent-promoting system based on the combination of Ce(III) salts and inorganic iodides provides a new approach for one-pot formation of nitrogen-containing heterocycles. In the course of our program aimed at studying new synergetic promoting system, we were able to develop the selective hetero-cyclocondensation to provide 2-substituted benzimidazoles.² The strategy has found application in our synthesis of Hoechst molecule **1**, which is useful for many different therapeutic and diagnostic purposes, as well as in the synthesis of other important building blocks in medicinal chemistry such as julolidine-type compound **2**, which has proved to have anticancer activity.³

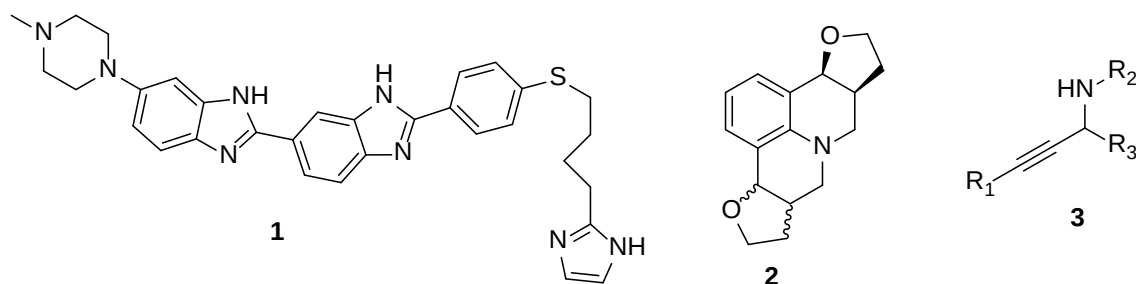


Figure 1.

Efficiency in synthesis of acyclic precursors is often the key factor in having good yield in target heterocycles: through the appropriate combination of the components of the promoting system, by A^3 coupling reaction⁴ we obtained also useful secondary propargylamines **3**, a class of building blocks involved in the synthesis of several important heterocyclic scaffolds.

References:

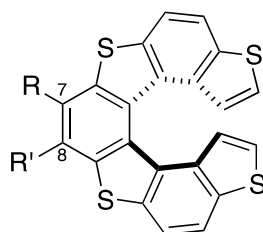
- [1] R. Properzi, E. Marcantoni, *Chem. Soc. Rev.* **2014**, 43, 779-791.
- [2] C. Cimorelli, M. Di Nicola, S. Diomedi, R. Giovannini, D. Hamprecht, R. Properzi, F. Sorana, E. Marcantoni, *Org. Biomol. Chem.* **2015**, 13, 11687-11695.
- [3] C. Cimorelli, S. Bordi, P. Piermattei, M. Pellei, F. Del Bello, E. Marcantoni, *Synthesis* **2017**, 49, 5387-5395.
- [4] C. Cimorelli, F. Navazio, F. V. Rossi, F. Del Bello, E. Marcantoni, *Synthesis* **2019**, in press.

Non photochemical route to functionalized thiophene-based [7]helicenes

S. Cauteruccio,^a V. Pelliccioli,^a E. Licandro^a

^aUniversità degli Studi di Milano, Dipartimento di Chimica, via Golgi 19, 20133 Milano
silvia.cauteruccio@unimi.it

Helicenes are an intriguing class of *ortho*-annulated polycyclic aromatic or heteroaromatic compounds endowed with inherent chirality owing to the helical shape of their π -conjugated system. These curved organic molecules provide unique opportunities for applications in manifold fields, including materials sciences, chiroptical devices, and asymmetric synthesis.¹ Among helicenes, thiahelicenes are emerging as one of the most popular class of heterohelicenes thanks to their unique characteristics combining the electronic properties of oligothiophenes, with the chiroptical properties of helical shape molecules.² For several years, we have been interested in the study of the synthesis and functionalization of thiahelicenes, such as tetrathiahelicene (7-TH) derivatives (Figure), that are configurationally stable and potentially very interesting for applications in optoelectronics,³ catalysis,⁴ and biology.⁵



R, R: aryl, heteroaryl

Figure: general structure of 7-TH derivatives

Recently, we have developed a versatile non-photochemical procedure to prepare functionalized thiahelicenes, including a novel class of 7,8-diaryl substituted 7-TH compounds. This strategy involves the synthesis of chiral heterobiaryl derivatives as key intermediates, whose configurational stability have been elucidated in order to design an asymmetric version for the synthesis of enantioenriched thiahelicenes.

References:

- [1] Y. Shen, C.F. Chen, *Chem. Rev.* **2012**, *112*, 1463-1535.
- [2] S. Cauteruccio, D. Dova, E. Licandro, *Adv. Heterocycl. Chem.* **2016**, *118*, 1-46.
- [3] A. Bossi, E. Licandro, S. Maiorana, C. Rigamonti, S. Righetto, G. R. Stephenson, M. Spassova, E. Botek, B. Champagne, *J. Phys. Chem. C* **2008**, *112*, 7900-7907.
- [4] S. Cauteruccio, A. Loos, A. Bossi, M. C. Blanco Jaimes, D. Dova, F. Rominger, S. Prager, A. Dreuw, E. Licandro, A. S. K. Hashmi, *Inorg. Chem.* **2013**, *52*, 7995-8004.
- [5] S. Cauteruccio, C. Bartoli, C. Carrara, D. Dova, C. Errico, G. Ciampi, D. Dinucci, E. Licandro, F. Chiellini, *ChemPlusChem* **2015**, *80*, 490-493.

Iodine-mediated deconstructive annulation of isoprenylchromenes to benzo[c]chromenes. Development of a one-step synthesis of cannabinal (CBN)

D. Caprioglio,^a D. Mattoteia,^a A. Minassi,^a O. Tagliatela-Scafati,^b G. Appendino^a

^a Dipartimento di Scienze del Farmaco, Università del Piemonte Orientale A. Avogadro, Lgo Donegani 2, 28100 Novara, Italy

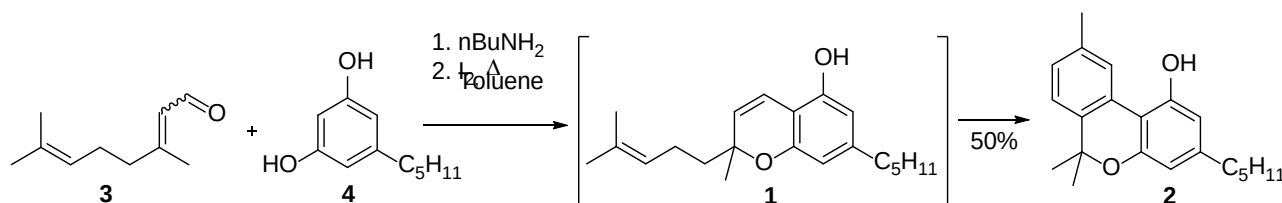
^b Dipartimento di Farmacia, Università di Napoli Federico II, Via Montesano 49, 80131 Napoli, Italy
diego.caprioglio@uniupo.it

Based on model reaction and calculations, the thermal degradation of the non-narcotic phytocannabinoid cannabichromene (CBC, **1**) has been suggested to generate a mixture of psychotropic tetrahydrocannabinols (THCs).¹ We found no evidence for this mechanistic and socially relevant conversion under a variety of pyrolytic conditions, but CBC could be converted in the benzochromene cannabinal (CBN, **2**) by refluxing with iodine.

Iodine can trigger the cyclization of isoprenylated chromenes to benzochromenes via a process that includes a couple of regiochemically distinct electroreversion and electrocyclization steps eventually evolving into a formal benzoannulation: the reaction involves cycloreversion of the chromene system to quinone methide, and this is next trapped in a hetero Diels-Alder fashion by the distal terminal isoprenyl double bond; the final iodine promoted aromatization terminates the reaction.²

Since isoprenylated chromenes are easily available by cyclo-condensation of phenolics with terpenyl aldehydes, the reaction has broad application for the preparation of natural- and non-natural products, as exemplified by an expeditious one-step synthesis of CBN from citral (**3**) and olivetol (**4**) that outperforms in terms of simplicity, scalability, and yield all its previous syntheses.

This deconstructive annulation is added to our meagre inventory of expedite benzochromene synthesis and of complex isoprenoids rearrangements involving aromatic moieties,³ and the remarkable atom-economy and simplicity of the reaction make it ideal to explore the chemical space of complex benzochromenes like cannabinoids and related bioactive biphenyls.



References:

- [1] A. Garcia, D. Borchard, C. Chang, M. J. Marsela, *J. Am. Chem. Soc.* **2009**, *131*(46), 16640-16641.
- [2] F. Pollastro, D. Caprioglio, P. Marotta, A. S. Moriello, L. De Petrocellis, O. Tagliatela-Scafati, G. Appendino, *J. Nat. Prod.* **2018**, *81*(3), 630-633.
- [3] A. Minassi, F. Pollastro, G. Chianese, D. Caprioglio, O. Tagliatela-Scafati, G. Appendino, *Angew. Chem. Int. Ed. Engl.* **2017**, *56*(27), 7935-7938.

Nitroso Diels-Alder chemistry on 1,2-dihydropyridines as a platform to obtain novel anti-diabetic agents

A. Menichetti,^a F. Berti,^a L. Favero,^a A. Nannini,^a S. Di Pietro,^a M. Pineschi^{*a}

^aDepartment of Pharmacy, University of Pisa, Via Bonanno 33, Pisa, Italy
andrea.menichetti@farm.unipi.it

Diabetes is among the most common and prominent diseases in various countries of the world, and in particular type-2 diabetes (T2DM) is prevalent in 90% of the population suffering from this pathology.¹ Glucagon-like peptide-1 (GLP-1) is an incretin hormone that enhances insulin release from pancreatic β -cells in both normal and type 2 diabetic subjects. GLP-1 receptor agonists and drugs that slow the degradation of active GLP-1 are therefore under development as novel treatments for T2DM. Some GLP-1 mimetics are now commercially available, but all of these are peptides with problems of stability and administration route.² For this reason, there is a huge interest in novel treatments that have similar physiological effects to GLP-1, but which can be administered orally and minimize side effects.

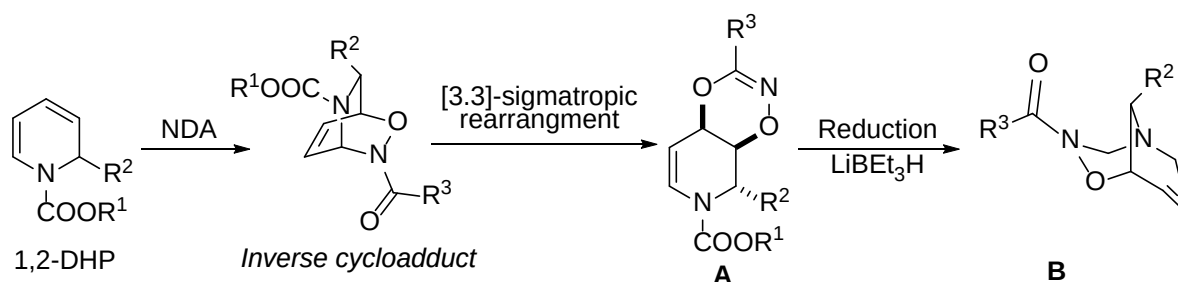


Figure 1: Synthesis of new bicyclic scaffold **B**.⁵

A previous deep study by our group about nitroso Diels-Alder reactions of 1,2-dihydropyridines and subsequent [3.3]-sigmatropic rearrangement of inverse cycloadducts afforded bicyclic dioxazines of type **A** (Figure 1).³ Reductive elaborations of a variety of compounds of type **A** allowed the obtainment of oxadiazabicyclo[3.3.1]nonene scaffolds of type **B**. The latter compounds have shown the ability to bind the GLP-1 receptor and they seem to be promising candidate to explore in terms of structure-properties relationship.^{4,5}

References:

- [1] F. Zaccardi, D. R. Webb, T. Yates, M. J. Davies, *Postgrad. Med. J.* **2016**, 92, 63-69.
- [2] C. Koole, K. Pabreja, E. E. Savage, D. Wootten, S. G. B. Furness, L. J. Miller, A. Christopoulos, P. M. Sexton, *Biochem. Soc. Trans.* **2013**, 41, 172-179.
- [3] F. Berti, A. Menichetti, V. Di Bussolo, L. Favero, M. Pineschi, *Chem. Het. Compd.* **2018**, 54, 458-468.
- [4] F. Berti, A. Menichetti, L. Favero, F. Marchetti, M. Pineschi, *J. Org. Chem.* **2018**, 83, 12221-12228.
- [5] F. Berti, A. Menichetti, M. Pineschi, Patent WO 2018/220542.

Direct and Chemoselective Transfer of the Difluoromethyl (CHF₂) Unit Into Carbon-Electrophiles under Nucleophilic Regime

A. Citarella,^a M. Miele,^b N. Micale^a and V. Pace^{b*}

^a Department of Chemical, Biological,
Pharmaceutical and Environmental Sciences
University of Messina

Viale F. Stagno D'Alcontres 31, I-98166 Messina

^b Department of Pharmaceutical Chemistry
University of Vienna

Althanstrasse, 14 A-1090 Vienna; [http: https://drugsynthesis.univie.ac.at/](http://drugsynthesis.univie.ac.at/acitarella@unime.it)
acitarella@unime.it; * vittorio.pace@univie.ac.at

The difluoromethyl group (CHF₂) plays a crucial role in synthetic chemistry because of the capability to act as an isoster of the carbinol group (CH₂OH), manifesting a remarkable hydrogen donor characteristic. As a consequence, difluoromethylated analogues of biologically active substances are strong, ideal candidates for pharmaceuticals.¹ In contrast to the lipophilic CF₃ group, the CHF₂ group is weakly acidic and exhibits a natural tendency to make strong H-bonding interactions.²

In line with Pace's group studies on nucleophilic halomethylations,^{3,4} the highly challenging introduction of a CH₂F group, herein we disclose a highly effective difluoromethylation – under nucleophilic regime – for the one-pot, straightforward formal transfer of a CHF₂ motif into a carbon electrophile. Tactic's development, optimization, and study of the scope – as well as the application in synthetic relevant transformations of the accessed structures – will be presented.⁵



References

- [1] D. E. Yerien, S. Barata-Vallejo, A. Postigo, *Chem. Eur. J.* **2017**, *23*, 14676-14701.
- [2] Y. Zhao, W. Huang, J. Zheng, J. Hu, *Org. Lett.* **2011**, *13*, 5342-5345.
- [3] L. Castoldi, S. Monticelli, R. Senatore, L. Ielo, V. Pace, *Chem. Commun.* **2018**, *54*, 6692-6704.
- [4] G. Parisi, M. Colella, S. Monticelli, G. Romanazzi, W. Holzer, T. Langer, L. Degennaro, V. Pace, R. Luisi, *J. Am. Chem. Soc.* **2017**, *139*, 13648-13651.
- [5] *Manuscript in preparation.*

A new biopolymer skeleton formed by a dimer of carbohydrate and aminoacid produced by *Rhizobium radiobacter* and useful for plant immunity evasion

A. Molinaro,^a I. Speciale,^a F. Di Lorenzo,^a C. De Castro^b

^aDepartment of Chemical Sciences, University of Napoli Federico II, Complesso Universitario Monte Santangelo, Via Cintia 4, I-80126 Napoli, Italy

^bDepartment of Agriculture Sciences, University of Naples 'Federico II', Via Università 100, 80055, Portici, Naples, Italy
molinaro@unina.it

Microbial surface antigens are key molecules for both symbiotic and pathogenic bacteria in the interaction with other organisms and in the physico-chemical interaction with the external environment. They are mostly carbohydrate based molecules such as glycolipids, glycoprotein and (capsular) polysaccharides. In Gram negative bacteria the lipopolysaccharide (LPS) represents the most important and the most abundant membrane/surface antigen. LPSs play a key role in the elicitation of innate immune response in all eukaryotes and is recognised as MAMP (Microbe Associated Molecular Pattern) by the eukaryotic immune system. LPS are amphiphilic essential outer membrane constituents of Gram negative bacteria, they comprise three chemically and genetically distinct regions: the endotoxic moiety termed Lipid A, the core region and the O-specific polysaccharide, which together form the so-called smooth(S)-form LPS; a rough(R)-form LPS (LOS) lacks, partially or totally, the O-specific polysaccharide. From a structural point of view, the O-specific polysaccharide, often referred to as the O-chain, is the predominant part of the LPS, usually it is a regular polysaccharide whose repeating unit is made up of a discrete number of residues, ranging from two to six.

In the present communication, it will be illustrated that the *Rhizobium radiobacter* strain expresses a polymer resulting to be a novel type of biopolymer in which the repeating unit is formed by a monosaccharide and an aminoacid derivative so that the whole molecule has alternating glycoside amide bonds.

Application of quantum chemical integrated multistep protocol in the stereochemical determination of natural products

A. Khalfaoui,^a M. G. Chini,^b M. Bouheroum,^a S. Belaabed,^a G. Lauro,^b S. Terracciano,^b M. C. Vaccaro,^b I. Bruno,^b S. Benayache,^b I. Mancini,^c G. Bifulco^b

^aDepartment of Chemistry, University Mentouri Constantine, Route Ain ElBey 25000, Constantine, Algeria.

^bDepartment of Pharmacy, University of Salerno, Via Giovanni Paolo II 132, Fisciano (SA) 84084, Italy.

^cDepartment of Physics, University of Trento, via Sommarive 14, I-38123 Povo- Trento, Italy.
mchini@unisa.it

The correct stereo-assignment of two metabolites as two atropisomeric forms (**1** (*M*, 10'*S*) and **2** (*P*, 10'*S*)) of the same glucopyranosylbianthrone (*Asphodelus tenuifolius*) was achieved applying a quantum chemical integrated multistep protocol (Fig. 1).¹ The correct assignment of the stereochemical pattern of **1** and **2** was resolved accounting two main issues, i.e., the atropisomerism around the biaryl axis and the configuration at C-10' as the unique point of difference between them.¹

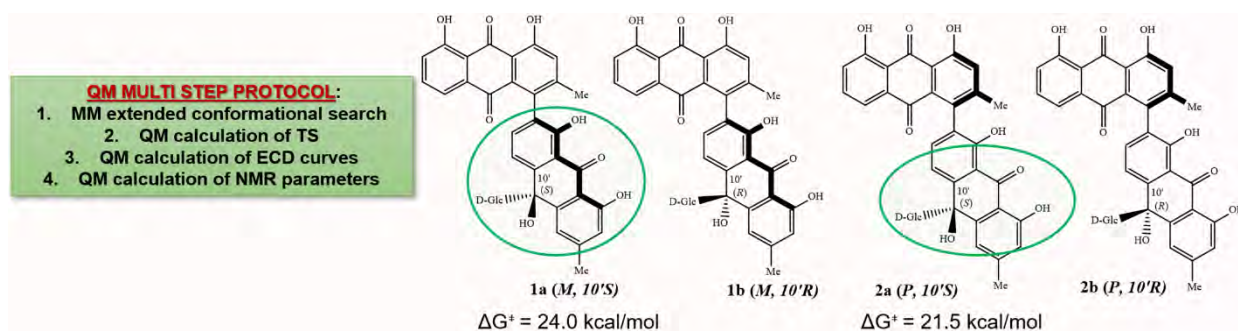


Figure 1: Schematic representation of the QM multistep protocol and molecular structures of the four possible diastereoisomers of **1** and **2** (**1a**, **1b**, **2a**, and **2b**).

With this aim, after defining the 2D structure of the two C-glucosidic metabolites and assuming the presence of a D-glucose, four different phases of the multistep protocol were applied, namely: 1) extended conformational search at empirical level; 2) computation of the rotational energy barrier related to the interconversion between the atropisomeric forms (*P* and *M*) for each possible isomer at C-10' (*R* and *S*) at DFT level, demonstrating their hindered interconversion; 3) computation and comparison of the experimental and calculated ECD curves of **1a**, **1b**, **2a**, **2b** suggesting that the Cotton effects are not influenced by the 3D arrangement at C-10'; 4) calculation and comparison between the experimental and calculated ¹³C NMR chemical shifts (DFT/NMR), singling out the better fit with the experimental data of **1a** and **2a**, and suggesting the (10'*S*) absolute configuration for both atropisomers. The results highlighted the elevated applicability and versatility of this integrated quantum chemical approach to a real case for resolving correct structure, stereochemistry and 3D arrangement of natural products (NP),² that represent a fundamental aspect for complete comprehension and rationalization of the molecular recognition events responsible for the biological activities of NPs.

References:

- [1] A. Khalfaoui, M. G. Chini, M. Bouheroum, S. Belaabed, G. Lauro, S. Terracciano, M. C. Vaccaro, I. Bruno, S. Benayache, I. Mancini, G. Bifulco, *J. Nat. Prod.* **2018**, 81, 1786-1794.
- [2] S. Di Micco, M. G. Chini, R. Riccio, G. Bifulco, *Eur. J. Org. Chem.* **2010**, 1411-1434.

Mn^{II}-complexation / Al¹⁸F-labeling of new AMP-based chelators for applications in Magnetic Resonance Imaging and Positron Emission Tomography

J. Martinelli,^a L. Russelli,^{a,b} C. D'Alessandria,^b L. Tei^a

^a Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale "Amedeo Avogadro", Viale T. Michel 11, 15121 – Alessandria, Italy

^b Nuclear Medicine Department, Klinikum Rechts der Isar, Technical University of Munich, Germany
jonathan.martinelli@uniupo.it

Magnetic resonance imaging (MRI) and positron emission tomography (PET) are non-invasive molecular imaging technologies constantly expanding, with a high demand for specific imaging probes. Contrast-enhanced MRI requires the use of suitable paramagnetic metals to increase the water-protons relaxation rate (R_1). Also, PET tracers based on $[Al^{18}F]^{2+}$ -complexes have been recently developed to label temperature-sensitive biomolecules. Thus, we designed pentadentate chelators based on the structure of aminomethylpiperidine (AMP) with acetic and/or hydroxybenzyl pendant arms, where the presence of the rigid piperidine cycle allowed to increase the metal complexes' stability.

Several AMP-based chelators were designed and synthesized: **2-, 3-, 4-AMPTA**; **2-, 3-, 4-AMPDA-HB**. All the ligands were characterized by HPLC-MS analysis and NMR spectroscopy. The relaxometric characterization of the Mn-complexes was performed by measuring the variation of R_1 as a function of pH, temperature and magnetic field strengths. The AlF-18 labeling reactions were performed at different pH values (4 and 5) and temperatures (rt, 37 and 80 °C); all the products were analyzed by radio-TLC and radio-HPLC and the stability of the tracers was investigated at 10-240 minutes *via* incubation in human serum, EDTA 5 mM, PBS and NaCl solutions. The MRI performance of the Mn-complexes is comparable to that of other mono-aquo Mn-based contrast agents. The Al¹⁸F radiolabeling efficiency at 37 °C was 60% for **2-AMPDA-HB** and 75% for **2-AMPTA**. High stability in human serum was measured for the ligand **2-AMPDA-HB** with a 90% of complexed Al¹⁸F, and 55% for **2-AMPTA** after 120 min. After 240 min in human serum the Al¹⁸F complexed by **2-AMPDA-HB** was 68%, and 33% for **2-AMPTA**.

In a preliminary screening of the reported chelators, promising results have been obtained in terms of radiolabeling efficiency at rt and 37 °C, and good stability in physiological conditions. The selection of the best chelator will lead to the synthesis of the bifunctional derivative followed by conjugation to temperature-sensitive biomolecules (e.g. Fab fragments and/or nanobodies), labeling and then *in vivo* applications.

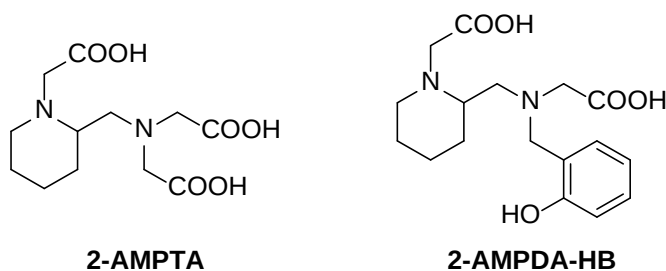


Figure 1: two of the ligands prepared and investigated to form MRI and PET contrast agents.

Ligand Based Identification of FABP4 Inhibitors:

Synthesis and Biological Screening

D. Gentile,^a G. Floresta,^a V. Patamia,^a A. Rescifina^a

^aDipartimento di Scienze del Farmaco, Università di Catania, Viale Andrea Doria 6, 95125 - Catania, Italy
davide.gentile@unict.it

Following on the recent publication of pharmacologically relevant effects, small molecule inhibitors of adipocyte fatty-acid binding protein 4 (FABP4) have attracted high interest.¹ FABP4 is mainly expressed in macrophages and adipose tissue, where it regulates fatty acid storage and lipolysis, being also an important mediator of inflammation. In this regard, FABP4 recently demonstrated an attractive molecular target for the treatment of type 2 diabetes, other metabolic diseases, and some cancers. In the past years, hundreds of effective FABP4 inhibitors have been synthesized. This communication describes our recent developments of a ligand-based (3D-QSAR model, Figure 1) approach for the identification of novel structures as FABP4 inhibitors. One hundred twenty of the already reported FABP4is were used to build the 3D-QSAR model. The development of the model has been undertaken with the use of Forge software using the PM3 optimized structure and the experimental IC₅₀ of each compound. The model was then employed to predict the activity of 3000 new isosteric derivatives of BMS309403.² The isosteric replacement was validated by the synthesis and the biological screening of three new compounds (AST_1–3).^{2,3} Their effective binding properties toward FABP4 were tested through a displacement assay and the three molecules results as FABP4 binders with an IC₅₀ between 3.70 and 5.79 μM.

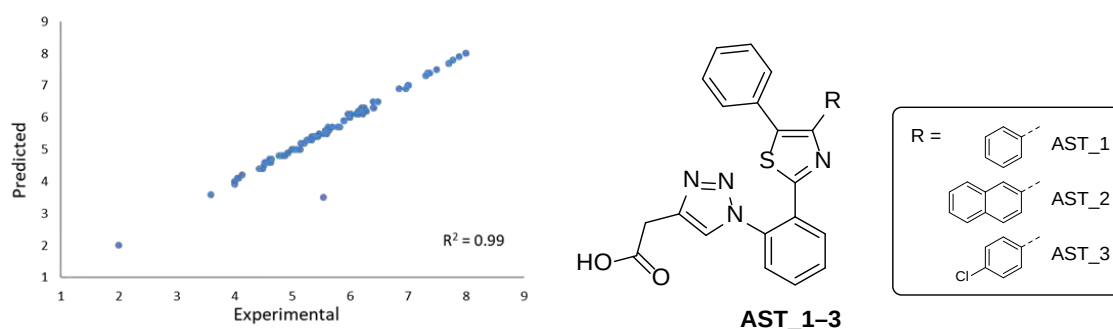


Figure 1: Left: 3D-QSAR model - Experimental vs. Predicted activity of the compounds in the training set. Right: Structures of AST_1–3.

References:

- [1] G. Floresta, V. Pistarà, E. Amata, M. Dichiarà, A. Marrazzo, O. Prezzavento, A. Rescifina, *Eur. J. Med. Chem.* **2017**, 138, 854-873.
- [2] G. Floresta, A. Cilibrizzi, V. Abbate, A. Spampinato, C. Zagni, A. Rescifina, *Bioorg. Chem.* **2019**, 84, 276-284.
- [3] G. Floresta, A. Cilibrizzi, V. Abbate, A. Spampinato, C. Zagni, A. Rescifina, *Data Brief.* **2019**, 22, 471-483.

Fungal phytotoxins with potential herbicidal activity for *Cenchrus ciliaris* biocontrol

M. Masi,^a F. Freda,^b A. Cimmino,^a M. Cristofaro,^{b,c} S. Meyer,^d A. Evidente^a

^a Dipartimento di Scienze Chimiche, Università di Napoli Federico II, Complesso Universitario Monte S. Angelo, Via Cintia 4, 80126 Napoli, Italy

^b BBICA onlus, Via A. Signorelli 105, 00123 Rome, Italy

^c ENEA C.R. Casaccia, SSPT-BIOAG-PROBIO, Via Anguillarese 301, 00123 Rome, Italy

^d U.S. Forest Service Rocky Mountain Research Station, Shrub Sciences Laboratory, 735 North 500 East, Provo, UT 84606, USA
marco.masi@unina.it

Cenchrus ciliaris, also known as buffelgrass or *Pennisetum ciliare*, is a plant native to the Old World which was intentionally introduced in many semi-arid regions of the world as a pasture grass. However, it has become highly invasive in western North America negatively affecting the native vegetation and altering the wildfire regime, especially in the Sonoran Desert of southern Arizona. Broad-spectrum herbicides have been extensively used to manage this weed with a negative environmental and ecological impact. Phytotoxins produced by weed pathogenic fungi might be an efficient alternative to these synthetic substances. Thus, some fungal pathogens, isolated from buffelgrass in North America, have been studied to evaluate their ability to produce phytotoxic metabolites that could be used to design natural and potential safe bioherbicides for *Cenchrus ciliaris* biocontrol. Fourteen secondary metabolites, belonging to different classes of natural compounds, have been isolated from *in vitro* cultures of *Cochliobolus australiensis* and *Pyricularia grisea*.¹⁻³ Some of these phytotoxins resulted to be new natural products and have been characterized by spectroscopic and chemical methods. Their relative and absolute configurations were also determined using a combination of spectroscopic, chiroptical and computational methods. When tested by leaf puncture assay on the host plant at different concentrations, radicinin and (10S, 11S)-*epi*-pyriculol (**1** and **2**, Fig. 1) proved to be the most promising compounds and their phytotoxic activity was also evaluated on non-host indigenous plants. Radicinin demonstrated high target-specific toxicity on buffelgrass, low toxicity to native plants, and no effects on zebrafish (*Brachydanio rerio*) embryos.⁴ This communication will give an overview on the work carried out and will illustrate the results obtained. The possibility to use radicinin for the development of a target-specific bioherbicide against buffelgrass will be also discussed.

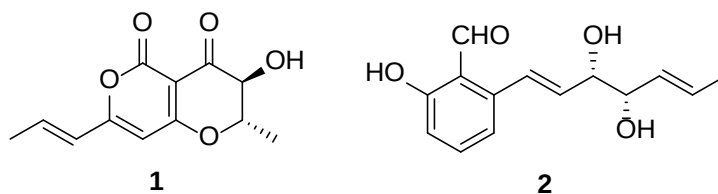


Figure 1: The structures of radicinin and (10S, 11S)-*epi*-pyriculol (**1** and **2**).

References:

- [1] M. Masi, S. Meyer, S. Clement, A. Cimmino, M. Cristofaro, A. Evidente, *J. Nat. Prod.* **2017**, *80*, 1241-1247.
- [2] M. Masi, S. Meyer, S. Clement, G. Pescitelli, A. Cimmino, M. Cristofaro, A. Evidente, *J. Nat. Prod.* **2017**, *80*, 2771-2777.
- [3] M. Masi, S. Meyer, M. Górecki, A. Mandoli, L. Di Bari, G. Pescitelli, A. Cimmino, M. Cristofaro, S. Clement, A. Evidente, *Chirality* **2017**, *29*, 726-736.
- [4] M. Masi, F. Freda, F. Sangermano, V. Calabrò, A. Cimmino, M. Cristofaro, S. Meyer, A. Evidente, *Molecules* **2019**, *24*, 1086.

Synthetic approaches to the development of new Antibody-Drug Conjugates charged with unconventional payloads

E. Petricci, F. Migliorini, F. Manetti, E. Cini, M. Taddei

Università degli Studi di Siena, Department of Biotechnology, Chemistry and Pharmacy, Via A. Moro, 2 - 53100 - Siena,

With more than 50 antibody–drug conjugates (ADCs) in clinical trials for cancer treatment, the ADC approach opens a new era of chemotherapy especially after Adcetris and Kadcyla approval for treatment of Hodgkin lymphoma and Her-2-positive metastatic breast cancer, respectively.¹ ADCs activity is strictly related to the chemical properties of both linker and payload, while the conjugation methodologies impact their homogeneity. Here we report our experience in the development of novel ADCs that can deliver to human tumors histone deacetylase (HDAC) inhibitors²⁻³ and other payloads (i.e. Smo inhibitors)⁴ with low cytotoxicity. Different payloads were prepared using both cleavable and non-cleavable linkers and conjugated to Cetuximab and Trastuzumab resulting in ADCs exhibiting unmodified ability to recognize EGFR and efficient internalization into tumor cells.²⁻³ Animal models of human solid tumors showed high anti-tumor efficacy of the conjugates without the toxicity of traditional ADCs charged with highly potent cytotoxic drugs. These new bioconjugates proved to be suitable for targeted epigenetic modulation possibly extending the ADC strategy to therapeutic applications beyond cancer.

References:

- [1] R. V. Chiari, *ACS Med. Chem. Lett.* **2016**, 7, 974-976.
- [2] E. Cini, V. Faltoni, E. Petricci, M. Taddei, L. Salvini, G. Giannini, L. Vesci, F. M. Milazzo, A. M. Anastasi, G. Battistuzzi and R. De Santis, *Chem. Sci.*, **2018**, 9, 6490-6496.
- [3] L. Vesci, R. De Santis, F. M. Milazzo, G. Giannini, M. Taddei, V. Faltoni, E. Petricci, Histone Deacetylase Inhibitors-based antibody drug conjugates (ADCs) and use in therapy. 27/03/2018 (EP 17163065.0)
- [4] S. Pietrobono, R. Santini, S. Gagliardi, F. Dapporto, D. Colecchia, M. Chiariello, C. Leone, M. Valoti, F. Manetti, E. Petricci, M. Taddei, B. Stecca, *Cell Death. Dis.* **2018**, 9, 142.

Technology-driven catalysis: (SLA) 3D-printed devices for organic synthesis

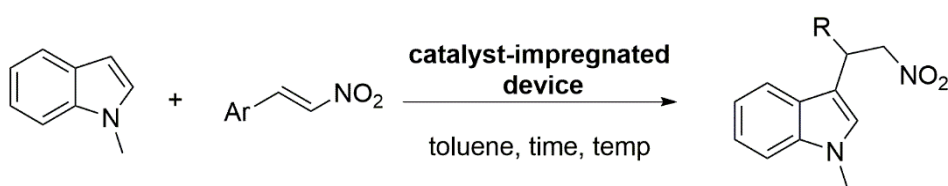
S. Rossi,^a M. Benaglia,^a

^aDipartimento di Chimica, Università degli Studi di Milano, Via Golgi 19, 20133, Milano
sergio.rossi@unimi.it

Three-dimensional (3D) printing has the capability to transform scientific ideas in bespoke and low cost devices that previously required expensive and dedicate facilities to make. By a simple additive manufacturing process, these appliances could be realized on a layer-by-layer basis through a series of cross-sectional slices.¹ Among all 3D Printing technologies developed to realize objects, FFF and SLA approaches are the most developed. Stereolithography (SLA) 3D printing technology involves the use of an ultraviolet laser that is focused onto a vat containing a photopolymer resin.

The manufacturing of a three-dimensional product from a computer-driven digital model (3D printing) has found extensive applications in several fields. In chemical sciences (FFF) 3D-printers were used to build research equipment, but had also a significantly impact in the field of fluidics devices for the realization of mesoreactors.² Despite all these developments, no examples of chemical-impregnated 3D printed devices realized with stereolithography technology are known. In this context, we focused our attention in the preparation of (SLA) 3D-printed catalyst-impregnated devices and their evaluation for batch and flow reactions in organic synthesis.

Using a low-cost SLA 3D printer and freeware design software, different devices were designed and printed using a photopolymerizable resin containing different organocatalysts. These devices were used to investigate different organic transformations such as the Friedel-Crafts alkylation of aromatic and heteroaromatic systems with nitroolefins leading to the formation of desired products with good results (Scheme 1).³ Furthermore, some 3D-printed mesoreactors have been employed in preliminary investigations of visible-light promoted reactions.



Scheme 1: Friedel-Crafts alkylation of aromatic systems with nitroolefins

References:

- [1] S. Rossi, A. Puglisi, M. Benaglia, *ChemCatChem* **2018**, 10, 1512-1525.
- [2] S. Rossi, R. Porta, D. Brenna, A. Puglisi, M. Benaglia, *Angew. Chem. Int. Ed.* **2017**, 56, 4290-4294.
- [3] S. Rossi, A. Puglisi, M. Benaglia, *unpublished results*.

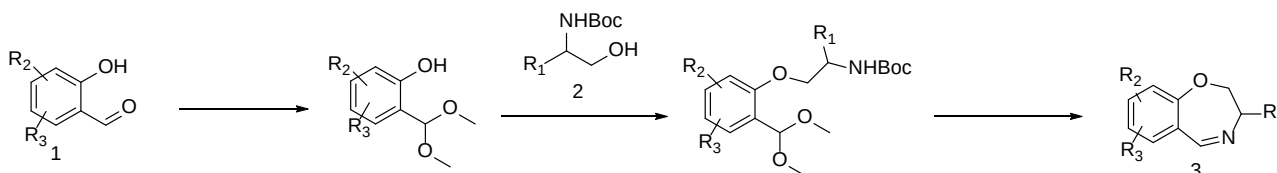
Synthesis of new chiral catalysts through multicomponent processes

A. Pinna, L. Banfi, C. Lambruschini

University of Study of Genoa, Department of Chemistry and Industrial Chemistry, via Dodecaneso 31, Genoa
e-mail: alessandro92.pinna@gmail.com

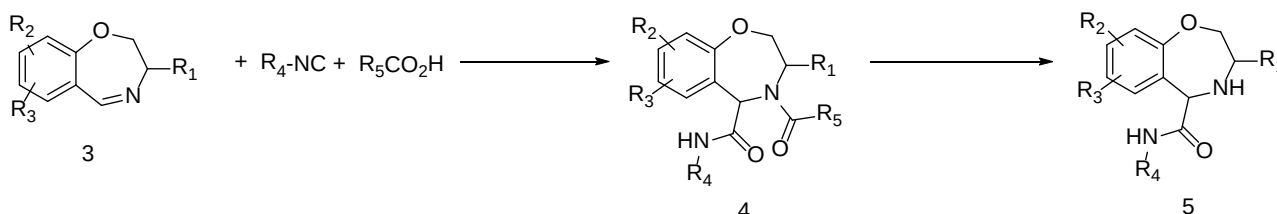
The examples of processes that are catalysed by secondary amines are many in the literature. They are involved in catalysis via enamine or iminium ion. The most famous and applied catalysts are proline derivatives, so finding an efficient method to synthesize new kind of catalysts would be desirable. The multicomponent reactions are ideal to get this goal in a combinatorial way, because they allow us to get a product in a single step, introducing various diversity inputs.¹

Recently a new methodology for the synthesis of chiral cyclic imines starting from salicylaldehydes **1** and Boc-amino-alcohols **2** has been developed (Scheme 1).²



Scheme 1: Synthesis of chiral cyclic imines

Involving these imines in a Ugi-Joullié reaction³ allows us to get easily the product with high diastereoselectivity. Although the product **4** has an amidic group in its structure, a method to get the free amino group can be found (Scheme 2).



Scheme 2: Synthesis of new potential organo-catalyst

References:

- [1] L. Banfi, R. Riva, A. Basso, *Synlett* **2010**, 23-41.
- [2] L. Banfi, A. Bagno, A. Basso, C. De Santis, R. Riva, F. Rastrelli, F. *European J. Org. Chem.* **2013**, 78, 5064-5075.
- [3] R. F. Nutt, M. M. Joullie, *J. Am. Chem. Soc.* **1982**, 104, 5852-5853.

Chemo-Enzymatic Cascades for the Synthesis of Heteroaromatic and Sulphur Containing Pharmaceutical Ingredients

D. Castagnolo

^aKing's College London, School of Cancer and Pharmaceutical Sciences,
150 Stamford Street, SE1 9NH, London, UK.
daniele.castagnolo@kcl.ac.uk

The use of biocatalysis in synthetic chemistry has grown exponentially in the last decade due to the tremendous progresses made in the field of gene cloning, DNA sequencing and protein expression. Biocatalysis represents nowadays a robust and sustainable method for the synthesis of many chemical tools and pharmaceutical ingredients under mild and more sustainable reaction conditions. However, one of the most intriguing challenges for chemists and biologists is still represented by the possibility to combine chemo- and biocatalysis in a concurrent fashion to outperform sequential transformations with a high degree of selectivity. Chemo-enzymatic cascade reactions are highly appealing for industrial processes as they can offer multiple benefits such as the immediate succession of individual transformations and the in-situ consumption of toxic or unstable intermediates without the requirement of intermediate isolation or functional group protection strategies, thus leading to safer processes and to the reduction of undesired side products. Our research group is interested in the development of novel chemo-enzymatic methods for the synthesis of drug-like compounds. Since most drugs contain a heteroaromatic ring, we developed a chemoenzymatic approach to access heterocycles such as pyrroles, pyridines and furans from appropriate aliphatic precursors through a ring-closing metathesis/enzymatic aromatization cascade. In parallel, we developed a photo-biocatalytic method for the synthesis of 1,3-mercaptoalkanols, a class of volatile flavouring compounds used as excipients in pharmaceutical preparations. The 1,3-mercaptoalkanols were synthesised from ketone precursors using KRED enzymes. Two different KRED biocatalysts with opposite enantioselectivity were identified in this study.

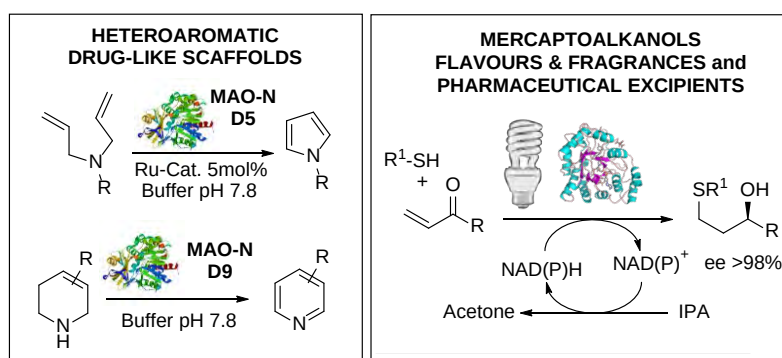


Figure 1. Chemoenzymatic approaches for the synthesis of aromatic heterocycles and mercaptoalkanols

References:

- [1] N. Scalacci, G. W. Black, G. Mattedi, N. L. Brown, N. J. Turner, D. Castagnolo, *ACS Catal.* **2017**, 7, 1295-1300.
- [2] A. Toscani, C. Risi, G. W. Black, N. L. Brown, A. Shaaban, N. J. Turner, D. Castagnolo, *ACS Catal.* **2018**, 8, 8781-8787.
- [3] K. Lauder, A. Toscani, Y. Qi, J. Lim, S. J. Charnock, K. Korah, D. Castagnolo, *Angew. Chem., Int. Ed.* **2018**, 57, 5803-5807.

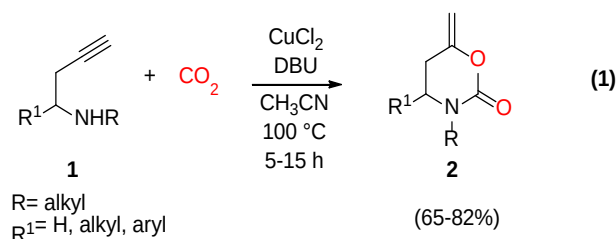
Synthesis of 1,3-oxazinan-2-ones
by catalytic incorporation of carbon dioxide into N-alkyl-3-yn-1-amines

I. Ziccarelli, R. Mancuso, B. Gabriele

*Laboratory of Industrial and Synthetic Organic Chemistry (LISOC)
Department of Chemistry and Chemical Technology, University of Calabria
Via Pietro Bucci, 12/C, 87036 Arcavacata di Rende (CS), Italy
idaziccarelli@gmail.com*

Carbon dioxide, continuously emitted in the atmosphere from the combustion of fossil fuels, is considered to be one of the major greenhouse gases responsible for increasing global temperature. For this reason, the efficient conversion of CO₂ into high value-added products currently represents one of the most innovative strategies for the valorization of this important waste.¹

In this contribution, we report a new synthetic process to obtain 1,3-oxazinan-2-ones, which are heterocycles of pharmaceutical interest,² using CO₂ as a key building block. In particular, starting from the results in the field of CO₂ fixation recently achieved in our research group,³ we have investigated the reactivity of N-alkyl-3-yn-1-amines **1** under carboxylation conditions for the synthesis of cyclic carbamates **2**, using CuCl₂ as simple and inexpensive catalyst (*Eq. 1*)



In the presence of 2 mol % of CuCl₂ and DBU (40 mol%), under relatively mild reaction conditions (100°C under 40 atm of CO₂), different N-alkyl-3-yn-1-amines **1** were converted into the corresponding 1,3-oxazinan-2-one **2**. Formation of **2** can be interpreted as occurring through an ordered sequence of steps, involving the initial DBU-promoted formation of a carbamate, followed by 6-*exo-dig* intramolecular nucleophilic attack of the carbamate oxygen on the triple bond coordinated to CuCl₂ and protonolysis.

The reaction is regioselective and leads to the oxazinan-2-one derivatives in good to high yields (65-82%)

References:

- [1] Q. Liu, L. Wu, R. Jackstell, M. Beller, *Nat. Commun.* **2015**, 6, Article number: 5933.
- [2] F. Aricò, S. Bravo, M. Crisma, P. Tundo, *Pure Appl. Chem.* **2016**, 88(3), 227-237.
- [3] M. Marchegiani, M. Nodari, F. Tansini, C. Massera, R. Mancuso, B. Gabriele, M. Costa, N. Della Ca', *J. CO₂ Util.* **2017**, 21, 553-561.

Highly Performing Iodoperfluoroalkylation of Alkenes Triggered by the Photochemical Activity of Perylene Diimides

C. Rosso,^a G. Filippini,^a P.G. Cozzi,^b A. Gualandi,^b M. Prato^{a,c,d}

^a University of Trieste, Via Licio Giorgieri 1, Trieste (Italy)

^b University of Bologna, Via Selmi 2, Bologna (Italy)

^c CIC BiomaGUNE, Paseo de Miramón 182, Donostia-San Sebastian (Spain)

^d Basque Fdn Sci, Ikerbasque, Bilbao (Spain)

gfilippini@units.it

Visible light photocatalysis has recently emerged as a powerful strategy for the implementation of radical chemical transformations.^[1] This approach relies on the ability of light-absorbing metal complexes and organic dyes (photocatalysts) to generate, upon direct visible-light excitation, reactive radicals from suitable precursors at ambient temperature. In 2014, the König group exploited the ability of perylene diimides (PDIs) to function as visible light photocatalysts for the reductive dehalogenation of aryl halides.^[2] Despite the excellent optical and redox properties of PDIs, their application in organic photochemistry remains rare.

Within this research field, we envisaged the use of PDIs as effective photocatalysts for atom-transfer radical addition (ATRA) reactions. Specifically, we describe a novel efficient photochemical procedure for the direct iodoperfluoroalkylation of terminal olefins (**1**, Figure 1).^[3] The process uses a simple and inexpensive perylenediimide (PDI) in an extremely low catalytic loading (0.05 mol%, corresponding to 500 parts per million) and occurs with visible light irradiation. The reported methodology is highly viable from a synthetic point of view, since it proceeds under mild reaction conditions with a significant rate of production. In addition, products (**3**) can be used as suitable building blocks to prepare new relevant chemical species by employing common organic synthetic methodologies.

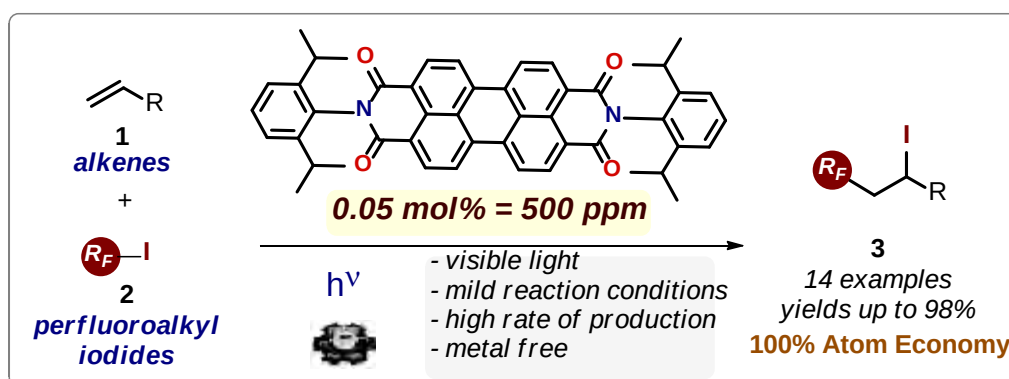


Figure 1: PDI initiated Atom Transfer Radical Addition (ATRA)

References:

- [1] N. A. Romero, D. A. Nicewicz D. A. *Chem. Rev.* **2016**, 116, 10075-10166.
- [2] T. Ghosh, J. Ghosh, I. Bardagi, B. König *Science* **2014**, 346, 725-728.
- [3] C. Rosso, G. Filippini, P. G. Cozzi, A. Gualandi, M. Prato, *ChemPhotoChem* **2019**, 3, doi: <https://doi.org/10.1002/cptc.201900018>

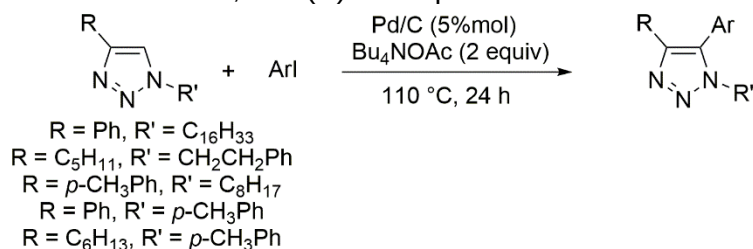
C–H Bond arylations of 1,2,3-triazoles by reusable Pd/C catalyst in solvent-free conditions

N. Zappimbulso,^a A. Punzi,^a G. M. Farinola^a

^aDepartment of Chemistry, University of Bari, Via Orabona 4, 70010 Bari, Italy
e-mail: nicola.zappimbulso@uniba.it

The 1,2,3-triazole ring represents a key structural motif in various applied areas, such as drug discovery,¹ bioconjugation,² and materials science.³ Among the known methods for the regioselective synthesis of fully substituted 1,2,3-triazoles, the Pd-catalyzed direct arylation of the easily available 1,4-disubstituted 1,2,3-triazoles turns out to be the most general approach.⁴ The major drawback of this synthetic methodology is still represented by the use of toxic solvents. Only few examples of direct arylation protocols of 1,4-disubstituted 1,2,3-triazoles based on the use of more sustainable conditions have been reported in the literature. For example, protocols for Pd-catalyzed direct arylations in environmentally-benign reaction media, such as polyethylene glycol (PEG)⁵ or biomass-derived γ -valerolactone, in the presence of reusable palladium catalysts, were developed by Ackermann and coworkers.

In the frame of our studies on triazole-based materials⁶ as well as on Pd-catalyzed reactions for the synthesis of heteroaromatic compounds,⁷ we report here in the first Pd-catalyzed direct arylation protocol of 1,4-disubstituted 1,2,3-triazoles that is performed in (i) solvent-free, (ii) non-anhydrous conditions, (iii) without exclusion of air, and (iv) in the presence of a reusable catalyst.



Then, with the aim of making the reaction conditions more sustainable, we evaluated the possibility of using only tetra-*n*-butylammonium acetate (Bu₄NOAc) as the base and the reaction medium, in the absence any other additive. Using Pd/C (5 mol %) as the catalyst, we examined the role of the halogen, reaction temperature and catalyst loading. To probe catalyst reusability, we recovered the Pd/C by a modified literature protocol and evaluated the catalytic activity of the recycled material in the subsequent run. We observed an unchanged catalytic activity of the recycled Pd/C until the third run, while a halving of its activity is detected at the fourth run. Having selected Pd/C (5 mol %) in the presence of neat Bu₄NOAc as the best reaction system, we investigate the substrate versatility reacting the 1,2,3-triazoles, having a different ring substitution pattern, with various aryl iodides.

References:

- [1] a) E. Bonandi, M. S. Christodoulou, G. Fumagalli, D. Perdicchia, G. Rastelli, D. Passarella, *Drug Discov. Today*, **2017**, 22, 1572-1581; b) D. Dheer, V. Singh, R. Shankar, *Bioorg. Chem.* **2017**, 71, 30-54.
- [2] C. J. Pickens, M. M. Pressnall, C. J. Berkland, J. Cory, *Bioconjugate Chem.* **2018**, 29, 686-701.
- [3] a) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, 36, 1249-1262; b) J.-F. Lutz, *Angew. Chem. Int. Ed.* **2007**, 46, 1018-1025.
- [4] C. Zhang, L. You, C. Chen *Molecules* **2016**, 21, 1268.
- [5] X. Tian, F. Yang, S. Warratz, L. Vaccaro, L. Ackermann, *Chem. Commun.*, **2016**, 52, 9777-9780.
- [6] A. Punzi, A. Ardizzone, I. Ratera, J. Veciana, G. M. Farinola, *Eur. J. Org. Chem.* **2016**, 15, 2617-2627.
- [7] a) A. Punzi, N. Zappimbulso, G. M. Farinola, *Monatshefte für Chemie-Chemical Monthly*, **2019**, 150, 59-66; b) A. Punzi, S. Di Noja, R. Ragni, N. Zappimbulso, G. M. Farinola, *J. Org. Chem.* **2018**, 83, 9312-9321.

Memory of Chirality Approach to the Synthesis of α -Quaternary Amino Acid Derivatives

F. Foschi,^a M. Penso^b

^a Università degli Studi dell'Insubria, Via Valleggio 9, Como

^b ISTM-CNR, Via Golgi 19, Milan
francesca.foschi@uninsubria.it

Quaternary amino acids have an essential role to play in the design of peptidase-resistant antibiotics and in the control of secondary structure in designed peptidomimetics.¹ In this communication we report the stereoselective conversion of a series of *N*-alkyl, *N*-aryl-sulphonyl- α -amino acid derivatives into the corresponding *N*-alkyl- α -aryl- α -amino esters (ee up to 98%). This methodology has been applied to the rearrangement of sulphonamides bearing different electron withdrawing functional groups *via* a 'memory of chirality' approach. The high enantioselectivities obtained indicate that the stereochemical information is transferred from the *N*-alkylated sulphonamide **1** to the final rearranged product **2** via a chiral nonracemic enolate **A**. This latter, evolves through a *Re*-face attack into a chiral spiro-Meisenheimer intermediate **B** that, in turn, undergoes the stereoselective *Ns*→*C α* migration of the aryl group and loss of sulphur dioxide (Figure 1).²

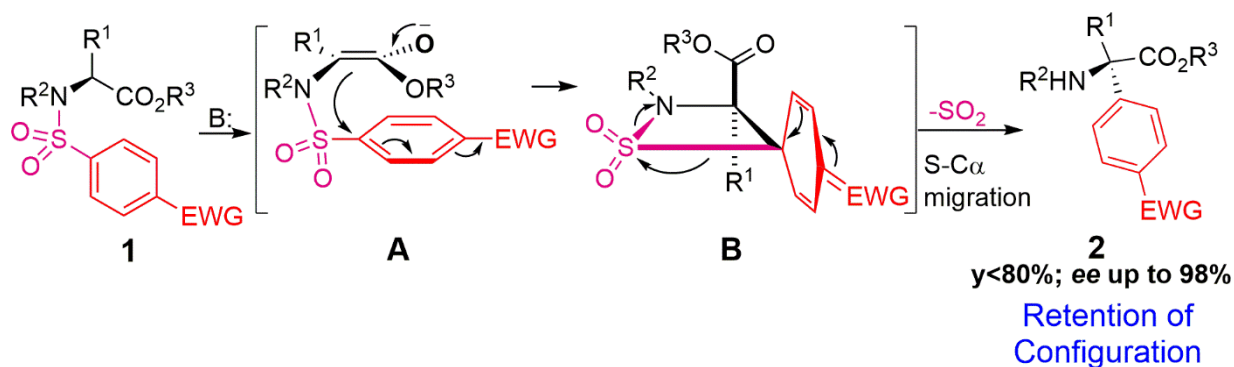


Figure 1

Interestingly, the pentafluoro sulphonamido derivatives do not promote the aryl migration reaction, but the ring closure, forming the correspondent sultam in high yield and enantiomeric excess.³

References:

- [1] C. Cativiela, M. D. Díaz-de-Villegas, *Tetrahedron: Asymm.* **2009**, *18*, 569-623.
- [2] a) V. Lupi, M.; Penso, F.; Foschi, F.; Gassa, V. Mihali, A.; Tagliabue, *Chem. Commun.* **2009**, 5012-5014;
b) F. Foschi, D. Landini, V. Lupi, V. Mihali, M. Penso, T. Pilati, A. Tagliabue, *Chem. Eur. J.*, **2010**, *16*, 10667-10670.
- [3] F Foschi, A. Tagliabue, V. Mihali, T. Pilati, I. Pecnikaj, M. Penso, *Org. Lett.* **2013**, *15*, 3686-3689.

Tetrachlorosilane mediated direct amidation method

E. Massolo,^a M. Benaglia^a

^aUniversità degli Studi di Milano, Via Golgi 19, Milano
elisabetta.massolo@unimi.it

The developments of general methods for sustainable direct amide formation is still one of the Key Green Chemistry Research Areas.¹ Several highly effective methods have already been reported, but they often suffer from drawbacks, including the need for harsh conditions, the involvement of expensive and/or toxic reagents and the formation of by-products that impede easy purifications.

Considering the relevance of the topic, our group developed a direct amidation method based on the use of tetrachlorosilane (SiCl₄)² as a mediator. Other silicon-based species have already been employed to promote the amide bond formation, but the most of them rely on organosilicon compounds,² intrinsically less effective in terms of atom economy.³ Tetrachlorosilane appears rather convenient, being cheap and readily available and implying the formation of inorganic by-products that are easily removed from the reaction crude during the work-up phase.

Conditions optimization allowed good yields for a wide substrate scope, including both aromatic and aliphatic amines; the desired amides were obtained clean upon aqueous work-up. An in-flow version of the method can also be implemented, leading to advantages from a productivity standpoint.

Control experiments have been carried out to gain an insight into the reaction mechanism.

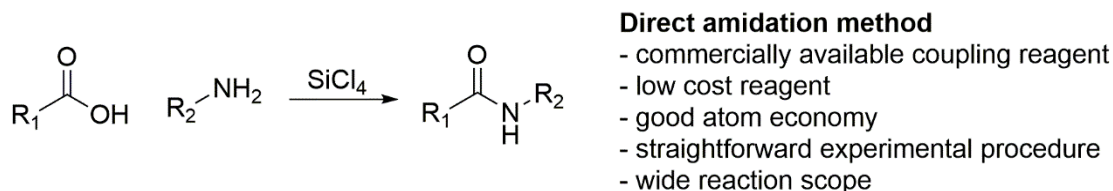


Figure 1: General reaction scheme for the developed amidation method

References:

- [1] M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Stevenh, F. J. Weiberth, *Green Chem.* **2018**, *20*, 5082-5103.
- [2] T. H. Chan, L. T. L. Wong, *J. Org. Chem.* **1969**, *34*, 2766-2767.
- [3] S. J. Aspin, S. Taillemaud, P. Cyr, A. B. Charette, *Angew. Chem. Int. Ed.* **2016**, *55*, 13833-13837.
- [4] D. C. Braddock, P. D. Lickiss, B. C. Rowley, D. Pugh, T. Purnomo, G. Santhakumar, S. J. Fussell, *Org. Lett.* **2018**, *20*, 950-953.

Straightforward Tactics and Enabling Technologies as useful tools for Fluoroalkylations

M. Colella^a, A. Tota^a, L. Degennaro^a, Y. Takahashi^b, A. Nagaki^b and R. Luisi^a

^aDepartment of Pharmacy – Drug Sciences, University of Bari “A. Moro” Via E. Orabona 4, 70125 – Italy
FLAME-Lab –Flow Chemistry and Microreactor Technology Laboratory;

^bDepartment of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Nishikyo-ku, Kyoto 615-8510, Japan
e-mail: marco.colella@uniba.it

Organofluorine compounds are interesting molecules with broad applications in medicinal chemistry, material chemistry and agrochemistry.^{1,2} The development of new synthetic strategies to access new molecules with fluorinated moieties still remains a challenge for organic chemists and a “hot topic” in modern synthesis. The importance of organofluorine chemistry is showcased by the presence of fluorine in nearly 20% of all pharmaceuticals and 35% of agrochemicals on the market.³ It is therefore noteworthy to develop effective synthetic strategies, either for the incorporation of fluorine atoms into organic scaffolds or for the preparation of fluorinated building blocks. In this communication, we report our contribute in the development of strategies for direct fluoroalkylation.⁴ The potential of flow microreactor technology in fluoroalkylation chemistry will be also reported.⁶

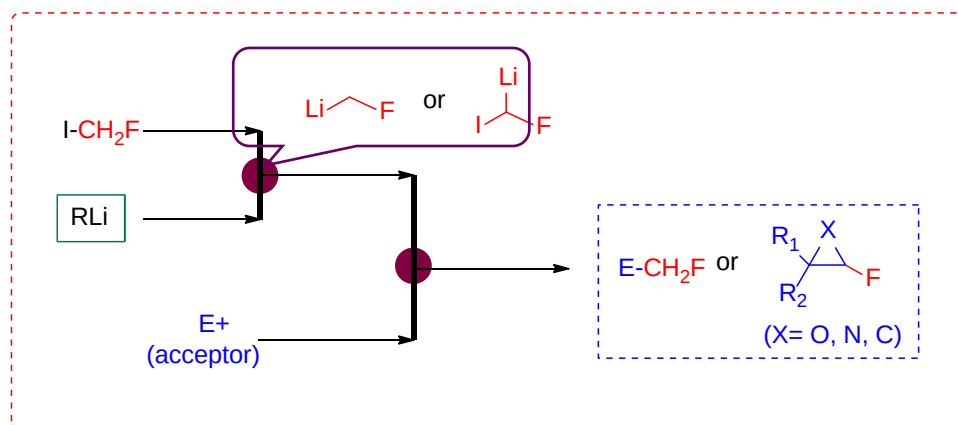


Figure 1: Flow Microreactor Technology as useful tool for Fluoroalkylations.

References:

- [1] J. M. Brown, V. Gouverneur, *Angew. Chem. Int. Ed.*, **2009**, *48*, 8610-8614.
- [2] T. Furuya, A. S. Kamlet, T. Ritter, *Nature*, **2011**, *473*, 470-477.
- [3] J. Wang, M. Sanchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.*, **2013**, *114*, 2432-2506.
- [4] G. Parisi, M. Colella, S. Monticelli, G. Romanazzi, W. Holzer, T. Langer, L. Degennaro, V. Pace, R. Luisi, *J. Am. Chem. Soc.*, **2017**, *139* (39), 13648-13651.
- [5] S. Monticelli, M. Colella, V. Pillari, A. Tota, T. Langer, W. Holzer, L. Degennaro, R. Luisi and V. Pace, *Org. Lett.* **2019**, *21*, 584-588.
- [6] L. Degennaro, F. Fanelli, A. Giovine, R. Luisi, *Adv. Synth. Catal.*, **2015**, *357* (1), 21-27.

Diversity-Oriented Synthesis and chemoinformatic analysis of sp^3 -rich molecular scaffolds using imine-based multicomponent reactions

E. Lenci, R. Innocenti, L. Baldini, G. Menchi, A. Trabocchi

Dipartimento di Chimica "Ugo Schiff", Università degli Studi di Firenze,
Via della Lastruccia 13, 50019, Sesto Fiorentino (FI), Italia
andrea.trabocchi@unifi.it

Modern chemical biology requires efficient synthetic processes to produce high-quality small-molecule collections as probes to investigate biological pathways. In this view, Diversity-Oriented Synthesis¹ (DOS) allows to explore the chemical space by generating structurally complex small molecule libraries, and multicomponent reactions (MCRs) represent a great tool to efficiently give a polyfunctional product for subsequent pairing reactions. In particular, imine-based MCRs, involving imines as a substrate or an intermediate, have gained considerable attention in recent years, due to substrate-dependent reactivity of imines, and commercial availability of several hundred amines and aldehydes to access a large number of imines.

Our contribution in this field involves the development of amino-acid derived molecular scaffolds, and to increase the complexity and the sp^3 character of the synthesized heterocyclic scaffolds, we recently applied the Petasis² and the copper-catalyzed A3 and KA2 reactions as imine-based MCRs to build novel structurally complex molecules. Chemoinformatic analysis demonstrated such MCRs being instrumental to access new areas of the chemical space, and to achieve molecular scaffolds possessing high F_{sp^3} ratio and three-dimensional complexity.

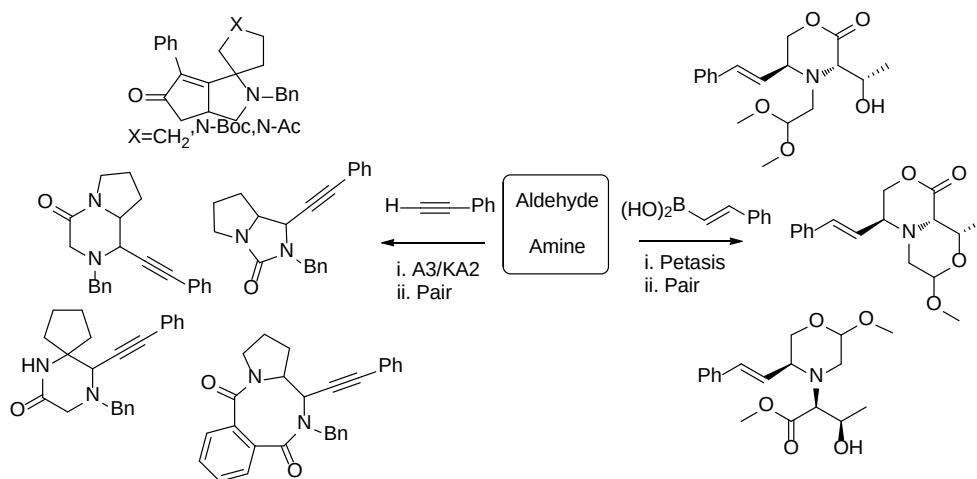


Figure 1: Petasis and A3/KA2 imine-based MCR reactions as coupling steps in couple-pair approaches.

References

- [1] a) S. L. Schreiber, *Science* **2000**, 287, 1964-1969; b) "Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology", A. Trabocchi, Ed.; Wiley and Sons, **2013**.
- [2] E. Lenci, A. Rossi, G. Menchi, A. Trabocchi, *Org. Biomol. Chem.* **2017**, 13, 9710-9717.

A new symmetric G-rich Oligonucleotides incorporating a 3'-3' inversion of polarity site as an interesting model for ligand binding studies.

M. Marzano,^{*a} N. Borbone,^a P. Dardano,^c A.P. Falanga,^a I. Rea,^c S. D'Errico,^a M. Terracciano,^c L. De Stefano,^c G. Piccialli,^a and G. Oliviero^b.

^aDepartment of Pharmacy, University of Naples Federico II, via D. Montesano 49, 80131 Naples, Italy.

^bDepartment of Molecular Medicine and Medicine Biotechnologies, University of Naples Federico II, via S. Pansini 5, 80131 Naples, Italy.

^cInstitute for Microelectronics and Microsystems, Consiglio Nazionale delle Ricerche, via P. Castellino 11, 80131 Naples, Italy.

maria.marzano@unina.it

G-quadruplexes are secondary structures of DNA, which are formed by guanine-rich oligonucleotides (GRO) annealed in the presence of monovalent cations such as Na^+ and K^+ . The basic unit of a G-quadruplex is the G-quartet or G-tetrad, which is composed of a planar arrangement of four guanine bases stabilized by eight Hoogsteen hydrogen bonds. GRO and G-quadruplex structures have attracted the attention of researchers in medicinal chemistry and more recently in supramolecular chemistry and nanotechnology. In recent years, G-quadruplexes have also been used to build supramolecular structures by exploiting the multimerization between several G-quadruplex units [1]. In accordance with the topological arrangement, in a previous work we have studied the ability of the 5'-CGGT-3'-3'-GGC-5' (Figure 1) to form long G-wires [2]. In this context, we have synthesized a new GRO incorporating the 3'-3' inversion of polarity site and have studied the interaction of this type of longer stacked G-wires assembly.

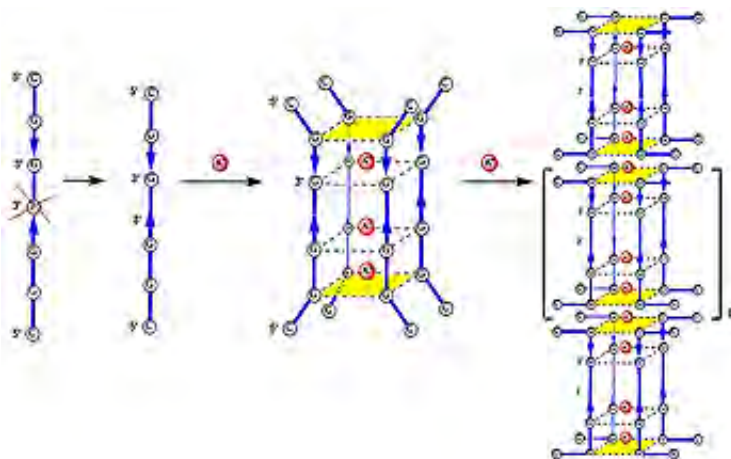


Figure 1. Formation of the G-quadruplex building block Q_1 and its multimerization into Q_n G-wire polymers.

References:

- [1] A. B. Kotlyar, N. Borovok, T. Molotsky, H. Cohen, E. Shapir, D. Porath, *Adv. Mater.* **2005**, *17*, 1901.
- [2] G. Oliviero, S. D'Errico, B. Pinto, F. Nici, P. Dardano, I. Rea, L. De Stefano, L. Mayol, G. Piccialli, N. Borbone, *Chemistry Open* **2017**, *6*, 599-605.

Synthesis and characterization of a PNA probe targeting the Bcl-2 gene promoter: a promising tool in anticancer treatment

A. P. Falanga,^a S. D'Errico,^b M. Marzano,^b G. Piccialli,^b N. Borbone,^b G. Oliviero^a

^aDepartment of Molecular Medicine and Medical Biotechnologies, University of Naples Federico II, Via Sergio Pansini 5, 80131 Naples, Italy

^bDepartment of Pharmacy, University of Naples Federico II, Via Domenico Montesano 49, 80131 Naples, Italy
andrea.patrizia.falanga@unina.it

Among several anti-gene strategies, the use of DNA analogues such as Peptide Nucleic Acids (PNA) represents a promising approach for the modulation of gene transcription. PNAs are mimics of DNA in which the sugar-phosphate backbone is replaced by the N-(2-aminoethyl)glycine moiety. The absence of charges on the PNA backbone allows the formation of PNA/DNA complexes provided with a higher stability than that of the corresponding natural DNA/DNA counterparts¹. We have recently demonstrated that the PNA complementary to the 7-mer longest loop of the G-quadruplex formed by the 23-mer bcl2midG4 sequence, located 52–30 bp upstream of the P1 promoter of Bcl-2 gene, is able to selectively bind the loop of the structure. The results have shown the ability of the PNA-coated OAd5 oncolytic vectors to load and transfect their PNA cargo with a high efficiency and also the synergistic cytotoxic effect against human A549 and MDA-MB-436 cancer cell lines². We have also demonstrated that the synthesized PNA does not interact with the corresponding duplex. With the aim of improving the target specificity we have investigated whether the length of the chosen PNA sequence could affect the type of interaction with the complementary DNA sequence. We extended the length of the pyrimidine-rich PNA from seven to ten bases complementary to the N_{10–19} tract of the bcl2midG4 sequence target. Additionally, we synthesized the 10-mer PNA-FITC labelled analogue. PAGE, CD and CD melting experiments were performed to investigate the interaction of the PNA and its analogue with the DNA target, in both quadruplex and duplex complexes. Moreover, molecular dynamics simulations were used to investigate the stability and the structural features of the target heterotriplexes. The drugability of the new PNAs was attested by fluorescence microscopy which showed that the FITC-labelled PNA specifically enters the cell nuclei, with no significant fraction being co-localized in the mitochondria or endoplasmic reticulum organelles. Finally, preliminary cytotoxicity assays confirmed the biological activity of the new anti Bcl-2 PNA. Overall, the studies here reported extend our knowledge about the structural properties of DNA₂-PNA heterotriplexes and provide the basis for the development of new PNA-based anticancer agents for the treatment of human cancers expressing high levels of the Bcl-2 protein.

References:

- [1] M. C. De Koning, G. A. Van Der Marel, M. Overhand, *Curr. Opin. Chem. Biol.* **2003**, 7, 734-740.
- [2] A. P. Falanga, V. Cerullo, M. Marzano, S. Feola, G. Oliviero, G. Piccialli, N. Borbone, *Bioconj. Chem.* **2019**, DOI 10.1021/acs.bioconjchem.8b00674.

Combined effect of amide protons and second sphere water molecules on the relaxivity of Gd(III)-DO3A-hydroxypropionamide complexes

L. Leone,^a M. Botta,^a Z. Baranyai,^b L. Tei^a

^aDipartimento di Scienze ed Innovazione Tecnologica, Università degli Studi del Piemonte Orientale "Amedeo Avogadro", Viale Teresa Michel 11, 15121 Alessandria, Italy

^bCentro Ricerche Bracco, Bracco Imaging SpA, SS14 Km 163.5, 34149, Basovizza (Trieste), Italy.
loredana.leone@uniupo.it

Gd(III) complexes with polyaminopolycarboxylic ligands are commonly used as MRI contrast agents (CAs) in the medical diagnosis. In particular, Gd(HP-DO3A) (ProHance®, **Figure 1**), one of the clinically approved MRI CAs, contains two sources of protons for transferring the paramagnetism of the Gd(III) ion to the bulk water, namely the coordinated water molecules and the proton on the coordinated hydroxyl group.¹ The objective of this study was the synthesis of different HPDO3A-like ligands, in which the methyl group in the ordinary arm of HP-DO3A was functionalized with electron-withdrawing amide groups. In particular, we have synthesized (**Figure 1**) HPA-DO3A ligands bearing, a primary, a secondary and a tertiary amide (**1-6**) as well as a dimeric (HPA-DO3A)₂ system (**7**).² Among the secondary amides, different options on the amidic moiety were also explored, such as hydrazides (**3**), 1,3-dihydroxypropyl (**4**) and methylphosphonic (**5**) functionalization.

As for their application as MRI CAs, the presence of electron-withdrawing amide groups and other hydrophilic groups near the metal centre have three effects: 1) it makes the –OH group in the hydroxypropyl arm more acidic; 2) it introduces an acid-catalyzed prototropic effect and 3) it makes possible the presence of water molecules in the second sphere of hydration. All these effects cause an improvement of the relaxation properties of Gd(HPA-DO3A) complexes (measured by ¹H and ¹⁷O NMR relaxometry), in particular at acidic pH. Moreover, as these chelates have to be stable for *in vivo* application, the stability constants and the kinetic inertness of Gd-HPA-DO3A complexes were determined by pH-potentiometry and spectrophotometry.

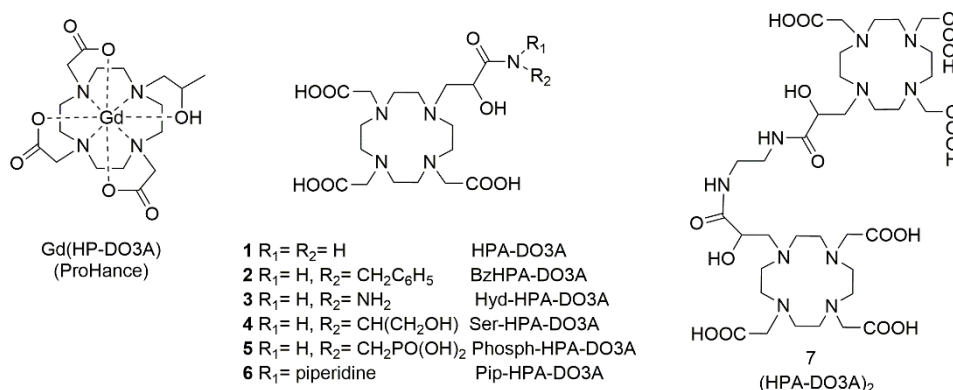


Figure 1: Structures of the ligands involved in this work.

References:

- [1] a) D. Delli Castelli, M.C. Caligara, M. Botta, E. Terreno, S. Aime, *Inorg. Chem.* **2013**, 52, 7130-7138; b) S. Aime, S. Baroni, D. Delli Castelli, E. Brücher, I. Fábíán, S. Colombo Serra, A. Fringuello Mingo, R. Napolitano, L. Lattuada, F. Tedoldi, Z. Baranyai, *Inorg. Chem.*, **2018**, 57, 5567-5574.
[2] L. Leone, G. Ferrauto, M. Cossi, M. Botta, L. Tei, *Front. Chem.* **2018**, 6, 158.

From microalgae to vaccine adjuvant: immunomodulant activity of sulfavants and its correlation with colloidal self-assembly

L. Fioretto,^{a,c} E. Manzo,^a C. Gallo,^a M. Ziaco,^{a,b} G. Nuzzo,^a M. Della Greca,^c L. Paduano,^c R. De Palma,^d A. Fontana^a

^aBio-Organic Chemistry Unit, CNR-ICB, Pozzuoli, Naples, Italy

^bBioSEARCH c/o R&D Site-ICB – CNR, Via Campi Flegrei, 34, 80078 Pozzuoli – Naples, Italy.

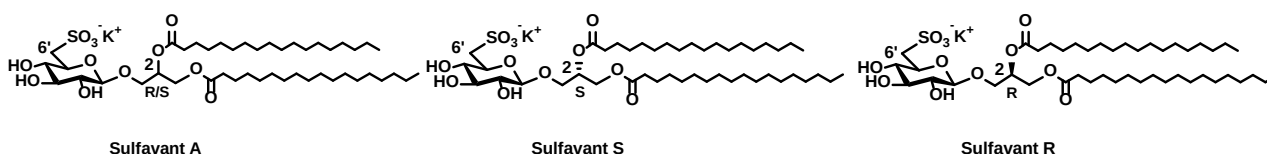
^cDept. of Chemical Sciences, University of Naples Federico II, Via Cinthia 4, 80136 Naples, Italy.

^dSecond University of Naples, Dept. of Precision Medicine, c/o II Policlinico, Via Pansini 5, 80131 Naples, Italy.

In the last decades, the improved understanding of how innate mechanisms influence the adaptive immunity system has prompted the research of new vaccine adjuvants by a rational design of new chemical entities.

Recently, we have searched for new immunomodulants in extracts of diatoms. This work led to isolation and characterization of α -sulfoquinovosides [1] as possible adjuvant candidates. These algal substances showed a promising activity and their biological optimization by structural modification led to the synthetic analog 1,2-O-distearoyl-3-O- β -D-sulfoquinovosyl glycerol named Sulfavant A. The synthetic product induces maturation of human dendritic cells (DCs) with no expression of inflammatory cytokines and, in vivo, boost of a immune protective response.[1] Later on, two other synthetic analogues of Sulfavant A (named Sulfavant S and Sulfavant R) were synthesized, and they showed the capability to elicit DC maturation at a concentration 1000 times lower than that the progenitor molecule.[2]

Investigation on the colloidal arrangement of Sulfavant A, R and S pointed out the formation of different kind of aggregates for the three molecules (Graph 1). The supramolecular interactions of these aggregates affect the different immunomodulant behavior of these molecules. [2]



Acknowledgments:

Authors thank European Union "PON Ricerca e Innovazione 2014-2020" for funding a Ph.D

References:

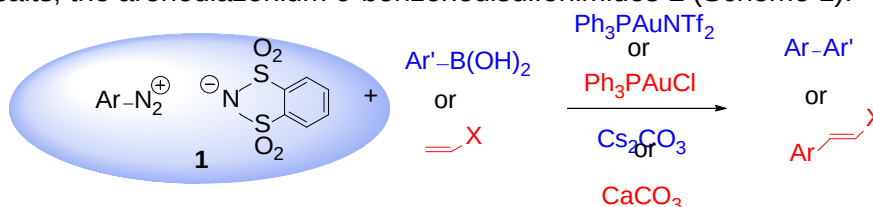
- [1] a) E. Manzo, A. Cutignano, D. Pagano, C. Gallo, G. Barra, G. Nuzzo, C. Sansone, A. Ianora, K. Urbanek, D. Fenoglio, F. Ferrara, C. Bernardi, A. Parodi, G. Pasquale, A. Leonardi, G. Filaci, R. De Palma, A. Fontana, *Sci. Rep.* **2017**, 7, 6286. b) A. Fontana, E. Manzo, A. Cutignano, R. De Palma, IT1417828 2015; PCT/IB2014/062098; c) E. Manzo, L. Fioretto, D. Pagano, G. Nuzzo, C. Gallo, R. De Palma, A. Fontana, *Mar. Drugs*, **2017**, 15, 288.
- [2] E. Manzo, C. Gallo, L. Fioretto, G. Nuzzo, G. Barra, D. Pagano, I. Russo Krauss, L. Paduano, M. Ziaco, M. Della Greca, R. De Palma, A. Fontana, *ACS Omega* **2019**, 4, 7807-7814.

Gold Catalysed Coupling Reactions of Arenediazonium *o*-Benzenedisulfonimides

S. Dughera^a, M. Barbero^a

^aDipartimento di Chimica dell'Università di Torino, Via P.Giuria 7, 10125, Torino.
stefano.dughera@unito.it

Gold catalysis is considered a fundamental topic in organic synthesis with several applications.¹ The high importance of gold catalysis is attributable to some peculiar qualities of gold which include good commercial availability, remarkable stability, functional groups and oxygen tolerance, tunability, minimal use of additive and excellent chemoselectivity. The use of oxidative gold catalysis as an effective means of facilitating C–C bond-forming reactions has been attracting increasing amount of attention in recent years.² The fact that Au (I) and Pd(0) are isoelectronics means that Au (I) species are able to catalyse reactions, including cross-coupling reactions, that are typically promoted by Pd(0). It is worth noting that strong oxidants were normally required in order to facilitate the Au (I)/Au (III) transition in the catalytic cycle. Some of our researches have resulted in a large family of dry diazonium salts, the arenediazonium *o*-benzenedisulfonimides **1** (Scheme 1).³



Scheme 1: Arenediazonium *o*-Benzenedisulfonimides **1** in gold catalysed Heck and Suzuki couplings

The properties of these compounds mean that they have great potential in numerous synthetic applications. In fact, they are easy to prepare and isolate, they are extremely stable, and they can be stored for an unlimited time. Moreover, they react easily both in water and in organic solvents, and *o*-benzenedisulfonimide can easily be recovered and reused at the end of the reactions.

Interestingly, arenediazonium salts have been recently used as electrophilic reactants in some Au (I) catalysed cross-coupling reactions, usually under fotoredox conditions.⁴ In fact, their capacity to undergo to a single-electron reduction under visible light and in the presence of photosensitizers means that they provide aryl radicals which give sequential oxidative additions onto Au (I) species. The subsequent reductive elimination from the resulting Au (III) complexes, produces the desired coupling adducts and regenerates the Au (I) catalyst.

In the light of these, we proposed mild, easy and efficient gold catalysed Heck and Suzuki couplings of arenediazonium *o*-benzenedisulfonimides **1**.⁵ The target products were generally obtained in satisfactory yields. It is worth noting the interesting role that the *o*-benzenedisulfonimide anion plays as an electron transfer agent in enabling a radical pathway that does not require the presence of photocatalysts or external oxidants.

References:

- [1] A. Arcadi, S. Di Giuseppe, *Curr. Org. Chem.*, **2004**, *8*, 795-812.
- [2] M. Joost, A. Amgoune, D. Bourissou, *Angew. Chem. Int. Ed.* **2015**, *54*, 15022-15045.
- [3] M. Barbero, S. Cadamuro, S. Dughera, *Org. Biomol. Chem.*, **2016**, *14*, 1437-1441.
- [4] X.-Z. Shu, M. Zhang, Y. He, H. Frei, F. D. Toste, *J. Am. Chem. Soc.*, **2014**, *136*, 5844-5847.
- [5] a) M. Barbero, S. Dughera, *Org. Biomol. Chem.* **2018**, *16*, 295; b) M. Barbero, S. Dughera, *Tetrahedron* **2018**, *74*, 5758-5769.

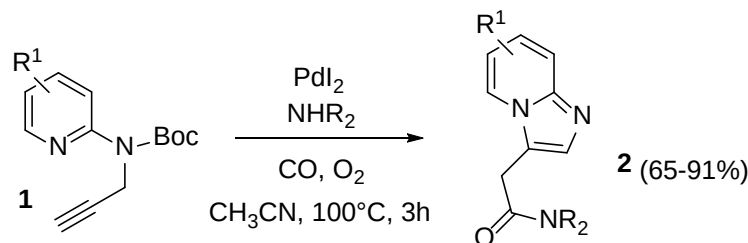
A Palladium Iodide – Catalyzed Oxidative Carbonylation Process for the Synthesis of Functionalized Imidazopyridines

L. Veltri,^a P. Russo,^a T. Prestia,^a B. Gabriele^a

^a *Laboratorio di Chimica Organica Sintetica e Industriale, Dipartimento di Chimica e Tecnologie Chimiche, Università della Calabria, Via P. Bucci 12/C, 87036 Rende (CS)*
lucia.veltri@unical.it

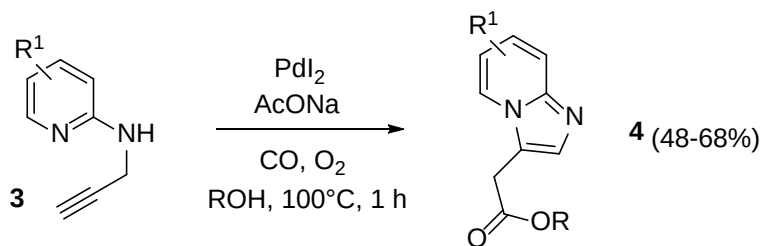
We report a novel PdI₂-catalyzed carbonylative approach to the synthesis of functionalized imidazo[1,2-*a*]pyridines starting from readily available (prop-2-yn-1-yl)pyridin-2-amine derivatives. Imidazo[1,2-*a*]pyridines are an important class of diheterocyclic derivatives, known to display a wide range of pharmaceutical activities (such as anticancer, antimycobacterial, antileishmanial, anticonvulsant, antimicrobial, antiviral, antidiabetic, proton pump inhibitor, and insecticidal activity).¹

The reaction takes place through the oxidative monocarbonylation of the terminal triple bond with C-H activation,² followed by intramolecular conjugated addition and double bond isomerization, to give 2-(imidazo[1,2-*a*]pyridin-3-yl)-*N,N*-dialkylacetamides **2** or alkyl 2-(imidazo[1,2-*a*]pyridin-3-yl)acetates **3**, depending on reaction conditions. In particular, amides **2** were obtained starting by *N*-Boc-protected-(prop-2-yn-1-yl)pyridin-2-amines **1** which underwent deprotection in situ and carbonylation when allowed to react with CO, O₂ (20 atm of a 4:1 mixture of carbon monoxide and air) and a secondary amine, in presence of catalytic amount of PdI₂ in conjunction with KI, in CH₃CN at 100° C° for 3 h (Scheme 1).



Scheme 1

On the other hand, *N*-unsubstituted (prop-2-yn-1-yl)pyridin-2-amines **3** were converted into esters derivatives **4** when the process was carried out in an alcoholic solvent in presence of AcONa as the base and the catalytic system PdI₂/KI, at 100°C for 1 h, under 16 atm di carbon monoxide and 4 atm of air (Scheme 2).



Scheme 2

References:

- [1] A. Deep, R. K. Bhatia, R. Kaur, S. Kumar, U. K. Jain, H. Singh, S. Batra, D. Kaushik, P. K. Deb, *Curr. Top. Med. Chem.* **2017**, 238-250.
- [2] B. Gabriele, R. Mancuso, G. Salerno, *Eur. J. Org. Chem.*, **2012**, 6825-6839.

Allylation of Aldehydes by Dual Photoredox and Nickel Catalysis

A. Gualandi,^a G. Rodeghiero,^{a,b} A. Faraone,^a F. Patuzzo,^a M. Marchini,^a F. Calogero,^a R. Perciaccante,^b T. P. Jansen,^b P. Ceroni,^a P. G. Cozzi^a

^aDip. di Chimica "G. Ciamician", ALMA MATER STUDIORUM Università di Bologna, Via Selmi 2, Bologna

^bCyanagen Srl, Via Stradelli Guelfi 40, Bologna
andrea.gualandi10@unibo.it

Addition of allyl organometallic reagents to aldehydes, ketones, and imines is a widespread used methodology in organic synthesis.¹ A plethora of organometallic reagents and conditions have been exploited for chemo- and stereo-selective allylation.² Normally, organometallic allylating reagents are obtained by redox reactions with metals in low oxidation state and suitable allyl precursors (e.g. allylbromides). Stoichiometric use of metals for preparing the organometallic reagent are therefore necessary and the final work-up of the reaction results in the production of waste.

Recently, the merging of transition metal catalysis and photoredox catalysis has become a hot topic in organic chemistry.³ Numerous examples of highly effective photocatalytic C(sp³) cross-coupling reactions were recently reported. Only few examples concerning the addition to polar functional groups, such as carbonyls or imines were described,⁴ and no examples of generation of nucleophilic nickel organometallic species were reported yet under the photocatalytic conditions.

In the present work, we have used photoredox synergistic catalysis for obtaining in mild conditions π -allylnickel, as an effective allylating agent of electrophiles. The methodology using inexpensive tertiary amine as sacrificial reductant, avoiding the use of metals such as magnesium, zinc, or manganese in stoichiometric amount. The reaction shows broad scope and it is quite tolerant regarding functional groups present.

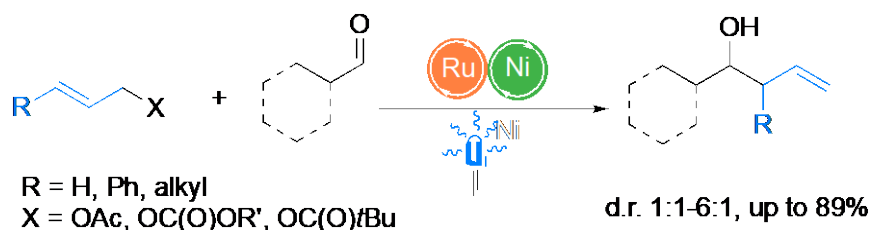


Figure 1.

References:

- [1] Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, 93, 2207-2293; P. V. Ramachandran, *Aldrichimica Acta* **2002**, 35, 23-35; S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, 103, 2763-2794; L. F. Tietze, T. Kinkel, C. Brazel, *Acc. Chem. Res.* **2009**, 42, 367-378
- [2] M. Yus, J. C. González-Gómez, F. Foubelo, *Chem. Rev.* **2011**, 111, 7774-7854.
- [3] J. Twilton, C. C. Le, P. Zhang, M. H. Shaw, R. W. Evans, D. W. C. MacMillan, *Nat. Rev. Chem.* **2017**, 1, 0052.
- [4] J. L. Schwarz, F. Schäfers, A. Tlahuext-Aca, L. Lückeimer, F. Glorius, *J. Am. Chem. Soc.* **2018**, 140, 12705-12709; (b) H. Mitsunuma, S. Tanabe, H. Fuse, K. Ohkubo, M. Kanai, *Chem. Sci.* **2019**, 10, 3459-3465.

Sustainable Catalytic Bromination of porphyrins

P. Galloni,^a G. Pomarico,^a V. Conte^a

^aDepartment of Chemical Science and Technologies, University of Rome Tor Vergata, via della ricerca scientifica snc 00133, Rome
e-mail galloni@scienze.uniroma2.it

Porphyrins represent the most famous compounds in the family of polypyrrolic macrocycles. The richness of properties of this class of molecules, allowed their exploitation in different fields of research, ranging from medicine¹ to catalysis,² chemical sensors³ or as dyes in DSSC.⁴ Among the different functionalizations of porphyrin scaffold, bromination represents one of the most important. On one hand, brominated derivatives represent the starting point for further modification of molecular framework achieved by cross coupling methodologies, such as Suzuki, Heck, Stille or Sonogashira reactions; on the other hand introduction of up to 8 bromine on the porphyrins scaffold varies significantly chemical, physical and geometrical properties. Common procedures require NBS or the corrosive and toxic Br₂ as Br source, and CHCl₃, CCl₄, o-dichlorobenzene or CH₃OH as solvents. We present a sustainable approach for the bromination of aromatic substrates based on a V(V) catalysed reaction, occurs in a two-phase medium and uses cheap and environmental friendly reagents such as H₂O₂ and KBr.⁵ With respect to the classical protocols for porphyrinoids bromination, this approach is based on milder and safer reaction conditions.

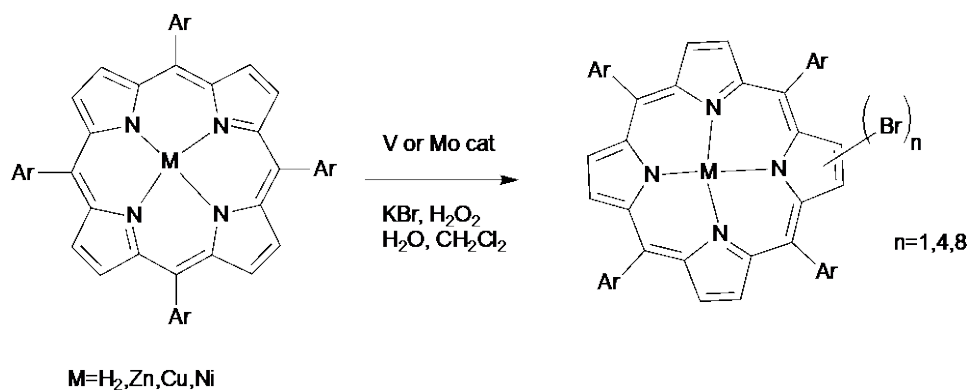


Figure 1: Catalytic Bromination of porphyrins using V or Mo catalysts.

By an accurate tuning of key parameters (H₂O₂ and KBr amount, catalyst), we are able to introduce one to eight Br atoms on β -pyrrolic positions of the porphyrin framework. While with Vanadium good results to obtain partially substituted porphyrins have been gained, the exploitation of the more active Molybdenum catalyst offered a better outcome in the achievement of complete halogenation of peripheral positions.

References:

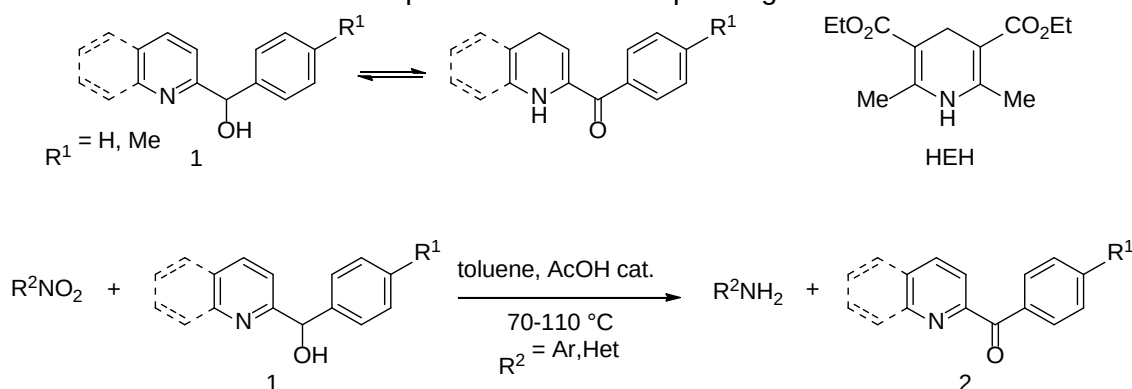
- [1] H. L. Pass, *J. Natl. Cancer Inst.* **1993**, 85, 443-456.
- [2] D. Intrieri, A. Caselli, E. Gallo, *Eur. J. Inorg. Chem.* **2011**, 5071-5081.
- [3] R. Paolesse, S. Nardis, D. Monti, M. Stefanelli, C. Di Natale, *Chem. Rev.* **2017**, 117, 2517-2583.
- [4] M. Urbani, M. Grätzel, M. K. Nazeeruddin, T. Torres, *Chem. Rev.* **2014**, 114, 12330-12396.
- [5] P. Galloni, M. Mancini, B. Floris, V. Conte, *Dalton. Trans.* **2013**, 42, 11963-11970.

Pyridyl and quinolyl methanols: applications in metal-free reductions of aromatic nitro compounds

J. Ceccarelli, A. Brandi, D. Giomi

Dipartimento di Chimica 'Ugo Schiff', Università degli Studi di Firenze
Via della Lastruccia 3-13, I-50019 Sesto Fiorentino, Italy
jacopo.ceccarelli@unifi.it

The weak acidity of the 'picoline type' hydrogen atom in 2-pyridyl- and 2-quinolyl-methanols **1** is responsible for their surprising reactivity as hydrogen donor allowing the metal-free reduction of aromatic and heteroaromatic nitro compounds to the corresponding amines.¹



Scheme 1: Metal-free reduction of R^2NO_2 with compounds **1**

In particular, the quinolyl system shows a higher reactivity with respect to the pyridyl one thanks to the low aromaticity of the bicyclic heterocycle. An easier access to the 1,4-dihydroquinoline form allows efficient metal-free reductions of aromatic nitro compounds and activated imines.

Ketones **2**, coming from the oxidation of **1**, can be easily recovered and converted back to **1** by simple reduction, making possible the recycling of the reducing agent and ascribing the process to sustainable friendly reactions.

Moreover, due to the inertness of Hantzsch Ester (HEH) as hydrogen donor towards nitro compounds, carbinols **1** may play a complementary role in the panorama of metal-free reducing agents.

Mechanistic aspects as well as synthetic applications of these new reactions will be properly discussed.

References:

- [1] a) D. Giomi, R. Alfini, A. Brandi, *Tetrahedron Lett.* **2008**, 49, 6977-6979. b) D. Giomi, R. Alfini, A. Brandi, *Tetrahedron* **2011**, 67, 167-172. c) D. Giomi, R. Alfini, J. Ceccarelli, A. Salvini, A. Brandi, *ChemistrySelect* **2016**, 1, 5584-5589.

A convenient access to imidazo[1,2-a]pyridines and fluorescent polycycles from nitrodienic building-blocks

A. Benzi,^a L. Bianchi,^a G. Giorgi,^b M. Maccagno,^a G. Petrillo,^a C. Tavani^a

^aDipartimento di Chimica e Chimica Industriale, Università di Genova, Via Dodecaneso 31, I-16146, Genova, Italy.

^bDipartimento di Biotecnologie, Chimica e Farmacia, Università di Siena, Via A. Moro, I-53100 Siena, Italy.
alice.benzi@edu.unige.it/alice.benzi93@gmail.com

When exploiting the reactivity of the versatile nitrodienic building-blocks **1**, originated by the ring-opening of a suitable nitrothiophenic precursor (**2**)^{1,2} towards 2-aminopyridine(s), it is possible to obtain a collection of 2-aryl-3-vinylimidazo[1,2-a]pyridines (**3**, **4**).

The formation of the final heterocyclic system occurs without the use of a catalyst and in mild condition, thanks to the particular functionalization of the conjugated system, that triggers a cascade process after the initial aza-Michael addition of the 2-aminopyridine on the nitrovinyl moiety.

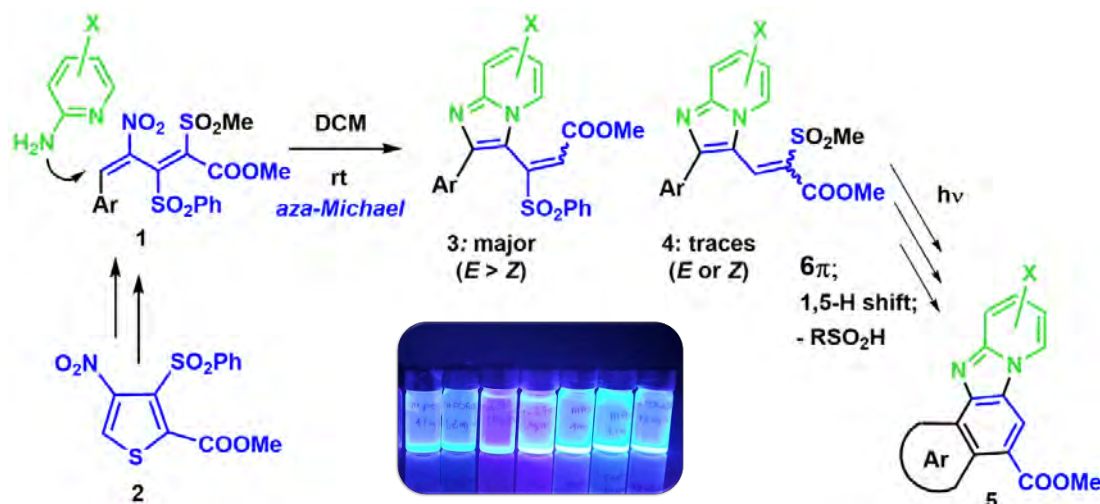


Figure 1: Fluorescence of compounds **5**.

Besides the general interest inherent to the pharmacological properties of imidazo[1,2-a]pyridine derivatives,³ the substituents present in the compounds herein allow an interesting photoinduced electrocyclization reaction, leading to the fluorescent heterocycles **5** with good yields. Latest achievements in the contest of this research project will be presented and discussed.

References:

- [1] C. Tavani, L. Bianchi, G. Giorgi, M. Maccagno, G. Petrillo *Eur. J. Org. Chem.* **2018**, 126-136.
- [2] L. Bianchi, M. Maccagno, G. Petrillo, E. Rizzato, F. Sancassan, E. Severi, D. Spinelli, C. Tavani, M. Viale *Targets in Heterocyclic Systems: Chemistry and Properties* (Eds.: O. A. Attanasi, D. Spinelli), Società Chimica Italiana, Rome, **2008**, 11 (2017), 1-20.
- [3] N. Devi, D. Singh, R. K. Rawal, J. Bariwal, V. Singh, *Curr. Top. Med. Chem. (Sharjah, United Arab Emirates)*, **2016**, 16, 2963-2994.

1,3-Dipolar Cycloaddition of Azides with Substituted Enaminones for Regioselective Synthesis of Trisubstituted 1,2,3-Triazoles.

L. Maiuolo,^a A. De Nino,^a V. Algieri,^a B. Russo,^a M. A. Tallarida,^a Manuel Pedron,^b T. Tejero,^c P. Merino^b

^a Dipartimento di Chimica e Tecnologie Chimiche, Università della Calabria, Ponte Bucci, cubo 12/C, 87036, Arcavacata di Rende (CS), Italy; ^b Instituto de Biocomputacion y Física de Sistemas Complejos (BIFI). Universidad de Zaragoza. 50009 Zaragoza (Spain); ^c Instituto de Síntesis y Catalisis Homogenea (ISQCH). Universidad de Zaragoza-CSIC. 50009 Zaragoza (Spain)

maiuolo@unical.it

1,2,3-Triazole derivatives represent a significant class of unsaturated nitrogen heterocycles that exhibit a number of important biological properties, such as antibacterial, antifungal, anticancer, antiviral, antitubercular, analgesic, anti-inflammatory, anticonvulsant, antidepressant and anti-arrhythmic activities.¹ Moreover, these compounds have also industrial applications as dyes, agrochemicals, corrosion inhibitors, and photostabilizers. In general, the synthetic strategies to obtain substituted triazoles are the catalyzed alkyne-azide cycloaddition or eliminative azide-olefin cycloaddition reaction (EAOC) between azides and olefins.

On the basis of our experience of cycloadditions in non-conventional reaction conditions,²⁻⁴ in this work we present the synthesis of trisubstituted 1,2,3-triazoles, substrates with high molecular diversity, by base mediated 1,3-dipolar cycloaddition between enaminones and azides. After an opportune screening to individuate the best Ionic Liquid and base, the synthesis are carried out with variously substituted enaminones and azides with excellent yields and in a regioselective manner (**Figure 1**). The final substrates maintain on their skeletal a versatile functional group such as carbonyl, susceptible to successive chemical manipulations.

In addition, theoretical calculations were made to clarify the reaction mechanism.

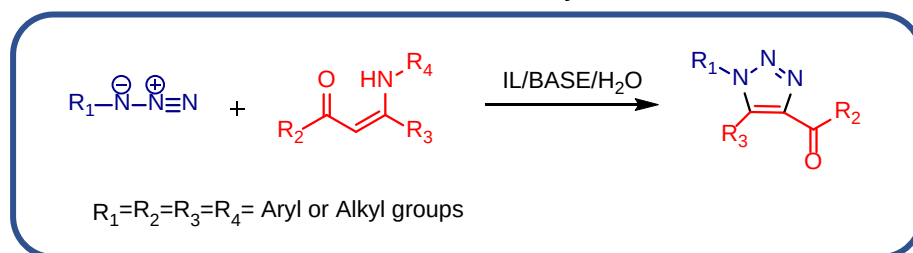


Figure 1: Base mediated 1,3-dipolar cycloaddition to synthesize trisubstituted 1,2,3-triazoles.

References:

- [1] C.-X. Wei, M. Bian G.-H. Gong, *Molecules* **2015**, *20*, 5528-5553.
- [2] A. De Nino, L. Maiuolo, P. Merino, M. Nardi, A. Procopio, D. Roca-López, B. Russo, V. Algieri, *ChemCatChem* **2015**, *7*, 830-835.
- [3] A. De Nino, P. Merino, V. Algieri, M. Nardi, M. L. Di Gioia, B. Russo, M. A. Tallarida, L. Maiuolo, *Catalysts* **2018**, *8*, 364.
- [4] L. Maiuolo, B. Russo, V. Algieri, M. Nardi, M. L. Di Gioia, M. A. Tallarida, A. De Nino, *Tetrahedron Lett.* **2019**, *60* (9), 672-674.

Divergent reactivity of *N*-allyl-2-aminophenols in domino reactions exploiting hypervalent iodine(III) reagents

S. Giofrè,^a M. S. Christodoulou,^a E. M. Beccalli^a

^a DISFARM, Sezione di Chimica Generale e Organica "A. Marchesini" Università degli Studi di Milano,
via Venezian 21, 20133 Milano, Italy.
e-mail: sabrina.giofre@unimi.it

In recent years, the functionalization of alkenes and alkynes makes use of hypervalent iodine(III) as a tool to reoxidize the transition metal catalysts¹ or to activate directly the unsaturated systems in a metal-free manner.²

The use of the *N*-allyl-2-aminophenols as building blocks allows us to report a divergent reactivity easily modulated by the reaction conditions. Indeed, the reaction performed in the presence of Pd(II)-catalyst and of a chiral ligand results in a stereoselective intramolecular alkoxylation through the incorporation of the nucleophile from the oxidizing agent (path A).

On the other hand, when the hypervalent iodine was employed in the absence of the metal, a new tricyclic product is observed, arising from an intramolecular Diels-Alder reaction coupled with the transfer of the nucleophile from the iodane (path B).

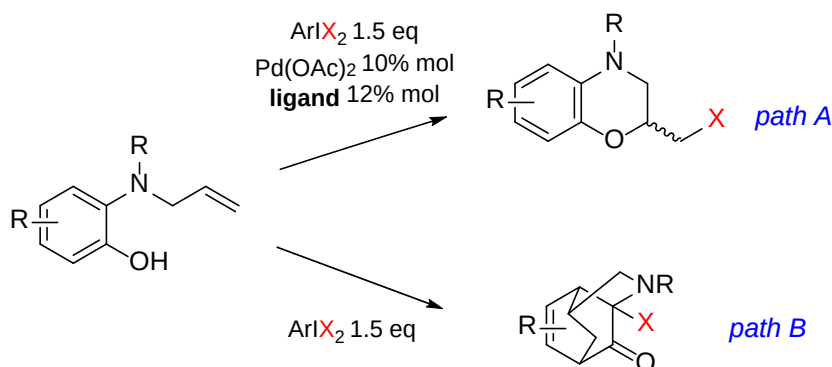


Figure. Hypervalent iodine-promoted a divergent reactivity of *N*-allyl-2-aminophenols.

References:

- [1] K. Muñiz, *Angew. Chem. Int. Ed.*, **2009**, *48*, 9412-9423.
- [2] X. Li, P. Chen, G. Liu, *Beilstein J. Org. Chem.* **2018**, *14*, 1813-1825.

Synthesis of 1,2,3-Triazole/MWCNT Conjugates for Environmental Application

R. Romeo,^a D. Iannazzo,^b A. Pistone,^b C. Celesti,^b S. V. Giofrè,^a

^aDepartment CHIBIOFARAM, University of Messina, Viale Annunziata, I-98168 Messina, Italy

^bDepartment of Engineering, University of Messina, Contrada Di Dio, I-98166 Messina, Italy
robromeo@unime.it

Functionalized carbon nanotubes (CNT) have attracted significant attention due to their unique electronic, optical, thermal, mechanical and chemical properties. The ability of these nanomaterials to undergo surface modification allows them to form nanocomposites with a wide range of materials such as polymers, metal nanoparticles and biomolecules.¹ Hybrid materials based on CNT have been developed for sustainable environment and green technology perspectives.

CNTs have been exploited for the development of a polyester-based gelcoat nanocomposite using as nanofiller multi-walled carbon nanotubes (MWCNT) conjugated with a biocidal 1,2,3-triazole to be used as a new eco-friendly antibiofouling coating. Ecotoxicological studies, performed on marine organisms, belonging to different evolutive classes, revealed the great biocidal properties of the synthesized nanocomposites. Differently from other investigated biocidal coatings, the antibiofouling properties of this system are not exerted by releasing drugs or other agents in the environment but simply inhibiting the replication of microorganisms on the nanocomposite surface.²

CNTs were also investigated for their ability to remove hazardous substances from aqueous media.³ Triazole based dendrimers were built directly to the MWCNT surface by click chemistry reactions, affording the MWCNT-TD chelating system (Fig.1a). The Moedritzer-Irani reaction performed on the amine groups of MWCNT-TD afforded the corresponding α -aminophosphonate chelating system MWCNT-TDP. Both nanosystems have been experimentally evaluated for their chelating ability towards Hg(II), Pb(II), Ni(II) and Ca ions by ICP-MS analyses and the complexation mode were investigated by DFT calculations (Fig.1 b).

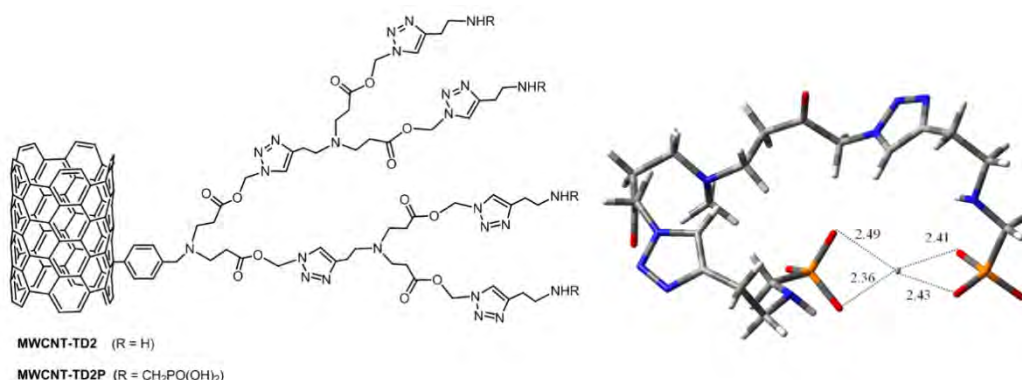


Figure 1: (a) Dendrimer-functionalized MWCNT; (b) 3D plot of a significant populated conformation of MWCNT-TD2P complexation mode.

References:

- [1] C. Vasile, *Materials*, **2018**, *11*, 1834.
- [2] D. Iannazzo, A. Pistone, A. Visco, G. Galtieri, S. V. Giofrè, R. Romeo, G. Romeo, S. Cappello, M. Bonsignore, R. Denaro and S. Galvagno, *Mater. Res. Express*, **2015**, *2*, 115001.
- [3] D. Iannazzo, A. Pistone, I. Ziccarelli, C. Espro, S. Galvagno, S. V. Giofrè, R. Romeo, N. Cicero, G. D. Bua, G. Lanza, L. Legnani, M. A. Chiacchio, *Environ. Sci. Pollut. Res.*, **2017**, *24*, 14735-14747.

Phosphine-catalyzed stereoselective dearomatization of 3-NO₂-indoles with allenates

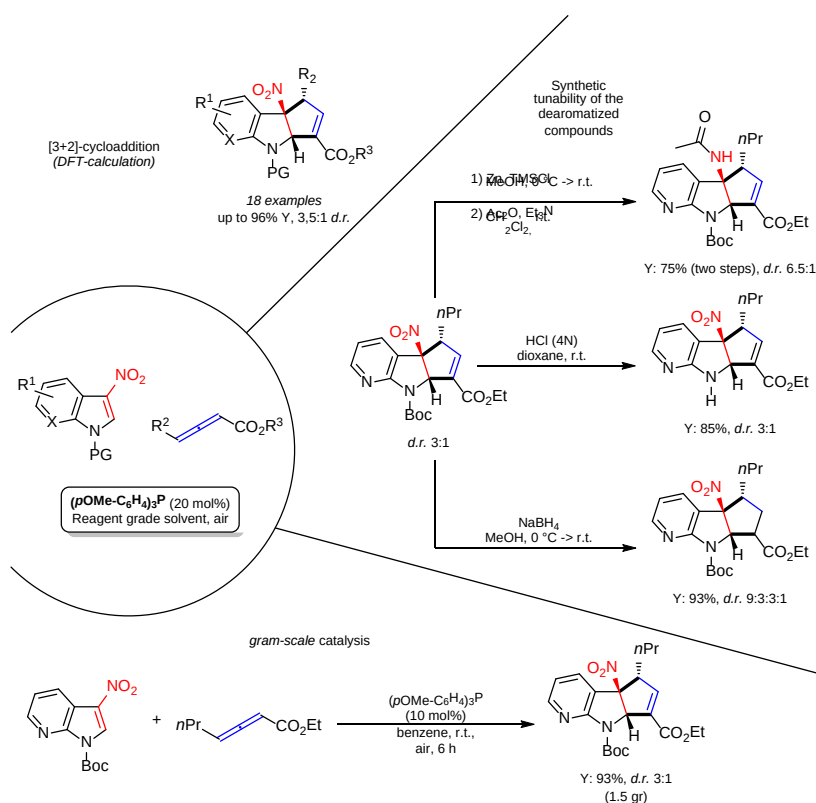
A. Cerveri,^a O. Nieto Faza,^b C. Silva López,^b S. Grilli,^a M. Monari^a and M. Bandini^a

^a Dipartimento di Chimica "G. Ciamician", Alma Mater Studiorum – Università di Bologna, Via Selmi 2, 4016, Bologna, Italy.

^b Departamento de Química Organica, Univesidad de Vigo, 36310 Vigo, Spain.

* e-mail: alessandro.cerveri2@unibo.it

In the last years new powerful methods for the desymmetrization of hetero-aromatic structures have been refined, giving the possibility of moving from simple 2D structure to a more complex chemical 3D space.[1] A current trend in the field encompasses the possibility to expand significantly the chemical diversity accessible via dearomative protocols by means of the so far less explored "dark-side" reactivity of electron-rich arenes.[2] Particularly, in this work the stereoselective phosphino-catalyzed dearomatization of 3-NO₂-indoles will be presented.



With this new methodology a range of densely functionalized indolines were synthesized in good to excellent yields and particular mild conditions (r.t., air, reagent grade solvent).

The mechanism of the catalytic process has been revealed to be a stepwise [3+2]-cycloaddition by means of computational and labelling studies (Figure 1).

Figure 1

References:

- [1] a) C. Romano, M. Jia, M. Monari, E. Manoni, M. Bandini, *Angew. Chem., Int. Ed.*, **2014**, 53, 13854-13857; b) M. Jia, M. Monari, Q.-Q. Yang, M. Bandini, *Chem. Commun.*, **2015**, 51, 2320-2323.
- [2] a) Q. Cheng, F. Zhang, Y. Cai, Y.-L. Guo, S.-L. You, *Angew. Chem. Int. Ed.* **2018**, 57, 2134-2138; b) D.-F. Yue, J.-Q. Zhao, X.-Z. Chen, Y. Zhou, X.-M. Zhang, X.-Y. Xu, W.-C. Yuan, *Org. Lett.* **2017**, 19, 4508-4511.

Dicationic Ionic Liquids: Synthesis, Characterization and catalytic Properties

C. Chiappe,^a C. S. Pomelli,^a L. Guglielmo,^a L. Guazzelli,^a A. Mezzetta,^a F. D'Andrea,^a A. Tredicucci,^b A. Toncelli^b

^aDept. of Pharmacy – University of Pisa, Via Bonanno 33, 56126 Pisa

^bDept. of Physics, Largo Pontecorvo 3, 56126 Pisa
christian.pomelli@unipi.it

The addition of a linker between two common ionic liquids' cations leads to a class of organised liquids, known as dicationic ionic liquids,^{1,2} which presents remarkable physical and chemical properties.

Several of these compounds have been synthesized, characterized by thermal analysis³ and various spectroscopic techniques including Thz spectroscopy. Furthermore, DFT studies on minimal neutral clusters (one dication and two anions) have been conducted to rationalize the experimental evidences.

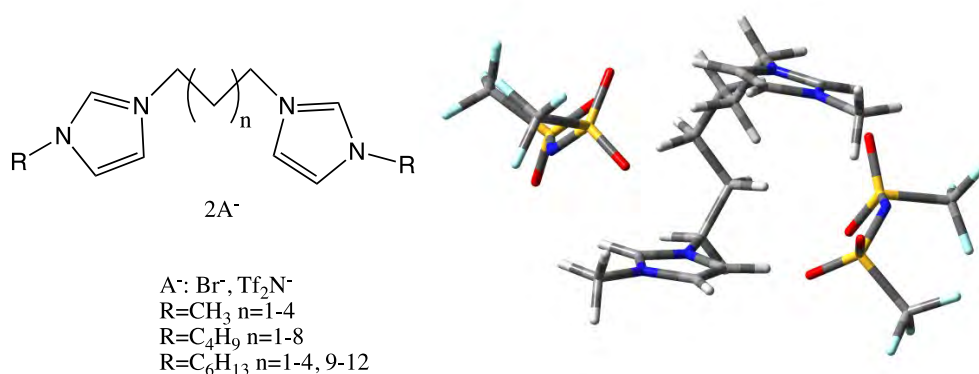


Figure 1: Left: some of the synthesized structures. Right: a DFT structure of a minimal neutral cluster.

Some of these ionic liquids have been used as catalysts for the cycloaddition reaction of CO_2 to epichlorohydrin.

References:

- [1] R. A. Patil, M. Talebi, C. Xu, S. S. Bhawal, D. W. Armstrong, *Chem. Mater.*, **2016**, 28, 4315-4323.
- [2] E. Priede, I. Nakurte, A. Zicmanis, *Synth. Comm.*, **2014**, 44, 1803-1809.
- [3] L. Guglielmo, A. Mezzetta, L. Guazzelli, C. S. Pomelli, F. D'Andrea, C. Chiappe, *Front. Chem.* **2018**, 6, 612.

Photocatalytic hydrogen production by means of Pt/brookite TiO₂ sensitized with dithienosilole-based organic dyes

O. Bettucci,^{a,b} T. Skaltsas,^c M. Calamante,^a A. Dessì,^a G. Reginato,^a A. Mordini,^a P. Fornasiero,^c L. Zani^a

^a Institute for the Chemistry of Organometallic Compounds (ICCOM), Consiglio Nazionale delle Ricerche (CNR), Via Madonna del Piano 10, 50019 Sesto Fiorentino (Italy)

^b Department of Biotechnology, Chemistry and Pharmacy, University of Siena, Via A. Moro 2, 53100 Siena (Italy)

^c Department of Chemical and Pharmaceutical Sciences, ICCOM-CNR Trieste Research Unit and INSTM bettucci.ottavia@gmail.com

The production of H₂ from sunlight and water is playing an increasingly important role in the production of clean fuels from sustainable and abundant energy sources¹. In this process, commonly referred as artificial photosynthesis, the role of the sensitizer, is critical for optimizing the harvesting of visible light and triggering the reduction reaction at the catalytic active site. Organometallic sensitizers have mainly been studied so far, however, thanks to recent advances and lower manufacturing costs, metal-free organic sensitizers have recently received increasing importance. On the basis of recent studies, concerning organic molecules applied on photoactivated H₂ production, appeared that those dyes well performing in DSSC are in most cases suitable for hydrogen production. For this reason, we selected a family of organic dyes having a dithienosilole core which are known to lead to high efficiencies in DSSC (10%, 7%)² as starting point to synthesize three new dyes (**OB1-3**) to study the influence of structural changes in the photoactivated H₂ evolution process. More in detail, the efficiency of some new organic D- π -A dyes in the H₂ production process has been investigated using the commercially available benchmark TiO₂ (P25) and the best performing dye was also used to sensitize a catalyst based on a different TiO₂ crystalline form, namely brookite/Pt. The aim of this work is to understand the possible correlation between structure and activity of such dyes, in particular the effect of introducing alkyl chains on the scaffold in order to affect several properties such as solubility, aggregation, shielding and wettability of the semiconductor and also the changes induced by the use of a different crystalline form of TiO₂.

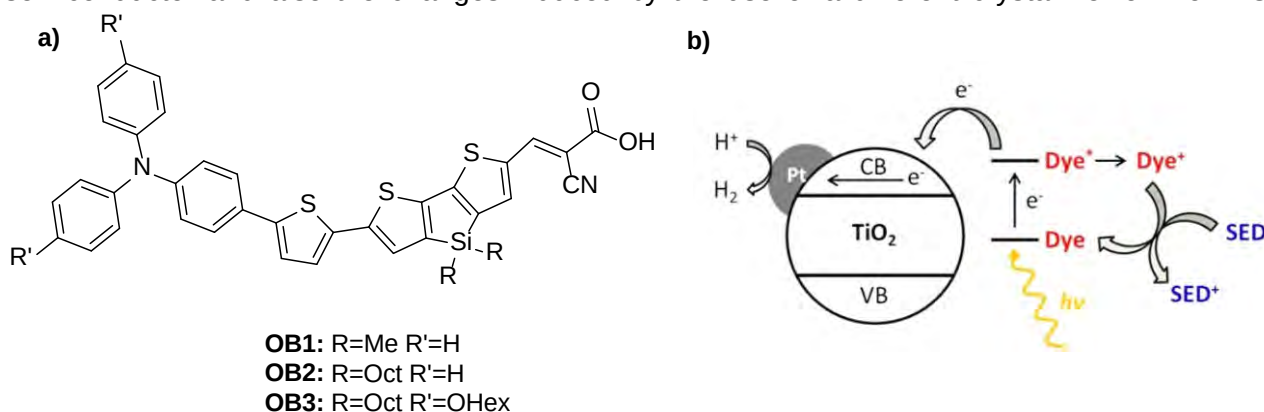


Figure 1: a) dyes synthesized in this work b) dye sensitizer H₂ production working principles

References:

- [1] N. Armaroli, V. Balzani, *Angew.Chem. Int. Ed.* **2007**, *46*, 52-66.
- [2] L. Lin, C. Tsai, K. Wong, T. Huang, L. Hsieh, S. Liu, H. Ling, C. Wu, S. Chou, S. Chen, A. Tsai, *J. Org. Chem.* **2010**, *75*, 4778-4785.

Copper-free methodologies for the multimerization of bioactive iminosugars

C. Matassini,^a C. Vanni,^a M. Marradi,^a F. Cardona,^a A. Goti^a

^a Department of Chemistry 'Ugo Schiff', University of Florence, via della Lastruccia 3-13, Sesto Fiorentino (FI), Italy
camilla.matassini@unifi.it

Glycosidases play a pivotal role in a variety of key biological processes. While the design of specific glycosidase inhibitors has attracted the interest of academics and pharmaceutical industry for a long time, only recently several efforts have been devoted to study the impact of the "multivalent effect" (defined as the increase of binding affinity compared to the traditional monovalent ligands) on glycosidase inhibition. A diversity of multivalent systems was synthesized essentially by using iminosugars (nitrogenated glycomimetics) as bioactive units and exploiting the copper-mediated azide–alkyne cycloaddition (CuAAC) reaction.¹ However, given that the cytotoxicity of copper is a potential drawback of the CuAAC approach, the need for alternative procedures is urgent.

In this context, we recently developed two copper-free methodologies for the multimerization of bioactive iminosugars. On one-hand, gold glyconanoparticles (sugar-coated gold nanoparticles, AuGNPs) were employed as novel scaffolds for the preparation of hybrid multivalent architectures decorated with pyrrolizidine (DAB-1)² or piperidines (DNJ) iminosugars and their biological activity was investigated towards different target glycosidases (Figure 1A). On the other hand, an innovative approach to multimerize DAB-1 was disclosed. The synthetic strategy involves a highly selective 1,3-dipolar cycloaddition performed onto a cyclic polyhydroxylated nitrone³ and is able to afford, in principle, a chiral enantiopure polyethylene glycol decorated with several pyrrolidine iminosugar units (Figure 1B). This methodology fully respects the principles of atomic economy and avoids the possible contamination of the final product with copper traces.

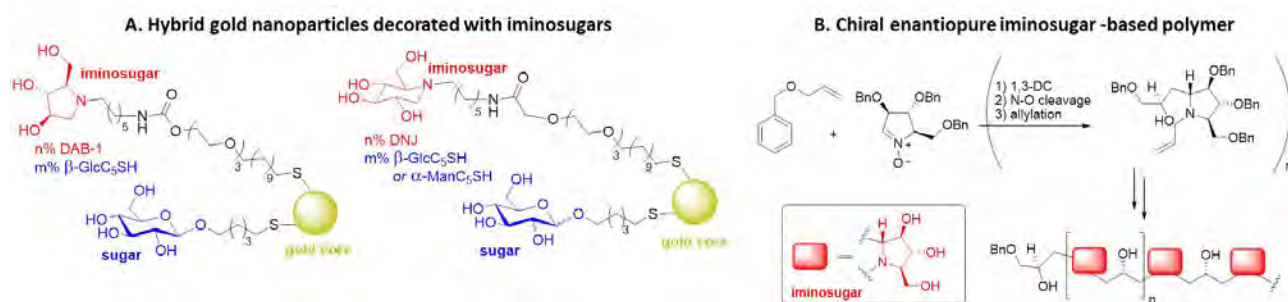


Figure 1: Copper-free methodologies for the preparation of novel multivalent iminosugars.

References:

- [1] C. Matassini, C. Parmeggiani, F. Cardona, A. Goti, *Tetrahedron Lett.* **2016**, 57, 5407-5415.
- [2] C. Matassini, C. Vanni, A. Goti, A. Morrone, M. Marradi, F. Cardona, *Org. Biomol. Chem.* **2018**, 16, 8604-8612.
- [3] D. Martella, G. D'Adamio, C. Parmeggiani, F. Cardona, E. Moreno-Clavijo, I. Robina, A. Goti, *Eur. J. Org. Chem.* **2016**, 8, 1588-1598.

Non-conventional technologies for copper heterogeneous catalysts production and its applications in organic synthesis

M. J Moran Plata,^a F. Calsolaro,^a K. Martina,^a G. Cravotto^a

^a Department of Drug Science and Technology, University of Turin, Via Pietro Giuria 9, 10125, Turin,
e-mail: mariajesus.moranplata@unito.it

During the last few years, conventional protocols have been replaced with intensified processes where alternative energy sources are used to achieve higher efficient and more sustainable procedures. Aiming to carry out methods lowering the energy and time consumption enabling technologies such as microwaves, ultrasounds and mechanochemistry have been successfully applied.

The use of truly efficient catalytic reactions is one of the most direct way to pursue green chemistry. In the last decade, copper heterogeneous catalysis gained more and more attention due to important advantages: (1) compared to other transition-metal, copper catalysts are inexpensive, readily available, insensitive to air, and can be easily handled (2) are extremely versatile and effective in different reaction types.

Here in we report the preparation of a new solid supported copper catalyst based on an efficient grafting of β -CD onto the inorganic silica surface. The use of non conventional techniques for the synthesis of this material, as well as for its use in click reactions, has played a very important role in terms of faster and more selective processes.

Moreover, an efficient synthesis of copper nanoparticles has been achieved. Ultrasound is known for its capacity in enhancing particles dispersion and favoring mechanical depassivation. In our study, copper nanoparticles supported over celite proved to be the ideal material for the transfer hydrogenation reaction of nitrobenzene in continuous flow.

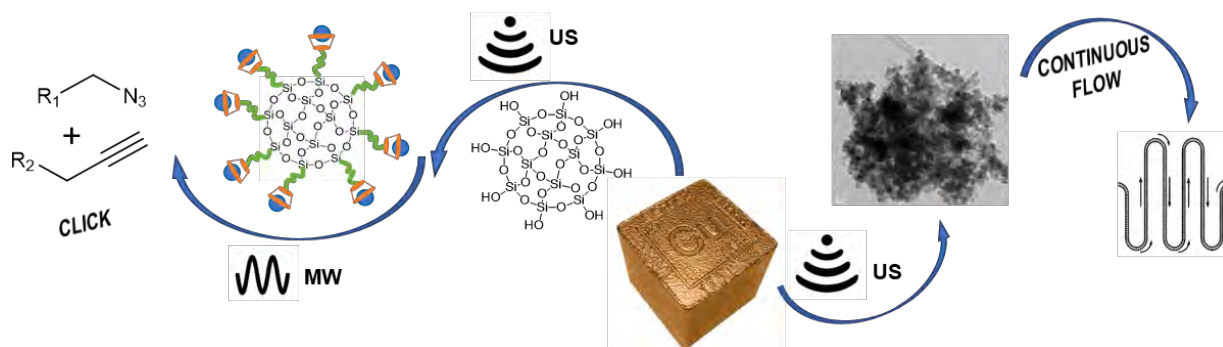


Figure 1: Microwave and ultrasound irradiations in copper heterogeneous catalysis.

Acknowledgments:

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 721290. This publication reflects only the author's view, exempting the Community from any liability. Project website: <http://cosmic-etn.eu/>

COMUNICAZIONI POSTER

Sessione 1

Study of milk proteins' digestibility: characterization of the peptide fraction released and potential impact on allergenicity

T. Tedeschi,^a A. Gasparini,^a S. Cutroneo,^a S. Sforza^a

^aUniversità degli Studi di Parma, Department of Food and Drug, Parco Area delle Scienze 17/A,
43124-Parma
tullia.tedeschi@unipr.it

Cow's milk is listed among the main food allergens: with fish, egg, crustacean/shellfish, nuts, peanuts, wheat and soy it is responsible for the 90% of food serious allergic reaction worldwide. The main milk allergens are caseins and the whey proteins α -lactalbumin and β -lactoglobulin. Milk proteins allergy is also the most prevalent allergy for young children with an incidence up to 2-7.5% of the population. One reason of this incidence might be the different protein composition between cow's and human milk, for instance β -lactoglobulin is not present in human milk while it is the main whey protein in cow's milk.

Milk undergoes several technological treatments to guarantee its safety and stability for human consumption. The application of high temperatures might affect milk proteins inducing structural and chemical modifications. The major common modification is the Maillard reaction.¹ This modification is promoted by the high temperatures and occurs between lactose, the main sugar present in milk, and the amino group of lysine residues in proteins. We previously identified modified sites on whey proteins by LC-MS spectrometry.² Through LTQ-Orbitrap and UPLC-MS analysis lactosylated residues were identified in the mixtures of peptides produced and compared with the known epitopes reported in literature confirming the presence of some modified lysines in these epitopes.

Recently, we approached further studies, in order to investigate how the digestibility of whey proteins can influence their allergenicity. Adopting the Minekus standard protocol³ suitable for food, kinetics studies were performed on whey proteins concentrates in order to obtain a digestion LC-MS profile for the whey proteins in their lactosylated forms. In particular we focused our attention on the identification of peptides released during the digestion, which are part of epitopes. In some cases it was found that the presence of the lactose linked to the molecule doesn't be affected by the digestive enzymes. The fact that the molecule remains stable until the end of the intestinal phase, raises the issue of the allergenic risk. Complete studies concerning dynamic simulation of digestion phases and peptide bioavailability and transfer through intestinal membrane phase should be performed, in order to better elucidate the role of this modified epitope.

Finally the chemical synthesis of the modified peptide sequence, identified in the digestion experiments, has been also approached and preliminary results will be showed and discussed.

References:

- [1] J. Meltretter, J. Wüst, and M. Pischetsrieder, *J. Agric. Food Chem.* **2014**, 62, 10903-10915.
- [2] S. Buhler, F. Solari, A. Gasparini, R. Montanari, S. Sforza, T. Tedeschi, *LWT--Food Sci. Techn.* **2019**, 105, 127-134.
- [3] M. Minekus, M. Alminger, P. Alvito, S. Ballance, T. Bohn, C. Bourlieu, F. Carrière, R. Boutrou, M. Corredig, D. Dupont, C. Dufour, L. Egger, M. Golding, S. Karakaya, B. Kirkhus, S. Le Feunteun, U. Lesmes, A. Macierzanka, A. Mackie, S. Marze, D. J. McClements, O. Ménard, I. Recio, C. N. Santos, R. P. Singh, G. E. Vegarud, M. S. Wickham, W. Weitschies, A. Brodtkorb, *Food Funct.* **2014**, 5, 1113-1124.

Design of novel organic hole transport materials for perovskite solar cells

C. Coppola,^a A. Dessì,^b L. Zani,^b G. Reginato,^b A. Sinicropi^{a,b}

^aDepartment of Biotechnology, Chemistry and Pharmacy, University of Siena,
via Aldo Moro 2, 53100 Siena

^bItalian National Council for Research - Institute for the Chemistry of OrganoMetallic Compounds (CNR-
ICCOM), Via Madonna del Piano 10, 50019 Sesto Fiorentino, Italy

carmencoppola19@gmail.com

Hole transport materials (HTMs) based on conductive small organic molecules are crucial components to prepare highly efficient perovskite solar cells (PSCs). Currently, the Spiro-MeOTAD is the most used HTM allowing for a conversion efficiency of 22%. Unfortunately, it has a series of drawbacks that prevent the commercialization of the cells prepared using this material¹. Therefore, fully organic molecules based on triphenylamine moieties have been proposed as alternative to Spiro-MeOTAD. In this work, the *in silico* design of four new triphenylamine-based HTMs (HTM1-4) is presented. Their electronic and molecular properties have been investigated by means of Density Functional Theory (DFT) and Time Dependent-DFT methods and they have been compared to those of the Spiro-MeOTAD² and other triphenylamine-based HTMs, e.g. PTZ2³, already present in literature (fig.1). Furthermore, a comparison with the experimental characterization of HTM1 is reported. The computed and experimental results suggest that HTM1-4 can be suitable candidates for the construction of potentially efficient PSCs.

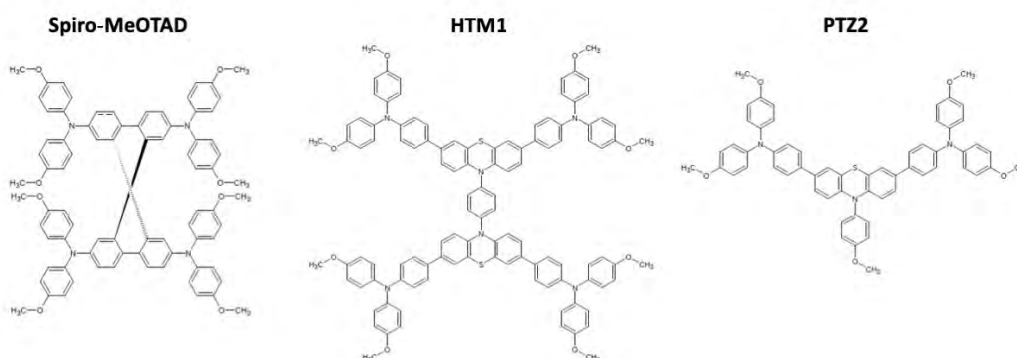


Figure 1: HTM1 molecular structure compared to Spiro-MeOTAD and PTZ2 molecular structures.

References:

- [1] P. Vivo, J. K. Salunke, A. Priimagi, *Materials* **2017**, 10 (9), 1-45.
- [2] S. Fantacci, F. De Angelis, M. K. Nazeeruddin, M. Grätzel, *J. Phys. Chem. C* **2011**, 115 (46), 23126-23133.
- [3] R. Grisorio, B. Roose, S. Colella, A. Listorti, G. P. Suranna, A. Abate, *ACS Energy Lett.* **2017**, 2 (5), 1029-1034.

Alternative Chemocatalytic Methods for Selective Conversion of Cellulose into Lactic Acid

S. Tallarico,^a P. Costanzo,^a S. Bonacci,^a M. Nardi,^a M.L. di Gioia,^b A. Procopio^a, M. Oliverio^a

^aDepartment of Health Sciences, University Magna Graecia of Catanzaro, Viale Europa, 88100-Catanzaro (CZ), Italy

^bDepartment of Pharmacy, Health and Nutritional Sciences, University of Calabria, Edificio Polifunzionale, 87036-Arcavacata di Rende (CS), Italy
sofia.tallarico@studenti.unicz.it

Lactic Acid (LA) is a chiral carboxylic acid traditionally used in food industry as acidulant, preservative and emulgator¹. It has the potential to become a precursor for the synthesis of α -amino acids, opening to the production of proteins from agricultural wastes via chemical routes in the future². In this work, we present alternative methods as microwaves combined with the reactor Q-tube and with ultrasounds to realize the selective hydrothermal conversion of cellulose into LA, under mild reaction conditions in presence of either ErCl_3 or grafted on MCM-41 silica surface. We decided to investigate: (i) the best MW/Q-tube conditions to perform the conversion of biomass derived hexoses with ErCl_3 , which at the best of our knowledge was never performed with this type of reactor, and (ii) the coupling of MW heating with US cellulose pre-treatment for its selective conversion into LA in the presence of heterogeneous catalyst. For all the substrates in both catalysis, lactic acid is the major product, together with lesser amounts of 5-hydroxymethylfurfural, furfural and levulinic acid. The best results in terms of yield and selectivity when Q-tube reactor was used, were reached at 165°C in 30 minutes. Thanks to the US-effect, cellulose MW-assisted conversion into LA with Er^{III} -MCM-41 was possible at 200°C and pressure under the water subcritical conditions with increased operational safety.

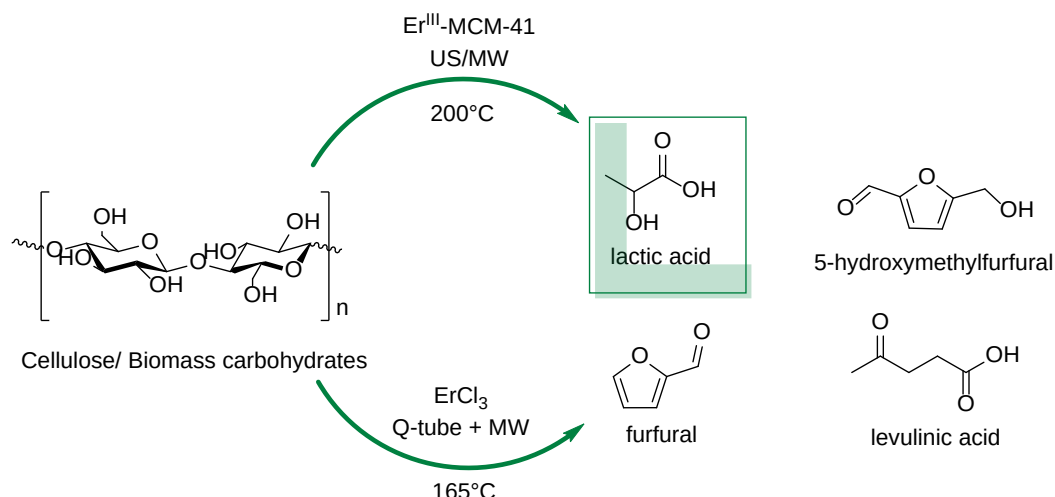


Figure 1: Catalytic hydrothermal conversion of cellulose and biomass carbohydrates.

References:

- [1] M. Dusselier, P. Van Wouwe, A. Dewaele, E. Makshina, B. F. Sels, *Energy Environ. Sci.*, **2013**, 6, 1415-1442.
- [2] W. Deng, Y. Wang, S. Zhanga K. M. Gupta, M. J. Hülsey, H. Asakura, L. Liu, Y. Han, E. M. Karp, G. T. Beckham, P. J. Dyson, J. Jiang, T. Tanakac, Y. Wang, N. Yan, *PNAS*, **2018**, 115 (20), 5093-5098.

Natural deep eutectic solvents as an efficient and versatile catalytic system for the Nazarov cyclization

S. Nejrotti, M. Iannicelli, S. S. Jamil, M. Blangetti, C. Prandi

^aDipartimento di Chimica, Università degli Studi di Torino, Via Pietro Giuria 7, 10125 Torino, Italy
stefano.nejrotti@unito.it

The Nazarov cyclization (NC) consists in a conrotatory electrocyclization of divinyl ketones to cyclopentenones, catalyzed by Brønsted or Lewis acids, and represents one of the most useful synthetic tools for the preparation of cyclopentenone motifs.¹ However, the reaction has some drawbacks, most prominently the use of strong Brønsted acids which are usually toxic and the use of volatile organic compounds (VOCs) as solvents. To date, advances on more sustainable versions of the NC are limited to very few reports.² Natural deep eutectic solvents (NaDES) have recently emerged as a new promising class of green solvents, not only because of their low cost, low toxicity and biodegradability, but also because they can have an active role in promoting organic reactions.³ Here, we report our study on the Nazarov cyclization performed in acidic deep eutectic solvents, employing non-toxic, naturally occurring carboxylic acids as components of the catalytic system. Various divinyl ketones, bearing different substituents and embedded in heterocycles, have been successfully cyclized, showing the versatility of the methodology.

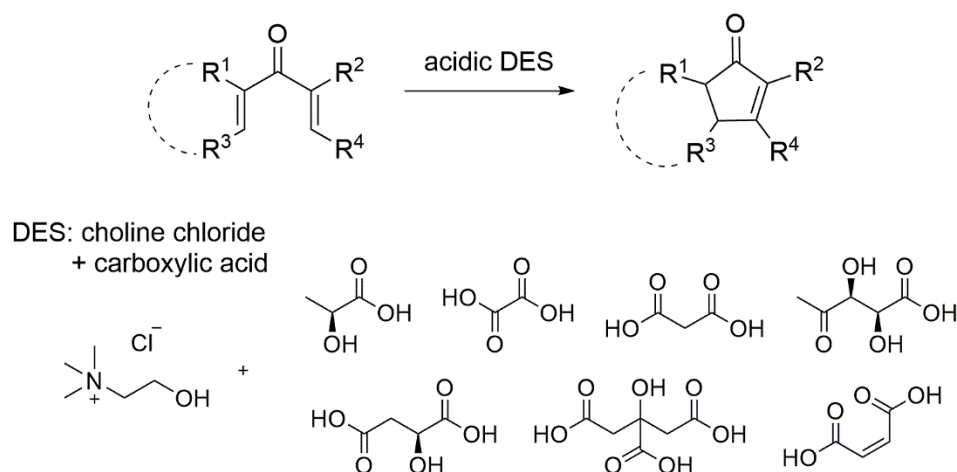


Figure 1: The Nazarov cyclization in acidic deep eutectic solvents.

References:

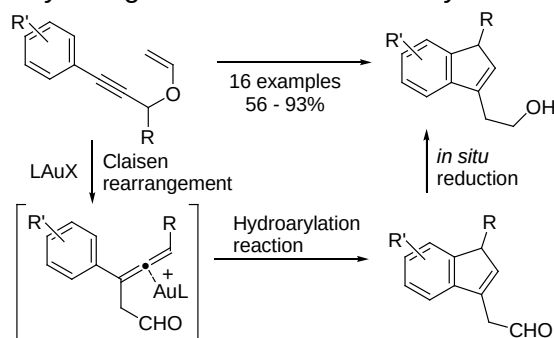
- [1] a) M. A. Tius, *Chem. Soc. Rev.* **2014**, *43*, 2979-3002; b) D. R. Wenz, J. Read de Alaniz, *Eur. J. Org. Chem.* **2015**, 23-37; c) M. G. Vinogradov, O. V. Turova, S. G. Zlotin, *Org. Biomol. Chem.* **2017**, *15*, 8245-8269.
- [2] a) M. Barbero, S. Cadamuro, A. Deagostino, S. Dughera, P. Larini, E. G. Occhiato, C. Prandi, S. Tabasso, R. Vulcano, P. Venturello, *Synthesis* **2009**, *13*, 2260-2266; b) Z. Daneshfar, A. Rostami, *RSC Adv.* **2015**, *5*, 104695-104707.
- [3] a) P. Liu, J.-W. Hao, L.-P. Mo, Z.-H. Zhang, *RSC Adv.* **2015**, *5*, 48675-48704; b) D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor, D. J. Ramón, *Eur. J. Org. Chem.* **2016**, 612-632.

Synthesis of Indenes by Tandem Gold(I)-Catalyzed Propargyl Claisen Rearrangement/Hydroarylation Reaction

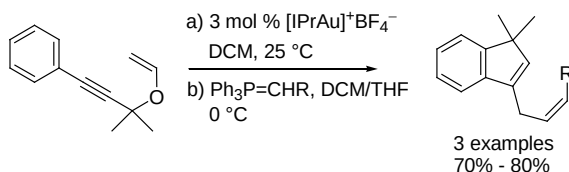
A. Rinaldi,^a V. Langé,^a D. Scarpi,^a E. G. Occhiato^a

^aDepartment of Chemistry "U. Schiff", Via della Lastruccia 3, Sesto Fiorentino (Italy)
antonio.rinaldi@unifi.it

As the indene framework is found in several natural products and it finds application in material science, and in the preparation of ligands for metal complexes, the development of efficient methodologies for the construction of indenenes plays an important role for organic synthesis¹. According to the previous works of our research group², we present a tandem gold(I)-catalyzed Claisen rearrangement/hydroarylation reaction of vinyl propargyl ethers³ which efficiently provides functionalized indenenes in good to excellent yields (Scheme 1). The reaction occurs under mild conditions with [IPrAuCl]/AgBF₄ as the best catalytic system. A variety of substituents and functional groups present on the substrate are tolerated. The effect of the aryl ring substituents and the results of a DFT computational study suggest that the final hydroarylation is the rate determining step of this cascade process. In order to increment the diversity of the products obtained, further *in situ* chain elongation can be carried out by Wittig olefination of the aldehyde functionality (Scheme 2).



Scheme 1: tandem gold(I)-catalyzed Claisen rearrangement/hydroarylation reaction.



Scheme 2: sequential Au(I)-catalyzed tandem process/Wittig olefination.

References:

- [1] For a review, see: B. Gabriele, R. Mancuso, L. Veltri, *Chem. Eur. J.* **2016**, *22*, 5056-5094.
- [2] a) A. Rinaldi, M. Petrovic, S. Magnolfi, D. Scarpi, E. G. Occhiato, *Org. Lett.* **2018**, *20*, 4713-4717. b) D. Scarpi, M. Petrović, B. Fiser, E. Gómez-Bengoa, E. G. Occhiato, *Org. Lett.* **2016**, *18*, 3922-3925. c) M. Petrović, D. Scarpi, B. Fiser, E. Gómez-Bengoa, E. G. Occhiato, *Eur. J. Org. Chem.* **2015**, *18*, 3943-3956.
- [3] A. Rinaldi, V. Langé, E. Gómez-Bengoa, G. Zanella, D. Scarpi, E. G. Occhiato, *J. Org. Chem.* **2019**, manuscript accepted.

PdI₂-Catalyzed Carbonylative Approach to Benzothiophene Derivatives from (2-Alkynyl)(methylthio)benzenes

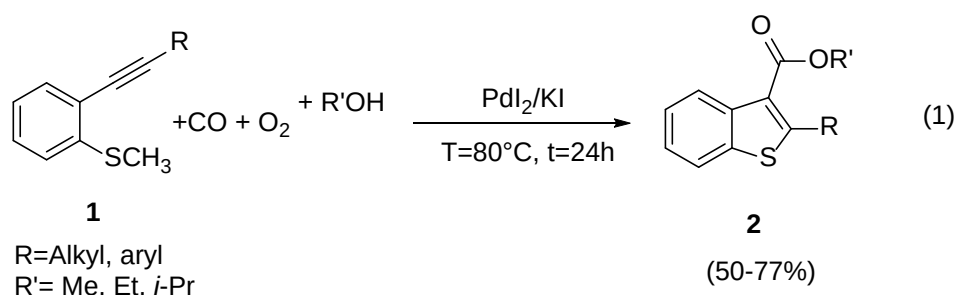
R. Mancuso, S. Cuglietta, B. Gabriele

Laboratory of Industrial and Synthetic Organic Chemistry (LISOC), Department of Chemistry and Chemical Technology, University of Calabria, Arcavacata di Rende (CS), Italy;
raffaella.mancuso@unical.it

It is known that carbonylation reactions are particularly efficient and convenient processes for the direct synthesis of carbonylated heterocycles¹

In the present communication we report that benzothiophene derivatives **2** can be conveniently synthesized by palladium-catalyzed intramolecular carbonylative heterocyclization of (2-alkynyl)(methylthio)benzenes **1** (Eq.1).

Benzothiophenes are an important classes of S-heterocycles in pharmaceutical science. They are used in a variety of drugs, pesticides and biologically active compounds².



Reactions are carried out at 80 ° C, in alcoholic solvents (R'=Me, Et, *i*-Pr.), in the presence of PdI₂ (1 mol%) in conjunction with KI (20 mol%) and under 40 atm of a 1: 4 mixture of CO / air. Benzothiophene derivatives **2** are obtained in good yields (50-77%).

References

- [1] B. Gabriele, R. Mancuso, G. Salerno, *Eur. J. Org. Chem.* **2012**, 6825-6839.
- [2] a) L. Berrade, B. Aisa, M. J. Ramirez, Galiano S, S. Guccione, L. R. Moltzau, F. O. Levy, F. Nicoletti, G. Battaglia, G. Molinaro, I. Aldana, A. Monge, S. Perez-Silanes, *J. Med. Chem.* **2011**, *54*, 3086-3090; b) H.-F. Guo, H.-Y. Shao, Z.-Y. Yang, S.T. Xue, X. Li, Z.-Y. Liu, X.-B. He, J.-D. Jiang, Y.-Q. Zhang, S.-Y. Si, Z.-R. Li, *J. Med. Chem.* **2010**, *53*, 1819-1829; c) I. Jarak, M. Kralj L. Šuman, G. Pavlović, J. Dogan, I. Piantanida, M. Žinić, K. Pavelić, G. Karminski-Zamola, *J. Med. Chem.* **2005**, *48*, 2346-2360; d) D. H. Boschelli, J. B. Kramer, S. S. Khatana, R. J. Sorenson, D. T. Connor, M. A. Ferin, C. D. Wright, M. E. Lesch, K. Imre, G. C. Okonkwo, D. J. Schrier, M. C. Conroy, E. Ferguson, J. Woelle, U. Saxena, *J. Med. Chem.* **1995**, *38*, 4597-4614.

Hybrid ionogels as potential antioxidant agents

C. Rizzo,^a F. Billeci,^a N. Tz. Dintcheva,^b R. Noto,^a S. Marullo,^a F. D'Anna^a

^aUniversità degli Studi di Palermo, Dipartimento STEBICEF, Sezione di Chimica, Viale delle Scienze Ed. 17, 90128, Palermo.

^bDipartimento di Ingegneria Civile, Ambientale, Aerospaziale, dei Materiali, Università degli Studi di Palermo, Viale delle Scienze Ed. 8, 90128 Palermo, Italy.
carla.rizzo03@unipa.it

The addition of natural antioxidant into polymeric materials has been proven fundamental to prevent or retard the oxidation of polymeric materials. However, the incorporation of these low molecular weight antioxidants results hard due to their low volatility, low efficiency and low chemical or photo-chemical stability. To overcome these issues, some anti-oxidant species have been physically adsorbed on carbon nanotubes (CNT) exerting an extremely high radical scavenging activity on the polymeric material.¹

Nevertheless, the obtainment of homogenous dispersions of CNT in a matrix is still challenging, for this reason we focused on the incorporation of functionalized carbon nanotubes on supramolecular gel matrix. It is well known that supramolecular gels are formed by low molecular weight molecules able to self-assemble through supramolecular interactions (hydrogen bonding, π - π stacking, van der Waals interactions) forming a 3D network in which a solvent is trapped. These soft materials can host several nanomaterials and, thanks to additional interactions between gelator molecules and nanomaterials, the resulting hybrid gels show improved properties. For example, it has been recently demonstrated that some nitrogen carbon nanodots were able to favor the gel formation and that the gelatinous matrix retained or improved carbon nanodots properties, showing a notable antiradical activity.²



Figure 1. Schematic representation of gelators and CNTs used to form hybrid gels.

In the present study, the influence of CNTs on the gelling ability of some carboxylate imidazolium gelators in ionic liquid solutions has been investigated. Hybrid gels properties such as critical gelation concentration, gel-sol temperature, morphology, rheology and self-repairing ability after disruption have been studied as function of gelator and solvent nature as well as in dependence of the different functionalization of CNTs. Hybrid gels exerted excellent radical scavenging activity, in addition, a small amount of gel can be incorporated in polymeric films warranting homogeneous dispersion of CNTs and good anti-oxidant properties of the film.

References:

- [1] L. Melk, N.; Emami, *Composites Part B: Engineering* **2018**, *146*, 20-27.
- [2] C. Rizzo, F. Arcudi, L. Đorđević, N. T. Dintcheva, R. Noto, F. D'Anna, M. Prato, *ACS Nano* **2018**, *12*, 1296-1305.

Gluconic acid for eco-friendly Ionic Liquids: chemical and biological investigations.

F. Billeci,^a H. Q. N. Gunaratne,^b N. V. Plechkova,^c K. R. Seddon,^d P. Cancemi,^a A. Forlino,^e R. Noto,^a F. D'Anna^a

^aUniversità degli Studi di Palermo, Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche, Viale delle Scienze, Ed. 17, 90128 Palermo, Italy

^bSchool of Chemistry and Chemical Engineering, Queen's University of Belfast, Stranmillis Road, Belfast, UK

^cSchool of Medicine, Dentistry And Biomedical Sciences, Queen's University of Belfast, Stranmillis Road, Belfast, UK

^dThe QUILL Research Centre, School of Chemistry and Chemical Engineering Queen's University of Belfast, Stranmillis Road, Belfast, UK

^eDepartment of Molecular Medicine, Biochemistry Unit, University of Pavia, Via C. Forlanini 6, 27100 Pavia, Italy
floriana.billeci@unipa.it

Ionic liquids (ILs) are employed in several fields thanks to their well-known properties. For a long time, ILs were considered the “green” alternative to conventional organic solvents.¹ However, the increasing attention on environmental health led to consider different ILs structures and alternative synthetic pathways. Considering the tunability of IL structures, new synthetic approaches with natural sources as starting materials were taken into account.² Here, new eco-friendly ILs were synthesised using gluconic acid. The structures carry gluconic moiety on the cation or as the anion (Figure 1). Hence, several OH groups decrease toxicity and shape a high coordinative site.

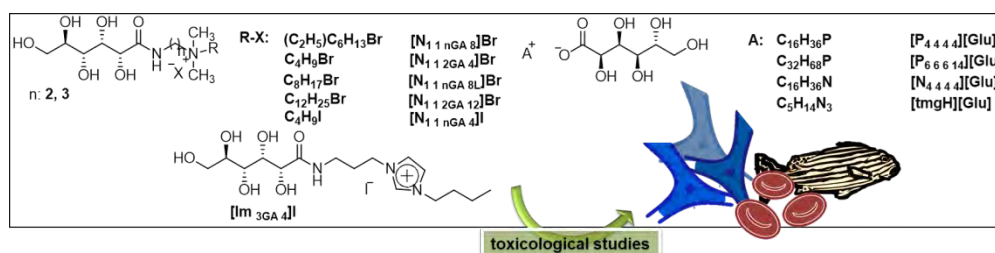


Figure 1: Structures of ILs synthesised and characterised in this work.

These new organic salts were fully characterised from a physico-chemical point of view. However, also, the study of their impact on the ecosystem health was performed. To this aim, three different cancer cell lines, Hela, HTC and MCF7 cells, were chosen to assess cytotoxicity effects of ILs.³ Moreover, haemolysis investigations were carried out to consider the effect on human blood cells. Finally, Zebrafisha organisms were used as an aquatic model for ILs toxicity.⁴ Indeed, the response by living organisms in an aquatic ecosystem gives additional information for dispose of ILs. In the aim of a sustainable approach, these ILs have been designed and analysed to achieve good materials with low environmental impact.

References:

- [1] R. M. Pagni *Ionic Liquids as Alternatives to Traditional Organic and Inorganic Solvents*, Vol. 92 Springer, **2003**, 105-127.
- [2] H. Ohno, K. Fukumoto, *Acc. Chem. Res.* **2007**, *40*, 1122-1129.
- [3] X. Xia, R. Wan, P. Wang, W. Huo, H. Dong Q. Du, *Ecotoxicol. Environ. Saf.* **2018**, *162*, 408-414.
- [4] S.-K. Ruokonen, C. Sanwald, M. Sundvik, S. Polnick, K. Vyavaharkar, F. Duša, A. J. Holding, A. W. T. King, I. Kilpeläinen, M. Lämmerhofer, P. Panula S. K. Wiedmer, *Environ. Sci. Technol.* **2016**, *50*, 7116-7125.

Conversion of carbohydrates into 5-HMF in Deep Eutectic Solvents under mild reaction conditions

S. Marullo, C. Rizzo, R. Noto, F. D'Anna

Dipartimento STEBICEF-Sezione di Chimica, Viale delle Scienze Ed. 17, 90128 Palermo
salvatore.marullo@unipa.it

Faced by pressing challenges like the depletion of fossil fuels, researchers are putting intense focus on the replacement of current feedstocks with renewable and sustainable sources, like lignocellulosic biomass, for the obtainment of industrially relevant chemicals.¹ To this aim, in agreement with the principles of Green Chemistry, the use of environmentally friendly and safe solvents, as well as mild reaction conditions are factors of paramount importance. In this context, the latest development is represented by Deep Eutectic Solvents (DES).² These are mixtures which, at a particular composition, display a definite melting point, lower than those of each individual component. Oftentimes they are composed of cheap and naturally occurring components and their preparation requires only a mixing process, without any synthetic or purification step.³ In the framework of our interest in biomass valorisation in non-conventional solvents,^{4,5} we studied the conversion of fructose and sucrose, into the chemical platform 5-hydroxymethylfurfural (5-HMF). The reactions were promoted by the resin Amberlyst 15, in a wide range of DES differing for the nature of the hydrogen bonding donating and accepting components (Figure 1).

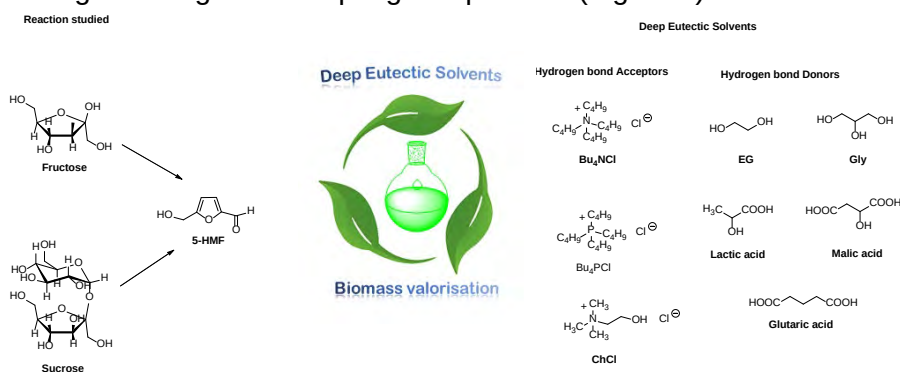


Figure 1: Reaction studied and DES used.

From our study, we found that coupling Amberlyst 15 with carboxylic acid-based DES allowed us to obtain high yields of 5-HMF under the relatively low temperature of 60 °C for fructose and 80 °C for sucrose, which are competitive with what reported in literature, but without using strong acids or transition metal salts as catalysts. The structure of the hydrogen bond donor dramatically affects the reaction outcome. Finally, we also investigated the recyclability of the best-performing DES.

References:

- [1] P. Gallezot, *Chem. Soc. Rev.* **2012**, *41*, 1538-1558.
- [2] E. L. Smith; A. P. Abbott; K. S. Ryder, *Chem. Rev.* **2014**, *114*, 11060-11082.
- [3] A. Paiva; R. Craveiro; I. Aroso; M. Martins; R. L. Reis; A. R. C. Duarte, *ACS Sustainable Chem. Eng.* **2014**, *2*, 1063-1071.
- [4] S. Marullo; C. Rizzo; F. D'Anna, *Front. Chem.* **2019**, *7*, 134.
- [5] S. Marullo; C. Rizzo; A. Meli; F. D'Anna, *ACS Sustainable Chem. Eng.* **2019**, *7*, 5818-5826.

Zinc oxide nanoparticles supported on halloysite nanotubes for environmental remediation

M. Massaro,^a S. Riela,^a G. Lazzara,^b G. Nicotra,^c C. Spinella,^c R. Noto^a

^a *Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche (STEBICEF), University of Palermo, Viale delle Scienze, Ed. 17, 90128 Palermo*

^b *Dipartimento di Fisica e Chimica (DiFC), University of Palermo, Viale delle Scienze, Ed. 17, 90128 Palermo*

^c *CNR-IMM, Zona industriale strada VIII, 5, 95121 Catania*
marina.massaro@unipa.it

Halloysite nanoclays (HNTs) are promising nanomaterials because of their versatile properties, such as hollow tubular morphology and tunable surface chemistry. HNTs are biocompatible, non-toxic and abundantly available at low cost. Due to these characteristics HNTs are suitable for development of hybrid sustainable materials, which are perspective for wastewater remediation, green packaging and drug delivery.^{1,2}

Functionalized halloysite constitutes a valuable support for metal nanoparticles, promoting catalytic applications with tunable properties. The peculiar tubular shape of HNTs favors the dispersion and surface availability of the supported metal nanoparticles that are active in the catalytic path. Moreover, the presence of an empty lumen opens new perspectives for the production of nanoarchitectures with synergistic catalytic effects, due to the increase in local concentrations and confinement.

Among the various alternative catalysts, zinc oxide received much attention due to its cheap, non-toxic, thermally stable, and amphoteric properties.

Herein we report the synthesis and characterization of a novel catalyst based on zinc oxide nanoparticles supported on halloysite nanotubes. The new material has been thoroughly investigated by means of several techniques. To evaluate the feasibility of the hybrid as a catalyst we studied the photodegradation of several organic dyes, chosen as pollutant models, using different experimental conditions. We also performed some recycling experiments to assess the stability of the material obtained.

References:

- [1] M. Massaro, G. Lazzara, S. Milioto, R. Noto, S. Riela, *J. Mater. Chem. B* **2017**, 5, 2867-2882.
- [2] M. Massaro, C.G. Colletti, G. Lazzara, S. Milioto, R. Noto, S. Riela, *J. Mater. Chem. A* **2017**, 5, 13276-13293.

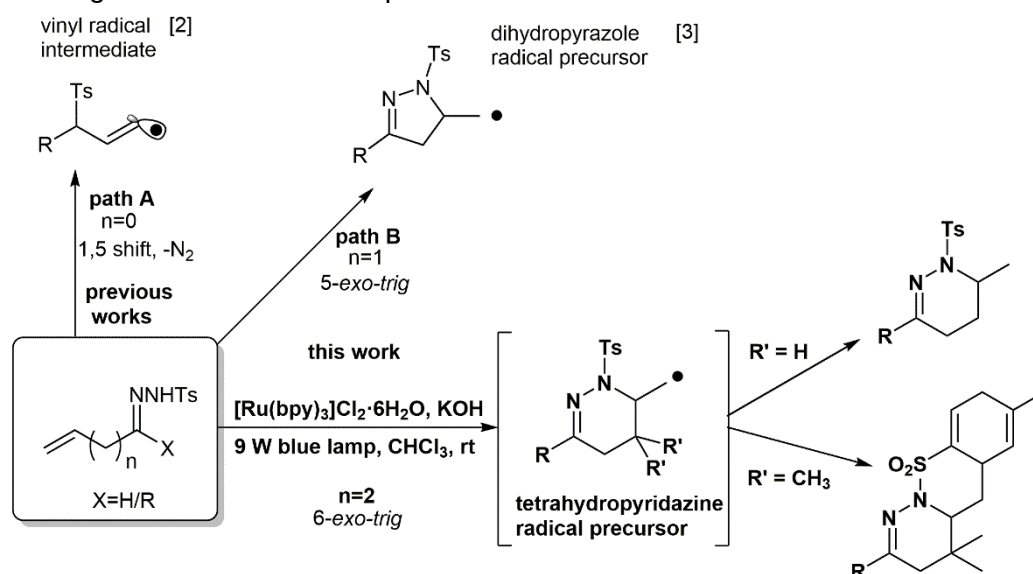
Visible-Light-Driven Synthesis of Tetrahydropyridazines from γ - δ Unsaturated *N*-Tosylhydrazones

E. Azzi, S. Parisotto, F. Pellegrino, V. Maurino and A. Deagostino

Dipartimento di Chimica, Università degli Studi di Torino, Via Pietro Giuria 7, 10125-Torino, Italia
emanuele.azzi@unito.it

Tetrahydropyridazines are six-membered aza-heterocycles which has proven to be biologically active. Many synthetic routes have been explored for their synthesis, such as the condensation of 1,4-keto carboxylic acid with hydrazine, followed by reduction, Diels–Alder reactions of 1,2-diaza-1,3-dienes with olefins and rearrangement reactions¹. Thanks to the previous experiences of our group with photocatalytic generation of highly reactive radical species from tosylhydrazones, we envisaged the possibility of an alternative visible light-mediated synthesis of these heterocycles.

Our group has described the first example of a visible-light-driven transformation of α,β -unsaturated sulfonylhydrazones leading to a vinyl radical intermediate (path A, Scheme 1)², while a previous work reported how β,γ -unsaturated sulfonylhydrazones undergo hydroamination reaction to generate a dihydropyrazoles radical precursor (path B, Scheme 1)³. We report how the further shift of the unsaturation to the γ - δ position lead to the formation of a tetrahydropyridazine radical precursor under photocatalytic conditions (this work, Scheme 1). Thus, we propose the first example of a photocatalytic synthesis of tetrahydropyridazines and tetrahydropyridazine-based complex structures through an eco-sustainable process and mild reaction conditions.



Scheme 1: Reactivity of different unsaturated *N*-tosylhydrazones.

References:

- [1] a) D. W. Combs, K. Reese, A. Phillips, *J. Med. Chem.* **1995**, 38, 4878-4879; b) O. A. Attanasi, G. Favi, F. Mantellini, S. Mantenuto, G. Moscatelli S. Nicolini, *Synlett* **2015**, 26, 193-196; c) R. F. Salikov, A. Yu. Belyy Y. V. Tomilov, *Tetrahedron Lett.* **2014**, 55, 5936–5939; d) S. Morita, J. Matsuo, *Tetrahedron Lett.* **2017**, 58, 932-934.
- [2] S. Parisotto, G. Garreffa, C. Canepa, E. Diana, F. Pellegrino, E. Priola, C. Prandi, V. Maurino, A. Deagostino, *ChemPhotoChem*, **2017** 1, 56-59.
- [3] X.-Q. Hu, J.-R. Chen, Q. Wei, F.-L. Liu, Q.-H. Deng, A. M. Beauchemin, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2014**, 53, 12163-12167; *Angew. Chem.* **2014**, 126, 12359-12363.

Synthesis and EPR investigation of a new stable diradical macrocycle

E. Mezzina, P. Franchi, C. Poderi, M. Lucarini

Department of Chemistry "Giacomo Ciamician", University of Bologna, Via S. Giacomo 11,
40126 Bologna, Italy.
elisabetta.mezzina@unibo.it

N-Oxyl compounds represent a versatile class of stable organic radicals with unique properties and reactivity. The diverse chemistry of these compounds has enabled the use of nitroxides in applications covering many fields of chemistry.¹ An interesting possibility is incorporating radicals in the molecular components of a synthetic molecular machine and using electron paramagnetic resonance (EPR) spectroscopy to investigate changes in the magnetic properties as the device operates. Rotaxanes containing nitroxide units have been described in the literature² by us, and in these cases the paramagnetic unit was used as spin probe and linked to the macrocycle or to the thread without participating to the recognition process. Recently, we prepared the first example of a nitroxide-containing bistable rotaxane **2** (Figure 1) in which the N-O• radical acts not only as EPR probe for the shuttling process, but is also directly involved in the recognition process of a molecular site.³ In the reported [2]rotaxane, the wheel consists of a 2,5-dimethyl-2,5-diphenylpyrrolidine-N-oxyl radical bound to a crown ether fragment at the *meta* positions of both aromatic rings (**1**, Figure 1). In this context, the presence of radical centres provide unusual functional addition to the diversity of templates available for assembling rotaxanes. For this reason we explored the possibility to introduce a second paramagnetic centre into a crown ether macrocycle in order to investigate the spectral communication changes between the two radicals arising from the complexation and the movements of the wheel occurring in a molecular machine upon an external input.

In the present contribution we report the synthesis of the diradical crown ether **3** and the EPR studies of the molecular assemblies of this new macrocycle with cationic organic guests.

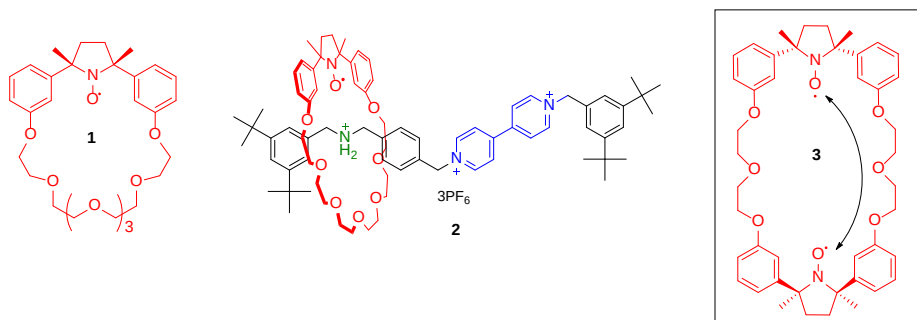


Figure 1: Structures of macrocycles **1**, **3** and rotaxane **2**.

References:

- [1] G. I. Likhtenshtein, J. Yamauchi, S. Nakatsuji, S. Smirnov, R. Tamura, in *Nitroxides: Applications in Chemistry, Biomedicine and Materials Science*, Wiley-VCH, Weinheim, **2008**.
- [2] V. Bleve, C. Schäfer, P. Franchi, S. Silvi, E. Mezzina, A. Credi, M. Lucarini, *ChemistryOpen* **2015**, *4*, 18-21.
- [3] V. Bleve, P. Franchi, E.; Konstanteli, L. Gualandi, S. M. Goldup, E. Mezzina, M. Lucarini, *Chem. Eur. J.* **2018**, *24*, 1198-1203.

Regio- and diastereoselective organo-zinc promoted arylation of *trans* 2,3-diaryloxiranes by arylboronic acids: stereoselective access to *trans* 2,3-diphenyl-2,3-dihydrobenzofuran.

T. Laurita, P. Lupattelli, L. Chiumminto, M. Funicello

Department of Sciences, University of Basilicata, Via dell'Ateneo Lucano, 10 85100 Potenza (Italy)
tlaurita@unisa.it

The 2,3-dihydrobenzofuran ring-system constitutes the core skeleton of numerous biologically active compounds, as resveratrol oligomers. Among them 2,3-diaryl-2,3-dihydrobenzofurans are the main dimers.¹ *Orto*-oxo substituted *trans* 2,3-diaryloxiranes, prepared taking advantage of the Corey-Chaykovsky reaction between the suitable *o*-substituted benzaldehyde and benzyldiene sulfur ylide², proved suitable starting materials for the first stereoselective access to *trans* 2,3-diphenyl-2,3-dihydrobenzofuran (Figure 1). The epoxides were regio- and stereoselectively opened by phenyl zinc reagent, which was obtained *in situ* from phenylboronic acid via a facile B-Zn exchange. Deprotection reactions of *orto*-oxo substituted affording the corresponding hydroxyphenols and the last Mitsunobu type cyclization with Ph₃P/DEAD afforded in high yield *trans* 2,3-diphenyl-2,3-dihydrobenzofuran. The use of enantioenriched starting diaryloxiranes resulted in no loss of stereochemical integrity in the final *trans* 2,3-dihydrobenzofuran, which was characterized for the first time in enantioenriched form³.

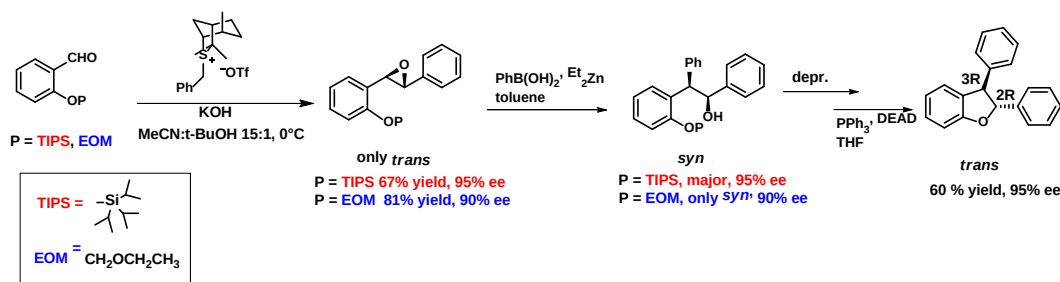


Figure 1

The reaction proved to be quite general using different aryl boronic acids as nucleophilic source and *orto*-ethoxymethoxy substituted *trans* 2,3-diaryloxirane as electrophilic acceptor. In particular, different *syn* aryl alcohols⁴ **A** were prepared in good yields. Scope and limitations of the method for the preparation of functionalized *trans* 2,3-diaryl-2,3-dihydrobenzofurans **B** (Figure 2) and mechanistic issues on ring-opening reaction will be discussed.

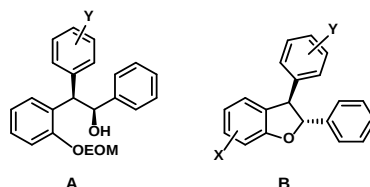


Figure 2

References:

- [1] M. H. Keylor, B. S. Matsuura, C. R. J. Stephenson, *Chem. Rev.* **2015**, *115*, 8976-9027.
- [2] P. Lupattelli, L. Chiumminto, M. Funicello, F. Tramutola, A. Marmo, N. Gliubizzi, D. Tofani, *Tetrahedron* **2015**, *71*, 5662-5668.
- [3] P. Lupattelli, L. Chiumminto, M. Funicello, T. Laurita, R. D'Orsi, D. Tofani, *manuscript submitted*.

Green and Mild Friedel-Crafts Benzylation of Arenes and Heteroarenes Under *On Water* Conditions

P. La Manna,^a A. Soriente,^a M. De Rosa,^a A. Buonerba,^a C. Talotta,^a C. Gaeta,^a P. Neri^a

^aDipartimento di Chimica e Biologia "A. Zambelli", Università di Salerno, Via Giovanni Paolo II 132, I-84084, Fisciano (SA), Italy.
plamanna@unisa.it

Among the most exploited reactions for the industrial synthesis of fine chemicals and pharmaceutical compounds, Friedel-Crafts¹ alkylation, and particularly benzylation, of arenes and heteroarenes plays a major role². Usually, metal-transition based catalysts are employed on industrial scale, with issues related to the sustainability and costs of the catalysts³. A greener approach involves the use of *on water* conditions⁴. It is known that under *on water* conditions hydrophobic effect⁵ drives catalyst and reactants to aggregate, leading to an amplification of secondary interactions, with amazing outcomes in catalysis^{6,7}. In the present communication, we will show that under *on water* conditions, C-undecyl-resorcin[4]arene **1** is able to catalyse Friedel-Crafts benzylation of several arenes and heteroarenes⁸ (Figure 1).

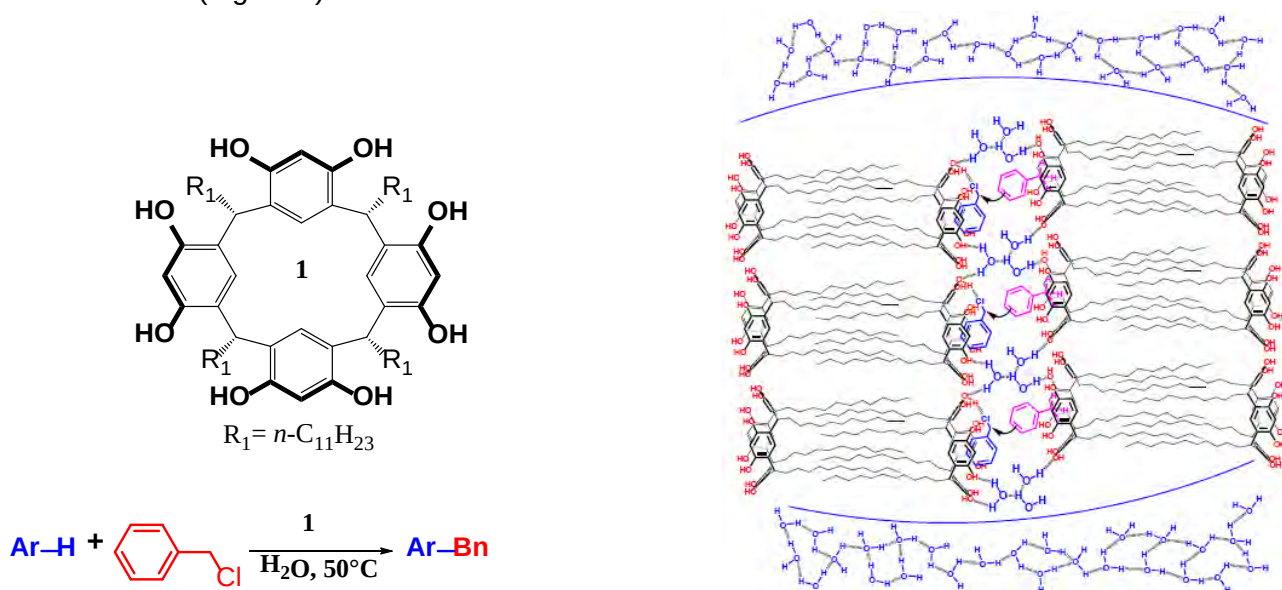


Figure 1. Left, Friedel-Crafts benzylation of arenes and heteroarenes promoted by resorcin[4]arene **1** under *on water* conditions; right, bilayer motif proposed as a model of the 3D packing of **1** in the solid state.

References:

- [1] C. Friedel, J. M. Crafts, *C. R. Hebd. Séances Acad. Sci.* **1877**, *84*, 1450-1454.
- [2] P. H. Groggins, S. B. Detwiler, *Ind. Eng. Chem.* **1952**, *44*, 2012-2015.
- [3] M. Rueping, B. J. Nachtsteim, *Beilstein J. Org. Chem.* **2010**, *6*, 6.
- [4] S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2005**, *44*, 3275-3279.
- [5] R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 159-164.
- [6] M. C. Pirrung, *Chem. Eur. J.* **2006**, *12*, 1312-1317.
- [7] J. H. Sim, C. E. Song, *Angew. Chem. Int. Ed.* **2017**, *56*, 1835-1839.
- [8] P. La Manna, A. Soriente, M. De Rosa, A. Buonerba, C. Talotta, C. Gaeta, P. Neri, *ChemSusChem*. doi:10.1002/cssc.201900137.

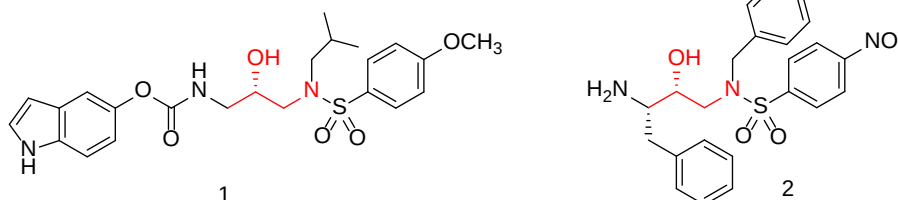
From HIV protease inhibitors to anticancer agents: diversity-oriented synthesis of new compounds with double biological activity

R. D'Orsi, L. Chiummiento, M. Funicello, P. Lupattelli, M. F. Armentano

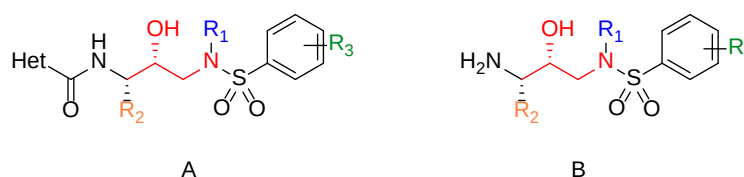
Department of Science, University of Basilicata, Via dell'Ateneo Lucano 10, 85100, Potenza, Italy
E-mail: rosarita.dorsi@gmail.com

Cancer is a complex disease and the main cause of death in developed countries. The success of some HIV protease inhibitors in treating HIV-related Kaposi's sarcoma proved the feasibility of developing approved anti-HIV drugs for cancer therapeutics.¹ Furthermore, the emergence of drug resistance prompts to produce novel substances with lower side effects and higher efficacy, especially if a double biological activity is possible. In a previous work we synthesized compound **1**, bearing an hydroxyethylaminic core linked to an heterocycle moiety, which showed both its biological activity against HIV protease² and its cytotoxicity on HepG2 cell lines³. Moreover, compound **2**, recently described in literature,⁴ which contains the free amino group in the hydroxyethylamine moiety, has proved to be important for anti-proliferative activity. Stimulated by the success of these molecules as antitumor agents, we prepared a library of compounds of general structure **A** and **B**, and tested their potential broad spectrum activities. The synthesis and biological results will be discussed.

Previous works



This work...



R1=H, iBu, Bn
R2=H, Ph
R3=4-OMe, 3,4-diOMe, 4-NO2

References:

- [1] a) W.A. Chow, C. Jiang, M. Guan, *Lancet Oncol.* **2009**, *10*, 61-71; b) Z. Lv, Y. Chu, Y. Wang, *Research and Palliative Cure* **2015**, *7*, 95-104.
- [2] F. Tramutola, M.F. Armentano, F. Berti, L. Chiummiento, P. Lupattelli, R. D'Orsi, R. Miglionico, L. Milella, F. Bisaccia, M. Funicello, *Bioorg. Med. Chem.* **2019**, *27*, 1863-1870.
- [3] F. Tramutola, M.F. Armentano, F. Berti, L. Chiummiento, P. Lupattelli, R. D'Orsi, R. Miglionico, L. Milella, F. Bisaccia, M. Funicello, manuscript in preparation.
- [4] V. Facchinetti, M. Moreth, C. R. B. Gomes, C. Pessoa, F. A. R. Rodrigues, B. C. Cavalcanti, A. C. A. Oliveira, T. R. Carneiro, I. L. Gama, M. V. N. de Souza, *Med. Chem. Res.* **2015**, *24*, 533-542.

New Molecules as Translational Readthrough Promoters of Nonsense Mutations: Rescuing the CFTR Protein

A. Campofelice,^a P. Ricco Galluzzo,^a L. Lentini,^a R. Melfi,^a M. Tutone,^a A. Di Leonardo,^a I. Pibiri,^a

^a *Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche -STEBICEF- Università degli Studi di Palermo, Viale delle Scienze Ed. 16-17, 90128, Palermo, Italy.*
ambra.campofelice@unipa.it

The presence of a nonsense mutation in the DNA frame encoding for a functional protein is one of the causes of severe genetic disease. In particular for Cystic fibrosis (CF), about 10% of CF patients worldwide possess a nonsense mutation in the CFTR gene, causing the absence of the CFTR protein expression and a more severe form of the disease.

Pharmaceutical approaches targeting the specific genetic defect have been faced and heterocyclic scaffolds rule the personalized medicinal approach, as proved by many studies in the CF field. In this context, a potential treatment approaching the genetic nonsense mutation is to promote translational readthrough of premature termination codons (PTCs) by translational readthrough promoters.

PTC124, also known as Ataluren, was launched by PTC Therapeutics to promote the readthrough of premature but not normal termination codons in HEK293 cells.¹

We reported a rationale for Ataluren promoted readthrough of PTCs by computational approach and GFP-reporter cell-based assay² and the observed enhancement of readthrough activity by some Ataluren derivatives.^{3,4,5} Moreover, recently we further investigated the possible targets for readthrough promoters.⁶

By using an integrated approach consisting of computational screening, synthesis and biological tests, we identified new small molecules showing high readthrough activity. We evaluated quantitatively the CFTR rescue after treatment with our derivatives in CF model systems and in cells expressing a *nonsense*-CFTR-mRNA.

References:

- [1] E. M. Welch, E. R. Barton, J. Zhuo, Y. Tomizawa, W. J. Friesen, P. Trifillis, S. Paushkin, M. Patel, C. R. Trotta, S. Hwang, R. G. Wilde, G. Karp, J. Takasugi, G. Chen, S. Jones, H. Ren, Y.-C. Moon, D. Corson, A. A. Turpoff, J. A. Campbell, M. M. Conn, A. Khan, N. G. Almstead, J. Hedrick, A. Mollin, N. Risher, M. Weetall, S. Yeh, A. A. Branstrom, J. M. Colacino, J. Babiak, W. D. Ju, S. Hirawat, V. J. Northcutt, L. L. Miller, P. Spatrick, F. He, M. Kawana, H. Feng, A. Jacobson, S. W. Peltz, H. L. Sweeney, *Nature* **2007**, *447*, 87-91.
- [2] L. Lentini, R. Melfi, A. Di Leonardo, A. Spinello, G. Barone, A. Pace, A. Palumbo Piccionello, I. Pibiri, *Mol. Pharm.* **2014**, *11*, 653-664.
- [3] I. Pibiri, L. Lentini, R. Melfi, G. Gallucci, A. Pace, A. Spinello, G. Barone, A. Di Leonardo, *Eur. J. Med. Chem.* **2015**, *101*, 236-244.
- [4] I. Pibiri, L. Lentini, M. Tutone, R. Melfi, A. Pace, A. Di Leonardo, *Eur. J. Med. Chem.* **2016**, *122*, 429-435.
- [5] I. Pibiri, L. Lentini, R. Melfi, M. Tutone, S. Baldassano, P. Ricco Galluzzo, A. Di Leonardo, A. Pace, *Eur. J. Med. Chem.* **2018**, *159*, 126-142.
- [6] M. Tutone, I. Pibiri, L. Lentini, A. Pace, A. M. Almerico, *ACS Med. Chem. Lett.* **2019**, *in press*. [DOI: 10.1021/acsmchemlett.8b00558]

A novel procedure for rapid and accurate quantification of amino functionalities bonded to solid porous matrices

F. Buonsenso,^a G. Manzi,^{a,c} O. H. Ismail,^a A. Ciogli,^a G. Siani,^b M. Pierini^a

^a Dipartimento di Chimica e Tecnologie del Farmaco, Università degli Studi di Roma "La Sapienza", Piazzale Aldo Moro 5, 00185 Roma (Italy)

^b Dipartimento di Farmacia, Università "G. d'Annunzio", Via dei Vestini 31, 66013 Chieti (Italy)

^c Present Address: Tide Microfluidics B.V., Capitoool 41, 7521 PL Enschede, The Netherlands
e-mail: fabio.buonsenso@uniroma1.it

Recently, solid porous matrices functionalized with amino groups have found wide use in the field of CO₂ capture and storage technologies¹ as well as in separation science for chromatographic applications. In fact, they are profitably used as stationary phases for HILIC (Hydrophilic Interaction Liquid Chromatography) separations², which allow the effective resolution of interesting compound classes (e.g. mixtures of mono- or oligo-saccharides). In this study, we developed a new method to quantify the density of basic sites on solid matrices (in particular amino groups). The procedure is fast and easy, and not destructive towards the analyzed material. The approach is based on the preventive salification of the basic groups linked to the solid by 3,5-dinitrobenzoic acid (DNBA). Quantification of the basic functionalities is then performed by an UV-spectrophotometric retro-titration of the salified solid matrix (or, alternatively, by reverse phase HPLC approach), resorting to a preventive either acid or basic displacement of DNBA from the solid material.

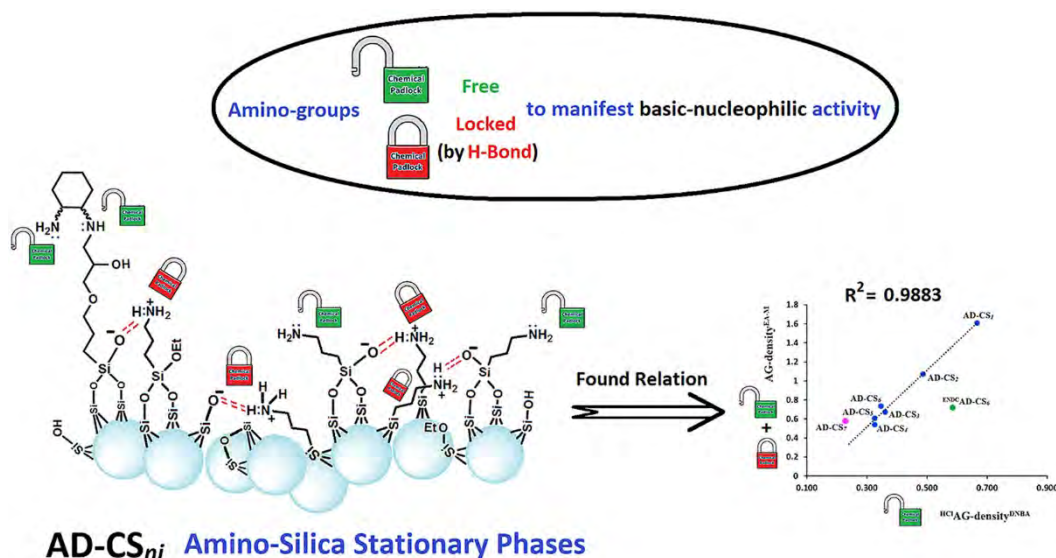


Figure 1: Left side: schematic representation of amino functionalities bonded to amino-silica stationary phases. Right side: plot of the linear correlation found between density values of basic sites chemically bonded to the surface of the AD-CS_{ni} silica samples determined by means of the EA-M and DNBA-M methods, the last one based on final acid displacement of DNBA.

References:

- [1] W. Chaikittisilp, J. D. Lunn, D. F. Shantz, C. W. Jones, *Chem. Eur. J.* **2011**, *17*, 10556-10561.
- [2] A. Cavazzini, A. Felinger, *Liquid Chromatography*, Elsevier Inc, 2013 Chapter 5.

Synthesis of new Water Reducer Plasticizers for concrete, gypsum and clay

C. Capacchione,^{a,b} C. Talotta,^a P. Neri,^a I. Bruno,^b A. Pauciulo,^b A. R. Bartiromo,^b R. Gliubizzi,^b C. Gaeta,^a

^aDipartimento di Chimica e Biologia "A. Zambelli", Università di Salerno, Via Giovanni Paolo II, Fisciano (SA),

^bBI-QEM Specialties SPA, Zona industriale - 84021 Buccino (SA) - Italia

e-mail: clcapacchione@unisa.it

Plasticizers are interesting chemicals admixtures used in materials engineering to improve both fresh concrete, gypsum and clay workability and mechanical properties of hardened materials. Their main function is to decrease the amount of needed mixing water and to control the setting time without losing fluidity of the pastes, which results in higher strength and better durability of final materials. Polymeric additives can cause dispersion of matrix particles due to their structure: indeed, plasticizers combine electrostatic repulsion effect of charged groups on their backbone and the steric hindrance effect of the linked side-chains.¹

In the late twenties the first-generation additives were developed from by-products obtained from the paper firm. Due their important applications in engineering field, research has been focused on the development of new and more performing plasticizers such as naphthalene/melamine sulfonate derivatives and polycarboxylate esters/ethers, which represent the second and third generation of additives.²

Dispersants gave an important and fundamental improvement in materials engineering during the 40 last years, however there is a serious environmental problem related to their use.³ In order to avoid that pollution problem, we propose to direct our research towards the development of new eco-sustainable and biodegradable superplasticizers from backbone based on cyclodextrins, polysaccharides and modified polycarboxylic derivatives as green alternatives to the existing petrochemical products.

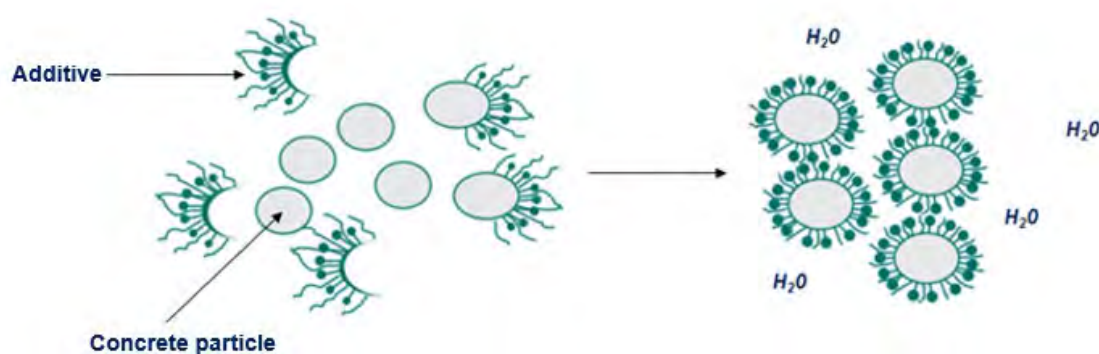


Figure 1: Action mechanism of plasticizers.

References:

- [1] L. Shenghua, L. Jingjing, Z. Qingfang, H. Ling, S. Ting, *Ind. Eng. Chem. Res.* **2014**, 53, 3908-3916.
- [2] H. Wu, H. Guo, J. Lei, R. Zhang, Y. Liu, *Front. Chem. China* **2007**, 2, 322-325.
- [3] S. Ruckstuhl, M. Suter, H. Kohler, W. Giger, *Environ. Sci. Technol.* **2002**, 36, 3284-3289.

Boron-functionalized benzodithiophenes

L. Menduti,^a A. Bossi,^b S. Arnaboldi,^a C. Baldoli,^{b*} E. Licandro^{a*}

^aDipartimento di Chimica, Università degli Studi di Milano. Via C. Golgi 19, 20133 Milano

^bCNR- Istituto di Scienze e Tecnologie Molecolari (ISTM). Via C. Golgi 19, 20133 Milano
luigi.menduti@studenti.unimi.it

Tricoordinate boron-functionalized molecules, such as triarylboranes, have recently emerged as a powerful new class of electron acceptors with great potential for application in optoelectronic n-type materials.^{1,2} This electron-accepting ability is the result of the p- π^* conjugation between the empty p orbital of boron atom and the π^* orbital of the π -conjugated framework. Furthermore, aromatic organo-boron systems often show fluorescence emission in the visible range of the electromagnetic spectrum. In recent years many examples of boron-functionalized molecules have been reported but, given their unique n-type semiconducting features, the design of new structures is still an attractive and relevant research topic.

We present the synthesis of new triarylboranes **1–4** containing linear or angular benzodithiophene (BDT) as core molecule and bearing one or two dimesityl boryl groups (Figure 1).

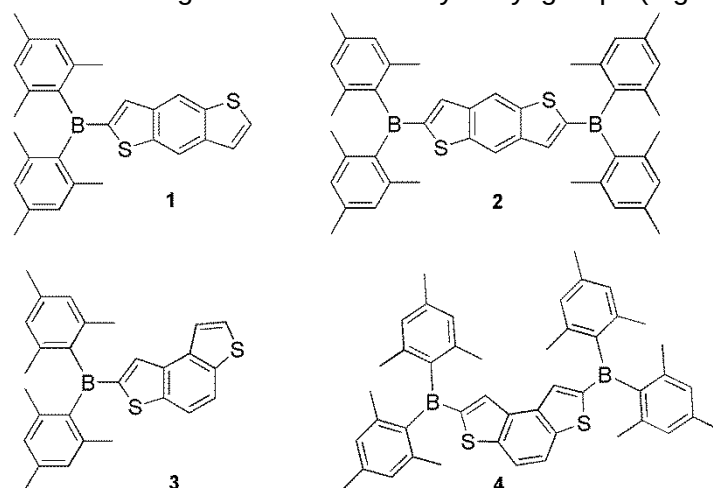


Figure 1. New BDT-based triarylboranes.

Photophysical and electrochemical studies were carried out to evaluate the potential of structures **1–4** as building blocks of materials for optoelectronic applications. In particular, compound **2** was selected as the most promising candidate since it shows good luminescence performances ($\lambda_{\text{max}} = 470 \text{ nm}$; $\Phi = 0.57$), redox properties and capability to detect fluoride anions.

References:

- [1] E. Von Grotthus, A. John, T. Kaese, M. Wagner, *Asian J. Org. Chem.* **2018**, 7, 37-53.
- [2] G. Turkoglu, M. E. Cinar, T. Ozturk, *Molecules* **2017**, 22, 1522-1546.

Development of new beta-lactam-based integrin ligands: Synthesis and Applications

M. Cirillo,^a G. Martelli,^a M. Baiula,^b S. M. Spampinato,^b D. Giacomini^{a,*}

^a Department of Chemistry "G. Ciamician", University of Bologna, Via Selmi 2, 40126 Bologna, Italy

^b Department of Pharmacy and Biotechnology, University of Bologna, Via Irnerio 48, 40126 Bologna, Italy
e-mail: martina.cirillo3@unibo.it

Integrins are adhesion receptors that mediate dynamic adhesive cell-cell and cell-matrix interactions; because of the important roles of integrins and their ligands in biological development, immune responses, leukocyte traffic, haemostasis, and cancer, their potential as therapeutic tools is now widely recognized.¹ Our research group recently developed a library of novel agonist integrin ligands characterized by a beta-lactam scaffold² and demonstrated that these compounds could promote integrin trafficking and endocytosis. Therefore the research group developed some conjugates of the most active agonist candidates with fluorescent tags (Rhodamine B and Fluorescein isothiocyanate) in order to evaluate by confocal microscopy analysis their internalization together with the integrin. The preliminary results are encouraging. Because of this behavior, we have been then focusing on the development and synthesis of two new beta-lactam compounds conjugated to cytotoxic agents (Figure 1), which could act as a drug-cargo for a selective delivery of cytotoxic molecules directly into cancer cells that overexpress integrins.

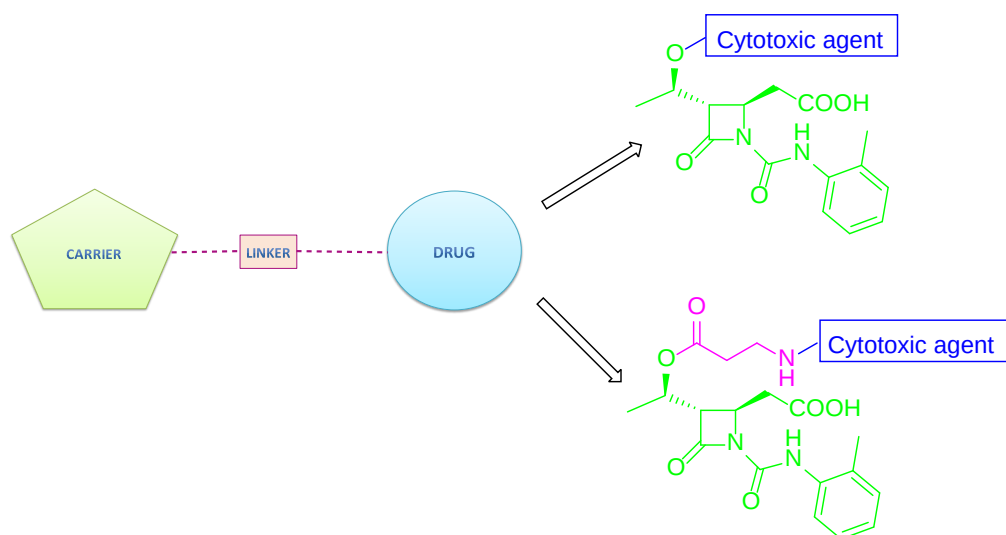


Figure 1: General scheme of targeted drug delivery system and development of two new beta-lactam-based integrin ligands conjugated to cytotoxic agents.

References:

- [1] A. Tolomelli, P. Galletti, M. Baiula, D. Giacomini, *Cancers*, **2017**, 9, 78.
- [2] M. Baiula, P. Galletti, G. Martelli, R. Soldati, L. Belvisi, M. Civera, S. D. Dattoli, S. M. Spampinato, D. Giacomini, *J. Med. Chem.* **2016**, 59, 9721-9742.

Enantioselective Desymmetrization of 1,4-Dihydropyridines by Oxidative NHC-Catalysis

A. Massi,^a G. Di Carmine,^a D. Ragno,^a A. Brandolese,^a O. Bortolini,^a D. Pecorari,^b A. Mazzanti^b

^aDepartment of Chemical and Pharmaceutical Sciences, University of Ferrara, Via L. Borsari 46, I-44121 Ferrara, Italy

^bDepartment of Industrial Chemistry "Toso Montanari", University of Bologna, V. Risorgimento 4, I-40136 Bologna, Italy
alessandro.massi@unife.it

According to Evans definition, 1,4-dihydropyridines (1,4-DHPs) are privileged structures endowed with a plethora of different biological activities depending on substitution of the heterocyclic scaffold. 1,4-DHPs are primarily used as calcium channel blockers for the treatment of vascular disorders, but also as antitumor and antidiabetic agents, and drugs to cure many other diseases. As with other pharmaceuticals, the role of C4 stereochemistry in chiral 1,4-DHPs is fundamental to modulate the biological activity and prevent adverse effects of these molecules. Additionally, optically pure DHPs are precious precursors of different chiral N-heterocycles and may serve as NADH mimetics in asymmetric reductions.

Herein, the unprecedented desymmetrization of prochiral dialdehydes catalyzed by N-heterocyclic carbenes (NHCs) under oxidative conditions has been applied to the highly enantioselective synthesis of 1,4-DHPs starting from 3,5-dicarbaldehyde substrates. Synthetic elaboration of the resulting 5-formyl-1,4-DHP-3-carboxylates allowed to access the class of pharmaceutically relevant 1,4-DHP-3,5-dicarboxylates (Hantzsch esters). DFT calculations suggested that the enantioselectivity of the process is determined by the transition state involving the oxidation of the Breslow intermediate by the external quinone oxidant.^[1]

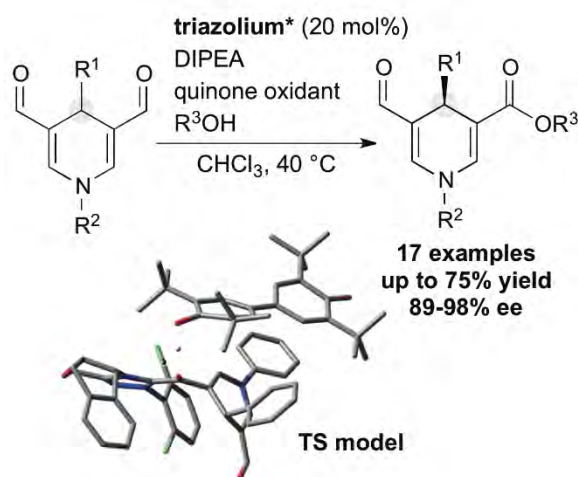


Figure 1: Desymmetrization process.

References:

- [1] G. Di Carmine, D. Ragno, A. Brandolese, O. Bortolini, D. Pecorari, F. Sabuzi, A. Mazzanti, A. Massi, *Chem. Eur. J.* **2019** (<https://doi.org/10.1002/chem.201901243>)

Functionalization of the BODIPY core with styryl carboranes: synthesis, characterization and photophysical properties.

C. Bellomo,^a M. Blangetti,^a R. Nuñez,^b C. Prandi^a

^aDipartimento di Chimica, Università di Torino, via P. Giuria 7, I-10125 Torino, Italy

^bICMAB-CSIC, Campus de la UAB, E-08193, Bellaterra, Barcelona (SPAIN)
chiara.bellomo@edu.unito.it

Carboranes are well-known interesting chemical species part of the boron cluster chemistry with unique physico-chemical features.¹ Many new synthetic procedures have been developed to functionalize these compounds, and the interest in studying their photoluminescent (PL) analogues in view of new applications in several fields has noticeably increased recently.² In fact, the carboranyl cage might influence the PL properties of the final material and gives an additional thermal stability, which is crucial in tuning the final properties of a certain material.

Owing to their unique spectroscopic properties and their easiness of functionalization, BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene) dyes have emerged as an interesting new class of fluorophores for boron clusters functionalization.³ As part of our studies aimed at tagging a class of biological relevant compounds using fluorescent probes for live-cell imaging applications, we recently reported the synthesis of carborane-BODIPY dyads through the optimization of a Heck coupling reaction between different (aza)BODIPYs and styryl (*ortho* and *meta*) carboranes.⁴ Starting from these grounds, we envisaged that the BODIPY might be functionalized with more than one styrene-containing carborane derivative and on different positions of the BODIPY core in order to tune the fluorescent properties. We herein report the synthesis of a small library of symmetric and asymmetric carborane-BODIPY triads by means of a Pd-catalyzed Heck coupling reaction (Figure 1). The characterisation, the spectroscopic and photochemical properties of these new compounds are also discussed.

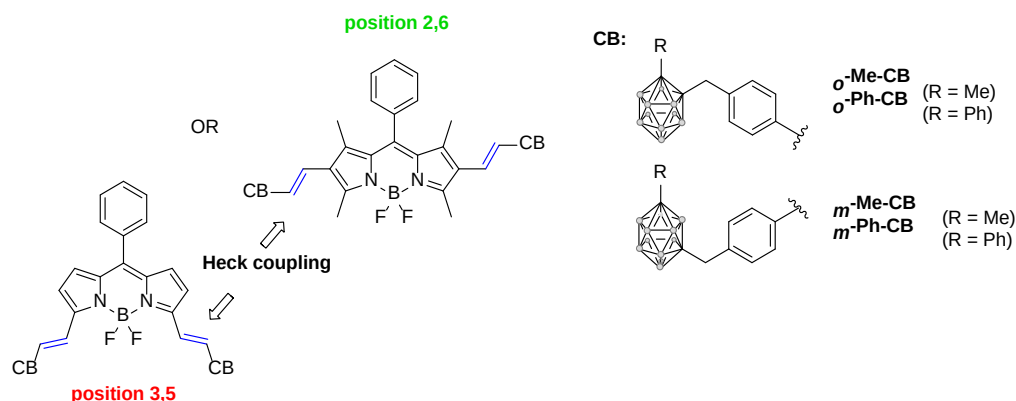


Figure 1: novel carborane-fluorophore triads by means of Heck coupling reaction.

References:

- [1] M. Scholz, E. Hey-Hawkins, *Chem. Rev.* **2011**, *111*, 7035-7062.
- [2] R. Núñez, M. Tarrés, A. Ferrer-Ugalde, F. F. de Biani, F. Teixidor, *Chem. Rev.* **2016**, *116*, 14307-14378.
- [3] S. Xuan, N. Zhao, Z. Zhou, F. R. Fronczek, M. G. H. Vicente, *J. Med. Chem.* **2016**, *59*, 2109-2117.
- [4] C. Bellomo, M. Chaari, J. Cabrera-Gonzalez, M. Blangetti, C. Lombardi, A. Deagostino, C. Vinas, N. Gaztelumendi, C. Nogues, R. Nunez and C. Prandi, *Chem. Eur. J.*, **2018**, *24*, 15622-15630.

Chemoselective Addition of Highly Polar Organolithium Reagents to Carboxamides in Deep Eutectic Solvents (DESs) Under Air: Novel Opportunities for the Synthesis of Ketones in Unconventional Solvents

M. Blangetti,^a S. Ghinato,^a G. Dilauro,^b F. M. Perna,^b V. Capriati,^b C. Prandi^a

^aDipartimento di Chimica, Università di Torino, via P. Giuria 7, I-10125 Torino, Italy

^bDipartimento di Farmacia, Scienze del Farmaco, Università di Bari "A. Moro", Consorzio C.I.N.M.P.I.S., Via E. Orabona 4, I-70125 Bari (Italy)
marco.blangetti@unito.it

Discovered at the beginning of the twentieth century, organolithium reagents are nowadays ubiquitous in organic synthesis both in academic research laboratories and in agrochemical and pharmaceuticals industries. However, these reagents usually require strictly controlled experimental conditions owing to their well-known sensitivity to moisture and air.¹ Recently, it has been reported the use of these reagents in nucleophilic addition to aromatic ketones, imines, nitriles and quinolines using highly polar solvents (DESs and water) at room temperature under open air conditions.² Nowadays we are extending this methodology to other electrophilic functional groups using organolithium reagents in DESs as an alternative synthetic strategy for the preparation of versatile building blocks under green conditions. In this context, direct 1,2-nucleophilic addition of hard organometallic reagents onto carboxylic acid derivatives suffers from a number of limitations depending mostly on the stability of the tetrahedral intermediate, including over-additions and reduction side-reactions. We herein investigate for the first time the potential benefits of using heterogeneous bio-based solvent mixtures in the treatment of several structurally diverse tertiary carboxamides with organolithium reagents in DES under air (Figure 1). Under these conditions, the nucleophilic acyl substitution reaction proceeds in a remarkable chemoselective fashion leading to ketones in moderate-to-high yields and with almost complete suppression of the undesired competitive pathways.

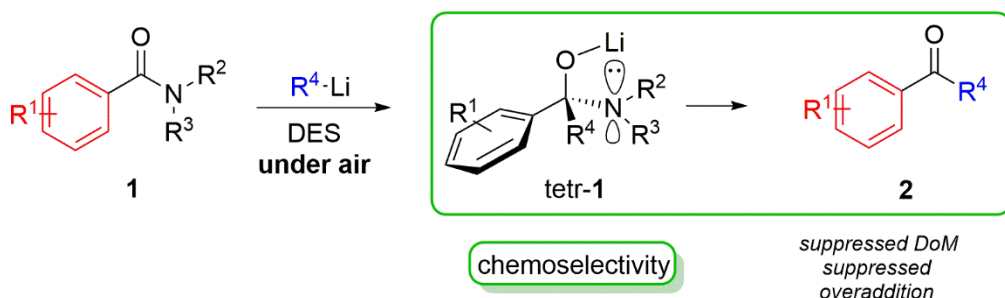


Figure 1: Chemoselective synthesis of ketones by nucleophilic addition of organolithium reagents to aromatic tertiary carboxamides

References:

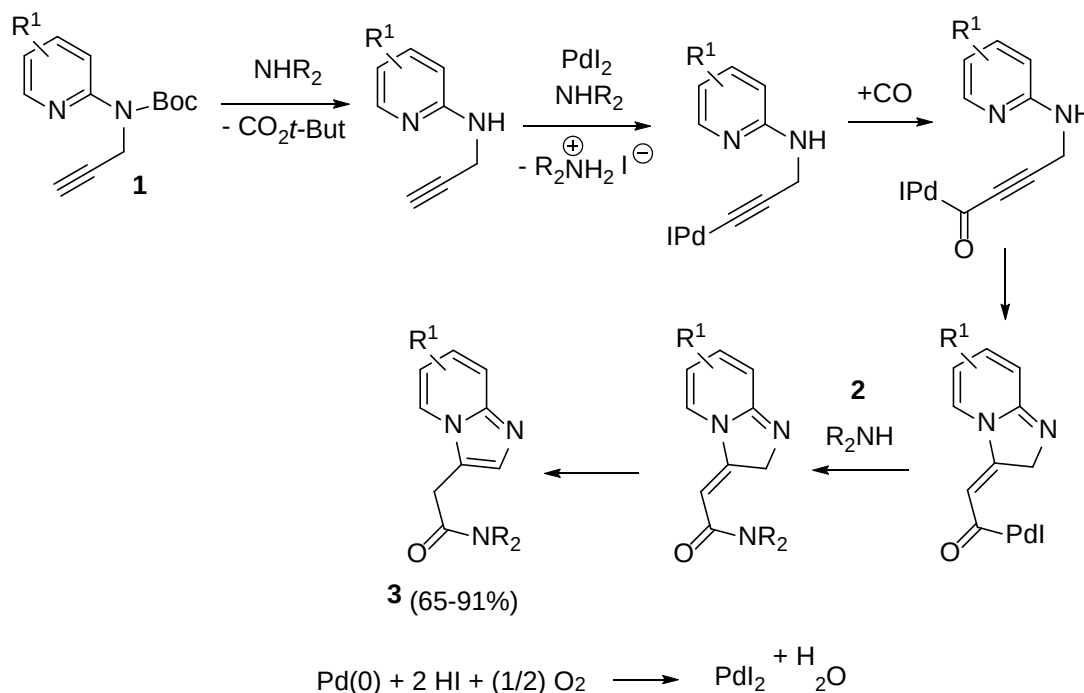
- [1] J. Clayden, *Organolithiums: Selectivity for Synthesis*, Pergamon, Oxford, **2002**.
- [2] J. García-Álvarez, E. Hevia, V. Capriati, *Chem. Eur. J.* **2018**, 24, 14854-14863.

A New Synthesis Of 2-(imidazo[1,2-a]pyridin-3-yl)acetamides By Palladium-Catalyzed Oxidative Aminocarbonylation Of (N-Prop-2-yn-1-yl)pyridin-2-amines

L. Veltri, T. Prestia, P. Russo, B. Gabriele

Laboratory of Industrial and Synthetic Organic Chemistry (LISOC), Department of Chemistry and Chemical Technology, University of Calabria, Arcavacata di Rende (CS), Italy
russopatrizio@outlook.it

Imidazo[1,2-a]pyridines are known as hypnotic sedative drugs which maintain the hypnotic effect without the onset of side effects and phenomena of pharmacological tolerance¹. In this communication we report a novel and simple Pd₂-catalyzed carbonylative approach to the synthesis of functionalized imidazo[1,2-a]pyridines. The method occurs in one step and consists in the deprotection of N-Boc-protected-(prop-2-yn-1-yl)pyridin-2-amines **1**, oxidative monoaminocarbonylation², conjugated addition and double bond isomerization. This methodology leads to 2-(imidazo[1,2-a]pyridin-3-yl)acetamides **3** to good-excellent yields (65-91%). Reactions were carried out in MeCN at 100 °C for 3 h, under 20 atm of a 4:1 mixture of carbon monoxide and air and in presence of catalytic amounts of PdI₂ (0.003 eq) in conjunction with KI (0.15 eq), using an excess of a secondary amine **2** as nucleophile. (**Scheme 1**).



Scheme 1

References:

- [1] A. K. Bagdi, S. Santra, K. Monir, A. Hajra, *Chem. Commun.* **2015**, 51, 1555-1575.
- [2] B. Gabriele, R. Mancuso, G. Salerno, *Eur. J. Org. Chem.* **2012**, 6825-6839.

An Unusually Divergent Reactivity of Basic Organolithium Compounds in Protic Unconventional Media: Novel Opportunities for the Synthetic Elaboration of Aryl Carboxyamides in Deep Eutectic Solvents

S. Ghinato,^a M. Blangetti,^a G. Dilauro,^b F. M. Perna,^b V. Capriati,^b C. Prandi^a

^aDipartimento di Chimica, Università degli Studi di Torino, via P. Giuria 7, I-10125 Torino, Italia

^bDipartimento di Farmacia–Scienze del Farmaco, Università di Bari “A. Moro”, Consorzio C.I.N.M.P.I.S., Via E. Orabona 4, I-70125 Bari, Italia
simone.ghinato@unito.it

The ability to activate a specific C-H bond and transform it into a more versatile functional group represents an important and long-standing goal in chemistry. Reactions of highly polar organometallic compounds of s-block elements are typically run in aprotic volatile organic solvents, under strictly anhydrous conditions and at low temperatures owing to their notorious air- and moisture-sensitivity¹. Spotting a gap in potential, the direct use of Grignard and organolithium reagents to promote nucleophilic additions to aromatic ketones, imines, nitriles and quinolines has proven to be surprisingly effective also in Deep Eutectic Solvents (DESs) and water, at room temperature and under hydrous conditions². Building on these achievements, we have now focused on the possible C-H bond activation of aromatic compounds by a directed *ortho*-metalation (DoM) approach using amides as direct metalation groups and organolithium reagents in DESs as alternative, environmentally friendly reaction media for the preparation of versatile building blocks. In this framework, we report an unprecedented chemoselective DoM or nucleophilic acyl substitution reaction taking place in DESs, as non-innocent reaction media, starting from the same tertiary carboxylic acid amide, according to the nature of the organolithium reagent (Figure 1).

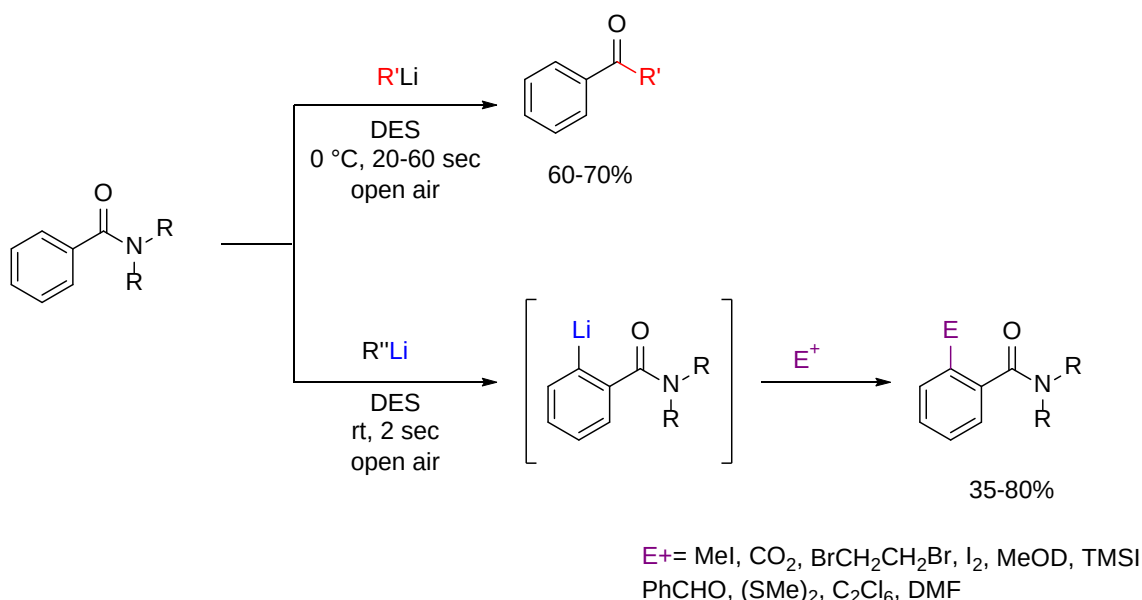


Figure 1: Chemoselectivity of organolithium reagents in deep eutectic solvents.

References:

- [1] a) J. F. Liebman, T. Holm, S. W. Slayden, *The Chemistry of Organomagnesium Compounds*, Patai Series, Wiley, Chichester, **2008**; b) V. Snieckus, *Chem. Rev.* **1990**, 90, 879-933.
[2] J. Garcia-Avarez, E. Hevia, V. Capriati, *Chem. Eur. J.* **2018**, 24, 14854-14863.

CI.O.E.: An automated workflow to simplify the early steps of Structure-Based Inverse Virtual Screening

S. De Vita, G. Lauro, S. Terracciano, R. Riccio, G. Bifulco

Department of Pharmacy, University of Salerno, Via Giovanni Paolo II 132, 84084, Fisciano, Salerno, Italy.
sdevita@unisa.it

Structure-Based Virtual Screening (SBVS) is highly used in the early stages of the drug discovery process to identify new putative lead compounds for a given target¹. However, it could happen that either a molecule elicits a biological effect, but its target is unknown, or the side effects observed cannot be explained by the proposed mechanism of action. In the last few years, a computational procedure, named Inverse Virtual Screening²⁻⁵, was developed to overcome these issues. It is based on docking the selected case-study molecule against panels of target proteins to select the most promising complexes and, accordingly, the most affine targets of interaction. Protein panels contain hundreds, or thousands of proteins and they must be correctly prepared to assure the best docking performance. The target preparation, if performed manually, may be costly in terms of time and efforts and can limit the efficacy of this method. Hence, we developed an automated workflow to shorten this time-consuming step and to speed up panel development. Briefly, online databases are analyzed to retrieve structural and functional information about each protein in the panel and the related crystal structure. Then, after performing an evaluation of the molecules present in the crystal, those are not strictly necessary to the protein function (e.g. crystallization buffer, solvents, etc.) are automatically deleted. Moreover, ligand molecules are recognized, their spatial coordinates are used to map the binding site surface using the software SiteMap^{6,7}, and finally the necessary input files for molecular docking calculations are generated (AutoDock Vina and Glide software). This protocol was applied to a panel of viral proteins to test its performance obtaining good results (only 3.26% of errors). In addition, we applied this workflow on a small set of available compounds synthesized in our laboratory against a panel of glycosyltransferase proteins, predicting tankyrase 2 as their target and validating the binding with surface plasmon resonance (SPR) experiments. This protocol represents a novelty in the field and is a useful tool for rapid identification of the interacting target for a bioactive compound. Also, it facilitates the reevaluation of known active compounds, addressing repurposing and polypharmacology concept.

References:

- [1] Q. Li, S. Shah, Structure-Based Virtual Screening, in: Protein Bioinformatics: From Protein Modifications and Networks to Proteomics, Springer New York, New York, NY, **2017**, 111-124.
- [2] Y. Chen, D. Zhi, *Proteins* **2001**, *43*, 217-226.
- [3] Y. Chen, C. Y. Ung, *J. Mol. Graphics Model.*, **2001**, *20*, 199-218.
- [4] G. Lauro, M. Masullo, S. Piacente, R. Riccio, G. Bifulco, *Biorg. Med. Chem.* **2012**, *20*, 3596-3602.
- [5] G. Lauro, A. Romano, R. Riccio, G. Bifulco, *J. Nat. Prod.* **2011**, *74*, 1401-1407.
- [6] T. Halgren, *Chem. Biol. Drug Des.* **2007**, *69*, 146-148.
- [7] T. Halgren, *J. Chem. Inf. Model.* **2009**, *49*, 377-389.

Unravelling the interactions between an antiproliferative 1,2,5-oxadiazole derivative and STAT3

A. Gelain,^a M. Mori,^a F. Meneghetti,^a A. Asai,^b and S. Villa^a

^aDipartimento di Scienze Farmaceutiche, Università degli Studi di Milano, via L. Mangiagalli 25, 20133 Milano, Italy

^bCenter for Drug Discovery, Graduate School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka, 422-8526, Japan
arianna.gelain@unimi.it

In our effort to develop novel direct STAT3 inhibitors¹, we identified the 1,2,5-oxadiazole **I** (Figure 1), which showed a promising inhibitory effect on the SH2 domain of STAT3 (inh % = 78.2 at 30 μ M, IC₅₀ = 8.2 μ M) and a significant antiproliferative activity in the LLC murine model (tumor growth inh % = 82.6 at 75 mg/kg as i.p. daily dose)². Since compound **I** is characterized by a pH-dependent enolization ratio, we decided to investigate whether the interactions with STAT3 could be related to its enolic form. Therefore, we designed several new derivatives (Figure 1) to shed light on this matter: for instance, we synthesized analogues lacking the NH₂ group or directly bearing an OH in substitution of the CO function. The results of the inhibition studies performed on these derivatives will be presented.

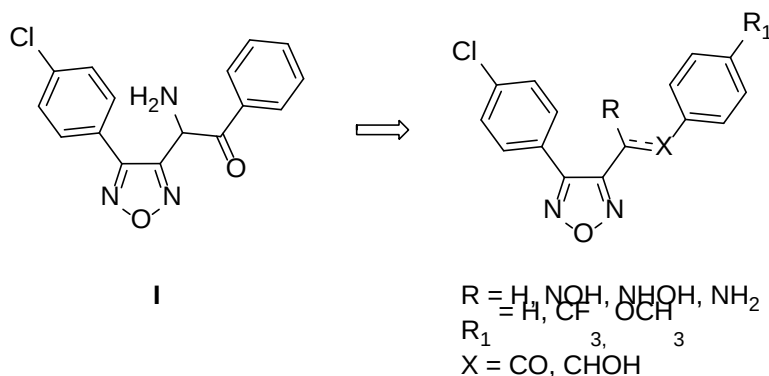


Figure 1: Product **I** and its derivatives (general structure)

References:

- [1] A. Gelain, M. Mori, S. Villa, F. Meneghetti, *Curr. Med. Chem.* **2018**, doi: <https://dx.doi.org/10.2174/0929867325666180719122729>.
- [2] F. Porta, G. Facchetti, N. Ferri, A. Gelain, F. Meneghetti, S. Villa, D. Barlocco, D. Masciocchi, A. Asai, N. Miyoshi, S. Marchianò, B.-M. Kwon, Y. Jin, V. Gandin, C. Marzano, I. Rimoldi, *Eur. J. Med. Chem.* **2017**, *131*, 196-206.

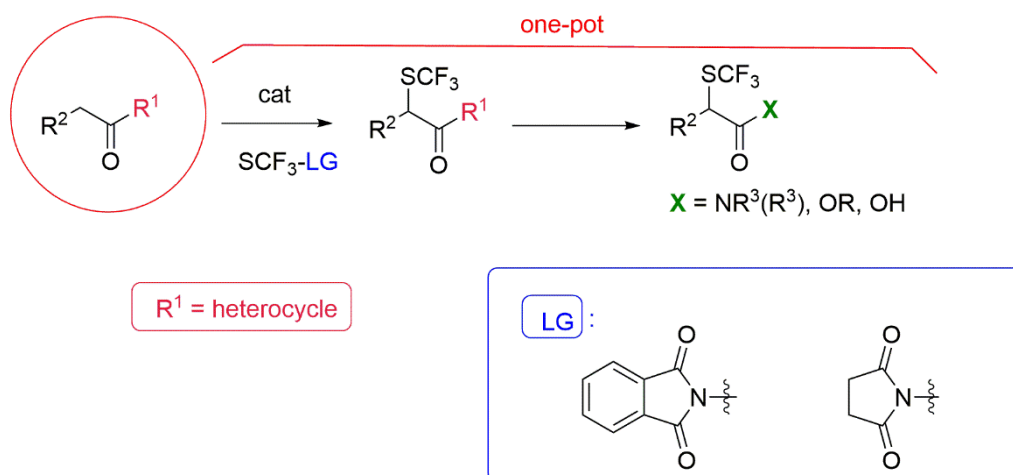
One-pot synthesis of α -trifluoromethylthiolated carboxylic acid derivatives

E. Franco,^a E. Massolo,^b M. Benaglia,^b A. Lattanzi^a

^aDipartimento di Chimica e Biologia, Università di Salerno, Via Giovanni Paolo II,
Fisciano, Italy

^bDipartimento di Chimica, Università degli Studi di Milano, Via Golgi, Milano, Italy
e-mail: ffranco@unisa.it

In the last decade, trifluoromethylthiolated compounds received significant interest both in academia and pharmaceutical/agrochemical industries. The strong electron-withdrawing ability and high lipophilicity of the SCF_3 group allow to modulate the properties of drug molecules.¹ Different methods for the introduction of trifluoromethylthio group at α -position of ketones have been intensively investigated.² The purpose of this work is the development of a mild methodology for the electrophilic incorporation of the SCF_3 group at the α -position of carboxylic acid derivatives such as amides or esters. Efforts are focused to employ ester surrogates as the starting reagents in a one-pot fashion (Scheme).



Scheme: One-pot approach for the α -trifluoromethylthiolation of carboxylic acid derivatives.

References:

- [1] S. Purser, P R. Moore; S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, 37, 320-330.
- [2] S. Rossi, A. Puglisi, L. Raimondi, M. Benaglia, *ChemCatChem* **2018**, 10, 2717-2733.

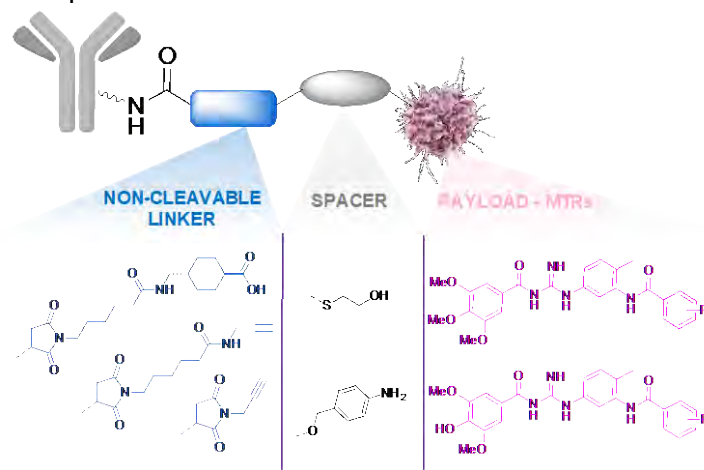
Synthesis and development of linker for bioconjugation of Smo inhibitors.

F. Migliorini,^a E. Petricci,^a M. Taddei,^a F. Manetti^a

^a Dipartimento di Biotecnologie, Chimica e Farmacia, Università di Siena, Via A. Moro 2, 53100 Siena
francesca.miglior@student.unisi.it

Antibody-drug conjugates (ADCs) represent a promising strategy in cancer therapy and for the treatment of different diseases. ADCs are composed by a monoclonal antibody (mAb) connected to a cytotoxic molecule through a properly designed linker. The mAb is responsible for selectively transporting the drug into target cells expressing the specific antigen,¹ thus significantly reducing the off-target toxicity of the drug.

Very potent inhibitors of the Hedgehog signaling pathway (HH) have been developed in our group by a virtual screening approach.²⁻⁴ These acylguanidine derivatives, called MRTs, show a very potent inhibitory activity on SMO receptor, being still very active in common mutant strains responsible for the tumor resistance observed in cancer therapy with HH inhibitors such as Vismodegib. MRT derivatives have interesting anticancer properties being active in the nanomolar range. However, acylguanidines lack a poor solubility and a low half-life.³ In order to overcome these issues, the bioconjugation of MRT derivatives has been explored to obtain a selective delivery of these inhibitors into HH sensitive tumor cells for the treatment of different types of cancers such as chronic myeloid leukemia, medulloblastoma and melanoma. Different synthetic strategies have been explored and developed to anchor differently substituted acylguanidines to lysine residues of mAb, through a traceless spacer introduced in a non-cleavable linker.



ADCs armed with MRT derivatives.

References:

- [1] A. Beck, L. Goetsch, C. Dumontet, N. Corvaia, *Nat. Rev. Drug Discovery* **2017**, *16*, 315-337.
- [2] A. Solinas, H. Faure, H. Roudaut, E. Traffort, A. Schoenfelder, A.; Mann, F. Manetti, M. Taddei, M. Ruat, *J. Med. Chem.* **2012**, *55*, 1559-1571.
- [3] L. Hoch, H. Faure, H. Roudaut, A. Schoenfelder, A.; Mann, N. Girard, L. Bihannic, O. Ayrault, E. Petricci, M. Taddei, D. Rognan, M. Ruat, *FASEB J* **2015**, *29*, 1817-1829.
- [4] S. Pietrobono, R. Santini, S. Gagliardi, F. Dapporto, D. Colecchia, M. Chiariello, C. Leone, M. Valoti, F. Manetti, E. Petricci, M. Taddei, B. Stecca, *Cell Death Dis.* **2018**, *9*(2), 1-16.

Synthesis of substituted 1,2-dihydropyridines by cerium(III) catalyzed amine-aldehyde polycondensation

D. Gentili, G. Lupidi, C. Paparoni, G. Pastore, M. Petrini, V. Vetri Buratti, E. Marcantoni

School of Sciences and Technologies, Università degli Studi di Camerino, 62032 Camerino, Italy
dario.gentili@unicam.it

Dihydropyridines are six-membered heterocyclic compounds having significant biological activities.¹ While the 1,4-dihydropyridine ring is present in various pharmacologically active compounds,² 1,2-dihydropyridine derivatives have been much less studied. One of the main reasons for this limit stems in the reduced availability of synthetic methods for their preparation.³ For this reason, we have directed our efforts toward the development of a new and efficient synthetic procedure for the preparation of substituted 1,2-dihydropyridines (**Figure 1**). The polycondensation between primary amines and aliphatic aldehydes, in the presence of a catalytic amount of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$, allowed us to obtain 1,2-dihydropyridines in good yield under mild reaction conditions.

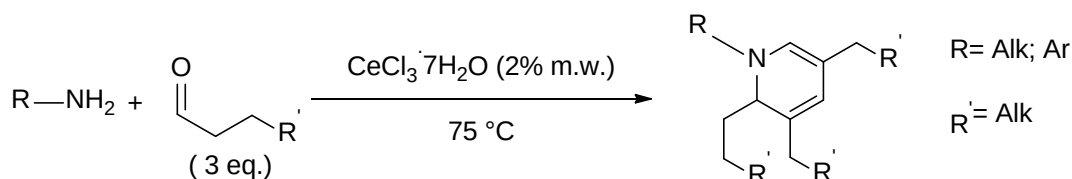


Figure 1.

Through common analytical techniques such as tandem mass spectrometry/chromatography and nuclear magnetic resonance it was possible to identify the expected products of condensation and related by-products. The target 1,2-dihydropyridine is obtained by a cascade process involving a preliminary aldehyde imination followed by a double aldol condensation and a final 6π azaelectrocyclization reaction⁴ (**Figure 2**).

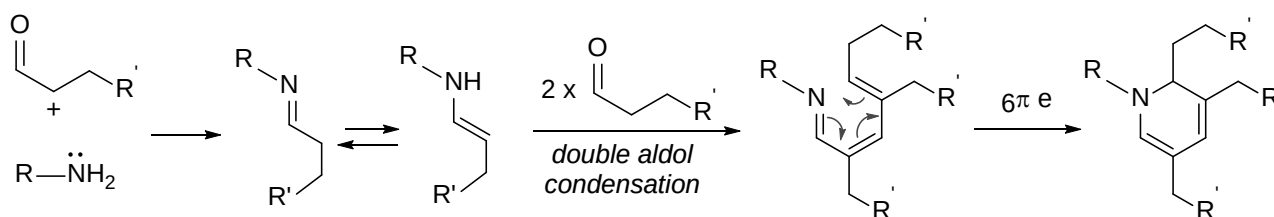


Figure 2.

References:

- [1] T. Salazar, A. Gonzalez, D. Bandyopadhyay, *J. Anal. Pharm. Res.* **2017**, 5:00148.
- [2] G. Swarnalatha, G. Prasanthi, N. Sirisha, C. Madhusudhana Chetty, *Int. J. ChemTech Res.* **2011**, 3, 75-89.
- [3] E. M. P. Silva, P. A. M. M. Varandas, A. M. S. Silva, F. E. M. P. Silva, *Synthesis* **2013**, 45, 3053-3089.
- [4] D. F. Vargas, E. L. Larghi, T. S. Kaufman, *Nat. Prod. Rep.* **2019**, 36, 354-401.

Resorc[4]arene-based site directed immobilization of antibodies for immunosensors development

C. Del Plato^{a,b}, F. Ghirga^a, C. Tortolini^b, D. Quaglio^b, L. Mangiardi^{a,b}, F. Polli^b, B. Botta^{*,b} and F. Mazzei^{*,b}.

^a Center for Life NanoScience, CLNS@Sapienza, Italian Institute of Technology (IIT), Viale Regina Elena 291, 00161 Rome, Italy.

^b Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, Piazzale Aldo Moro 5, 00185 Rome, Italy.

E-mail: cristina.delplato@uniroma1.it

One of the main problems in the development of immunosensors is to overcome the complexity of binding antibody to the surface of the sensor. In fact, antibodies need to be immobilized with a high density and good orientation to allow the easy detection of antigens. The influence of nonspecific bindings should be minimized to improve the detection performance. Most of immobilizing methods lead to randomly oriented antibodies on the surface, which results in a low density of binding sites and alleviation of immunoaffinity of the antibodies. Therefore, oriented immobilization is required for the improvement of the performance enhancement.

Calix[4]arene derivatives have been proposed as an alternative tool for the oriented immobilization of antibodies thanks to their particular structure of lower and upper rims.¹

To ensure the orientation control of antibodies on the sensor surface, we synthesized several resorc[4]arene derivatives able to self-assemble onto gold surface thanks to the thiol groups present on their structure.² Resorc[4]arene, a type of calixarene, is a macrocycle oligomer based on the condensation of resorcinol and aldehyde. The immobilization characteristics of these artificial linkers have been evaluated by means of Surface Plasmon Resonance (SPR) technique comparing the results obtained with a random immobilization method based on EDC/NHS and an oriented immobilization with boronic acid derivatives of insulin antibody for the development insulin immunosensors. The results obtained put in evidence that the synthesized compounds show an enhancement of the insulin-insulin antibody interaction, resulting in a significative increase of the immunosensor sensitivity.

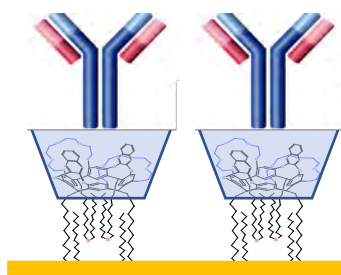


Figure 1: Immobilization on the sensor surface.

References:

- [1] H. Chen, F. Liu, F. Qi, K. Koh, K. Wang, *Int. J. Mol. Sci.* **2014**, *15*, 5496 -5507.
- [2] H. Chen, M. Lee, S. Choi, J. H. Kim, H. J. Choi, S. H. Kim, J. Lee, K. Koh, *Sensors* **2007**, *7*, 1091-1107.

The marine worm *Hermodice carunculata* is a promising biocatalyst for aldol reactions

S. Righi^a, M.R. Cramarossa^a, D. Prevedelli^a, R. Simonini^a, L. Forti^a

^aDepartment of Life Sciences, University of Modena and Reggio Emilia, via G. Campi 103, 41125 Modena
luca.forti@unimore.it

Recently, increasing efforts have been made to develop low-energy dependent and eco-sustainable enzyme-catalyzed procedures, with the aim to replace existing expensive and polluting manufacturing processes with new environmentally-friendly catalysts. The use of enzymes can frequently lead to the design of new products, otherwise unavailable by classical chemical synthesis. Generally, a relatively crude preparation is far more stable than a highly purified enzyme [1]. Crude extracts of annelids seem promising biocatalysts for various organic synthesis, but the available data only concern an earthworm species [2]. To improve the existing knowledges, in our study a crude extract of the marine worm *Hermodice carunculata* was used as biocatalyst for asymmetric aldol reactions on an assortment of aldehyde acceptors. The reactions showed moderate to good yields and stereoselectivity, and their chemical progress was affected by water concentration and temperature. The catalytic activity was present in the crude extracts obtained from different parts of the body of *H. carunculata*, even if the greatest conversion values were found with the dorsal body wall (32-45%). Our results confirm that crude annelid extract may be used as energy-efficient, safe, cheap and stable catalyst.

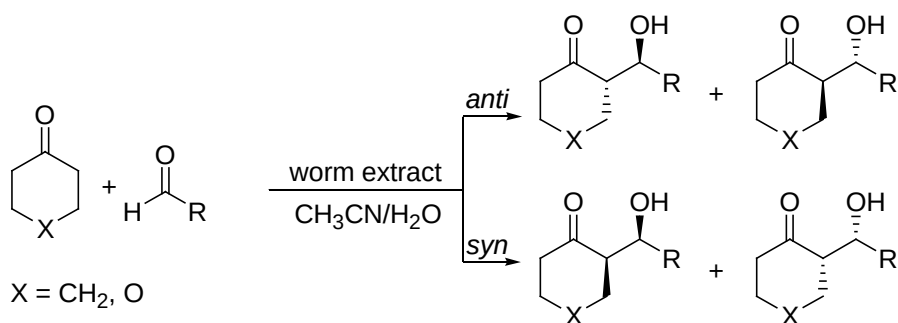


Figure 1: Aldol reactions catalysed by the crude extracts of *H. carunculata*.

References:

- [1] K. Faber, *Biotransformation in Organic Chemistry*. Springer, **2018**.
- [2] Z. Guan, Y.N. Chen, Y. Yuan, J. Song, D.C. Yang, Y. Xue, Y. H. He, *PLoS ONE* **2014**, 9(8), e105284.

Chemical Derivatisation of Tannins for Functional Materials

L. Zongo,^a L. Zhen,^a H. Lange,^{a,b} C. Crestini^{a,c}

^a University of Rome 'Tor Vergata', Department of Chemical Sciences and Technologies
Via della Ricerca Scientifica, 00133 Rome, Italy

^b University of Naples 'Federico II', Department of Pharmacy
Via Domenico Montesano 49, 80131 Naples, Italy

^c University of Venice Ca' Foscari, Department of Molecular Sciences and Nanosystems
Via Torino 155, 30170 Venice Mestre, Italy
luc.zongo@uniroma2.it

The efficient use of all available biomass components is of utmost interest with respect to a sustainable use of renewable resources. Tannins represent one of the most versatile polyphenolic compounds of biomass.¹ Although being not as abundant as lignin, they are much more widely used already due to their unique functional features: i) unique π -stacking and complexing properties; ii) high general biocompatibility; iii) antioxidant activity; iv) ability to absorb UV light; v) anti-inflammatory activity; vi) anti-microbial activity and vii) anti-tumoral activity *via* control of reactive oxidant species (ROS).¹

The yet unprecedented controlled functionalisation of commercially available tannins is a promising strategy that holds the potential to significantly broaden the actual scope of tannins used as natural antioxidant and antimicrobial agents -into innovative active ingredients and functional materials. Functionalised monomeric or oligomeric products serve as starting materials adding to the classical tannin features aspects necessary for targeted industrial applications in home and personal care products.

We will present the formation of a wide variety of functional tannins obtained *via* simple chemical protocols² that are optimised on the basis of detailed structural NMR analyses of starting materials.³⁻⁵ Products include charged, chargeable, zwitterionic and copolymeric substances. Control of degrees of functionalisation allows for targeted tuning of macroscopic characteristics of the novel tannin-based substances.

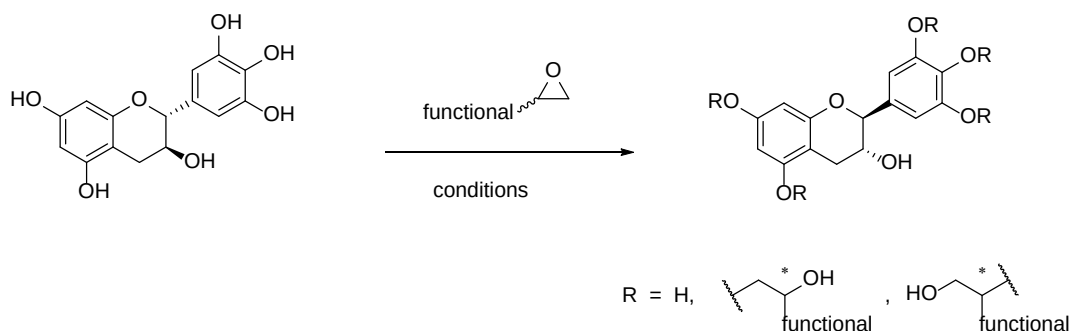


Figure 1: General functionalisation of tannins, shown using gallocatechin as one representative example.

References:

- [1] K. Khanbabaee, T. van Ree. *Nat. Prod. Rep.* **2001**, 18, 641-649.
- [2] L. Zongo, L. Zhen, H. Lange, C. Crestini, *manuscript in preparation*.
- [3] C. Crestini, H. Lange, G. Bianchetti, *J. Nat. Prod.* **2016**, 79, 2287-2295.
- [4] F. Melone, R. Saladino, H. Lange, C. Crestini, *J. Agric. Food Chem.* **2013**, 61, 9316-9324.
- [5] F. Melone, R. Saladino, H. Lange, C. Crestini, *J. Agric. Food Chem.* **2013**, 61, 9307-9315.

Stability Profiles of Lignin Microcapsules

L. Zongo,^a H. Lange,^{a,b} C. Crestini^{a,c}

^a University of Rome 'Tor Vergata', Department of Chemical Sciences and Technologies
Via della Ricerca Scientifica, 00133 Rome, Italy

^b University of Naples 'Federico II', Department of Pharmacy
Via Domenico Montesano 49, 80131 Naples, Italy

^c University of Venice Ca' Foscari, Department of Molecular Sciences and Nanosystems
Via Torino 155, 30170 Venice Mestre, Italy
luc.zongo@uniroma2.it

The efficient use of all available biomass components is of utmost interest with respect to a sustainable use of renewable resources. Almost one third of lignocellulosic biomass is comprised of polyphenolic oligomers and polymers, which are for the most part lignins.¹ The valorisation of lignin waste streams from pulp and paper and modern biorefinery processes is a crucial step for the development of circular sustainable economy. One very promising application of lignins is their use as shell material in ultrasonication-based generation of micro- and nanocapsules^{2,3} for biomedical and agricultural applications.⁴

In light of various potential applications, stimuli responsive behaviour of lignin microcapsules (LMCs) has been investigated along with the detailed characterisation of their stability profiles.⁵ The disassembly of LMCs was found to reflect kosmotropic and chaotropic characteristics of buffer systems and physiological solutions. A connection between the Hofmeister series and the stability profile of lignin micro-scaled materials can be delineated. LMCs showed excellent stability in water and under high temperature and pressure (autoclaving conditions). Active release is efficiently triggered by pH-changes and balancing chaotropic and kosmotropic effects via salinity tuning.

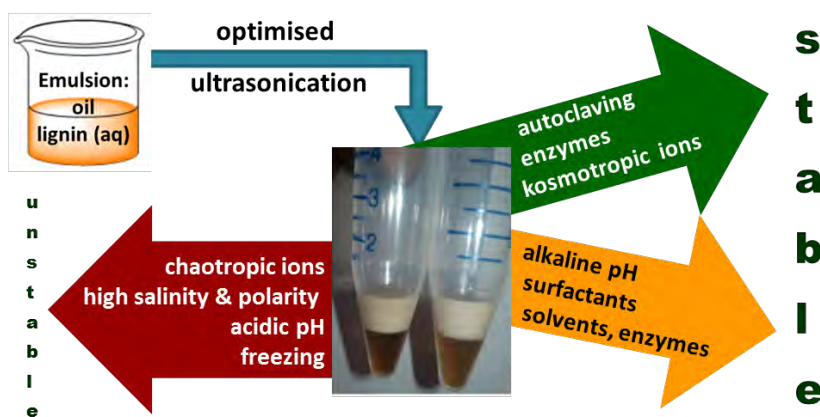


Figure 1: Lignin microcapsule stability – general overview.

References:

- [1] G. T. Beckham (ed.), Lignin Valorization: Emerging Approaches. Royal Chemical Society, Cambridge **2018**.
- [2] E. D. Bartzoka, H. Lange, K. Tiehl, C. Crestini, *ACS Sustainable Chem. Eng.* **2016**, 4, 5194–5203.
- [3] M. Tortora, F. Cavalieri, P. Mosesso, F. Ciaffardini, F. Melone, C. Crestini, *Biomacromolecules* **2014**, 15, 1634–1643.
- [4] M. H. Sipponen, H. Lange, C. Crestini, A. Henn, M. Österberg, *ChemSusChem* **2019**, accepted.
- [5] L. Zongo, H. Lange, C. Crestini, *ACS Omega* **2019**, 10.1021/acsomega.8b03510.

Bio-based renewable polymeric materials from research to industrial point of view

G. Pastore,^a R. Ballini,^a S. Gabrielli,^a C. Luciani,^b A. Menchi,^a L. Paniccia,^b E. Marcantonio^a

^aSchool of Science and Technology, Università degli Studi di Camerino, Via S. Agostino 1, 62032 Camerino

^bIndustria Chimica Adriatica (ICA), Via Sandro Pertini 52, 62019 Civitanova Marche

e-mail: genny.pastore@unicam.it

The current model of production and consumption relies on fossil-based resources. Climate change and environmental pollution are the main effects of this system.

National governments are developing a more sustainable economy based on biomass to overcome the negative impact of the fossil-based model. The bio-economy convert biomass into energy, feed and bio-based products, reducing the CO₂ emissions.¹

Bio-based polymers found their application in different fields from packaging to wood coating. Aliphatic polyesters such as polylactic acid derived from renewable resources has been extensively used in packaging, medical implant and drug delivery systems.² PLA can be synthesized through ring-opening polymerization of lactide and polycondensation of lactic acid using different catalysts. Among them the most common used for the synthesis of high molecular weight PLA are tin-based compounds, despite the difficulties in removing the catalyst from the polymer. Moreover, the presence of tin ions in polymeric matrix has adverse effects on living organism cells.³

A new non-toxic and eco-sustainable catalytic system, CeCl₃·7H₂O/NaI, is used for the synthesis of PLA, in order to achieve a molecular weight close to that obtained with tin compounds.

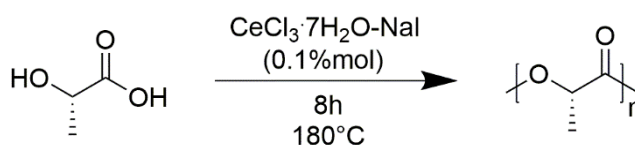


Figure 1: Synthesis PLA.

Together with lowering CO₂ emissions, a crucial role is played by reducing the release of VOCs. Development and production of acrylic and polyurethane resins for water-based paints, starting from biomass waste, lead to a reduction of VOCs emission while keeping the chemical-physical properties very close to those of synthetic resins.

References:

- [1] S. Lambert, M. Wagne, *Chem. Soc. Rev.* **2017**, 46, 6855-6871.
- [2] L. T. Lim, R. Auras, M. Rubino, *Prog. Polym. Sci.* **2008**, 33, 820-852.
- [3] A. A. Bakibaev, A. M. Gazaliev, S. K. Kabieva, V. I. Fedorchenko, G. Ya. Guba, E. I. Smetanina, I. R. Dolgov, R. O. Gulyaev, *Procedia Chem.* **2015**, 15, 97-102.

Novel Synthetic Analogues of Climacostol as Potent Anticancer Nature-Inspired Small Molecules

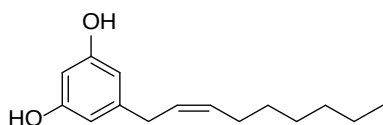
G. Lupidi,^a C. Cimarelli,^a F. Buonanno,^b E. Catalani,^c D. Cervia,^c D. Gentili,^a C. Ortenzi,^b E. Marcantoni^a

^aSchool of Sciences and Technologies, Università degli Studi di Camerino, 62032 Camerino, Italy

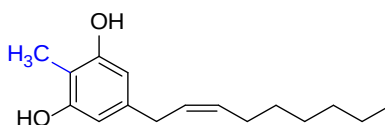
^bLaboratory of Protistology and Biology Education, Department of Education, Cultural Heritage and Tourism (ECHT), Università degli Studi di Macerata, 62100 Macerata, Italy

^cDepartment for Innovation in Biological, Agro-food and Forest Systems (DIBAF), Università degli Studi della Tuscia, 01100 Viterbo, Italy
gabriele.lupidi@unicam.it

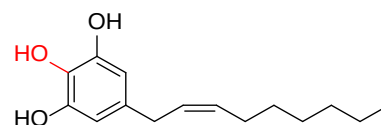
Climacostol (5-[(2Z)-non-2-en-1-yl]benzene-1,3-diol, **1**) is a natural toxin isolated from the freshwater ciliated protozoan *Climacostomum virens* and belongs to resorcinolic lipids, a group of compounds that show antiparasitic, antimicrobial and anticancer activities.¹ After developing a straightforward strategy to synthetically obtain Climacostol,² we recently developed the synthesis of two analogues, compounds **2** and **3** with the aim of improving the activity of the native toxin. Results showed that the analogue **2** exhibited higher toxicity against pathogen microbes, while molecule **3** is able to induce programmed cell death in protistan cells.³



1

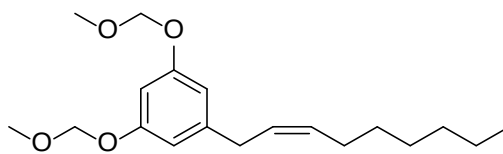


2



3

The choice of MOM protection of the free hydroxyl groups was a crucial step for the synthesis, since it allowed us to obtain the *Z*-isomer in a selective way through a Wittig olefination, avoiding the formation of the biologically inactive *E*-diastereomer. Moreover, the mild acidic condition for its deprotection, proved compound **4** to be a promising prodrug that is efficiently activated in the mild extracellular acidosis.⁴



4

References:

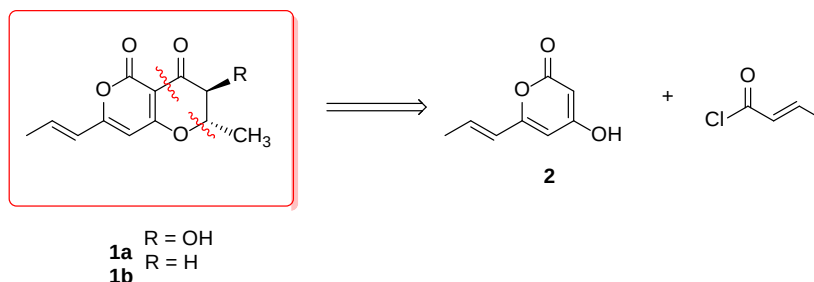
- [1] C. Perrotta, F. Buonanno, S. Zecchini, A. Giavazzi, F. Proietti Serafini, E. Catalani, L. Guerra, M. C. Belardinelli, S. Picchietti, A. M. Fausto, S. Giorgi, E. Marcantoni, E. Clementi, C. Ortenzi, D. Cervia, *Sci. Rep.* **2016**, 6:27281.
- [2] D. Fiorini, S. Giuli, E. Marcantoni, L. Quassinti, M. Bramucci, C. Amantini, G. Santoni, F. Buonanno, C. Ortenzi, *Synthesis* **2010**, 9, 1550-1556.
- [3] F. Buonanno, E. Catalani, D. Cervia, F. Proietti Serafini, S. Picchietti, A. M. Fausto, S. Giorgi, G. Lupidi, F. V. Rossi, E. Marcantoni, D. Petrelli, C. Ortenzi, *Toxins* **2019**, 11, 42.

Synthesis of the fungal metabolites radicinin and its natural precursor deoxyradicinin: potential bioherbicides for invasive species control.

G. Marsico, S. Ciccone, S. Superchi, P. Scafato

Dipartimento di Scienze, Università degli Studi della Basilicata, Via dell'Ateneo Lucano 10, 85100, Potenza
giuliamar86@hotmail.it

Radicinin (**1a**) is a fungal natural product first isolated in 1953 from *Stemphylium radicinum* (*Alternaria radicina*),¹ the fungus responsible for black rot disease of carrots and, since then, from a variety of other plant-associated fungi. Such secondary metabolite displays different phytotoxic and antibiotic properties.² Indeed, it shows phytotoxic activity against several kind of plants such as buffelgrass (*Pennisetum ciliare* or *Cenchrus ciliaris*), cress (*Lepidium sativum*) and Job's tears (*Coix lachryma-jobi*) as well as antifungal activity against *Magnaporthe grisea*, also known as rice blast fungus, and *Valsa mali*, a plant pathogen fungus. It also exhibits a strong antibacterial activity against the Gram-negative bacterial phytopathogen *Xylella fastidiosa*, that causes many devastating plant diseases. The recent growing interest for radicinin is mainly due to the possibility to use this compound as potential natural herbicides against buffelgrass, a perennial grass that has become highly invasive in the Sonoran Desert of southern Arizona. Radicinin demonstrated high target-specific toxicity on such weed, low toxicity to native plants, and no teratogenic, sub-lethal, or lethal effects on zebrafish (*Brachydanio rerio*) embryos.³ In order to develop a target-specific bioherbicide for that invasive species, it is necessary to have quantities of radicinin much greater than those obtainable from natural sources and, for this reason, the development of an efficient total synthesis of this compound becomes mandatory. Moreover, the availability of racemic **1a** as well as of the deoxygenated derivative **1b** can also allow to carry out detailed structure-activity studies on the role of the absolute and relative stereochemistry and of the α -oxygen on the bioactivity of this compound. Accordingly, the synthetic approach to ($\pm$)-radicinin (**1a**) and its precursor ($\pm$)-deoxyradicinin (**1b**) described in Scheme 1 is reported in this communication. Such approach is based on the disconnection of their structure into pyranone **2**⁴ and crotonyl chloride.



Scheme 1: Retrosynthetic analysis.

References:

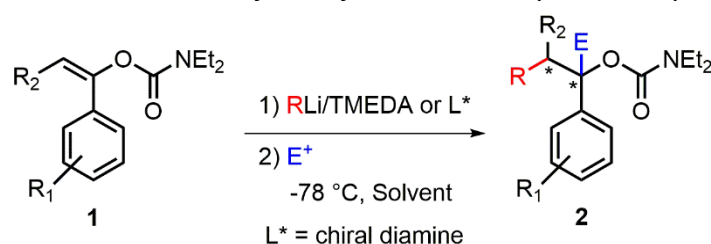
- [1] D. D. Clarke, F. F. Nord, *Arch. Biochem. Biophys.* **1953**, 45, 469-470.
- [2] M. Suzuki, E. Sakuno, A. Ishihara, Jun-ichi Tamura, H. Nakajima, *Phytochemistry* **2012**, 75, 14-20.
- [3] M. Masi, F. Freda, F. Sangermano, V. Calabrò, A. Cimmino, M. Cristofaro, S. Meyer, A. Evidente, *Molecules* **2019**, 24, 1086-1095.
- [4] T. Bach, S. Kirsch, *Synlett* **2001**, 12, 1974-1976.

Enantioselective Carbolithiation-Trapping Reaction of 1-Aryl-1-Alkenyl Carbamates

G. Marsico, P. Scafato, S. Superchi

Dipartimento di Scienze, Università degli Studi della Basilicata, Via dell'Ateneo Lucano 10, 85100, Potenza
giuliamar86@hotmail.it

Carbolithiation reactions of styrenyl olefins represent an attractive synthetic methodology, offering pathways for the preparation of highly functionalized aromatic compounds. This transformation generates a benzyllithium species which, through a tandem carbolithiation-trapping reaction, can be reacted with carbon electrophiles, allowing the efficient regioselective formation of two new C-C bonds and of one or two new stereocenters. A potential limitation to the application of carbolithiation as a synthetic method derives from the difficulty of tempering the reactivity of the obtained organolithium intermediate towards the starting unsaturated substrate avoiding to trigger an unwanted anionic polymerization process. Therefore, despite its synthetic appeal, this class of reactions has not gained much synthetic attention. For synthetically useful carbolithiation reactions, a special stabilization of the benzyl lithium intermediate is in fact required. Such a stabilization can be obtained either by *intra*- or *inter*-molecular organolithium coordination which, at the same time, prevents polymerization and promotes the carbolithiation reaction.¹ This coordination occurs in the presence of chelating groups proximal to the reacting alkene and/or in the presence of bidentate ligands such as diamines. The aim of this study was to investigate the carbolithiation of 1-aryl-1-alkenyl *N,N'*-dialkylcarbamates (**1**) as a useful tool for the synthesis of multi-functional compounds, also in optically active forms.¹ The organolithium intermediate obtained after the carbolithiation step was then reacted with several electrophiles, obtaining trisubstituted benzyl carbamates (**2**) as direct precursors of tertiary benzylic alcohols. The tandem carbolithiation-trapping with electrophiles was also carried out in an enantioselective manner, in the presence of chiral diamines as chelating agents,² obtaining enantioenriched tertiary benzyl carbamates (Scheme 1).



Scheme 1: Carbolithiation-trapping reaction.

References:

- [1] S. Superchi, N. Sotomayor, G. Miao, B. Joseph, M. G. Campbell, V. Snieckus, *Tetrahedron Lett.* **1996**, 37, 6061-6064.
- [2] J. G. Peters, M. Seppi, R. Fröhlich, B. Wibbeling, D. Hoppe, *Synthesis* **2002**, 3, 381-392.

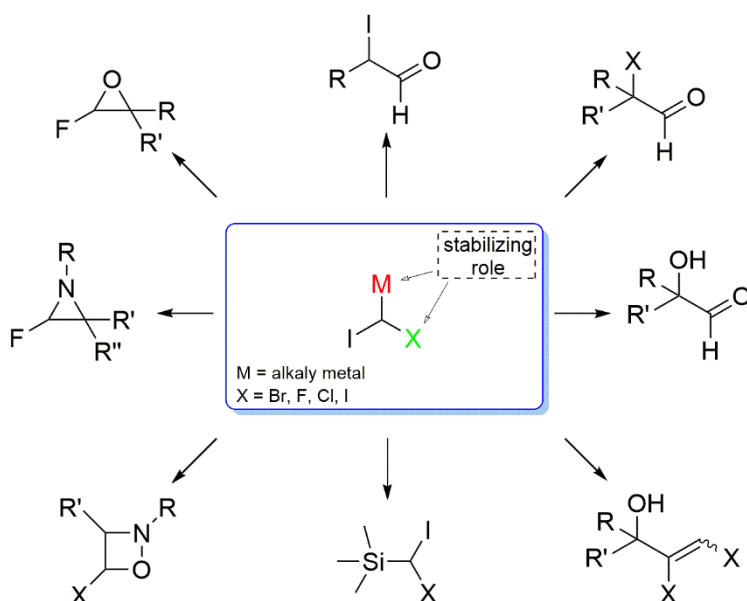
Intriguing role of iodine on the reactivity and stability of dihalomethylithium carbenoids

P. Musci,^a L. Degennaro,^a R. Luisi^a

^aDepartment of Pharmacy - Drug Science, University of Bari 'Aldo Moro' Via E. Orabona 4, 70125 Bari, Italy
pantaleo.musci@uniba.it

Halo and dihalomethylithium carbenoids represent attractive tools in organic synthesis due to their dichotomic reactivity as nucleophiles and electrophiles. Generally, genesis (Li-halogen exchange or deprotonation) and *in-situ* trapping require cryogenic conditions (usually below -78°C),^{1,2,3,4,5} although microfluidic reactors are able to control the thermal (and chemical) instability allowing external quenching even at higher temperatures.⁶ Recent works demonstrate that iodinated lithium carbenoids could react with electrophiles after 20 minutes at -78°C in batch conditions.⁷

Motivated by these promising results and by the shortage of detailed studies, we analyzed the reactivity and stability of dihalomethylithium carbenoids, highlighting the role of iodine atom on the carbenoid properties. Herein, the reactivity of dihalomethylithiums (LiCHIBr, LiCHIF, LiCHICl, LiCHI₂) is investigated, disclosing interesting synthetic pathways depending on the nature of the electrophile.



References

- [1] G. Parisi, M. Colella, S. Monticelli, G. Romanazzi, W. Holzer, T. Langer, L. Degennaro, V. Pace, R. Luisi, *J. Amer. Chem. Soc.* **2017**, *139* (39), 13648-13651.
- [2] S. Monticelli, M. Colella, V. Pillari, A. Tota, T. Langer, W. Holzer, L. Degennaro, R.; Luisi, V. Pace, *Org. Lett.* **2019**, *21* (2), 584-588.
- [3] A. Hafner, V. Mancino, M. Meisenbach, B. Schenkel, J. Sedelmeier, *Org. Lett.* **2017**, *19* (4), 786-789.
- [4] V. Pace, W. Holzer, N. De Kimpe, *Chem. Rec.* **2016**, *16* (4), 2061-2076.
- [5] M. Colella, A. Tota, A. Großjohann, C. Carlucci, A. Aramini, N. S. Sheikh, L. Degennaro, R.; Luisi, *Chem. Commun.* **2019**, 55, 8430-8433.
- [6] L. Degennaro, F. Fanelli, A. Giovine, R. Luisi, *Adv. Synth. Catal.* **2014**, *357* (1), 21-27.
- [7] J. A. Bull, J. J. Mousseau, A. B. Charette, *Org. Lett.* **2008**, *10* (23), 5485-5488.

Diastereoselective synthesis of axially chiral styrenes

M. Barbero,^a S. Dughera,^a G. Ghigo,^a D. Marabello^{a,b}

^aDipartimento di Chimica, Via P. Giuria 7, Torino

^bCrisDi (Interdepartmental Center for Crystallography), Via P. Giuria 7, 10125 Torino
margherita.barbero@unito.it; giovanni.ghigo@unito.it

Recently, we have reported a new synthesis of 3-vinylindoles based on a clean and direct dehydrative coupling reaction between acetophenones and indoles in the presence of catalytic amounts of aryl-(3-indolyl)methylm tetrafluoroborates as Lewis acid catalysts.¹ 3-Vinylindoles feature the 1,1-diarylethene scaffold often present in molecules showing strong biological activities; furthermore, 3-vinylindole and derivatives have been used as complex building blocks in the asymmetric synthesis of substituted indoles.²

Owing to the wide interest in these compounds, we decided to extend the reaction to alkyl aryl ketones other than acetophenones and, subsequently, to other aromatic and heteroaromatic nucleophiles. The reaction requires an acidic catalyst and we tested both the above Lewis acid carbocations and simple Brønsted acids. The expected dehydrative coupling products were, in this case, α -aryl- β -alkyl (or aryl) α -indol-3-ylethenes containing two stereogenic elements; they are axially chiral styrene derivatives, achievable as a mixture of *E* or *Z* diastereomers, as already reported in literature when prepared by similar synthetic methods.³ In preliminary results, in our conditions, we obtained predominantly *Z*-diastereomers, as confirmed by spectroscopic and X-ray diffraction measures. The computational study reproduced and explained the observed diastereoselectivity.

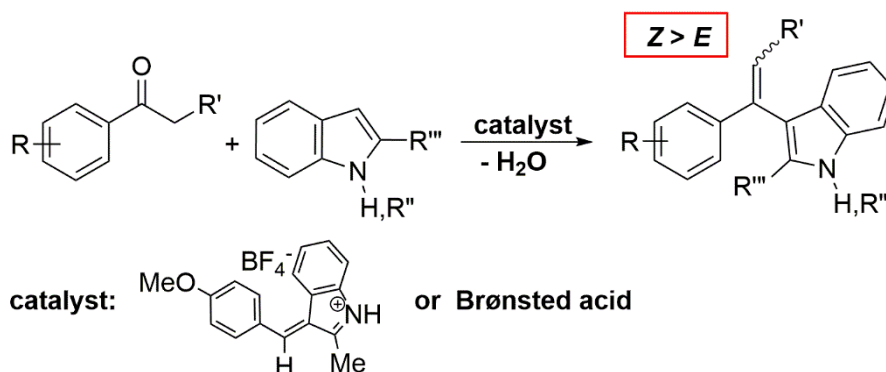


Figure 1: Dehydrative coupling reaction for the synthesis of axially chiral styrenes.

References:

- [1] M. Barbero, S. Dughera, S. Alberti, G. Ghigo, *Tetrahedron* **2019**, 75, 363-373.
- [2] a) T. Naret, O. Provot, M. Alami, A. Hamze, *Asian J. Org. Chem.* **2017**, 6, 1509-1518; b) M.-Y. Chang, Y.-H. Huang, H.-S. Wang, *Tetrahedron* **2016**, 72, 3022-3031; c) J.-H. Xue, M. Shi, F. Yu, X.-Y. Li, W. Ren, L.-N. Fu, Q.-X. Guo, *Org. Lett.* **2016**, 18, 3874-3877.
- [3] a) P. Jaisankar, P. C. Srinivasan, *Synth. Commun.* **2005**, 35, 923-927; b) V. V. Angeles-Dunham, D. Nickerson, D. Ray, A. E. Mattson, *Angew. Chem. Int. Ed.* **2014**, 53, 14538-14541. c) A. Taheri, C. Liu, B. Lai, C. Cheng, X. Pana, Y. Gu, *Green Chem.* **2014**, 16, 3715-3719.

GLYCOG Lab 4.0, the sweet nanofiller: a tangible case of transfer of technology (TOT)

G. Toniolo,^{a,b} J. Tricomi,^{a,b} B. Richichi,^{a,b} S. Cicchi,^{a,b} A. Borio,^{a,b} G. Biagiotti^{a,b}

^a Consorzio Interuniversitario Nazionale Per la Scienza e Tecnologia dei Materiali (INSTM), Via Giusti 9, 50121 Firenze, Italy

^b Department of Chemistry "Ugo Schiff", Università degli Studi di Firenze, via della Lastruccia 3-13, 50019 Sesto Fiorentino, Firenze, Italy
giacomo.biagiotti@unifi.it

In the last ten years, companies have been often faced with stringent environmental regulations imposed by the European Legislation related to the use of hazardous chemicals in final products. Most of these chemicals are used as preservatives, thus, they are crucial additives ensuring the durability of end products. Therefore, environmental issues are forcing the industry to steadily updated and, in particular, manufactures are dealing with the need of high-quality products not only in terms of technical performance but also in terms of controlled impact on health and environment. Moreover, the development of innovative and eco-friendly solutions, providing a lower impact to human health and environment, is one of the top priorities for industry.

Carbon based nanocomposites are an emerging technology that have generated great expectations as demonstrated by the significant number of companies involved in the commercialization of these materials,¹ by the huge amount of private and EU funding opportunities (e.g. Graphene flagship)² and by the substantial body of publications from academia. However, despite many impressive achievements in the preparation of carbon-based nanocomposite with tailor-made properties,³⁻⁴ the main industrial applications rely on the use of raw materials.⁵ Indeed, the main issues related to the transfer of technology (TOT), in the field of functionalized nanomaterials, concern the scale up and the final physiochemical properties of the products.

GLYCOG Lab 4.0, a close partnership between industry and academia, arises from the necessity to answer these issues, guaranteeing the highest level of innovation and research. In particular, we report here on the development of a novel smart and multifunctional carbon-based nanocomposite containing a new eco-friendly biopolymer as a case study of transfer of technology. Indeed, the strong point of the proposed nanomaterial is the possibility to be applied by a wide range of companies (e.g. textile, naval and construction paint industries) that deal with the issue of long-term UV-shielding and bio-deterioration combined with the optical, mechanical and electronic properties of the functionalized glyco-nanomaterial. The nanoadditive was designed employing glycopolymers as biocompatible component and water as main solvent, in accordance with the green chemistry guidelines. Moreover, the scale-up of the process on the gram scale dealing with the problem of the technological transfer from basic research to applied science has been taken into account by GLYCOG Lab 4.0.

References:

- [1] J. Hu, Y. Ji, Y. Shi, F. Hui, H. Duan, M. Lanza, *Ann. J. Materials Sci. Eng.*, **2014**, 1, 16.
- [2] <http://graphene-flagship.eu/>
- [3] M. J. Nine, M. A. Cole, D. N. H. Tran, D. Losic, *J. Mater. Chem. A*, **2015**, 3, 12580-12602.
- [4] a) K. S. Novoselov, V. I. Fal'ko, L. Colombo, P. R. Gellert, M. G. Schwab, K. Kim, *Nature*, **2012**, 490, 192-200; b) Y. Zhu, S. Murali, W. Cai, X. Li, J. W. Suk, J. R. Potts, R. S. Ruoff, *Adv. Mat.*, **2010**, 22, 3906-3924 and references cited therein.
- [5] A. Zurutuza, C. Marinelli, *Nat. Nanotechnol.* **2014**, 730-734.

Accelerating water exchange in Gd^{III}-DO3A-acetophenone derivatives by favouring the dissociative mechanism through hydrogen bonding

L. Leone,^a M. Milanesio,^a S. Camorali,^a C. Platas Iglesias,^b D. Esteban-Gómez,^b L. Tei^a

^aDipartimento di Scienze ed Innovazione Tecnologica, Università degli Studi del Piemonte Orientale "Amedeo Avogadro", Viale Teresa Michel 11, 15121 Alessandria, Italy

^bCentro de Investigaciones Científicas Avanzadas (CICA) and Departamento de Química Fundamental, Facultade de Ciencias, Universidade da Coruña, E-15071, A Coruña, Galicia, Spain
loredana.leone@uniupo.it

MRI contrast agents (CAs), usually Gd^{III} or Mn^{II} complexes, are often used to increase the diagnostic information of the image by enhancing the signal intensity and the contrast between normal and diseased tissues.¹ A reduction of the doses used in clinical practice could be beneficial and this can be obtained through the development of more efficient CAs with fast exchange rates (k_{ex}) of the coordinated water molecule(s), which lead to high relaxivity values. We have recently shown that Gd(DO3A-o-HAP), a DO3A-like ligand with a fourth pendant arm consisting of a 2'-hydroxyphenacyl group, has a hydrogen-bond acceptor in the periphery of the coordinated water molecule that accelerates dramatically the water exchange rate, as measured by ¹H and ¹⁷O NMR relaxometry.² Furthermore, a Density Functional Theory (DFT) study confirmed that intramolecular hydrogen-bonding interactions with the peripheral phenolate group favour the exchange of the coordinated water molecule, thereby accelerating k_{ex} . A single crystal of GdDO3A-oHAP was also obtained and the X-ray diffraction analysis showed that complex presents a square antiprismatic coordination around the metal centre with a cis/trans disordered 2-hydroxyacetophenone moiety at 20/80 ratio. The phenolic OH forms an intermolecular H-bond in *trans* conformation while an intramolecular water assisted H-bond is observed in the *cis* conformation.

Then, in order to evaluate the effect of different hydrogen-bond acceptors in this family of phenacyl-based complexes, we also synthesized and characterized via ¹H and ¹⁷O NMR relaxometry two novel macrocyclic ligands, bearing a 2'-aminophenacyl (DO3A-An-AP) and a 2',4'-dihydroxyphenacyl (DO3A-DHAP) group as the fourth pendant arm (**Figure 1**).

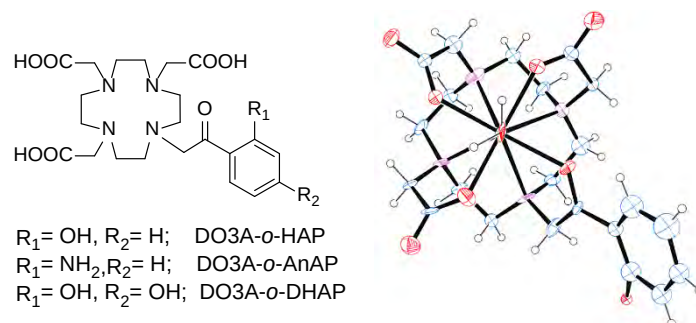


Figure 1: left: chemical structures of the ligands involved in this work; right: molecular structure of the major *trans* conformation of GdDO3A-o-HAP viewed along Gd-water bond

References:

- [1] *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*, Eds. A. Merbach, L. Helm and E. Toth, Wiley, Chichester, 2nd ed., **2013**.
- [2] L. Leone, D. Esteban-Gómez, C. Platas-Iglesias, M. Milanesio L. Tei, *Chem. Commun.* **2019**, 55, 513-516.

Mixed phenolate/carboxylate AAZTA-like ligands for MRI applications

J. Martinelli, L. Tei

Dipartimento di Scienze e Innovazione Tecnologica, Università del Piemonte Orientale "Amedeo Avogadro",
Viale T. Michel 11, 15121 – Alessandria, Italy
jonathan.martinelli@uniupo.it

Magnetic resonance imaging (MRI) is a leading technique in modern clinical diagnostics. Contrast-enhanced MRI requires the use of suitable paramagnetic metals (e.g. Gd^{3+}) that increase the water-protons relaxation rate (R_1). We have designed new ligands based on the AAZTA platform (Figure),^[1] since it has proved to chelate lanthanide and *p*-block ions with excellent thermodynamic stability and kinetic inertness, which is crucial to ensure *in vivo* safety. GdAAZTA possesses optimal parameters to attain a high MRI performance, particularly two water molecules coordinated to the metal center ($q = 2$), affording a R_1 -enhancement per millimolar Gd -concentration (relaxivity, r_{1p}) of $7.1 \text{ mM}^{-1} \text{ s}^{-1}$ at 20 MHz and 25 °C. Our novel ligands (Figure) contain one (**L1** and **L2**) or two (**L3**) phenolic moieties in addition to traditional acetate arms. Phenolate anions can be strong donor groups, and macrocyclic and acyclic chelates functionalized with hydroxyphenyl units are widely reported in the literature as ligands for transition-metal ions. However, their applications as lanthanide chelators are very uncommon, particularly for use in aqueous environments: only a few cases are reported for Gd^{III} .^[2] The synthesis of **L1-L3** (Figure) involves a nitro-Mannich cyclization with a suitable disubstituted ethylenediamine to obtain a 6-nitroperhydro-1,4-diazepine, followed by reduction of the nitro-group and mono- or dialkylation of the resulting primary amine with *t*-butyl bromoacetate. The phenolic moieties are introduced by reacting the primary or secondary amine(s) with 2-(bromomethyl)phenyl acetate or salicylaldehyde. The ligands are obtained upon deprotection of the acetate and hydroxybenzyl arms. Gd^{3+} -complexations and a preliminary relaxometric characterization (20 MHz, 25 °C) allowed to determine r_{1p} values of 7.2, 5.7 and $4.9 \text{ mM}^{-1} \text{ s}^{-1}$ for GdL1 , GdL2 and GdL3 respectively, with the first confirming a $q = 2$ as for GdAAZTA . Further and more advanced investigations (^{17}O -measurements, interaction with HSA and endogenous anions etc.) have been carried out on these promising chelators and their potential MRI applications.

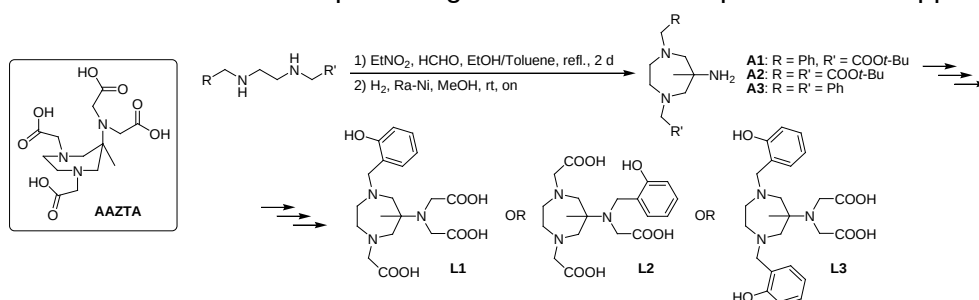


Figure: AAZTA-ligand and synthetic pathway for ligands **L1-L3**.

References:

- [1] S. Aime, L. Calabi, C. Cavallotti, E. Gianolio, G. B. Giovenzana, P. Losi, A. Maiocchi, G. Palmisano, M. Sisti, *Inorg. Chem.* **2004**, 43, 7588-7590.
[2] a) M. Woods, G. E. Kiefer, S. Bott, A. Castillo-Muzquiz, C. Eshelbrenner, L. Michaudet, K. McMillan, S. D. K. Mudigunda, D. Ogrin, G. Tircsó, S. Zhang, P. Zhao, A. D. Sherry, *J. Am. Chem. Soc.*, **2004**, 126, 9248-9256; b) M. I. Tsionou, C. E. Knapp, C. A. Foley, C.R. Munteanu, A. Cakebread, C. Imberti, T. R. Eykyn, J. D. Young, B. M. Paterson, P. J. Blower, M. T. Ma, *RSC Adv.*, **2017**, 7, 49586-49599.

Targeting mPGES-1 by a combinatorial approach: identification of 2-aminobenzothiazoles as scaffold for new PGE₂ modulator in human cancer cells

E. Colarusso,^a M. G. Chini,^a A. Giordano,^b M. C. Vaccara,^a M. Potenza,^a S. Terracciano,^a I. Bruno,^a R. Riccio,^a O. Werz,^c A. Koeberle,^c G. Bifulco^a

^aDepartment of Pharmacy, University of Salerno, Fisciano, Italy

^bInstitute of Biomolecular Chemistry (ICB), Consiglio Nazionale delle Ricerche (CNR), Napoli, Italy

^cInstitute of Pharmacy, Friedrich Schiller University Jena, Germany

e-mail: ecolarusso@unisa.it

Microsomal prostaglandin E₂ synthase-1 enzyme (mPGES-1) has emerged as an attractive target for the discovery and development of new efficient anti-inflammatory and anticancer drugs¹. This enzyme is responsible for the production of inducible prostaglandin PGE₂, and its inhibition is an alternative option to control PGE₂-related pathologies with respect to the strategies targeting the upstream cyclooxygenases². For these reasons, inhibition of mPGES-1 represents an attractive strategy for developing new anti-inflammatory and anti-cancer drugs with reduced side effects. Design of these inhibitors was done following a computational protocol; the synthones 2-amino-6-bromobenzothiazole and 2-amino-5-bromobenzothiazole were combined with 318 acid-chlorides at position 2 and 570 boronates at position 6 or 5, respectively, obtaining 181,260 molecules for each library, using *CombiGlide* software³. Docking calculations were performed using *Glide* software. In particular, different levels of Glide sampling and scoring precision algorithms were accounted (HTVS, SP, and XP modes). The best-selected compounds (**3-20**) were synthesized, using Pd-catalyzed Suzuki-Miyaura cross-coupling between 3-(hydroxymethyl)phenylboronic acid and 2-amino-6-bromobenzothiazole or 2-amino-5-bromobenzothiazole followed by acylation. mPGES-1 inhibitory activity of synthesized compounds was evaluated *in vitro* performing cell-free and cell-based assays⁴. The effects of synthesized molecules against mPGES-1 activity were studied by monitoring the enzymatic conversion of the substrate PGH₂ to PGE₂ in a cell-free assay using microsomes of IL-1β-stimulated A549 cells as a source of mPGES-1, disclosing **3, 5, 8, 12, 20** as active compounds able to inhibit the target at low micromolar concentrations (IC₅₀ < 3.0 μM). Afterwards, the evaluation of melanoma cancer cell vitality disclosed **3, 5, 12** as the most promising hits with IC₅₀ < 20.0 μM.

References:

- [1] J. G. Luz, S. Antonysamy, S. L. Kuklish, B. Condon, M. R. Lee, D. Allison, X.-P. Yu, S. Chandrasekhar, R. Backer, A. Zhang, M. Russel, S. S. Chang, A. Harvey; A. V. Sloan; M. J. Fisher, *J. Med. Chem.* **2015**, *58*, 4727-4737.
- [2] A. Koeberle, S. A. Laufer, O. Werz, *J. Med. Chem.* **2016**, *59*, 5970-5986.
- [3] CombiGlide, Schrödinger, LLC, New York, NY, **2017**.
- [4] A. Koeberle, U. Siemoneit, U. Buehring, H. Northoff, S. Laufer, W. Albrecht, O. Werz, *J. Pharmacol. Exp. Ther.* **2018**, *326*, 975-982.

Unprecedented use of a deep eutectic solvent as hydrogen source for Ru(II)-catalyzed transfer hydrogenation of carbonyl compounds under mild conditions

M. Cavallo,^a C. Prandi,^a R. Figliolia,^b M. Ballico,^b W. Baratta,^b S. Baldino^{a*}

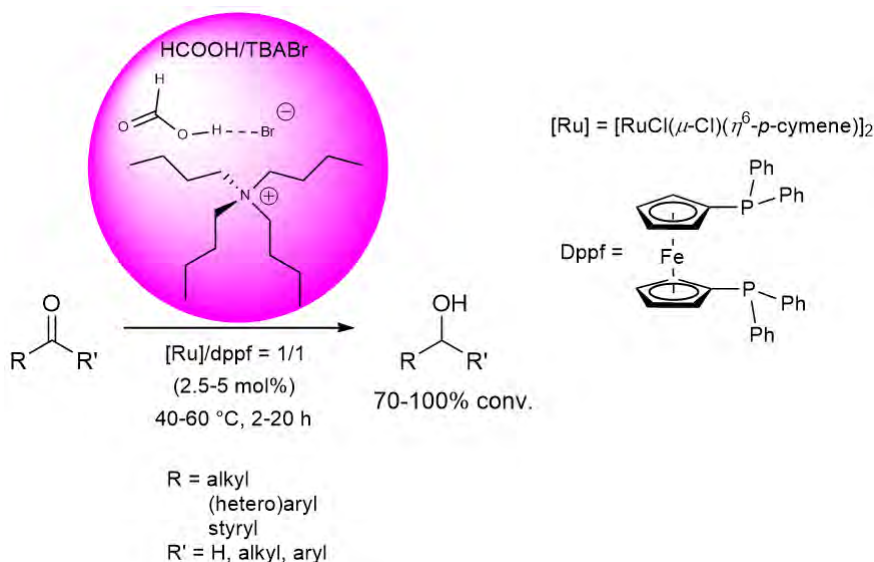
^aDipartimento di Chimica, Università di Torino, Via P. Giuria, 7, 10125 Torino, Italy

^bDI4A, Università di Udine, Via Cotonificio 108, 33100 Udine, Italy

e-mail: *salvatore.baldino@unito.it

Deep eutectic solvents (DESs)¹ are systems formed from a eutectic mixture of Lewis or Brønsted acids and bases which can contain a variety of anionic and/or cationic species. They have emerged in the last two decades as a promising alternative to volatile organic compounds (VOCs).² They have recently been used as unconventional solvents in several and diverse synthetic transformations,^{2a} such as transition metal catalyzed hydrogenation,^{2b} often showing novel reactivity, selectivity and efficiency compared to traditional VOCs. In addition, DESs are not volatile, non-toxic, non-flammable, completely biodegradable and easy to handle and synthesize. Given their peculiar properties, in our pursuit of simple and efficient catalysts for the Ru(II)-mediated reduction of carbonyl compounds,³ we envisaged the possibility to employ DESs both as reaction media and hydrogen sources, combining readily accessible Ru-precursors with different diphosphane and diamine ligands.

Herein we report the unprecedented use of the eutectic mixture HCOOH/TBABr as hydrogen source in the transfer hydrogenation of commercial-grade carbonyl substrates to their corresponding alcohols, catalyzed by the in situ generated system $[\text{RuCl}(\mu\text{-Cl})(\eta^6\text{-p-cymene})]_2$ / dppf under mild conditions.



References:

- [1] E. L. Smith, G. Capper, A. P. Abbot, K. S. Ryder, *Chem. Rev.* **2014**, *114*, 11060-11082.
- [2] a) D. A. Alonso, A. Baeza, R. Chinchilla, G. Guillena, I. M. Pastor, D. J. Ramón, *Eur. J. Org. Chem.* **2016**, 612-632; b) J. García-Álvarez, *Eur. J. Inorg. Chem.* **2015**, 5147-5157.
- [3] G. Chelucci, S. Baldino, W. Baratta, *Coord. Chem. Rev.* **2015**, *300*, 29-85.

Quinoline cyclic tripeptoids as novel DNA bis-intercalating agents

A. D'Amato,^a I. Izzo,^a F. De Riccardis^a

^aUniversity of Salerno, Department of Chemistry and Biology "A. Zambelli", 84084 Fisciano (SA), Italy
asdamato@unisa.it

Bis-intercalators are a class of secondary metabolites produced by several bacteria species.¹ The main interest in these compounds is due to their remarkable anti-tumor activity, as well as the unique DNA binding mode, which usually is enhanced by GC-rich DNA sequences. Non-covalent DNA binders exert their function via intercalation of a polyaromatic unit between two bases; this interaction can be enhanced by a positively charged nitrogen atom on the intercalator scaffold (which usually is a cyclic peptide or depsipeptide) and the oxygen atom of the phosphodiester group of DNA.² The chromophores face out from the scaffold and are constituted either by a quinoline or a quinoxaline unit; the intercalation causes severe alteration in the replication or transcription of the DNA, which results in the cytotoxic effect.³

Cyclic peptoidic systems, oligomers of *N*-alkyl glycines,⁴ have already proven to be remarkably promising as small molecules mimicking the activities of natural cyclodepsipeptidic counterparts.⁵ Our approach to a synthetic class of bis-intercalators consists in the functionalization of a cyclic trimeric peptoid core with two or three quinoline appendages, in order to evaluate the effect of a free amino group, potentially able to interact with the DNA's phosphodiester group. In this communication we will report both the synthesis and the activities of our compounds as cytotoxic agents against human cancer cell lines.

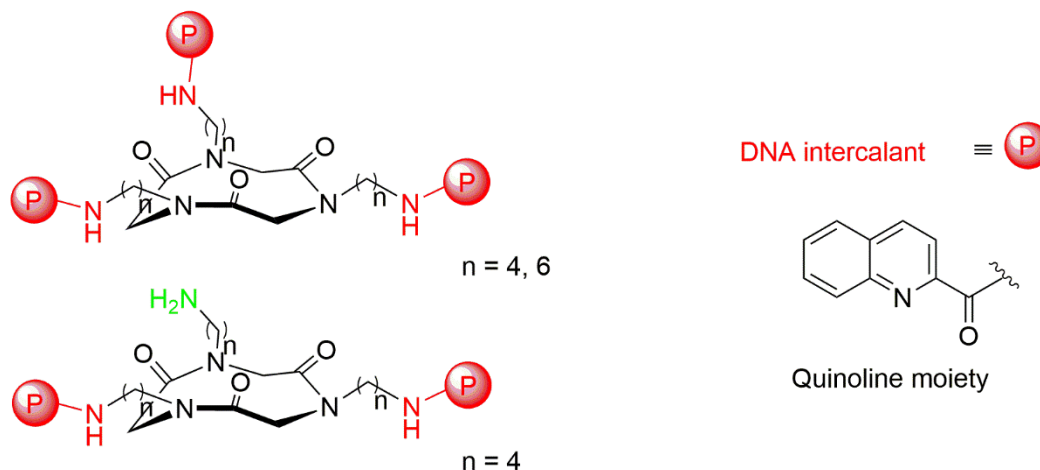


Figure 1. Cyclic tripeptoids examined in this communication.

References:

- [1] O. E. Zolova, A. S. A. Mady, S. Garneau-Tsodikova, *Biopolymers* **2010**, 93, 777-790.
- [2] A. Rescifina, C. Zagni, M. G. Varrica, V. Pistarà, A. Corsaro, *Eur. J. Med. Chem.* **2014**, 74, 95-115.
- [3] J. Fernández, L. Marín, R. Álvarez-Alonso, S. Redondo, J. Carvajal, G. Villamizar, C. J. Villar, F. Lombó, *Mar. Drugs* **2014**, 12, 2668-2699.
- [4] N. Maulucci, I. Izzo, G. Bifulco, A. Aliberti, C. De Cola, D. Comegna, *Chem. Commun.* **2008**, 33, 3927-3929.
- [5] a) A. D'Amato, R. Volpe, M. C. Vaccaro, S. Terracciano, I. Bruno, M. Tosolini, C. Tedesco, G. Pierri, P. Tecilla, C. Costabile, G. Della Sala, I. Izzo, F. De Riccardis, *J. Org. Chem.* **2017**, 82, 8848-8863; b) A. D'Amato, G. Della Sala, I. Izzo, C. Costabile, F. De Riccardis, Y. Masuda, *Molecules* **2018**, 23, 1779-1794.

COMUNICAZIONI POSTER

Sessione 2

Modulation of biological target selectivity through an appropriate scaffold decoration

S. Terracciano,^a D. Ruggiero,^a M. G. Chini,^a R. Riccio,^a G. Bifulco,^a I. Bruno^a

^aDepartment of Pharmacy, University of Salerno, Via Giovanni Paolo II 132, 84084 Fisciano (SA), Italy
sterracciano@unisa.it

Small-molecules are powerful tools both as therapeutics and as probes for investigating key cellular processes governed by biological macromolecules.¹ With the aim of disclosing new molecular entities able to selectively modulate strategic therapeutic targets involved in both cancer and inflammatory pathologies, here we describe a valuable combined approach for generating new chemical hits. In particular, starting from a versatile synthetic strategy we had access to a wide variety of highly functionalized heterocyclic scaffolds representing the initial seed for investigating protein-ligand interactions involved in key biological processes. A computational approach by molecular docking calculations drove the strategic synthesis of selective molecules able to interact with a specific target.^{2,3} Our purpose was the optimization of synthetic strategy leading to a fused heterocyclic ring as building block *via* suitably functionalized starting materials. These advanced intermediates could further derivatized, by nucleophilic aromatic substitution as well as by Palladium catalyzed Suzuki-Miyaura reactions, in order to obtain the whole series of designed compounds.⁴ Following these strategies, the easy and fast preparation of a wide number of new potential bioactive compounds is allowed. The synthesized molecules were screened to confirm their biological profile.

References:

- [1] M. Aeluri, S. Chamakuri, B. Dasari, S.K.R. Guduru, R. Jimmidi, S. Jogula, P. Arya, *Chem. Rev.* **2014**, *114*, 4640-4694.
- [2] S. Di Micco, S. Terracciano, V. Cantone, K. Fischer, A. Koeberle, A. Foglia, R. Riccio, O. Werz, I. Bruno, G. Bifulco, *Eur. J. Med. Chem.* **2018**, *143*, 1419-1427.
- [3] CombiGlide, version 3.8, Schrödinger, LLC, New York, NY, 2015.
- [4] B. Jafari, M. Ospanov, S.A. Ejaz, N. Yelibayeva, S. Khan, S.T. Amjad, *Eur. J. Med. Chem.* **2018**, *144*, 116-127.

A multistep computational protocol towards the identification of 2-amino-1,3,4-thiadiazole-based molecules as novel mPGES-1 inhibitors

M. Potenza,^a M. G. Chini,^a A. Giordano,^{a,b} M.C. Vaccaro,^a S. Terracciano,^a I. Bruno,^a R. Riccio,^a O. Werz,^c A. Koeberle,^c and G. Bifulco^{a,*}

^aDepartment of Pharmacy, University of Salerno, Fisciano, Italy

^bInstitute of Biomolecular Chemistry (IBC), Consiglio Nazionale delle Ricerche (CNR), Via Campi Flegrei 34, I-80078, Pozzuoli, Napoli, Italy

^cInstitute of Pharmacy, Friedrich Schiller, University of Jena, Jena, Germany
e-mail: mpotenza@unisa.it

In light of the well-known involvement of microsomal Prostaglandin E₂ Synthase-1 (mPGES-1) in the development of inflammatory and tumor diseases, the mentioned protein target is recently getting one of the most investigated towards the individuation of novel drugs for the treatment of both the pathologies.¹ The synthase, in fact, catalyzes the conversion of the unstable peroxide prostaglandin H₂ (PGH₂) in prostaglandin E₂ (PGE₂), and it is over-expressed in inflammation and cancer.¹ Thus, a structure-based multistep computational protocol coupled to a previously selected synthetic approach was applied, with the main purpose of identifying novel promising hits.

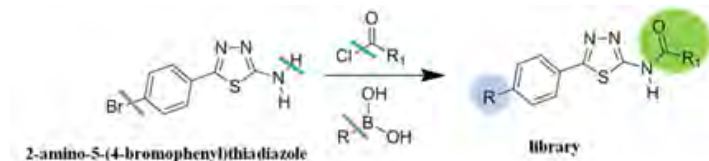


Figure 1: Generation of the library.

In detail, commercially available acyl chlorides were introduced on the amino group at position 2 of 2-amino-5-(4-bromophenyl)thiadiazole (Figure 1), as a substitution reaction is the first step of the chemical route (Figure 2), while commercially available boronic acids, involved in the Suzuki coupling reaction, were used for the replacement of the bromine. A new library of 181,260 *N*-(5-(4-arylphenyl)-1,3,4-thiadiazol-2-yl)arylcaboxamides was generated *in silico*, and a *Virtual Screening Workflow* for the docking studies (*Glide software*)² onto the crystal structure of mPGES-1 was performed, affording a final selection of 9 promising compounds for the synthetic step. All the compounds were synthesized applying the reported synthetic strategy. Performed cell-free and cell-lines assays confirmed the inhibitory activity on the enzyme of 3 among the synthesized compounds, presenting an IC₅₀ < 3 μM in the cell free assay.

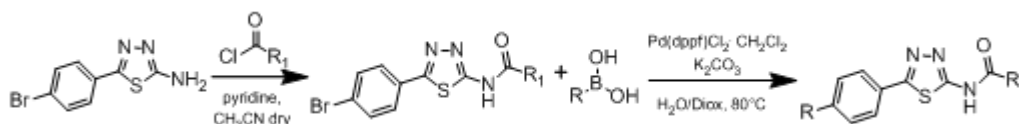


Figure 2: Selected and applied synthetic strategy.

References:

- [1] J. G. Luz, S. Antonysamy, S. L. Kuklish, B. Condon, M. R. Lee, D. Allison, X.-P. Yu, S. Chandrasekhar, R. Backer, A. Zhang, M. Russel, S. S. Chang, A. Harvey; A. V. Sloan; M. J. Fisher, *J. Med. Chem.* **2015**, *58*, 4727.
- [2] *Glide*, version 6.8, Schrödinger, LLC, New York, NY, **2015**.

Synthesis of bifunctional inhibitors to address type 2 diabetes by dual enzyme targeting

C. Matassini,^a X. Ferhati,^a A. Goti,^a A. Morrone,^b P. Paoli,^c A. J. Moreno-Vargas,^d F. Cardona^a

^a Department of Chemistry 'Ugo Schiff', University of Firenze, Sesto Fiorentino (FI), Italy

^b Paediatric Neurology Unit and Laboratories, Neuroscience Department, Meyer Children's Hospital, and Department of Neurosciences, Pharmacology and Child Health, University of Florence, Italy

^c Department of Experimental and Clinical Biomedical Sciences, University of Florence, Italy

^d Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Spain
francesca.cardona@unifi.it

The diffusion of type 2 diabetes (T2D) throughout the world represents one of the most important health problems of this century and the development of new anti-diabetic drugs remains an urgent challenge. Indeed, none of the currently marketed drugs is capable of reproducing the physiological action of insulin and often they have several side effects. Multi-target drugs could offer new therapeutic opportunities for the treatment of T2D. [1] α -Glucosidases and Protein Tyrosine Phosphatase 1B (PTP1B) are considered important targets for the treatment of T2D: the first enzymes digest oligo- and disaccharides in the gut, while the latter regulates the insulin-signaling pathway. With the aim of generating new drugs able to inhibit both enzymes, we synthesized a series of bifunctional compounds bearing both a nitro aromatic group and an iminosugar moiety (Figure 1). [2] The synthesis relies on the connection of an iminosugar key intermediate to the nitroaromatic moiety through the CuAAC approach or via an amide bond.

The results of tests carried out both *in vitro* and in a cell-based model, show that these bifunctional compounds maintain activity on both target enzymes and, more importantly, two of them showed a good insulin-mimetic activity in *ex-vivo* assays, increasing phosphorylation levels of Akt in the absence of insulin stimulation. These compounds could be used to develop a new generation of anti-hyperglycemic drugs useful for the treatment of patients affected by T2D.

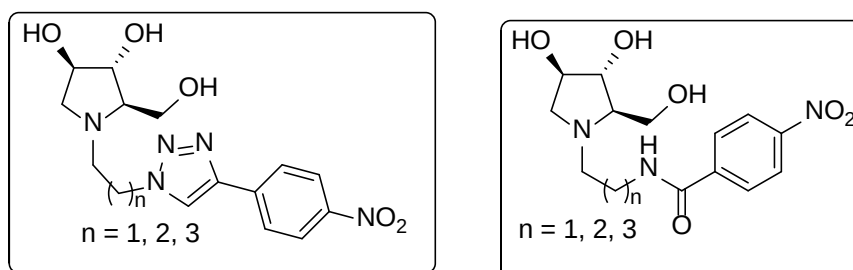


Figure 1: The bifunctional compounds designed to inhibit both α -Glucosidases and Protein Tyrosine Phosphatase 1B (PTP1B) enzymes

References:

[1] J Thrasher, *Am. J. Cardiol.* **2017**, 120, S4-S16.

[2] X. Ferhati, C. Matassini, M. G. Fabbrini, A. Goti, A. Morrone, F. Cardona, A.-J. Moreno-Vargas, P. Paoli, *Bioorg. Chem.* **2019**, 87, 534-549.

Micellar Assisted Synthesis of Chalcones as Intermediates for Bipyridines

P. Quagliotto, M. M. H. Desoky, N. Barbero, C. Barolo, G. Viscardi

Dipartimento di Chimica e Centro NIS "Superfici ed Interfacce Nanostrutturate", via P. Giuria 7, Torino
pierluigi.quagliotto@unito.it

Chalcones are well known molecules, having several applications as intermediates and drugs.¹ They are often easily obtained by performing aldol reaction in solvents, with good yields. They are essential intermediates for the Kröhnke reaction, which give access to pyridines, bipyridines and terpyridines.² The bipyridine structural motif is often exploited as a ligand to form metal complexes which showed electrochemical CO₂ reduction activity.³ In order to produce chalcones for the preparation of bipyridine ligands, we tried a green chemistry approach. While the solvents used for this reaction are in general mild (often alcohols are used), the use of water by surfactant assistance is an attractive alternative, which is not new but in the last few years it reached important results from the preparative point of view.⁴ The aldol reaction was studied and applied to the synthesis of a few chalcones, useful for the preparation of bipyridine ligands. Several surfactants were used and among them, PTS, Nok and TPGS-750-M are truly green surfactants.⁴ The use of surfactants shortened the reaction time and increased the yield. Whether the chalcone is sufficiently soluble in the micellar medium, the reaction can proceed with a Michael addition on the chalcone. The chalcone was easily isolated by filtration when it was slightly soluble in the micellar solution. Reactions performed in presence of a cosolvent (10% ethanol), showed an increased yield and gave pure solids by simple filtration (yields: 76-91%). The scope of the reaction was studied, and also the less deactivated substrates reacted easily. The chalcones were used to prepare some bipyridine derivatives, with Kröhnke reaction, under both standard conditions (acetic acid and ammonium acetate at 80°C) and an original and green way, performed in water.

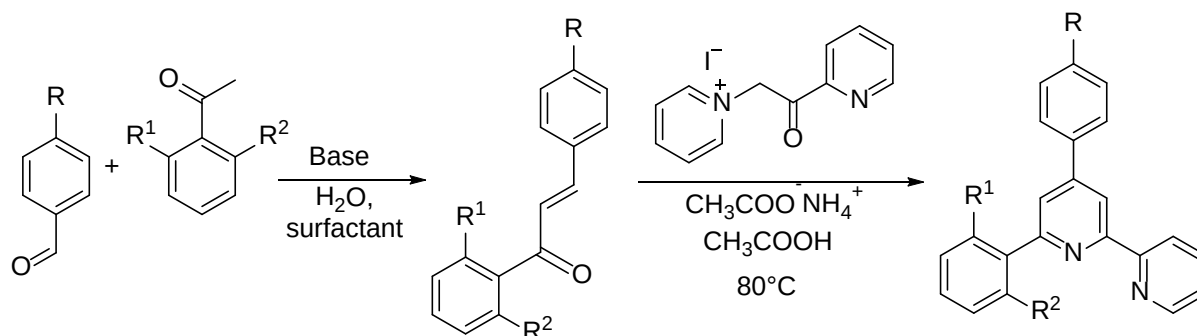


Figure 1: Synthetic Pathway to chalcones in surfactant medium and to bipyridines by Krohnke reaction.

References:

- [1] M. N. Gomes, E. N. Muratov, M. Pereira, J. C. Peixoto, L. P. Rosseto, P. V. L. Cravo, C. H. Andrade, B. J. Neves, *Molecules* **2017**, 22 (8), 1210.
- [2] I. Sasaki, *Synthesis* **2016**, 48 (13), 1974-1992.
- [3] a) C. Sun, R. Gobetto, C. Nervi, *New J. Chem.* **2016**, 40 (7), 5656-5661; b) C. Sun, S. Prosperini, P. Quagliotto, G. Viscardi, S. S. Yoon, R. Gobetto, C. Nervi, *Dalton Trans.* **2016**, 45 (37), 14678-14688.
- [4] B. H. Lipshutz, *J. Org. Chem.* **2017**, 82 (6), 2806-2816.

Synthesis and characterization of polymers as HTMs for perovskite solar cells

M.M.H. Desoky,^a P. Quagliotto,^a C. Barolo,^a M. Bonomo,^a G. Viscardi,^a A. Di Carlo,^b N. Yaghoobi Nia^b

^aDipartimento di Chimica, Università degli Studi di Torino, via P. Giuria 7, Torino, 10125, Italy

^bCHOSE. (Centre for Hybrid and Organic Solar Energy),
University of Rome "Tor Vergata", via del Politecnico 1, Rome 00133, Italy
mohamedmgadyhassan.desoky@unito.it

Among alternative energy sources, Perovskite Solar Cells (PSC), raising in efficiency from 3.2% to 22-23% in only few years,¹ are the new frontier of the photovoltaic research. The polymeric Hole Transport Materials (HTM) extract holes and protect perovskite from moisture degradation due to their superior sealant ability.² We prepared several P3HT and PTAA conductive polymers. P3HT structure was modulated in molecular weight (20 to 300 kDa) and regioregularity (78-100%), to search for correlations between structure and solar cell efficiency.³ The P3HT were prepared by different synthetic methods (oxidative,⁴ C-H activation⁵ and Grignard Methatesis⁶).

The PTAA were prepared by polymerization of dibromo-substituted linkers with different anilines, with a Pd catalyst bearing a NHC ligand,⁷ obtaining polymers with short to medium molecular weight. Upon characterization, the polymers showed a very good stability and the estimation of energy levels was compatible with the most common perovskites used in perovskite solar cells. Those HTMs were used in crystal engineering perovskite⁸ solar cells, reaching a photoconversion efficiency of 17% and 13.4% respectively, confirming their good potential as HTMs for PSCs.

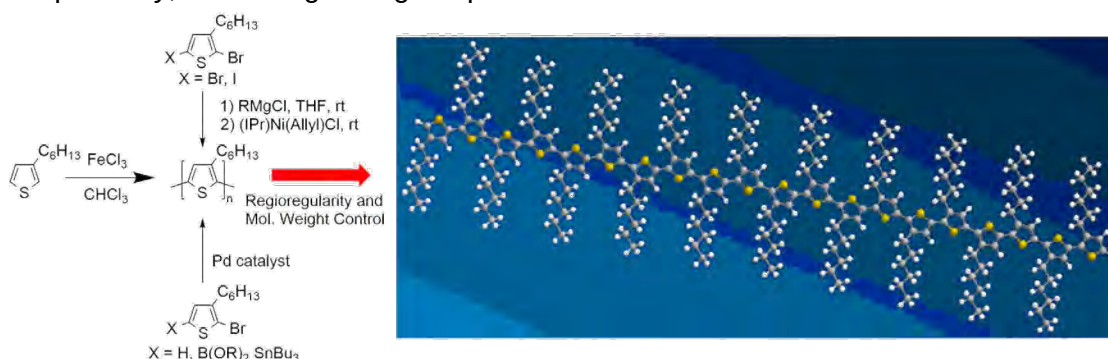


Figure 1: Different synthetic methods for P3HT.

Acknowledgements

This work was supported by the Italian Ministry of Economic Development in the framework of the Operating Agreement with ENEA for Research on the Electric System.

References:

- [1] M. Green, A. Ho-Baillie, *ACS Lett.* **2017**, 2, 822-830.
- [2] W. Zhou, Z. Wen, P. Gao, *Adv. Energy Mater.* **2018**, 1702512.
- [3] P. Quagliotto, A. Fin, *Lett. Org. Chem.* **2018**, 15, 991-1006.
- [4] M. R. Andersson, D. Selse, M. Berggren, H. Jaervinen, T. Hjertberg, O. Inganaes, O. Wennerstroem, J.E. Oesterholm, *Macromolecules* **1994**, 27, 6503-6506.
- [5] A. E. Rudenko, B. C. Thompson, *J. Polym. Sci. Part A: Polym. Chem.* **2015**, 53, 135-147.
- [6] X. Shi, A. Sui, Y. Wang, Y. Li, Y. Geng, F. Wang, *Chem. Commun.* **2015**, 51, 2138-2140.
- [7] R. S. Sprick, M. Hoyos, O. Navarro, M. L. Turner, *React. Funct. Polym.* **2012**, 72, 337-340.
- [8] N. Yaghoobi Nia M. Zendehtdel, L. Cina F. Matteocci A. Di Carlo, *J. Mater. Chem. A*, **2018**, 6, 659-671.

Synthesis of a donor-acceptor polymer for perovskite solar cells

M.M.H. Desoky, P. Quagliotto, N. Barbero, C. Barolo, M. Bonomo, G. Viscardi

Dipartimento di Chimica, Università degli Studi di Torino, via P. Giuria 7, Torino, 10125, Italy
mohamedmagdyhassan.desoky@unito.it

The increasing world energy demanding makes compulsory the search of energy sources alternative to fossil fuels. Among alternative energy source, the solar energy is green, renewable and not exhaustible. Perovskite Solar Cells (PSC), which rose in efficiency from the 3.2% (2012) to 22-23% in only 5-6 years,¹ are the new frontier of the photovoltaic research. Unfortunately, perovskites show instability towards moisture, which rapidly deteriorates the device performances. The use of polymeric Hole Transporting Material (HTMs) layers on the perovskite surface seems to overcome those problems, granting a good stability increase, since the optimal filming properties of hydrophobic polymers.

Most HTMs need to be doped to show good conductivity levels, useful for PSC cells, but doping agents are detrimental for cell stability since they are hygroscopic and, through them, water can reach the perovskite layer. Recently, we prepared P3HT and PTAA as HTM, but we are also interested into polymeric HTMs showing an inherent high conductivity, which recently became the new HTM research hot topic, the “dopant-free” conductive polymers.² To prepare a promising dopant-free polymer, a donor-acceptor monomer (**1**) was prepared by Suzuki coupling on a dibromoaldehyde derivative, followed by Knoevenagel condensation with malononitrile under microwaves. The final polymerization using FeCl₃ gave a red colored polymer (**2**). The polymer was characterized by NMR, GPC, UV, Fluorescence, CV, thermal analysis (TGA and DSC). A high molecular weight polymer was obtained, showing very good thermal stability. The HOMO and LUMO levels, obtained by electrochemistry and spectroscopy, showed that the polymer can be considered an interesting HTM for perovskite solar cells.

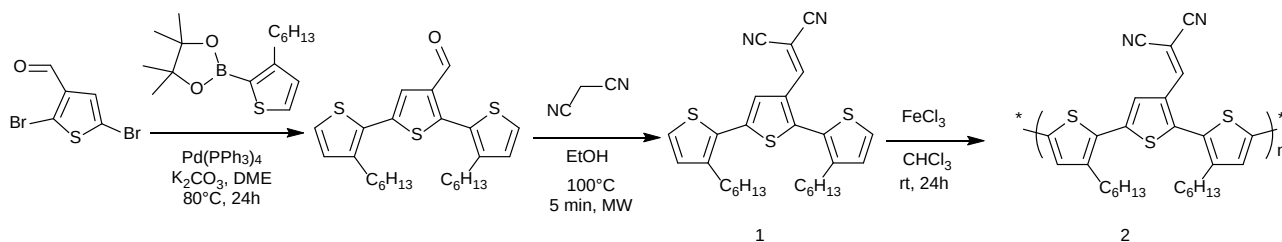


Figure 1: Scheme for the synthesis of the monomer (**1**) and the polymer (**2**).

Acknowledgements:

This work was funded by ASI, through the project PEROSKY.

References:

- [1] M. Green, A. Ho-Baillie, *ACS Lett.* **2017**, 2, 822-830.
- [2] W. Zhou, Z. Wen, P. Gao, *Adv. Energy Mater.* **2018**, 1702512.

Azodyes based polymers for 3D printing

M. Gastaldi,^a A. Fin,^b N. Barbero,^a I. Roppolo,^c A. Chiappone,^c S. Bordiga,^a M. Zanetti,^a F. Frascella,^c C. Barolo,^a G. Viscardi^a

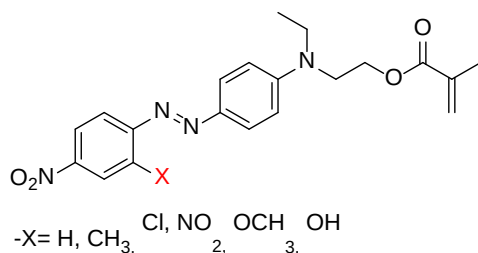
^aDipartimento di Chimica e Centro Interdipartimentale NIS, Università di Torino, Via Pietro Giuria 7, 10125-Torino, Italy

^bDipartimento di Scienza e Tecnologia del Farmaco, Università di Torino, Via Pietro Giuria 9, 10125-Torino, Italy

^cDipartimento di Scienza Applicata e Tecnologia, Politecnico di Torino, C.so Duca degli Abruzzi 24, 10129-Torino, Italy
matteo.gastaldi@unito.it

Three-Dimensional Printing (3DP) is one of the most promising innovative technologies, used not only in prototyping, but also in the production processes. The main advantages of this new technique are the high versatility, the progressive printers' price knock off and the considerable saving of raw materials. The exploitation of new functional materials, for example temperature-, light- and pH-responsive polymers, is one of the most interesting survey field¹. Azo-based scaffolds have been reported to provide well-defined either photohardening or photosoftering 3D devices².

a)



b)

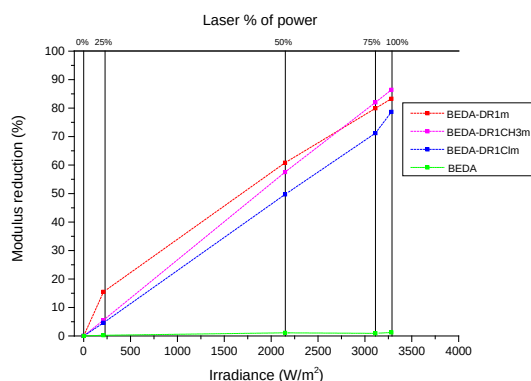


Figure a) Molecular scaffold of the azo monomers; b) Elastic modulus reduction as a function of laser irradiance

In the present work, we designed, synthesized and characterized dye-functionalized polymethacrylates for Digital Light Processing (DLP). Our attention was focused on the azo-benzene methacrylate monomers, because they give mechanical responses, upon irradiation, probably due to the *trans-cis* isomerization. Various substituents (Figure 1a) have been introduced, in *ortho* position to the azo moiety, to tune the monomer/polymer properties, both by steric and electronic effects. We have noticed that the polymers glass-transition temperature (T_g) and the elastic modulus have shown remarkable variations, as a function of the laser power at 532 nm (Figure 1b).

References:

- [1] Z. X. Khoo, J. E. M. Teoh, Y. Liu, C. K. Chua, S. Yang, J. An, K. F. Leong, W. Y. Yeong, *Virtual and Phys. Prototyp.*, **2015**, 10, 103-122.
- [2] I. Roppolo, A. Chiappone, A. Angelini, S. Stassi, F. Frascella, C. F. Pirri, C. Ricciardi, E. Descrovi, *Mater. Horiz.*, **2017**, 4, 396-401.

Squaraine dyes: interaction with bovine serum albumin to investigate supramolecular adducts with aggregation-induced emission (AIE) properties

C. Butnarasu,^a N. Barbero,^b S. Visentin,^a C. Barolo,^b G. Viscardi^b

^aDepartment of Molecular Biotechnology and Health Sciences, University of Torino,
via Gioacchino Quarello 15A, 10135 Torino

^bDepartment of Chemistry, NIS Interdepartmental and INSTM Reference Centre, University of Torino,
via Pietro Giuria 7, 10125 Torino
cosminstefan.butnarasu@unito.it

In the last decades great attention was dedicated to the development of new dyes as markers in biological applications. Squaraines are a class of highly fluorescent near-IR dyes with potential applications as sensors. Even though squaraines have favourable properties relevant in several fields (Dye-Sensitized Solar Cells, organic solar cells, organic light emitting diodes and biomedicine),¹ their poor solubility in aqueous media and the formation of non-emissive aggregates heavily hampered their utilization under biological conditions.² However, squaraines exhibited fluorescence enhancement after non-covalently binding with bovine serum albumin (BSA).

In the present study, BSA-squaraine supramolecular adducts with aggregation-induced emission (AIE) properties were prepared and investigated by spectroscopic methods. AIE is a photophysical phenomenon exhibited when non-emissive luminogens are induced to emit by the aggregate formation.³ While squaraine dyes showed very low fluorescence quantum yield in water, a great enhancement in the fluorescence of the aggregated BSA adducts was achieved due to the abnormal aggregation-induced emission properties of squaraines.⁴ The adducts formation was studied from a kinetic point of view and we observed that the dye backbone structure as well the length of the alkyl chain play a crucial role in the kinetics of the interaction (Figure 1).

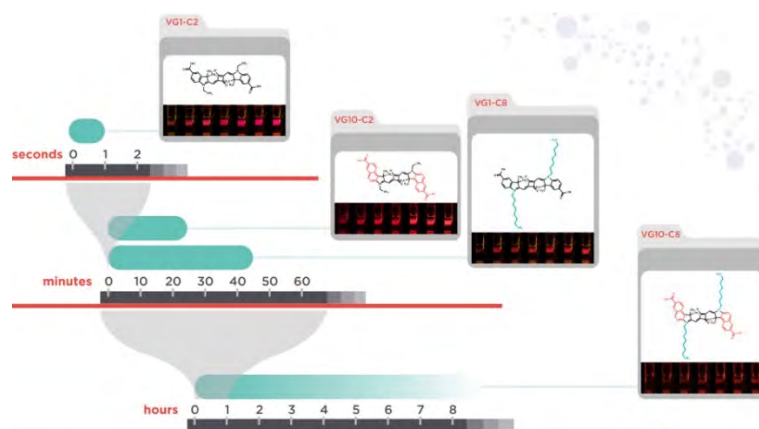


Figure 1: kinetic behaviour of the four BSA-squaraine complex formation

References:

- [1] G. M. Paternò, L. Moretti, A. J. Barker, C. D'Andrea, A. Luzio, N. Barbero, S. Galliano, C. Barolo, G. Lanzani, F. Scotognella, *J. Mater. Chem. C* **2017**, 5, 7732-7738.
- [2] F.-P. Gao, Y.-X. Lin, L.-L. Li, Y. Liu, U. Mayerhöffer, P. Spenst, J.-G. Su, J.-Y. Li, F. Würthner, H. Wang, *Biomaterials* **2014**, 35, 1004-1014.
- [3] J. Mei, N. L. C. Leung, R. T. K. Kwok, J. W. Y. Lam, B. Z. Tang, *Chem. Rev.* **2015**, 115, 11718-11940.
- [4] N. Barbero, C. Butnarasu, S. Visentin, C. Barolo, *Chem. Asian J.* **2019**, 14, 896-903.

Sigma-1 Receptors: Computational Model to Predict the Agonist/Antagonist Effect

V. Patamia, D. Gentile, G. Floresta, C. Barbaraci, M. Dichiarà, E. Amata, A. Marrazzo, A. Rescifina

*Dipartimento di Scienze del Farmaco, Università di Catania, Viale A. Doria 6, 95125, Catania
vincenzo.patamia@unict.it*

Originally mistaken for a subtype of opioid receptors, sigma receptors (σ_R) are now considered as an enigmatic and distinct receptor class. Widely distributed as two subtypes (σ_1 and σ_2), in the central nervous system, and also found in peripheral tissues including liver, kidney, heart, eye, and endocrine, immune and reproductive tissue;¹ furthermore, σ_1 and σ_2 receptors were over-expressed in several tumour cell lines.²

Despite its increasing importance in human physiology and disease, the molecular architecture of the σ_1 receptor and mechanisms of action remain, in some aspects, unanswered.

At present, the classification of σ_1 ligands as agonists and antagonists is based on modulation of typical pharmacological responses, defining agonists as ligands that induce specific effects through binding to σ_1 , while antagonists are σ_1 ligands that inhibit or decrease these responses.

It has been shown that the different oligomeric states of σ_1 receptors are significantly influenced by the different interaction with agonists and antagonists. The agonists decrease the oligomer state, while the antagonists increase the stability of the oligomer state.³

Through computational methods, our research group has recently identified new potent and selective sigma receptor ligands.⁴ In an attempt to study the conformational changes of σ_1 receptors with MD simulation methods provided by antagonists and agonists, we have developed a computational protocol capable of predicting the physiological activity of different ligands. This computational approach could facilitate the task of pharmaceutical chemists for the rational synthesis of new drugs with σ_1 activity.

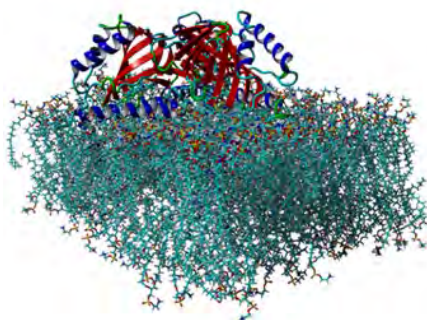


Figure 1: Viewed to the transmembrane domain of the human σ_1 receptor.

References:

- [1] J. A. Fishback, M. J. Robson, Y. T. Xu, R. R. Matsumoto, *Pharmacol. Ther.* **2010**, *127*, 271-282.
- [2] H. Kashiwagi; J. E. McDunn, P. O. Simon, P. S. Goedegebuure, J. Xu; L. Jones, K. Chang, F. Johnston, K. Trinkaus, R. S. Hotchkiss, *Mol. Cancer*. **2007**, *6*, 48.
- [3] K. A. Gromek, F. P. Suchy, H. R. Meddaugh, R. L. Wrobel, L. M. LaPointe, U. B. Chu, J. G. Primm, A. E. Ruoho, A. Senes and B. G. Fox, *J. Biol. Chem.* **2014**, *289*, 20333-20344.
- [4] G. Floresta, E. Amata, G. Barbaraci, D. Gentile, R. Turnaturi, A. Marrazzo, A. Rescifina, *Mar. Drugs* **2018**, *16*, 384.

Flow technology for the preparation of Active Pharmaceutical Ingredients

C. Carlucci,^a S. De Angelis,^a P. Celestini,^b G. Rebuzzini,^b L. Degennaro,^a R. Luisi^a

^a Flow Chemistry and Microreactor Technology FLAME-Lab; Dipartimento di Farmacia - Scienze del Farmaco, Università degli Studi di Bari, Via Orabona 4, 70125 Bari, Italy

^b COSMA S.p.A, Via Colleoni 15/17, Ciserano, BG 24040, Italy
claudia.carlucci@uniba.it

The continuous flow synthesis has attracted interest in chemical and pharmaceutical industries as it guarantees lower production costs, better safety and a greater sustainability. In many cases, it has been demonstrated that some economic savings can be achieved in the production chain if some processes or the entire production could be transferred in continuous flow microreactors.[1-3]

A continuous-flow reduction of (*R*)-2-hydroxy-*N*-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide, a direct precursor of Mirabegron, has been developed, demonstrating the possibility to safely handle BH₃ within microfluidic reactors using 2-MeTHF as greener alternative to traditional solvents.[4]

A fast, sustainable and environmental friendly synthesis of the β -blocker Propranolol, has been developed by using a continuous flow process. The synthetic routes tested show that, within microreactors, it is possible to realize a more sustainable synthesis of pharmaceutical targets, with higher yields, purity and productivity if compared to batch processing.

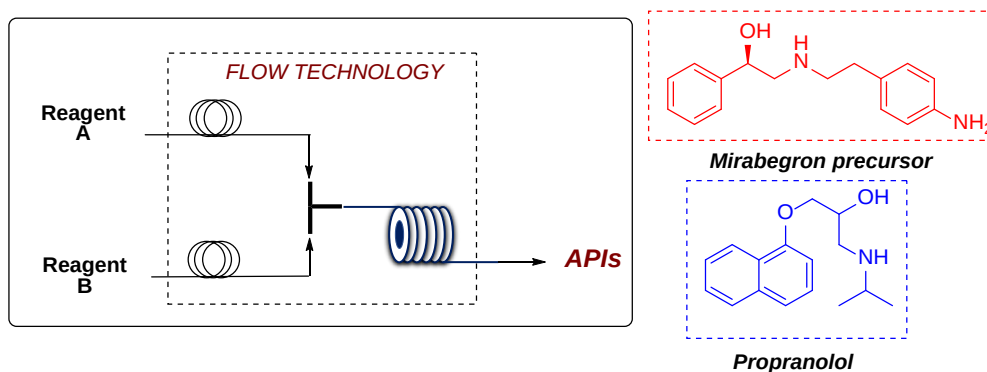


Figure 1: Flow technology for the synthesis of APIs.

References:

- [1] P. Poehlauer, J. Colberg, E. Fisher, M. Jansen, M. D. Johnson, S. G. Koenig, M. Lawler, T. Laporte, J. Manley, B. Martin, A. O'Kearney-McMullan, *Org. Process Res. Dev.* **2013**, 17, 1472-1478.
- [2] L. Degennaro, C. Carlucci, S. De Angelis, R. Luisi, *J. Flow Chem.* **2016**, 6, 136-166.
- [3] M. Colella, C. Carlucci, R. Luisi, *Top. Curr. Chem.* **2018**, 376:46.
- [4] S. De Angelis, C. Carlucci, M. de Candia, G. Rebuzzini, P. Celestini, M. Riscazzi, R. Luisi, L. Degennaro, *Catal. Today* **2018**, 308, 81-85.

Zwitterionic Natural Deep Eutectic Solvents as green alternative for the CO₂ capture

G. Siani,^a V. Canale,^a M. Tiecco,^b P. Di Profio,^a A. Fontana^a

^aDipartimento di Farmacia, Università "G. d'Annunzio", Via dei Vestini 31, 66023 Chieti

^bDipartimento di Chimica, Biologia e Biotecnologie, Via Elce di Sotto 8, Università degli Studi di Perugia,
06123 Perugia
siani@unich.it

The increase in emission of greenhouse gases is largely responsible for global warming, with carbon dioxide, CO₂, being the main contributor, as a consequence of human activities such as the burning of oil, coal and gas, as well as deforestation. The capture of CO₂ is a valid option to reduce emission and many technologies based on the use of solid and liquid sorbents or membranes¹ have been proposed. Among these technologies, the chemical absorption using aqueous amine solutions seemed to be the most effective, due to their high affinity for CO₂.² However, the amine-based method has some negative aspects such as corrosion and high energy consumption. For this reason, the development of alternative technologies for CO₂ capture and storage is the most relevant goal to be achieved and is receiving significant attention by researchers. Recently, classical³ and amine-based⁴ deep eutectic solvents (DESs) have been investigated as sorbents for CO₂ capture. DESs are obtained by combining solid compounds, generally a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD), capable to self-associate, and form liquid mixtures having a melting point that lies below those of the individual starting materials. DESs are often related to ionic liquids (ILs), with which they share many physicochemical characteristics such as thermal stability, low vapor pressure, non-flammability and a great solvating ability. These properties can be tuned simply by changing the nature or the ratio of the constituents, to obtain the most appropriate HBD-HBA combination for a target application. The major advantage of DESs over ILs is that their synthesis is very simple, safe and environmentally benign. Some DESs have been synthesized by natural metabolites such as organic acids, amino acids and sugars. These Natural Deep Eutectic Solvents (NADESs), have gained much attention especially in the green chemistry area due to their biodegradable properties and their safe components.

In the present work, we have investigated the CO₂-capture ability of some zwitterionic NADES based on N,N,N-trimethylglycine (TMG) and carboxylic acids as the HBA and HBD component, respectively. The solubility of CO₂ in the DES was measured gravimetrically at different temperatures in the range 298.15 - 333.15 K, and different pressures in the range 0.1 - 4 MPa. It can be observed that the solubility of CO₂ in the DES increases as the pressure increases while it decreases as the temperature increases. The highest uptake has been observed for phenylacetic acid/TMG DES at 313.15 K and 4 MPa (45.5 g CO₂/g DES). The same DES has been reused in two successive cycles with a consequent decrease in CO₂ capture efficiency (up to 27% less).

References:

- [1] L. Espinal, D. L. Poster, W. Wong-Ng, A. J. Allen, M. L. Green, *Environ. Sci. Technol.* **2013**, 47, 11960-11975.
- [2] G. T. Rochelle, *Science* **2009**, 325, 1652-1654.
- [3] R. B. Leron, M. H. Li, *Thermochim. Acta* **2013**, 551, 14-19.
- [4] I. Adeyemi, M. R. M. Abu-Zahra, I. Alnashef, *Energy Procedia* **2017**, 105, 1394-1400.

Bioactive metabolites produced by the fungal pathogens *Diplodia fraxini* and *Hymenoscyphus fraxineus* isolated from infected *Fraxinus* spp. trees

R. Di Lecce^a M. Masi^a A. Cimmino^a B. T. Linaldeddu,^b L. Maddau,^c A. Evidente^a

^a Dipartimento di Scienze Chimiche, Università di Napoli Federico II, Complesso Universitario Monte S. Angelo, Via Cintia 4, 80126 Napoli, Italy

^b Dipartimento Territorio e Sistemi Agro-Forestali, Università di Padova, Viale dell'Università 16, 35020 Legnaro, Padova, Italy

^c Dipartimento di Agraria, Sezione di Patologia Vegetale ed Entomologia, Università degli Studi di Sassari, Viale Italia 39, 07100 Sassari, Italy
roberta.dilecce@unina.it

During the last two decades widespread ash population decline has happened in Europe. This epidemic disease, commonly known as ash dieback, is the result of biological invasions by the two ascomycetes fungi *Diplodia fraxini* and *Hymenoscyphus fraxineus*. On *Fraxinus* spp. both fungi are able to cause the same symptoms, corresponding to the typical ones due to the infections of *Diplodia* species on woody hosts characterized by V-shaped necrotic sector visible in cross section.¹

D. fraxini is a fungus belonging to the Botryosphaeriaceae family. It was found to be a pathogen associated to symptomatic *Fraxinus angustifolia* trees in South Europe and isolated also from branch and twigs of *Fraxinus excelsior* in initial and advanced stages of dieback in Poland.

A new phytotoxic isochromanone, named fraxitoxin (**1**, Fig. 1), was isolated together with (–)-mellein and tyrosol, already known toxic fungal metabolites, from the organic extract of the *D. fraxini* culture filtrates.¹ The structure of fraxitoxin was characterized using spectroscopic methods (essentially NMR and HR-EI-MS) while its absolute configuration was assigned by electronic circular dichroism (ECD) measurements and calculations.

H. fraxineus is a fungus belonging to the Helotiaceae family. It was identified as the pathogen causing the *F. excelsior* dieback in Europe. *H. fraxineus* was introduced in Europe from Asia and has gradually spread from East to West continental Europe including the British Isles.² Viridiol (**2**, Fig. 1) was isolated as the most abundant and phytotoxic metabolite, from the organic extract of the *H. fraxineus* culture filtrates.³ The purification and chemical and biological characterization of these two metabolites as well as those of other related compounds will be illustrated in this communication.

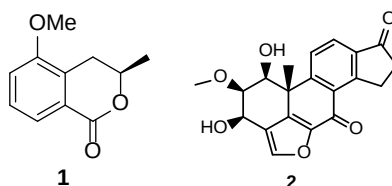


Figure 1: The structures of fraxitoxin and viridiol (**1** and **2**).

References:

- [1] A. Cimmino, L. Maddau, M. Masi, B.T. Linaldeddu, G. Pescitelli, A. Evidente, *Chem. Biodiversity* **2017**, *14*, e1700325
- [2] F. Surupa, S. Halecker, M. Nimtz, S. Rodrigo, B. Schulz, M. Steinert, M. Stadler, *Steroids* **2018**, *35*, 92-97.
- [3] S. Helecker, F. Surup, E. Kuhnert, K. I. Mohr, N. L. Brock, J. S. Dickschat, C. Junker, B. Schulz, M. Stadler, *Phytochemistry* **2014**, *100*, 86-91.

Natural products as stimulants and inhibitors of parasitic seed germination and radical growth

R. Zatout,^a M. Masi,^a A. Evidente,^a M. Fernandez-Aparicio,^b A. Cimmino^a

^aDipartimento di Scienze Chimiche, Complesso Univ. Monte Sant'Angelo, Via Cintia, Napoli, Italia

^bInstitute for Sustainable Agriculture, Spanish National Research Center, Cordoba, Spain 2, Address, City
marco.masi@unina.it

A number of parasitic plants have adapted to agricultural environments becoming weedy and posing a serious threat to important crops. Available control measures rely heavily on use of synthetic herbicides. The side effects on environmental pollution and food health of chemical control prompted studies to find alternative strategies based on the use of natural products.

Some sesquiterpene lactones named inuloxins A-D, belonging to different subgroup as germacrane, eudesmane and seco-eudesmane, were isolated from the aerial parts of *Dittrichia viscosa* (family Asteraceae) and showed to stimulate seed germination leading to suicidal germination, or inhibit germination or disrupting germling growth and haustorium development.^{1,2}

The absolute configuration (AC) of inuloxin A was determined by chiroptical and computational methods.³ The same methods were successively used to assign the AC to inuloxin C,⁴ while studies are in progress to assign that of inuloxin D. Recently, considering the potential herbicidal activity of inuloxin A, it was formulated in β -cyclodextrins to overcome its low water solubility and preserving its ability to inhibit *Phelipanche ramosa* seed germination.⁵

In this communication, the purification of other germination stimulants and/or inhibitors of parasitic seed germination, isolated from the same plant, will be illustrated as well as the results of structure-activity relationship studies comparing the biological activity of the natural sesquiterpenoids to that of some their hemisynthetic derivatives.

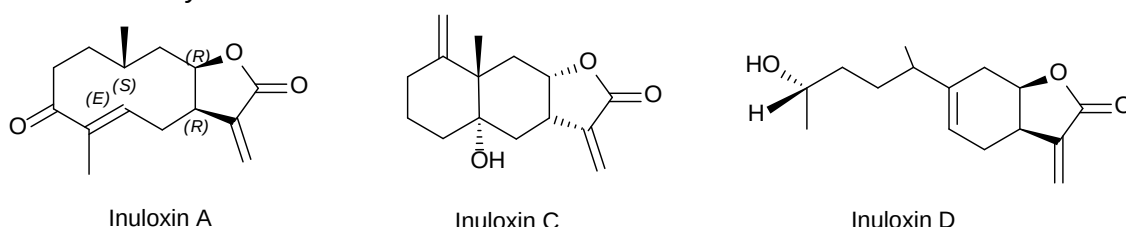


Figure 1: Structures of inuloxins A, C and D.

References:

- [1] A. Cimmino, M. Fernández-Aparicio, A. Andolfi, S. Basso, D. Rubiales, A. Evidente, *J. Agr. Food Chem.* **2014**, 62, 10485-10492.
- [2] A. Cimmino, M. Masi, D. Rubiales, A. Evidente, M. Fernández-Aparicio, *Nat. Prod. Commun.* **2018**, 13, 289-294.
- [3] E. Santoro, G. Mazzeo, A. G. Petrovic, A. Cimmino, A., J. Koshoubu, A. Evidente, N. Berova, S. Superchi, *Phytochemistry* **2015**, 116, 359-366.
- [4] J. L. Johnson, V. Raghavan, A. Cimmino, A. Moeini, A. G. Petrovic, E. Santoro, S. Superchi, N. Berova, A. Evidente, P. L. Polavarapu, *Chirality* **2018**, 30(11), 1206-1214.
- [5] A. Moeini, M. Masi, M. C. Zonno, A. Boari, A. Cimmino, O. Tarallo, M. Vurro, A. Evidente, *Org. Biomol. Chem.* **2019**, 17(9), 2508-2515.

New degradation products of Irbesartan: Analysis and identification from a simulated chlorinated disinfection treatment¹

G. Luongo,^a D. Palatucci,^a A. Siciliano,^b L. Saviano,^b M. Guida,^b G. Di Fabio,^a A. Zarrelli^a

^aDepartment of Chemical Sciences, University of Napoli Federico II, Via Cintia 4, I-80126 Napoli

^bDepartment of Biology, University of Naples Federico II, via Cintia 4 (ed. 7), I-80126 Napoli
zarrelli@unina.it

A wide range of pharmaceutical compounds is used for the treatment of various diseases in both humans and domestic animals. These compounds and their metabolites are excreted through urine and faeces into domestic wastewater and make their way to wastewater treatment plants (WWTPs). Some of them are not totally removed in the WWTPs and remain in the effluents entering surface waters² and even groundwater.³ The potential for a drug to reach the aquatic environment depends on three factors: the sales amount, the pharmacokinetic behaviour (half-life, urinary and faecal excretion, metabolism, etc.) and the rate of its degradation in the sewage system and WWTPs. In the meantime, a high amount of drugs and related metabolites have been detected in the aquatic environment and the list is continuously increasing.⁴ One non-extensively investigated drug is Irbesartan, used alone or together with other medicines to treat high blood pressure, on the market for about 19 years and with an annual production of about 20,000 kg. Irbesartan is an orally active substance that is rapidly and effectively absorbed, reaching peak plasma after approximately 2 hours. After its biological effect, Irbesartan, following hepatic metabolism, is mainly eliminated through the faeces, even if a share of about 20% is found in the urine. Here the degradation pathway of Irbesartan has been investigated by simulating the chlorination process normally used in a WWTPs to reduce similar emerging pollutants.⁵ The structures of the isolated degradation by-products have been determined from the crossing of MS and 1D-2D NMR data and justified by a proposal mechanism of formation. The new by-products, together with Irbesartan, have been assayed on different living organisms (*C. elegans* and *Daphnia magna*), to test their acute and chronic toxicity.

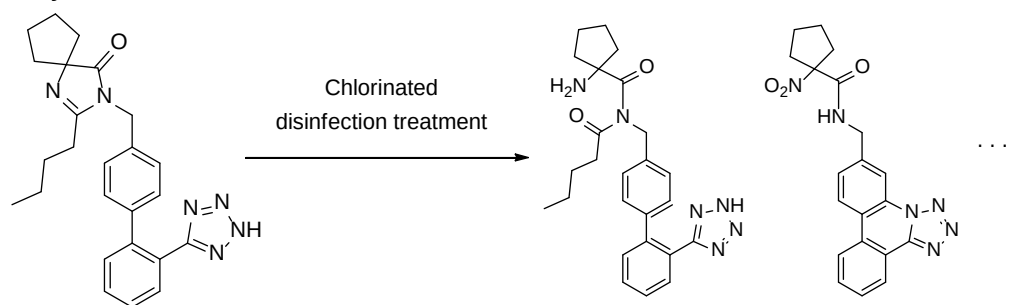


Figure 1: Structures of Irbesartan and some its degradation by-products

References:

- [1] These studies were supported by the AIPRAS Onlus (<http://www.aipras.org/>).
- [2] S. A. González, M. Catalá, R. R. Maroto, J. L. R. Gil; A. G. de Miguel, Y. Valcárcel, *Environ. Int.* **2010**, *36*, 195-201.
- [3] F. Einsiedl, M. Radke, P. Maloszewsky, *J. Contam. Hydrol.* **2010**, *117*, 26-36.
- [4] C. Boix, M. Ibáñez, J. V. Sancho, J. R. Parsons, P. de Voogt, F. Hernández, *J. Hazard. Mat.* **2016**, *302*, 175-187.
- [5] V. Romanucci, A. Siciliano, E. Galdiero, M. Guida, G. Luongo, R. Liguori, G. Di Fabio, L. Previtera, A. Zarrelli, *Molecules* **2019**, *24*, 693-704.

Sulfur, Selenium, and some silicon: A new access to disulfides and mixed chalcogenides with GPx-like activity

D. Tanini, A. Capperucci, S. Menichetti, C. Viglianisi

Department of Chemistry "Ugo Schiff" University of Florence, Via Della Lastruccia 3-13, I-50019, Sesto Fiorentino, Firenze, Italy
damiano.tanini@unifi.it

Omo-disulfides (RSSR) and diselenides (RSeSeR) are of paramount importance for their applications in material sciences and for their involvement in biological chemistry.^{1,2} At the same time, mixed-dichalcogenides (RSSeR) represent a synthetic challenge while maintaining their relevance at biological level.³

Recently, bringing together our expertise in sulfur and selenium chemistry,⁴ we have developed new procedures for the synthesis of disulfides (RSSR)⁵ and selenylsulfides (RSSeR).⁶ Using N-thiophthalimide derivatives as electrophilic sulfur transfer reagents and a selenosilane, or selenols, as nucleophiles, we could easily access both classes of compounds with a huge variability and tolerance of the substituents (Figure 1).

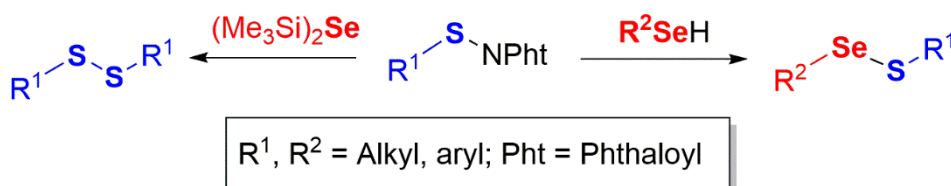


Figure 1: Synthesis of disulfides and selenenylsulfides

The scope and limitation of these new procedures as well as the stability and the properties of the obtained disulfides and selenylsulfides will be discussed in the communication.

References:

- [1] B. Mandala, B. Basu, *RSC Adv.*, **2014**, 4, 13854-13881, and references cited therein.
- [2] V. A. Potapov, in *Chemistry of Organic Selenium and Tellurium Compounds* (Eds: Patai, S.; Rappoport, Z.), **2013**, vol. 4 (Part. 1), 765-843, and references therein.
- [3] a) Q. Cheng, T. Sandalova, Y. Lindqvist, E. S. J. Arnér, *J. Biol. Chem.* **2009**, 284, 3998-4008; b) D. P. Gamblin, P. Garnier, S. van Kasteren, N. J. Oldham, A. J. Fairbanks, B. G. Davis, *Angew. Chem. Int. Ed.* **2004**, 43, 828-833; c) L. A. Wessjohann, A. Schneider, *Chem. Biodivers.* **2008**, 5, 375-388.
- [4] a) G. Capozzi, C. Falciani, S. Menichetti, C. Nativi, *J. Org. Chem.* **1997**, 62, 2611-2615; b) D. Tanini, A. Capperucci, A. Degl'Innocenti, *Eur. J. Org. Chem.* **2015**, 357-369; c) D. Tanini, C. Tiberi, C. Gellini, P. R. Salvi, A. Capperucci, *Adv. Synth. Catal.* **2018**, 360, 3367-3375.
- [5] a) C. Viglianisi, C. Bonardi, E. Ermini, A. Capperucci, S. Menichetti, D. Tanini, *Synthesis*, **2019**, 51, 1819-1824; b) C. Viglianisi, K. Vasa, D. Tanini, A. Capperucci, R. Amorati, L. Valgimigli, A. Baschieri, S. Menichetti, *Chem. Eur. J.*, **2019**, 10.1002/chem.201901537.
- [6] D. Tanini, C. Bonardi, C. Viglianisi, A. Capperucci, S. Menichetti, *Catalysts*, **2019**, 9, 333 (1-11).

New Phosphate-Linked Tyrosol Dimers: Synthesis, antioxidant activity, metal chelating capacity and effect on A β aggregation¹

M. Giordano,^a V. Romanucci,^a R. Bernini,^b M. Clemente,^b S. García-Viñuales,^c D. Milardi,^c M. Iuliano,^a G. De Tommaso,^a A. Zarrelli,^a G. Di Fabio^a

^aDepartment of Chemical Sciences, University of Napoli Federico II, Via Cintia 4, 80126 Napoli

^bDepartment of Agriculture and Forest Sciences (DAFNE), University of Tuscia, 01100 Viterbo

^cInstitute of Crystallography, National Research Council, Via Paolo Gaifami 8, 95126 Catania
difabio@unina.it

Phenylpropanoids are secondary metabolites widely distributed in plants. They are believed to protect human cells against oxidative stress and in turn, to prevent various diseases associated with it, such as cancer, cardiovascular, and neurodegenerative disorders as well.^{2,3} Recently, many natural phenylpropanoids have emerged as a particularly promising class of small molecules able to inhibit β -amyloid aggregation and disrupt preformed amyloid fibrils that represent important targets in the development of pharmacological treatments of Alzheimer's disease (AD).⁴ Unfortunately, natural phenylpropanoids often have poor pharmacokinetic properties and low bioavailability. In this frame an interesting approach in the design of new bioactive compounds could be the combination of two or more polyphenolic "fragments". This "natural-fragment-based drug-discovery" approach would allow the assembly, also in a combinatorial manner, of libraries based on complex polyphenols in a few steps. This strategy provides us with the possibility of easily modifying both scaffold and decorations and modulating pharmacodynamic and pharmacokinetic properties.⁵ Therefore, we planned to join two "tyrosol-fragments" by a phosphodiester bridge to obtain a new class of phosphate-linked compounds,⁶ which are potentially more bioactive than the corresponding precursors.

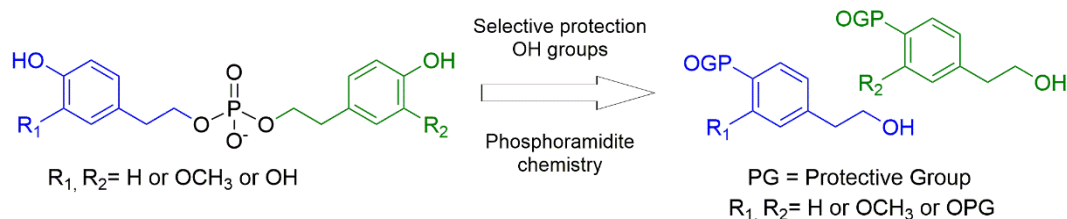


Figure. Retrosynthetic scheme of phosphate-linked tyrosol dimers.

We report here the general synthetic strategy to obtain new phosphate-linked tyrosol dimers in good yield and their full characterization. Since oxidative stress, as well as metal ion dyshomeostasis, are known to play important roles in AD pathogenesis, preliminary studies are focused on the evaluation of their antioxidant activity, metal chelating ability and their ability to inhibit β -amyloid aggregation.

References:

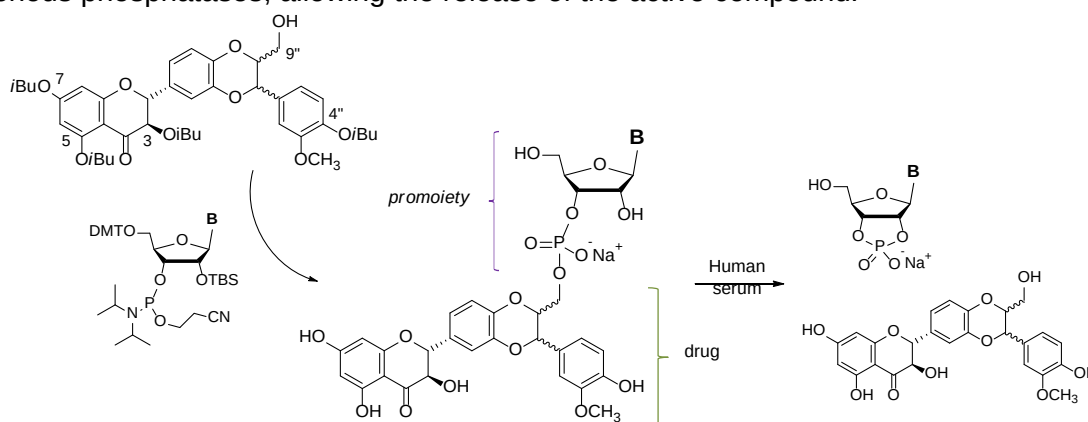
- [1] These studies were supported by the AIPRAS Onlus (<http://www.aipras.org/>).
- [2] S. Quideau, D. Deffieux, C. Douat-Casassus, L. Pouységu, *Angew. Chem. Int. Ed.* **2011**, 50, 586-621.
- [3] R. Bernini, N. Merendino, A. Romani, F. Velotti, *Curr. Med. Chem.* **2013**, 20, 655-670.
- [4] C. Lambruschini, D. Galante, L. Moni, F. Ferraro, G. Gancia, R. Riva, A. Traverso, L. Banfi, C. D'Arrigo, *Org. Biomol. Chem.* **2017**, 15, 9331-9351.
- [5] B. Over, S. Wetzel, C. Grütter, Y. Nakai, S. Renner, D. Rauh, H. Waldmann, *Nat. Chem.* **2013**, 5, 21-28.
- [6] V. Romanucci, R. Gravante, M. Cimafronte, C. Di Marino, G. Mailhot, M. Brigante, A. Zarrelli G. Di Fabio, *Molecules* **2017**, 22, 1323.

A general synthetic strategy and preliminary investigations of *pro*-drug Silibinin conjugates¹

V. Romanucci, M. Giordano, D. Palatucci, G. Luongo, A. Zarrelli, G. Di Fabio

Department of Chemical Sciences, University of Napoli Federico II, Via Cintia 4, I-80126 Napoli
difabio@unina.it

Silibinin is the major component of an extract, known as Silymarin, obtained from the seeds of the milk thistle (*Silybum marianum*). Structurally, Silibinin is diastereoisomeric equimolar mixture of two flavonolignans (Silybin A and Silybin B). As extensively reported in literature, Silibinin displays multiple biological activities, most of them related to its radical scavenging activity. In the past two decades, in addition to hepatoprotective effects, Silibinin has demonstrated remarkable anti-cancer as well as cancer chemopreventive efficacy in pre-clinical cell culture and animal models of several epithelial cancers, including skin, bladder, colon, prostate, and lung.² Oral administration of chemotherapeutic agents is the mainstay for the treatment of disease. Sustained release formulations have been crucial for the safe and effective dosing of orally administered drugs.³ In this frame, the synthesis of phosphodiester derivatives can improve the oral bioavailability of poorly water-soluble metabolites maintaining their pharmacologic activity.^{4,5} Here, we reported the synthesis of new Silibinin conjugates with 3'-ribonucleotide units. The phosphodiester junction is typically used in *pro*-drug strategies, in which the phosphate group is susceptible to hydrolysis by endogenous phosphatases, allowing the release of the active compound.



Scheme: Synthesis of ribonucleotide-Silibinin conjugates and their cleavage by serum nucleases.

The new conjugates were prepared in few steps and in good yields, starting from the suitable Silibinin or Silybin building blocks and nucleotide phosphoramidites. All compounds were fully characterized by NMR and Maldi-TOF and their serum stability was evaluated by HPLC analyses.

References:

- [1] These studies were supported by the AIPRAS Onlus (<http://www.aipras.org/>).
- [2] G. Deep, R. Agarwal, *Cancer Metastasis Rev.* **2010**, 29, 447-463.
- [3] K. Moodley, V. Pillay, Y. E. Choonara, L. C. Du Toit, V. M. K. Ndesendo, P. Kumar, S. Cooppan, P. Bawa, *Int. J. Mol. Sci.* **2012**, 13, 18-43.
- [4] M. J. Palte, A. K. F. Davis, N. A. McGrath, C. A. Spiegel, R. T. Raines, *ChemMedChem* **2012**, 7, 1361-1364.
- [5] V. Romanucci, C. Agarwal, R. Agarwal, C. Pannecouque, M. Iuliano, G. De Tommaso, T. Caruso, G. Di Fabio, A. Zarrelli, *Bioorg. Chem.* **2018**, 77, 349-359.

Structural modification of pyridine-containing ligands: customize optical and electrochemical properties of Cu complexes

V. Leandri,^a D. Franchi,^a R. Pizzichetti,^a B. Xu,^a W. Zhang,^a L. Sun,^{a,b} L. Kloo,^a J. Gardner^a

^aDepartment of Chemistry, KTH Royal Institute of Technology, SE-10044 Stockholm, Sweden.

^bState Key Laboratory of Fine Chemicals, DUT Dalian University of Technology, 116024 Dalian, China.
danielef@kth.se

Organometallic Cu(I) complexes with diimine ligands have tuneable optical and electrochemical properties suitable for applications in the field of Dye-Sensitized Solar Cells (DSSCs) as both redox shuttle and photoactive media.¹ The balance between the electron withdrawing/donating character and the structural properties of the heteroaromatic ligand rule over the redox potentials of the Cu(I/II) couple and the visible light absorption of the Cu(I) complexes.²

In his work, we report different strategies for the modification of the canonical 2,2'-bipyridine and 1,10-phenanthroline ligands to insert substituents with relevant electronic and steric effects. The diversification of the ligands structures (Figure 1) allowed us to prepare two small libraries of Cu(I) complexes (homoleptic and heteroleptic) which exhibit a broad spectrum of optical and electrochemical properties.

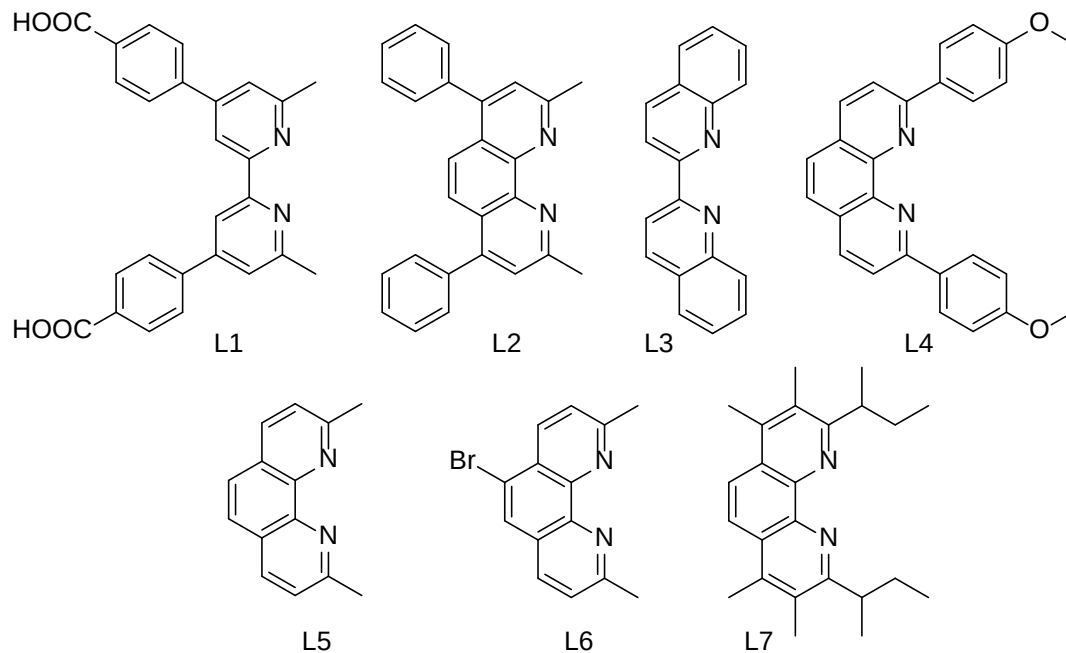


Figure 1: Synthesized ligands bearing substituents with relevant electronic and steric effects.

The comparison of the two libraries, in terms of the complexes properties, showed a good correlation but diverse patterns were found for the absorption maxima and the half-wave potential. This highlights the individual dependence of each property by some of the ligands features and sets the bases for the prediction of the properties of heteroleptic complexes.

References:

- [1] M. Karpacheva, F. J. Malzner, C. Wobill, A. Büttner, E. C. Constable, C. E. Housecroft, *Dyes and Pigments*, **2018**, 156, 410-416.
- [2] A. Lavie-Cambot, M. Cantuel, Y. Leydet, G. Jonusauskas, D. M. Bassani, N. D. McClenaghan, *Coordi. Chem. Rev.* **2008**, 252, 2572-2584.

Luminescent rhenium(I)-peptide nucleic acids conjugates for microRNA targeting

S. Cauteruccio,^a M. Panigati,^a L. Veronese,^a N. Zaffaroni,^b M. Folini,^b E. Licandro^a

^aDipartimento di Chimica, Università degli Studi di Milano, via C. Golgi 19, I- 20133, Milan

^b Dipartimento di Ricerca Applicata e Sviluppo Tecnologico, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, via G. A. Amadeo, 42, I-20133, Milan
emanuela.licandro@unimi.it

Peptide Nucleic Acids (PNA) are a quite unique example of mimics of native nucleic acid structures able to target natural DNA or RNA with high sequence specificity and affinity and are therefore potential excellent candidates in diagnostics and antisense and antigene therapy. In place of the ribose phosphodiester backbone of DNA and RNA, PNA contain a pseudopeptide backbone, composed of *N*-(2-aminoethyl)glycine units, on which the four nucleobases are inserted (Figure).¹ Unmodified PNAs display low cellular uptake,² and this feature constitutes a drawback towards its effective use in therapy. One of the strategy to overcome this problem is the conjugation of PNA to metal complexes that can modify their intrinsic chemico-physical and spectroscopic properties.^{3,4}

Within our research on PNA, we have prepared some bioorganometallic PNA-dirhenium complexes (Figure), which have been used to target a specific microRNA, that is miRNA-21 in the DU145 prostate cancer cell line. Thanks to the presence of the dirhenium fragment, these bioconjugates are luminescent and act as fluorescent probes to track the cell uptake of PNA that is easily taken up by the above mentioned cells, thus showing that the Re(I) complexes are indeed useful tools for the intracellular delivery of PNA.

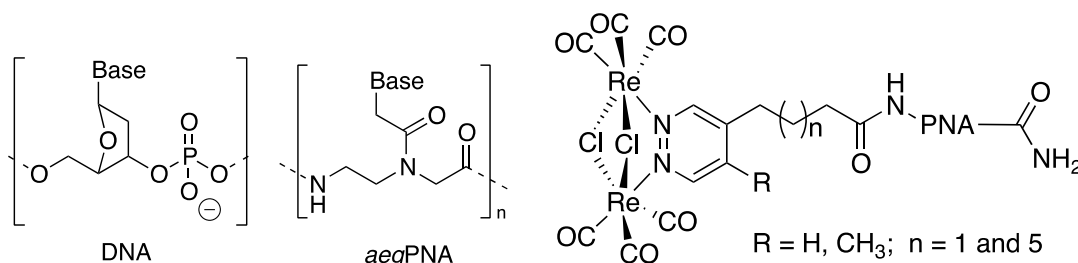


Figure.

References:

- [1] P. E. Nielsen, M. Egholm, R. H. Berg, O. Buchardt, *Science* **1991**, 254, 1497-1500.
- [2] U. Koppelhus, S. K. Awasthi, V. Zachar, H. U. Holst, P. Ebbesen, P.E. Nielsen, *Antisense Nucleic Acid Drug Dev.* **2002**, 12, 51-63.
- [3] G. Gasser, A. M. Sosniak, N. Metzler-Nolte, *Dalton Trans.* **2011**, 40, 7061-7076.
- [4] S. Cauteruccio, M. Panigati, L. Veronese, N. Zaffaroni, M. Folini, E. Licandro, *J. Organomet. Chem.* **2019**, 887, 32-39.

Synthesis and characterization of chiral bis-benzo[1,2-*b*:4,3-*b'*]dithiophenes

V. Pelliccioli,^a S. Cauteruccio,^a R. Franzini,^b C. Villani,^b G. Mazzeo,^c G. Longhi,^c S. Abbate,^c E. Licandro.^a

^a Dipartimento di Chimica, Università degli Studi di Milano, via Golgi 19, I-20133, Milano

^b Dipartimento di Chimica e Tecnologie del Farmaco, Sapienza Università di Roma, Piazzale Aldo Moro 5, 00185 Roma

^c *Dipartimento Medicina Molecolare e Traslazionale, Università degli Studi di Brescia, Viale Europa 11, 25123 Brescia*

valentina.pelliccioli@unimi.it

Thiophene-containing fused aromatic compounds are a versatile class of π -conjugated systems with applications in functional organic materials.¹ Among them, benzo[1,2-*b*:4,3-*b'*]dithiophene (**BDT**) and its derivatives are widely studied, for instance as units in mono and polydisperse oligomers in materials science,² and as π -spacers in push-pull organic chromophores for photovoltaic applications.³ Moreover, **BDT** is a key intermediate for the synthesis of inherently chiral helical systems such as tetrathia[7]helicenes.⁴ In our ongoing studies on the synthesis and functionalization of **BDTs**,⁵ we have developed a strategy to prepare new chiral atropoisomeric heterobiaryl derivatives **2-4** starting from bromides **1** (Figure).

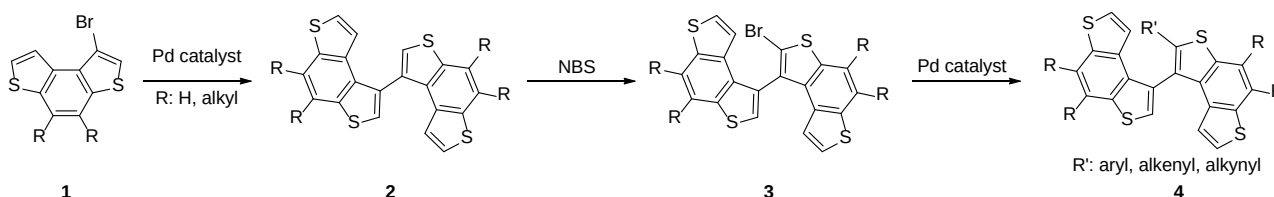


Figure: general synthesis of chiral bis-benzo[1,2-*b*:4,3-*b'*]dithiophenes.

The configurational stability of these systems have been fully elucidated by experimental and theoretical studies, and thanks to their chiroptical properties, some of these atropoisomers will be exploited as useful intermediates for the enantioselective synthesis of the corresponding tetrathia[7]helicene derivatives.

References:

- [1] J. Roncali, *Acc. Chem. Res.* **2009**, *42*, 1719-1730.
- [2] Y. Nishide, H. Osuga, M. Saito, T. Aiba, Y. Inagaki, Y. Doge, K Tanaka, *J. Org. Chem.* **2007**, *72*, 9141-9151.
- [3] E. Longhi, A. Bossi, G. Di Carlo, S. Maiorana, F. De Angelis, P. Salvatori, A. Petrozza, M. Binda, V. Roiati, P. R. Mussini, C. Baldoli, E. Licandro, *Eur. J. Org. Chem.* **2013**, 84-94.
- [4] E. Licandro, C. Rigamonti, M. T. Ticozzelli, M. Monteforte, C. Baldoli, C. Giannini, S. Maiorana, *Synthesis* **2006**, *21*, 3670-3678.
- [5] a) S. Cauteruccio, D. Dova, C. Graiff, C. Carrara, J. Doulcet, G. R. Stephenson, E. Licandro, *New J. Chem.* **2014**, *38*, 2241-2244; b) G. R. Stephenson, S. Cauteruccio, J. Doulcet, *Synlett*. **2014**, *25*, 701-707.

Lipase catalyzed oxidation in sugar-derived Natural Deep Eutectic Solvents

P. Galletti,^a C. Samorì,^a M. Vagnoni^a

^aDipartimento di Chimica "Giacomo Ciamician", Università di Bologna
martina.vagnoni3@unibo.it

Chemoenzymatic oxidations offer a valid alternative to the oxidative processes normally used in industries that show problems in terms of safety and waste disposal. Lipases are very versatile enzymes that thanks to their high selectivity, good stability and mild reaction conditions, can represent a valid and sustainable alternative to classic chemical catalysts. In the field of oxidations, lipases act as perhydrolases to produce peracids in situ, which subsequently act as catalysts for oxidation reactions.¹

In the present work we show results obtained using *Candida antarctica* lipase B (CAL B) for the epoxidations of alkenes and for the conversion of ketones to esters or of aldehydes to acids (Baeyer-Villiger). These reactions have been carried out in DES (Deep Eutectic Solvents), taking advantage of the fact that these sustainable solvents can increase the stability of the supported enzymes.²

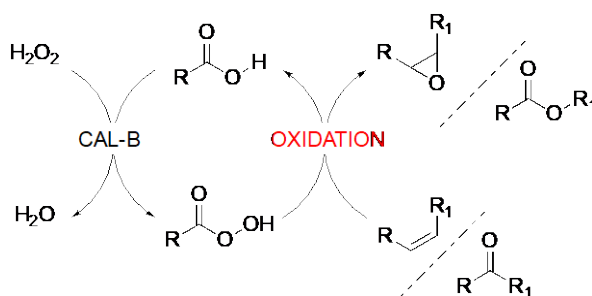


Figure 1: Chemoenzymatic oxidations investigated.

Some of the crucial parameters for obtaining high substrate conversions have been found to be the nature and the amount of the peracid precursor and the nature of DES. The best results were obtained with medium-long chain carboxylic acids such as octanoic acid or dodecanoic acid. The best yields in all types of reactions tested were obtained using a NaDES (Natural DES) consisting of sugar mixtures capable of increasing the stability of the CAL B with respect to other tested NaDES and with respect to organic solvents or aqueous reaction media. Moreover, some of the DES studied (especially those containing Choline Chloride, with and without the addition of a superbases) have also been shown to be systems that catalyze the incorporation of CO₂ into epoxides for the synthesis of cyclic carbonates.³

References:

- [1] Y. Xu, N. Ranong, B. J. Khaw, Z. Li, *Green Chem.* **2009**, *11*, 2047-2051.
- [2] S. H. Kim, S. Park, H. Yu, J. H. Kim, H. J. Kim, Y.-H. Yang, Y. H. Kim, K. J. Kim, E. Kan, S. H. Lee, *J. Mol Catal. B: Enzym.* **2016**, *128*, 65-72.
- [3] A. Zhu, T. Jiang, B. Han, J. Zhang, Y. Xie, X. Ma, *Green Chem.* **2007**, *9*, 169-172.

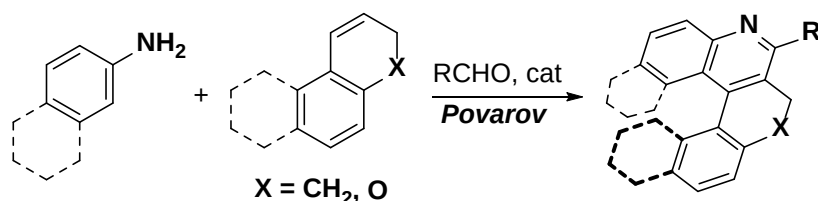
Synthesis of heterohelices through the Povarov reaction

S. Menichetti,^a C. Viglianisi,^a S. Nardini,^a C. Villani,^b R. Franzini^b

^aDepartment of Chemistry 'U. Schiff', University of Florence, Via Della Lastruccia 3-13, 50019 Sesto Fiorentino, Italy.

^bDepartment of Chemistry and Technology of Drugs, University 'La Sapienza' Roma, P.le A. Moro 5 - 00185 Roma, Italy.
stefano.menichetti@unifi.it

Helicenes and heterohelices are challenging chiral structures that continuously stimulate new interest and find new applications. From just a chemical curiosity due to their inherent chirality, these compounds are now commonly used in asymmetric synthesis, materials science and medicinal chemistry.¹ On the other hand, among imino cycloadditions, the Povarov reaction, *i.e.* the reaction of electron-rich olefins with *N*-aryl imines, provides a straightforward and modular entry to tetrahydroquinolines and, after oxidation, quinolines, in turn very useful heterocyclic systems.²



In this communication, we report how, with the proper choice of electron-rich olefins and *N*-aryl imines, under lanthanide salts catalysis, the Povarov reaction can be exploited for the synthesis of aza- and azaoxaheterohelices.³ Scope and limitation of the procedure as well as a study on the resolution of helical shaped quinolines obtained will be presented.

References:

- [1] a) Y. Shen, C-F. Chen, *Chem. Rev.* **2012**, *112*, 1463–1535 ; b) M. Gingras, *Chem. Soc. Rev.* **2013**, *42*, 968-1006.
- [2] a) X. Jiang, R. Wang, *Chem. Rev.* **2013**, *113*, 5515-5546; b) G. Masson, C. Lalli, M. Benohoud, G. Dagousset, *Chem. Soc. Rev.* **2013**, *42*, 902-923; c) M. Fochi, L. Caruana, L. Bernardi, *Synthesis* **2014**, *46*, 135-157.
- [3] C. Viglianisi, C. Biagioli, M. Lippi, M. Pedicini, C. Villani, R. Franzini, S. Menichetti, *Eur. J. Org. Chem.* **2019**, 164-167.

Sustainable and Water-Soluble Non-Fullerene Acceptors for Bulk Heterojunction Solar Cells

G. Forti,^a A. Nitti,^a R. Po,^b G. Bianchi,^b D. Pasini^a

^a Department of Chemistry, University of Pavia, Viale Taramelli, 10, 27100 Pavia, Italy

^b Solar Energy Department, Decarbonization & Environmental R&D, Eni SpA, Via G. Fauser, 4 - 28100 Novara, Italy

giacomo.forti01@universitadipavia.it

Bulk Heterojunction solar cells (BHJ), are very promising amongst emerging technologies for solar energy conversion for their unique properties, such as flexibility, low cost and possibility to be printed on plastic substrates. They are composed of an intrinsic mixture, organized at the nanoscale, of an Acceptor and Donor organic material in the photoactive, photon absorbing active layer¹. Traditionally, fullerene derivatives, possessing good electron transporting capability, have been used. Recently, a new class of non fullerene Acceptors (NFAs) they have boosted BHJ cells efficiencies in terms of solar energy conversion to over 17%.² The most efficient molecular scaffold, the ITIC family, has optimal properties with respect to range of absorption, and morphology in the active layer. Materials for BHJ have several problems linked to their non-sustainable synthesis: a) they often require Stille cross couplings, which produce toxic by-products in stoichiometric quantities; b) they require toxic solvents for processing into thin films over the substrate. We present our results on the synthesis of novel NFAs for which innovation will be brought on two levels: a) synthesis of sustainable NFAs using cascade or one-pot methodologies such as multicomponent reaction or Domino Direct Arylation-Cross Aldolization³ and b) functionalization of NFAs with hydrophilic side chains (poly(ethylene glycols) (PEG), hyperbranched glycerols (HBP), or alkylsulfonates), in order to increase their solubility in green solvents for processing.

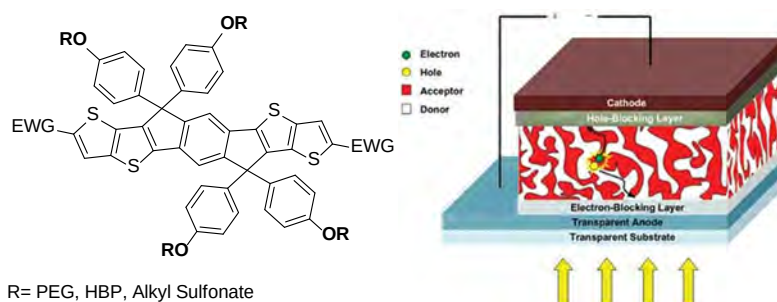


Figure 1

References:

- [1] H. Zhou†, L. Yang, W. You, *Macromolecules*, **2012**, 45, 607-632.
- [2] H. Li, Z. Xiao, L. Ding, J. Wang. *Science*, **2018**, 63, 340-342.
- [3] a) A. Nitti, G. Bianchi, R. Po, T. M. Swager, D. Pasini, *J. Am. Chem. Soc.* **2017**, 139, 8788-8791; b) A. Nitti, M. Signorile, M. Boiocchi, G. Bianchi, R. Po, D. Pasini, *J. Org. Chem.*, **2016**, 81, 11035-11042; c) A. Nitti, G. Bianchi, R. Po, D. Pasini, *Synthesis*, **2019**, 51, 677-682.

Influence of flat and helical peptide spacers on the redox properties of two covalently bound, ferrocenyl moieties

S. Santi, A. Bisello, R. Cardena, S. Tomelleri, F. Formaggio

Department of Chemistry, University of Padova, via Marzolo 1, 35131 Padova, Italy
fernando.formaggio@unipd.it

The conjugation of ferrocene (Fc) with biomolecules has been exploited to create new systems endowed with both organometallic and bio-properties¹ or to investigate electron transfer processes through peptide backbones.² In this contribution we report the synthesis and preliminary electrochemical studies of new Fc-peptide systems. Thanks to the appropriate placement of Fc redox probes along a peptide chain, we aim at modulating the electronic properties as a function of the applied potential.

For the synthesis of our peptide spacers we relied on two amino acid building blocks, namely 2,3-diaminopropionic acid (Dap) and 2-amino-2-methylpropionic acid (Aib), and on two Fc derivatives characterized by a carboxylic (Fc-COOH) or an amino (Fc-NH₂) function (Figure 1).

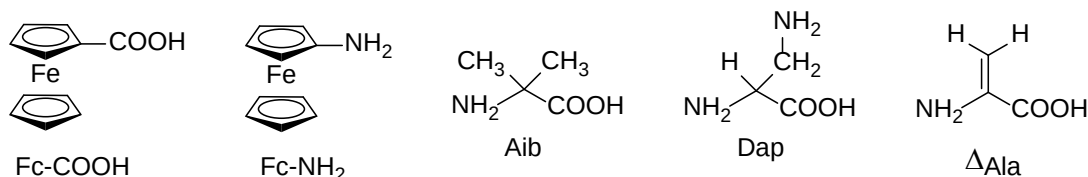
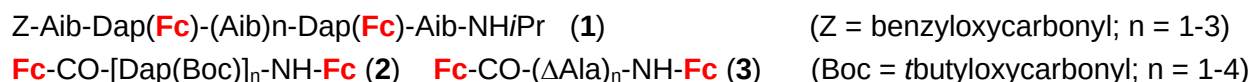


Figure 1: Molecular structures of Fc-COOH, Fc-NH₂, Aib, Dap and ΔAla.

The use of Dap offers two opportunities: (i) incorporation along the peptide chain of a Fc probe by exploiting the amino group on the side chain; (ii) synthesis of dehydroalanine (ΔAla)³, through a Hofmann elimination of the amino function of Dap, thus obtaining a flat, all sp² molecule.

The structures of the hybrid systems designed for goals (i) and (ii) are, respectively:



The peptide of series **1**, helical thanks to Aib, allows to locate the two Fc on the same or on opposite faces. Thus, we will be able to determine the influence of distance, mutual orientation and peptide macrodipole on the Fc...Fc interactions. On the other side, the flexible peptides **2** and the flat peptides **3** have no dipole moments, but the latter possess a conjugated π system that could promote a very efficient electron transfer.

References:

- [1] N. Metzler-Nolte, M. Salmain. In *Ferrocenes: Ligands, Materials and Biomolecules*; P. Stěpnička Ed., 499-639, Wiley, **2008**.
- [2] A. Donoli, V. Marcuzzo, A. Moretto, M. Crisma, C. Toniolo, R. Cardena, A. Bisello, S. Santi, *Biopolymers* **2013**, *100*, 14-24.
- [3] M. Crisma, F. Formaggio, C. Toniolo, T. Yoshikawa, T. Wakamiya, *J. Am. Chem. Soc.* **1999**, *121*, 3272-3278.

Squaraine-Based Porous Organic Polymers Containing Trigonal Linkers

O. Yildirim,^a C. Atzori,^a A. Fin,^b F. Bonino,^a M. Chierotti,^a M. Zanetti,^{a,c} C. Barolo,^{a,c} G. Viscardi^a

^a Department of Chemistry and NIS Interdepartmental Centre and INSTM Reference Centre, University of Turin, via Pietro Giuria 7, 10125/Torino, Italy

^b Department of Drug Science and Technology, University of Turin, via Pietro Giuria 9, 10125/Torino, Italy

^c ICxT Interdepartmental Centre, Lungo Dora Siena 100, 10153/Torino Italy
onur.yildirim@unito.it

Porous organic polymers (POPs) are a type of organic polymers with large surface area, tunable skeleton and high thermal and chemical stability¹. They are attractive for applications in the fields of gas storage and separations, catalysis, optoelectronic and energy storage^{2,3}. There are various methodologies reported for the preparation of porous polymers. Among them, Schiff base reaction is one of the most adjustable ways owing to facile, one-pot, catalyst-free, quantitative synthesis⁴. Squaraines are appealing dyes with a zwitterionic resonance structure and have extensive applications in areas such as imaging, nonlinear optics, photovoltaics, photodynamic therapy, and ion sensing⁵. For example, squaraine-toluidine motif, through the condensation of squaric acid with *p*-toluidine, exhibits planar zigzagged zwitterionic resonance structure⁶ (Figure a). There have been no studies about squaraine-bridged POPs containing different tritopic linkers. Our goal focuses on the syntheses of these squaraine-bridged POPs using tritopic linkers such as: TAPT, TAPB, TAPA and TAPM (Figure b). We have synthesized these polymers through Schiff base reaction by refluxing a tritopic linker with the squaric acid. These 2D-materials containing trigonal building blocks can have different chemical and electrochemical properties suitable for important developments.

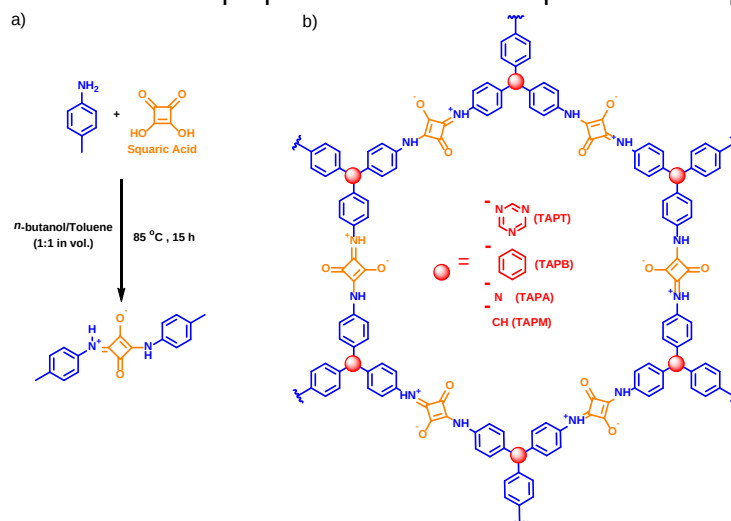


Figure: a) Model compound of SQ-Toluidine, b) SQ-POP based on different tritopic linkers.

References:

- [1] D. Wu, F. Xu, B. Sun, R. Fu, H. He, K. Matyjaszewski, *Chem. Rev.* **2012**, 112, 3959-4015.
- [2] P. Puthiaraj, S. M. Cho, Y. R. Lee, W. S. Ahn, *J. Mater. Chem. A* **2015**, 3, 6792-6797.
- [3] M. Dogru, T. Bein, *Chem. Commun.* **2014**, 50, 5531-5546.
- [4] Y. Jin, Y. Zhu, W. Zhang, *CrystEngComm* **2013**, 15, 1484-1499.
- [5] a) W. Ziegenbein, H. E. Sprenger, *Angew.Chem.* **1966**, 78, 937-937; b) W. Ziegenbein, H. E. Sprenger, *Angew.Chem. Int. Ed.* **1966**, 5, 893-894.
- [6] A. Nagai, X. Chen, X. Feng, X. Ding, Z. Guo, D. Jiang, *Angew.Chem. Int. Ed.*, **2013**, 52, 3770-3774.

Coinage-metal catalyzed functionalizations of propargylic amine derivatives

V. Marsicano,^{a,b} A. Arcadi,^a V. Michelet^b

^a Dipartimento di Scienze Fisiche e Chimiche, Università di L'Aquila, Via Vetoio, 67010 Coppito (AQ), Italy

^b University Côte d'Azur, Institut de Chimie de Nice, UMR 7272 CNRS, Parc Valrose, Faculté des Sciences, 06100 Nice, France
vincenzo.marsicano@graduate.univaq.it

Coinage-metals, especially those belonging to the group 11 of the modern Periodic Table, have always been used by mankind in the production of jewellery and currency; in contrast, the past decades have seen an increase in the use of these metals as efficient catalysts for organic transformations. In particular, Au and Ag have been widely employed in the activation of unsaturated C-C bonds towards several types of transformations, such as nucleophilic additions and cycloisomerization reactions, thanks to their strong π -Lewis acidity.¹

As C-C unsaturated bonds, alkynes bearing proximal nitrogen atoms, such as propargylamines, are very interesting building blocks in synthetic organic chemistry because of the presence of both electrophilic and nucleophilic moieties that enable the generation of complex structural architectures and some transformations have already been described in literature.²

Considering our interest in innovative metal-catalyzed transformations and the collaboration between our two research groups,³ we would like to report the results of our study on the use of these substrates to access valuable chemical compounds by means of coinage-metal catalysis (Figure 1).

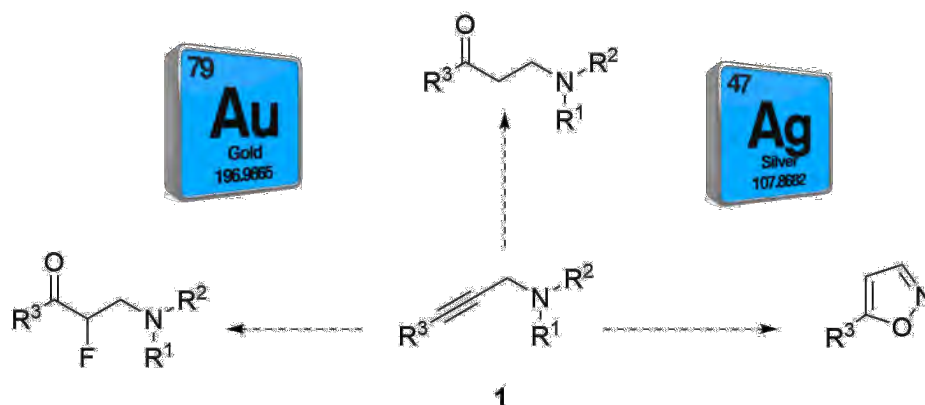


Figure 1: Metal-catalyzed reactions of functionalized propargylic derivatives **1**.

References:

- [1] a) A. M. Echavarran, N. Jiao, V. Gevorgyan, *Chem. Soc. Rev.* **2016**, 45, 4445-4447; b) *Gold Catalysis: An Homogeneous Approach* (Eds.: F. D. Toste, V. Michelet), Imperial College Press, London, **2014**; c) *Modern Gold Catalyzed Synthesis* (A. S. K. Hashmi, F. D. Toste), Wiley VCH, **2012**.
- [2] K. Lauder, A. Toscani, N. Scalacci, D. Castagnolo, *Chem. Rev.* **2017**, 117, 14091-14199.
- [3] a) A. Arcadi, M. Chiarini, L. Del Vecchio, F. Marinelli, V. Michelet, *Eur. J. Org. Chem.* **2017**, 16, 2214-2222; b) A. Arcadi, M. Chiarini, L. Del Vecchio, F. Marinelli, V. Michelet, *Chem. Commun.* **2016**, 52, 1458-1461; c) A. Arcadi, E. Pietropaolo, A. Alvino, V. Michelet, *Org. Lett.* **2013**, 15, 2766-2769; d) N. D. Rode, A. Arcadi, A. Di Nicola, F. Marinelli, V. Michelet, *Org. Lett.* **2018**, 20, 5103-5106.

Spectroscopic elucidation and antimicrobial screening of myrtogalloyl glycosides from *Myrtus communis*

O. Celaj,^a A. Garcia Duran,^b V. Graziani,^a R. Marasco,^a E. Buommino,^c B. D'Abrosca,^{a,d} A. Fiorentino^{a,d}

^aDipartimento di Scienze e Tecnologie Ambientali Biologiche e Farmaceutiche (DiSTABiF), Università degli Studi della Campania "Luigi Vanvitelli", via Vivaldi 43, Caserta, Italy

^bDepartment of Organic Chemistry, University of Cadiz, C/ Republica Saharaui, 7, 11510-Puerto Real (Cádiz), Spain

^cDepartment of Pharmacy, University of Naples Federico II, 80131- Naples, Italy

^dDepartment of Marine Biotechnology Stazione Zoologica Anton Dohrn, Villa Comunale, Naples 80121, Italy
odeta.celaj@unicampania.it

After the "golden era", when almost all groups of important antibiotics were discovered, the history repeats itself nowadays and these antimicrobial agents are in danger of losing their efficacy because of the occurrence of microbial resistance¹. In this scenario, natural products are of great interest since a large part of antibiotics derive from natural sources.

Myrtus communis has already attracted attention for its peculiar molecules, myrtucommulone acylphloroglucinol and analogues compounds with several pharmacological properties, including antimicrobial activities².

In this communication, we explored the antimicrobial potential of *Myrtus communis* leaves collected from Sardinia, with the ultimate goal to find new antimicrobial metabolites. NMR-based metabolomic approach³ can be an excellent tool in order to identify the metabolic composition of bioactive extract. In fact, metabolomics seeks to identify and quantify the complete set of metabolites, which can be measured by NMR, requiring shorter times and rapid sample preparation. Therefore, the antimicrobial potential of myrtle crude extract has been assessed against a panel of gram-positive and gram-negative bacteria, while NMR-based metabolomic screening of the myrtle crude extract, thanks to 1D and 2D NMR experiments, reveals from the a complex metabolic profile. It is already possible to highlight the presence of two glycosylated myricetins and some non-prenylated acylphloroglucinols.

Based on the encouraging antimicrobial results, especially against gram-positive bacteria, a detailed bio-guided fractionation led to the isolation of four new myrtogalloyl glycosides elucidated based on NMR experiments (HSQC, CIGAR-HMBC, DQ-COSY, and NOESY) and spectrometric techniques (ESI-Q-TOF). These insights pave the way to future experiments that will focus on assessing the antibacterial properties of this purified compounds with the ultimate goal of identifying new antimicrobial agents.

References:

- [1] M. Balouiri, M. Sadiki, S. Koraichilbnsouda, *J. Pharm. Anal.* **2016**, 6, 71-79.
- [2] G. Appendino, F. Bianchi, A. Minassi, O. Sterner, M. Ballero, S. Gibbons, *J. Nat. Prod.* **2002**, 65, 334-338.
- [3] V. Graziani, M. Scognamiglio, V. Belli, A. Esposito, B. D'Abrosca, A. Chambery, R. Russo, M. Panella, Russo, F. Ciardiello, T. Troiani, N. Potenza, A. Fiorentino, *Sci. Rep.* **2018**, 8, 5309.

Collagen capped halloysite nanotubes as multifunctional drug carriers

K. Fidecka,^a J. Giacoboni,^a R. Vago,^b E. Licandro^a

^a Department of Chemistry, University of Milan, Via Camillo Golgi 19, 20133, Milan, Italy

^b San Raffaele Hospital, Urological Research Institute, Via Olgettina 60, 20132 Milano, Italy
kasia.fidecka@wp.pl

In the past decade, the investigation of nanoparticles usage in medicine has revolutionized the universal viewpoint of drug delivery. Such submicron materials characterize with potential for crossing biological barriers, reducing toxicity and site effects of incorporated drugs as well as providing protection for such immobilized therapeutics from fast hydrolytic and enzymatic degradation in the body¹.

From a multitude of nanoparticles under current investigation, halloysite nanotubes (HNTs) stand out as biofriendly, inorganic nanoparticles with drug-loading capabilities and drug release characteristics. The complexity of HNT's morphology results in variation of inner and outer surfaces' properties, endowing their site-specific modification, towards various methodologies for therapeutics incorporation².

Herein we report two strategies for immobilization of model drugs, aspirin and epirubicin within HNT's inner lumen. In the forward step we present encapsulation of drug loaded HNTs in natural polymer, collagen. Such collagen capping has a multifunctional effect: it allows to entrap immobilized drug until nanoconstructs reach the suffering organ; allows to control the duration and speed of drug release as well as allows to trigger therapeutics release in response to decreased pH and enzymes activity. The proposed collagen coating has another exceptional feature: it is bioresorbable and moreover it is potentially capable of selective wounds, fibrotic tissues and tumour cells targeting, since collagen is recognized by several receptors of pathological cells³. We have focused on qualitative as well as quantitative characterization of formed nanoconstructs, to finally complete our studies with biological tests.

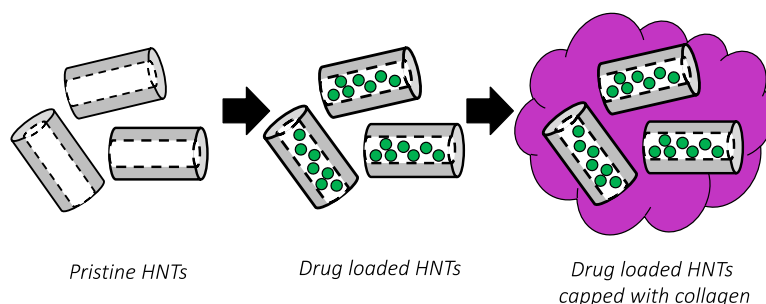


Figure 1: Illustration of halloysite nanotubes loading with a drug and forward nanoconstructs' encapsulation in collagen shell.

References:

- [1] S. Tran, P.-J. DeGiovanni, B. Piel, P. Rai, *Clin. Transl. Med.* **2017**, 6, 1-21.
- [2] E. Abdullayev, Y. Lvov, *J. Mater. Chem. B* **2013**, 1, 2894-2903.
- [3] C. Zeltz, D. Gullberg, *J. Cell Sci.* **2016**, 129, 653-664.

Visible-Light Promoted Dearomatizing Spirocyclizations of Ynone-Tethered Indoles

A. Pagano,^a H. E. Ho,^b R. J. K. Taylor,^b W. Unsworth^b

^aDepartment of Chemistry and Industrial Chemistry, University of Genova, via Dodecaneso, 31, 16146 Genova, Italy.

^bDepartment of Chemistry, University of York, Heslington Road, YO10 5DD York, U.K.
angela_pagano@alice.it

Dearomatizing spirocyclizations are an effective means to generate three-dimensional scaffolds starting from simple aromatic precursors. Spiroindolines and spiroindoles are an important class of spirocyclic compounds present in a wide range of pharmaceuticals and natural alkaloids.¹

We have recently reported a one-pot protocol for the dearomatizing spirocyclization/cross-coupling of alkyne-tethered indoles/pyrroles, where palladium complexes generated in situ act as both π -acid and cross-coupling catalysts (Figure 1a).²

The dearomatization strategy described herein is based on a thiyl radical cascade process mediated by visible light which enables the simultaneous metal-free preparation of synthetically challenging spirocyclic carbons and tetrasubstituted alkenes, converting indole derivatives **1** into spirocycles **2** under operationally simple reaction conditions (Figure 1b).³

This highly efficient radical cyclisation process is compatible with a wide range of ynone-tethered indoles and thiols.

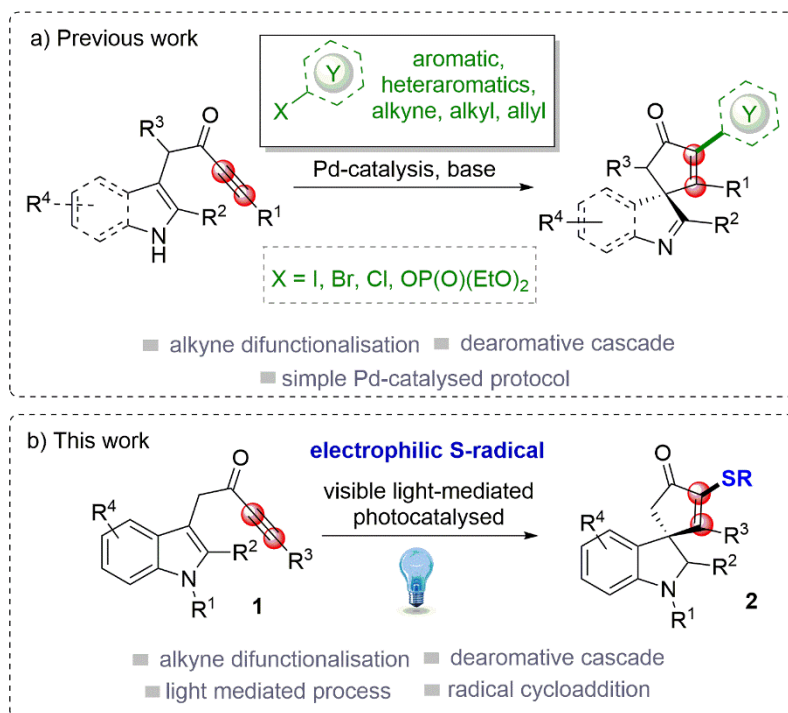


Figure 1: a) merged π -acid spirocyclization/Pd-catalyzed cross coupling; b) light promoted radical cascade spirocyclization.

References:

- [1] J. Bariwal, L. G. Voskressensky, E. V. Van der Eycken, *Chem. Soc. Rev.* **2018**, 47, 3831-3848.
- [2] H. E. Ho, T. C. Stephens, T. J. Payne, P. O'Brien, R. J. K. Taylor, W. Unsworth, *ACS Catal.* **2019**, 9, 504-510.
- [3] A. Pagano, H. E. Ho, R. J. K. Taylor, W. Unsworth, *manuscript in preparation*.

Plasticizers from Natural Resources

F. Trapani,^{a,b} M. Grillo,^a S. Gastaldello,^a C. Maran,^a L. Tassoni,^a A. Palumbo Piccionello,^b A. Pace^b

^aATPr&d S.r.l., Via Piersanti Mattarella 14, 36043 Camisano Vicentino (VI)

^bUniversità degli Studi di Palermo – Dipartimento STEBICEF, Viale delle Scienze Ed. 17, 90128 Palermo
fed.trapani@gmail.com

A plasticizer, according to the IUPAC council, is defined as “a substance or a material incorporated into a plastic to increase its flexibility, workability or distensibility.”¹ The most widely plasticized polymer is poly(vinyl chloride) (PVC) because of its excellent plasticizer compatibility characteristics and it is applied in packaging, toys, wires, cables, clothes and healthcare devices. The largest class of plasticizer for the PVC are phthalic acid esters that found applications for the first time in 1920. Nevertheless, concerns and controversy have been raised regarding their use. They exhibit a migration phenomenon and are suspected to produce bioaccumulation in the environment, justifying restrictive regulations in several countries about the use of phthalates as plasticizer.² With the growing interest for plasticizers with low migration levels and low toxicity, researchers are paying more attention to bio-based plasticizers. Many plasticizers can be prepared from different agricultural resources: cereals, oleaginous plants, trees, fruits, and vegetables or their wastes. In particular, vegetable oils coming from soybean, linseed, palm, castor bean, permit to elaborate several plasticizers after chemical modifications. They have various compositions of fatty acids depending on the plant and the growing conditions, can intersperse and intercalate between polymer chains, increase intermolecular spacing and bring mobility, and they have the ester groups can interact with polymer chains (van der Waals interactions for instance) and bring compatibility.³ In this communication we want to evaluate the synthesis of new bio-plasticizers for PVC derived from vegetable resources for a possible industrial use.

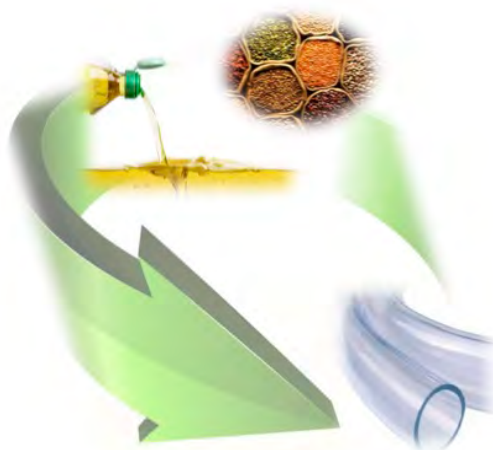


Figure 1: Plastics derived from natural resources.

References:

- [1] C. E. Wilkes, J. W. Summers, C. A. Daniels, PVC Handbook, Akron, Ohio, **2005**.
- [2] O. Fenollar, L. Sanchez-Nacher, D. Garcia-Sanoguera, J. Lopez, R. Balart, *J. Mater. Sci.* **2009**, *44*, 3702-3711.
- [3] M. Bocque, C. Voirin, V. Lapinte, S. Caillol, J. Robin, *J. Polymer Sci. Part A: Polym. Chem.* **2016**, *54*, 11-33.

Synthesis of Pre-cannabinoid Terpenyl esters, an Unexplored Class of Native Phytocannabinoids

F. Pollastro,^a G. Appendino,^a F. Rogati,^a O. Tagliatela-Scafati^b

^aDepartment of Pharmaceutical Sciences, University of Piemonte Orientale, Novara, Italy

^bDepartment of Pharmacy, University of Naples Federico II, Napoli, Italy
federica.pollastro@uniupo.it

Phytocannabinoids occur in *Cannabis* mainly in carboxylated form (pre-cannabinoids), that undergo decarboxylation upon prolonged storage or heating and generate the neutral phytocannabinoids.¹ The bioactivity profile of pre-cannabinoids is significantly different from the one of their corresponding neutral analogues, although their further development is hampered by decarboxylation-related overlapping of their biological profile with the one of their neutral analogues. On the other hand, *Cannabis* contains also esters of pre-cannabinoids with terpenyl alcohols (mono- and sesquiterpenes) that are stable toward decarboxylation, but whose biological profile is unexplored because of the difficulties of their isolation. Thus, these compounds are trace constituents of *Cannabis*, occurring in concentration <<0.1% of the plant material, and occur as very complex mixtures from which single compounds are difficult to obtain.¹ For these reasons, we have investigated the esterification of pre-cannabinoids with a selection of primary-, secondary- and tertiary terpenyl alcohols to capture the chemical diversity of these compounds, largely elusive by isolation.

The presence of the *ortho-para* dioxygenation makes the chemistry of the carboxylate group idiosyncratic, as manifested by the facility of decarboxylation, a feature absent in *ortho*- and *para*-hydroxybenzoic acids, rationalizing the failure of all the most common esterification procedures based on either alcohol or acyl activation. After considerable experimentation, a protocol involving the use of carbodiimides in the presence of Brønsted acids was found to give satisfactory results. Although preceded in the literature,² this esterification method has very rarely been used, and is mechanistically distinct from the Keck esterification that involves the combined use of DMAP and acids. Its application was validated by the preparation of a library of pre-cannabinoid terpenyl esters, and its other difficult cases of esterification of phenolic acids were also explored.

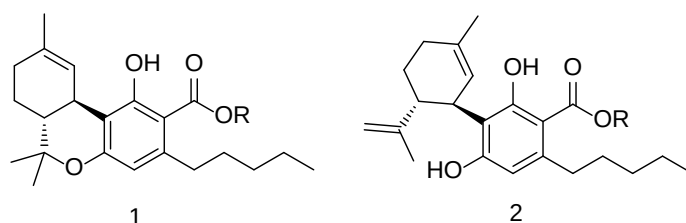


Figure 1: General formula of pre-THC (1) and pre-CBD (2) terpenyl esters (R = mono or sesquiterpene residue)

References:

- [1] L. O. Hanuš, S. M. Meyer, E. Muñoz, O. Tagliatela-Scafati, G. Appendino, *Nat. Prod. Rep.* **2016**, 33, 1357-1392.
- [2] K. Holmberg, B. Hansen, *Acta Chem. Scand. B* **1979**, 33, 410-412.

Molecular Editing of Cannabichromene (CBC)

D. Mattoteia, D. Caprioglio, D. Del Prete, A. Minassi, G. Appendino

Dipartimento di Scienze del Farmaco, Largo Donegani 2, 28100 Novara, Italy
daiana.mattoteia@uniupo.it

Phytocannabinoids can modulate the endocannabinoid system directly, by interaction with the cannabinoid receptors (CB1 and CB2), or indirectly by potentiation of the endocannabinoid tone, an activity mediated by the interaction with the enzymes responsible for the production and degradation of the endocannabinoids anandamide (AEA) and 2-arachydonoylglycerol (2AG). The most potent indirect phytocannabinoid is cannabichromene (CBC), a compound available by total synthesis via the condensation of citral and olivetol (Figure 1), that can selectively inhibit the degradation of 2AG by the enzyme monoacylglycerol lipase (MAGL). The therapeutic potential of non-narcotic boosters of the endocannabinoid tone provided a rationale to investigate the generality of this tandem Knoevenagel-electrocyclic reaction to edit the CBC chemotype.

The modification investigated were the oligomerization of the isoprenyl aldehydes (from C-5 to C-20), the substitution and the isosteric heterocyclic replacement of the resorcinyl core, and the nature of the promotion (acidic, basic, nucleophilic, electrophilic, microwave, NHC). The reaction turned out to be synthetically useful only for disubstituted resorcinols, and a different course was observed with heterocyclic substrates. Surprisingly, the C-15 isoprenyl aldehyde (farnesal) failed to generate its corresponding chromene.

A second set CBC analogues was prepared by modification of the chromene core by alkylation, oxidation and reduction, identifying more potent inhibitors of MAGL worth additional pre-clinical evaluation.

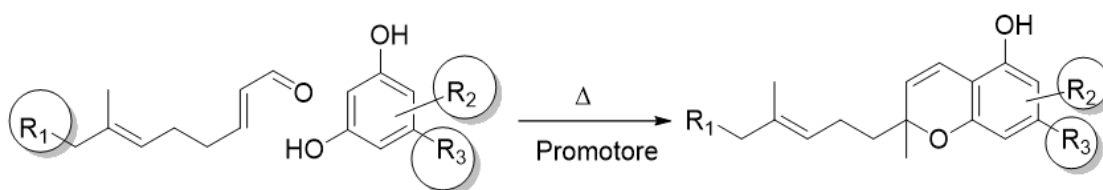


Figure 1: synthesis of CBC analogues (CBC: R₁= R₂ =H, R₃ = nC₅H₁₁)

References:

- [1] L.O Hanuš, S. M. Meyer, E. Muñoz, O. Tagliabatella-Scafati, G. Appendino, *Nat. Prod. Rep.* **2016**, 33, 1357-1392.
- [2] F. Pollastro, D. Caprioglio, D. Del Prete, F. Rogati, A. Minassi, O. Tagliabatella-Scafati, E. Munoz, G. Appendino, *Nat. Prod. Commun.* **2018**, 13, 1189-1184.

Synthesis of Nucleobase-Containing 1,2,3-Triazoles with Potential Biological Activity through Metal Catalyzed Azide-Alkyne 1,3-Dipolar Cycloaddition

V. Algieri,^a L. Maiuolo,^a A. De Nino,^a B. Russo,^a M. A. Tallarida,^a M. Nardi,^b M. L. Di Gioia.^c

^a Dipartimento di Chimica e Tecnologie Chimiche, Università della Calabria, Ponte Bucci, cubo 12/C, 87036, Arcavacata di Rende (CS), Italy;

^b Dipartimento di Scienze della Salute, Università Magna Graecia, Viale Europa, 88100 Germaneto, CZ, Italy

^c Dipartimento di Farmacia e Scienze della Salute e della Nutrizione, Edificio Polifunzionale, Università della Calabria, 87036 Rende, CS, Italy.
vincenzo.algieri@unical.it

1,2,3-triazoles are five-member *N*-heterocyclic compounds bearing three nitrogen atoms in the ring. They are an important nucleus for the development of drugs because they are resistant to oxidation, reduction, and hydrolysis in both acidic and basic conditions for their aromatic nature.¹ Thanks to their active participation in hydrogen bond formation, dipole–dipole, and π -stacking interactions they can mimic peptide bonds, enhancing their binding ability with different biological targets. Therefore, triazoles represent a significant class of nitrogen compounds with important biological properties, such as antibacterial, anticancer, antiviral, antimalarial, anti-inflammatory, and antituberculosis. In particular, 1,2,3-triazoles have found a broad spectrum of biological applications such as β -lactam antibiotic tazobactam, cefatrizine, and anticancer compound carboxyamidotriazole (CAI), which are some drugs available on the market.² In addition, the presence of nucleobase portion bonded on triazole core increase the biological activity because these compounds mimic the natural nucleosides exercising enzyme inhibition, viral toxicity and cytotoxicity.³

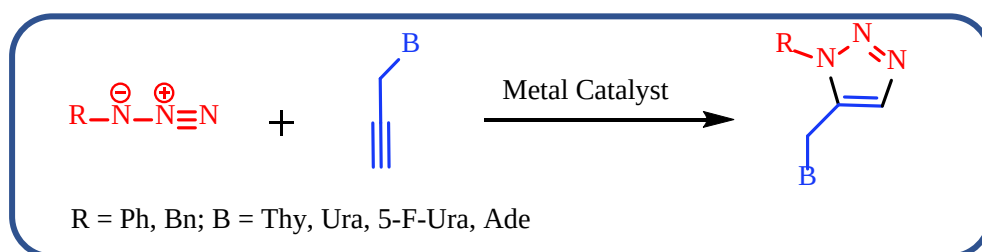


Figure 1: 1,3-dipolar cycloaddition reaction for nucleobase-containing 1,2,3-triazoles

In this work, our research group has designed and synthesized a new class of nucleobase-containing 1,2,3-triazoles (**Figure 1**) through 1,3-dipolar cycloaddition reaction using azides as 1,3-dipoles and propargyl nucleobases as dipolarophiles. The reaction is catalyzed with metal Lewis acid and the products are obtained with high yields and excellent regioselectivity because only 1,5-disubstituted 1,2,3-triazoles are obtained.

References:

- [1] A. De Nino, P. Merino, V. Algieri, M. Nardi, M. L. Di Gioia, B. Russo, M. A. Tallarida, L. Maiuolo, *Catalysts*, **2018**, 8, 364.
- [2] L. Maiuolo, B. Russo, V. Algieri, M. Nardi, M. L. Di Gioia, M. A. Tallarida, A. De Nino, *Tetrahedron Lett.*, **2019**, 60 (9), 672-674.
- [3] L. Maiuolo, G. Feriotto, V. Algieri, M. Nardi, B. Russo, M. L. Di Gioia, E. Furia, M. A. Tallarida, C. Mischiati, A. De Nino, *MedChemComm*, **2018**, 9, 299-304.

Preparation and characterization of graphene oxide foils for applications in the biomedical field

A. Fontana,^a A. Di Crescenzo,^a A. Ventrella,^a P. Di Profio,^a S. Zara,^a M. Passacantando,^b A. Cataldi^a

^aDepartment of Pharmacy, University "G. d'Annunzio", Via dei Vestini, Chieti

^b Department of Physical and Chemical Science, University of L'Aquila, Via Vetoio, Coppito 1, L'Aquila
fontana@unich.it

Graphene oxide (GO) is the oxidized derivative of graphene. It retains some of the exceptional features of graphene and the capacity to be well dispersed in water.¹ The good *in vitro* biocompatibility of GO has paved the way for investigating it in numerous biomedical applications.²

In the present study we report the synthesis of GO foils, characterized by cross-linked GO sheets that impart to the foil an extraordinary stiffness and strength,³ with the aim of exploiting their capacity to induce differentiation of Dental Pulp Stem Cells (DPSCs) towards the osteogenic/odontogenic lineage.⁴ The obtained foils have been investigated in terms of structure via Scanning Electron Microscopy (SEM) measurements, surface topography and nanomechanical characterization via Atomic Force Microscopy (AFM) measurements and stability in aqueous fluids. After proper sterilization, DPSCs were cultivated on GO foils for 28 days and conventional cell viability assays were performed to follow the growth process. DPSCs differentiation towards the osteoblastic lineage was investigated by measuring alkaline phosphatase (ALP) activity.

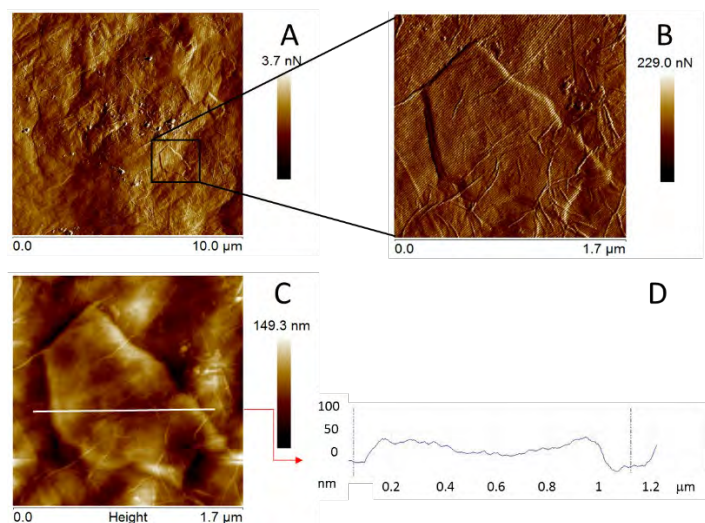


Figure 1: AFM images of GO foil obtained with Peak Force QNM reporting: A) peak force error (10 μm $\times$ 10 μm), B) inset of image A; C) and D) high of the inset B in planar and trace profile, respectively.

References:

- [1] D. R. Dreyer, S. Park, C. W. Bielawski, R. S. Ruoff, *Chem. Soc. Rev.* **2010**, 39, 228-240.
- [2] V. Ettore, P. De Marco, S. Zara, V. Perrotti, A. Scarano, A. Di Crescenzo, M. Petrini, C. Hadad, D. Bosco, B. Zavan, L. Valbonetti, G. Spoto, G. Iezzi, A. Piattelli, A. Cataldi, A. Fontana, *Carbon* **2016**, 103, 291-298.
- [3] D. A. Dikin, S. Stankovich, E. J. Zimney, R. D. Piner, H. B. G. Dommett, G. Evmenenko, S. T. Nguyen, R. S. Ruoff, *Nature* **2007**, 448, 457-460.
- [4] A. Di Crescenzo, S. Zara, C. Di Nisio, V. Ettore, A. Ventrella, B. Zavan, P. Di Profio, A. Cataldi, A. Fontana, *ACS Appl. Bio Mater.* **2019**, 2, 1642-1651.

Developing new ways to introduce the boron atom in organic molecules by ring-opening reactions

A. Menichetti,^a C. Boldrini,^a C. Cammarella,^a M. Pineschi^{*a}

^aDepartment of Pharmacy, University of Pisa, Via Bonanno 33, Pisa, Italy
andrea.menichetti@farm.unipi.it

Introducing boron atom in organic molecules in a regio- and stereoselective fashion is a fascinating challenge for the organic chemist. In fact, boronic acids and esters are important intermediates in synthetic organic chemistry and have a wide range of applications in medicinal chemistry.¹ After seminal contributions about the ring opening of vinyl epoxides and vinyl aziridines with nucleophilic diboron reagents,² some other advances in the field of borylative ring opening of epoxides and aryl aziridines using diboron reagents have been quite recently made.³ However, a general approach for the borylative ring opening of alkyl aziridines is still lacking.

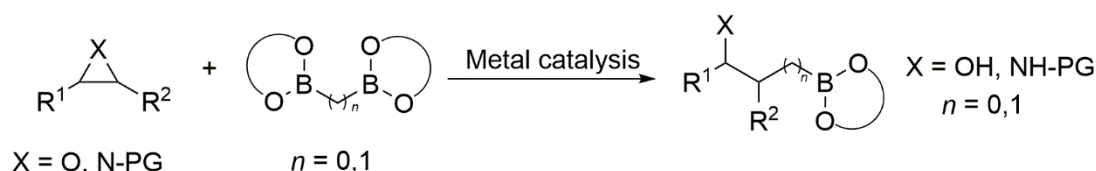


Figure 1: Ring-opening reactions with boron-containing reagents.

We herein report our study about the individuation of reaction conditions able to open a variety of alkyl aziridines using diboron reagents ($n = 0$, Figure 1) and diborylmethane derived reagents ($n = 1$).

References:

- [1] W. Yang, X. Gao, B. Wang, *Med. Res. Rev.* **2003**, 23, 346-368.
- [2] a) S. Sebelius, V. J. Olsson, K. J. Szabó, *J. Am. Chem. Soc.*, **2005**, 127, 10478-10479; b) S. Crotti, F. Bertolini, M. Macchia, M. Pineschi, *Org. Lett.* **2009**, 11, 3762-3765; c) Review: M. Pineschi, *Synlett* **2014**, 25, 1817-1826.
- [3] a) Y. Takeda, A. Kuroda, W. M. C. Sameera, K. Morokuma, S. Minakata, *Chem. Sci.* **2016**, 7, 6141-6152; b) E.-A. M. A. Ahmed, X. Lu, T.-J. Gong, Z.-Q. Zhang, B. Xiao, Y. Fu, *Chem. Comm.* **2017**, 53, 909-912.

Synthesis of fluorinated curcumin-based molecules for detecting amyloid plaques by ^{19}F -MRI

R. Stefania,^a L. Tei,^b F. Garelo,^a I. Hawala,^a G. Forloni,^c A. Deluigi,^c C. Balducci,^c G. Digilio,^b E. Terreno^a

^aDepartment of Molecular Biotechnology and Health Sciences, University of Torino, Via Nizza 52, 10126-Torino, Italy

^b Department of Sciences and Technologic Innovation, Università del Piemonte Orientale, Alessandria, Italy

^c IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Department of Neuroscience, Milan
rachele.stefania@unito.it

The detection of A β plaques is one strategy for Alzheimer's Disease (AD) diagnosis. Amyloid imaging can be successfully pursued by ^{19}F -MRI using fluorinated curcumin-based compounds.¹ The developed probes contained a limited number of ^{19}F atoms/molecule, and, furthermore, they were directly conjugated to the aromatic portion of the molecule, thus potentially reducing the detection sensitivity due to the broadening of the ^{19}F signal. This work aims at synthesizing a series of novel F-containing curcumins with a high number of ^{19}F nuclei, suitably spaced from the aromatic part of the molecule. The preparation of F-containing curcumins (Fig. 1) started from the synthesis of mono and bi-carboxylic acid derivatives of curcumin followed by an amide coupling with two different perfluorinated amines, one of them incorporated a carboxylic functional group to improve solubility. All the compounds obtained were dissolved at 10 mg/mL in DMSO or in a mixture of normal saline and Cremophor® and characterized by ^1H and ^{19}F NMR. The deposition of the compounds on brain slices explanted from APP-PS1 mice (transgenic AD model) showed a reduced affinity of the derivatives with respect to the parent curcumin. However, a qualitative assessment of the fluorescent signal allowed to rank the affinity of the compounds towards the plaques in the order: mono-F9 > mono-carboxy-F9 > bi-F18 > bi-carboxy-F18. Most likely, the higher affinity showed by the mono-derivatives is due to the preservation of one phenolic group in the aromatic portion of the structure involved in the binding to the plaque. On this basis, compound mono-F8 appears to be the more promising to be tested in vivo on preclinical AD models for amyloid imaging by ^{19}F -MRI.

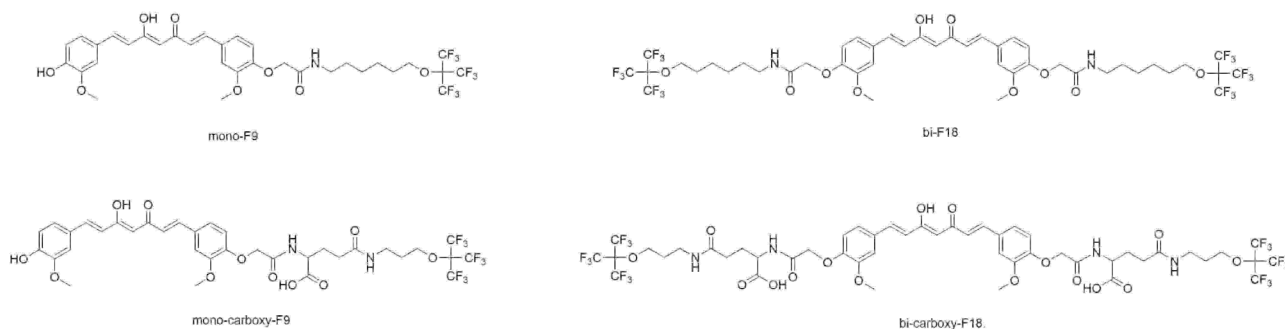


Figure 1: Chemical structures of Curcumin derivatives.

References:

- [1] I. Tooyama, D. Yanagisawa, H. Taguchi, T. Kato, K. Hirao, N. Shirai, T. Sogabe, N. F. Ibrahim, T. Inubushi, S. Morikawa, *Ageing Res. Rev.* **2016**, 30, 85-94.

Ruthenium-catalyzed ring transformation of 4,4-disubstituted isoxazolin-5-ones to different heterocyclic systems

M. S. Christodoulou, E. M. Beccalli, S. Giofrè

DISFARM, Sezione di Chimica Generale e Organica "A. Marchesini" Università degli Studi di Milano, via Venezian 21,
20133 Milano, Italy.

e-mail: Michael.Christodoulou@unimi.it

Isoxazol-5-ones have been identified as a versatile building block for the preparation of a variety of functionalized molecules, exploiting their high reactivity and the relative ease of ring opening.¹ The isoxazolone derivatives were object of studies by our research group for a long time, regarding their reactivity and the ring transformation in different heterocycles.² We report here the reactions of the isoxazol-5-ones bearing an unsaturated system in position 4 under ruthenium catalysis. The results are depending on the different substituents present on the ring and different reaction conditions. The novel reactivity by using ruthenium-complexes provides a step-economic strategy towards benzo[*f*]indole-4,9-diones, and 2,3,4,5-tetrasubstituted pyrroles, through a decarboxylative ring-opening and ring closure.

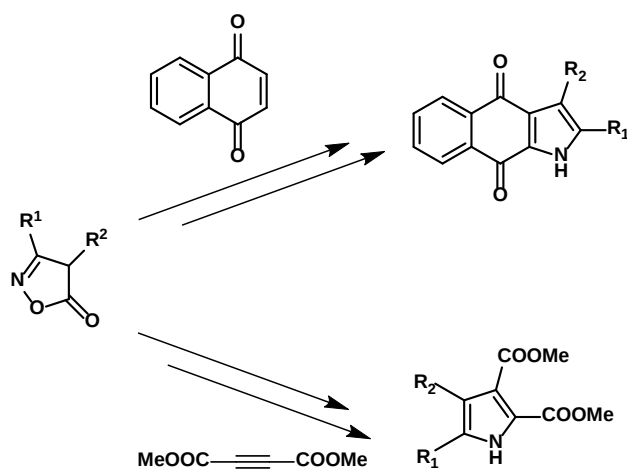


Figure. Isoxazol-5-ones ring transformation

References:

- [1] A. F. da Silva, A. A. G. Fernandes, S. Thurow, M. L. Stivanin, I. D. Jurberg, *Synthesis* **2018**, 50, 2473-2489.
- [2] E. M. Beccalli, D. Pocar, C. Zoni, *Targets in Heterocyclic Systems* **2003**, 7, 31-63.

***N,N*-bis-Triazol-Sulfenamides: A New Family of Halogen Free Flame Retardants**

S. V. Giofrè,^a D. Iannazzo,^b C. Celesti,^b A. Pistone,^b R. Romeo,^a

^a *Dipartimento di Scienze chimiche, biologiche, farmaceutiche ed ambientali, Università di Messina, Via S.S. Annunziata, 98168 Messina, Italy*

^b *Dipartimento di Ingegneria, Università di Messina, Contrada Di Dio, 98166 Messina, Italy*
sgiofre@unime.it

In response to the urgent need to develop new high-performance and halogen-free fire resistant materials with low environmental impact,¹ different alternative flame retardant (FR) systems have been introduced. In many applications, traditional inorganic, non-halogenated flame retardants such as ammonium polyphosphate (APP) and aluminum or magnesium hydroxides (ATH, MDH) are widely used, but there is still a need to find more effective solutions. The proposed alternatives are mainly based on the employment of different reactive or additive organophosphorus or nitrogen containing additives that can act in gas phase and/or in condensed phase. In addition, various families of radical generators have been prepared and their viability in a series of polymer applications has been recently demonstrated.²

We have developed a new class of sulfenamides linked to the triazole systems. This specific group of compounds is characterized by the presence of a bond between a divalent sulfur atom and a trivalent nitrogen atom, which by homolytic cleavage generates aminyl and thiyl radicals, and by the presence of the triazole unit able to generate nitrogen and ammonia by splitting, thus providing excellent flame retarding properties to polymer substrates.

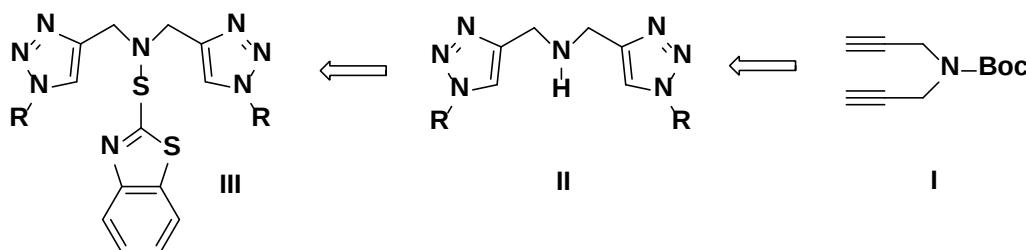


Figure 1: Retrosynthetic approach for the synthesis of *N,N*-bis-Triazol-Sulfenamide derivatives.

The general synthetic procedure have been developed through two key substrates as shown in the retrosynthetic scheme (Figure 1): the protected dipropargylamine **I** and the bis-triazolyl derivative **II** which is subsequently converted into the final product **III**.

The obtained products were investigated by thermogravimetric analysis (TGA) to evaluate their thermal stability and the best compounds were incorporated in polypropylene (PP). Flame stability of the composite thus obtained was evaluated.

References:

- [1] C. A. De Wit, *Chemosphere* **2002**, 46, 583-624.
- [2] T. Tirri, M. Aubert, W. Pawelec, A. Holappa, C. E. Wilén, *Polymers* **2016**, 8, 360.

Decoration of carbon nanotubes for the combined therapy of cancer

M. C. Ligi,^a G. Biagiotti,^{a,b} F. Pisaneschi,^{b*} F. Machetti,^{a,c} P. Paoli,^d S. Cicchi^{a,c*}

^a Department of Chemistry "Ugo Schiff", Università degli Studi di Firenze, via della Lastruccia 3-13, 50019 Sesto Fiorentino, Firenze, Italy

^b Department of Cancer Systems Imaging, Division of Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, 1881 East Road, 77054 Houston, TX, USA

^c Istituto di Chimica dei Composti Organometallici (ICCOM), Consiglio Nazionale delle Ricerche (CNR), Via Madonna del Piano 10, 50019 Sesto Fiorentino, Italy

^d Department of Biomedical, Experimental and Clinical Science "Mario Serio", Università degli Studi di Firenze, viale Morgagni 50, 50134 Firenze, Italy
mariacristina.ligi@unifi.it

A drug delivery system (DDS) for combined therapy, based on a short oxidized multiwalled carbon nanotube, is reported. It was prepared exploiting a synthetic approach which allowed loading of two drugs, doxorubicin and metformin, the targeting agent biotin and a radiolabeling tag, to enable labeling with Ga-68 or Cu-64 in order to perform an extensive biodistribution study by PET/CT. The DDS biodistribution profile changes with different administration methods. Once administered at therapeutic doses, the DDS showed a marginal beneficial effect on 4T1 tumor bearing mice, a syngeneic and orthotopic model of triple negative breast cancer, with survival extended by 1 week and 2 days in 20% of the mice. This is encouraging given the aggressiveness of the 4T1 tumor. Furthermore our DDS was well tolerated, ruling out concerns regarding the toxicity of carbon nanotubes.

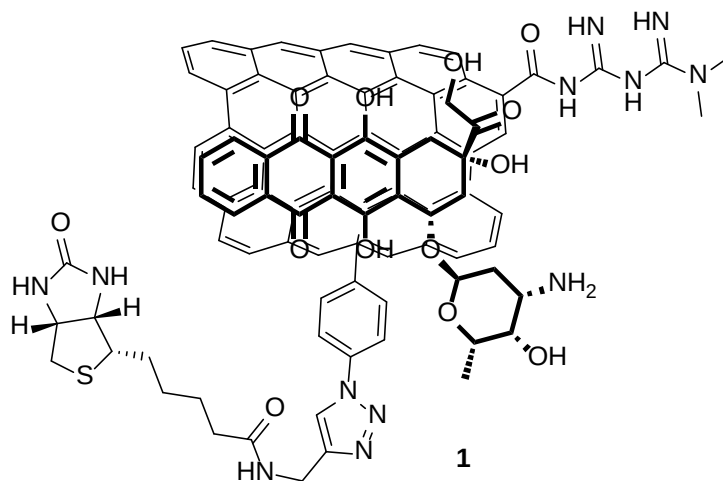


Figure 1: Structure of the drug delivery system loaded with doxorubicin and metformin.

References:

- [1] G. Biagiotti, S. Fedeli, G. Tuci, L. Luconi, G. Giambastiani, A. Brandi, F. Pisaneschi, S. Cicchi, P. Paoli, J. Mater. Chem. B **2018**, 6, 2022-2035.

Synthesis of new amphiphilic Zn-Salophen complexes derivatized by bile acids

V. Raglione,^a B. Droghei,^a A. Zerbini,^a M. Neri,^b A. Dalla Cort,^a A. D'Annibale^a

^aUniversità di Roma "La Sapienza", Piazzale Aldo Moro 5, Roma

^bUniversità di Parma, Dipartimento SCVSA, Parco area delle scienze 11A, Parma
venanzio.raglione@uniroma1.it

The amphiphilic Zn-salophen complexes have lately been receiving attention due to their aggregation behaviour, dependent upon some experimental parameters, such as concentration and polarity of solvents.¹ The possibility to control their aggregation morphologies, and their well known capability to accept one axially coordinated donor species make them suitable candidates for the development of new materials with applications in sensing.² The search of new amphiphilic derivatives of Zn-salophenes is thus an active research field. Our group have recently been working on the functionalization of bile acids which are an important class of natural surfactants showing amphiphilic properties strictly related to their rigid backbones. We prepared new derivatives linking natural bile acids to other natural compounds, such as sugars and aminoacids. The aggregation properties of the resulting derivatives were studied, and interesting aggregates and nanostructures were observed, making these compounds ideal building blocks for the bottom up synthesis of new materials for applications in the field of materials chemistry, in pharmacology and in the field of nanotechnologies, also thanks to the morphological variability.³ Thus here we describe the functionalization of metal-salophen complexes with substituted bile acids to obtain complex derivatives, in principle able to aggregate both thanks to the metal salophenic core, and bile acid subunit.

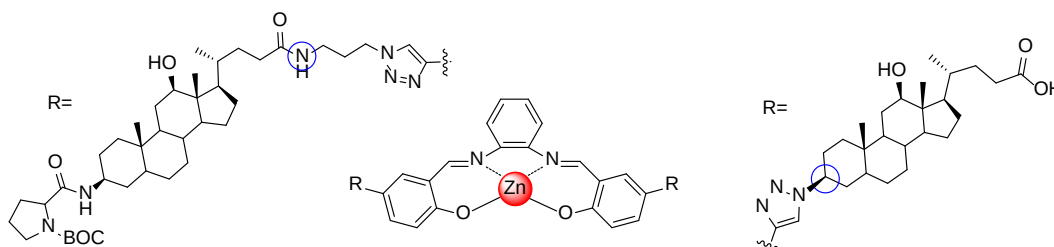


Figure 1: new amphiphilic Zn-Salophen compounds.

The strategies to functionalize bile acid backbone at C-3 or at its side chain to afford are discussed (**Figure 1**).

References:

- [1] G. Consiglio, S. Failla, P. Finocchiaro, I. P. Oliveri, R. Purrello, S. Di Bella, *Inorg. Chem.* **2010**, 49, 5134-5142.
- [2] A. Dalla Cort, L. Mandolini, C. Pasquini, K. Rissanen, L. Russo, L. Schiaffino, *New J. Chem.* **2007**, 31, 1633-1638.
- [3] U. Nonappa, U. Maitra, *Org. Biomol. Chem.* **2008**, 6, 657-669.

Napthochromenones as Cross-Border Light Photoredox Catalysts

J. Mateos,^a F. Rigodanza,^a A. Vega-Peñaloza,^a A. Sartorel,^a M. Natali,^b X. Companyó,^a M. Bonchio,^a L. Dell'Amico^a

^aDepartment of Chemical Sciences, University of Padova, Via Marzolo 1, Padova

^b Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Via Luigi Borsari 46, Ferrara
javier.mateoslopez@phd.unipd.it

During the last decade photochemistry has experienced an exponential growth. This, pushed by the development and utilisation of an increasing number of photocatalysts (PCs) in synthetic and material chemistry. Despite their cost and scarce sustainability, Ru- and Ir-based PCs have played a dominant role. This can be mainly ascribed to their easy use under common light sources irradiation (LEDs or CFL bulbs) that guarantees reagents and products stability. On the other hand, UV-light absorbing PCs generate wider redox windows which potentially result in broader applications.¹ Unfortunately, the use of highly energetic photons hampers their utilisation in diverse photoreactions. The identification of a general PC that combines the advantages of visible-light absorption with a redox window as wider as possible, efficiently catalysing the highest number of transformations is crucial to the future development of the field.

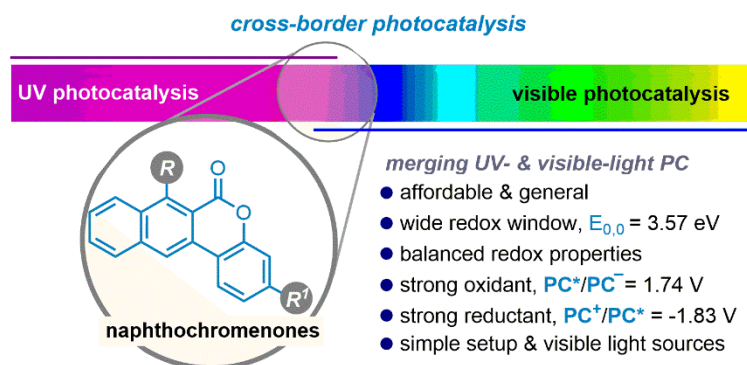


Figure 1: Napthochromenone photocatalysts as a new class of fully organic PCs.

I herein present a novel class of purely organic PCs, with a distinctive absorption across UV- and visible-light regions. Thanks to a robust microfluidic light-driven synthetic protocol their synthesis can be easily accomplished starting from readily available benzophenones and coumarins.² Remarkably, naphthochromenone PCs combine the benefits of an extremely wide redox window, $E_{0,0} =$ up to 3.57 eV, typical of UV-absorbing PCs, to the advantages of the use of simple setup and product stability of visible-light photocatalysis. Their well-balanced excited state redox potentials, $PC^+/PC^* =$ up to +1.74 V and PC^{**}/PC^* up to -1.83 V vs SCE, ensure the ability of performing diverse challenging photoredox transformations through both reductive and oxidative quenching cycles.³

References:

- [1] N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075-10166.
- [2] J. Mateos, A. Cherubini-Celli, T. Carofiglio, M. Bonchio, N. Marino, X. Companyó, L. Dell'Amico, *Chem. Commun.* **2018**, *54*, 6820-6823.
- [3] *Submitted manuscript.*

Microfluidic Dearomatisation of Indoles by a Light-Driven [2+2] Paternò-Büchi Process

A. Vega Peñaloza,^a P. Franceschi,^a J. Mateos,^a L. Dell'Amico^a

^aDepartment of Chemical Sciences, University of Padova, Italy
alberto.vegapenaloza@unipd.it

Excited state molecules can react in unconventional ways, offering synthetic opportunities that cannot be realized under classical thermal activation.¹ For this reason, the field of light-mediated synthetic chemistry has recently witnessed a tremendous growth.² The advancements of different technologies including new light sources, such as: high-power LEDs or compact fluorescent light bulbs, have been key for boosting the development of novel photochemical transformations.³ However, the use of a microfluidic photoreactor setup (MFP) offers decisive advantages with respect to photochemical batch protocols – improving the efficiency and selectivity of diverse light-driven processes.⁴

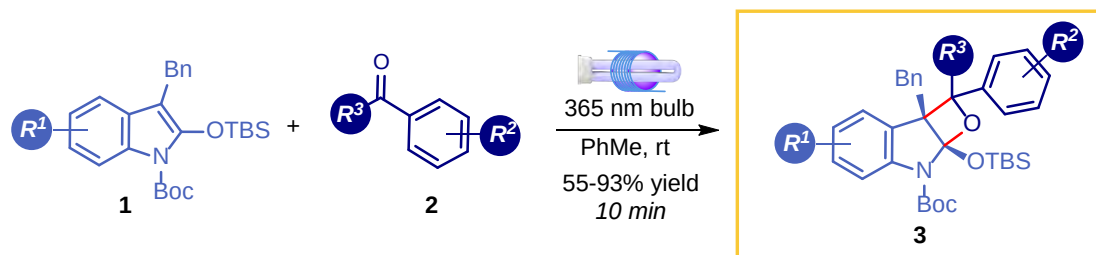


Figure 1: Dearomatisation of indoles by a Paternò-Büchi reaction.

I herein present our progress towards novel microfluidic dearomatisation of indoles triggered by a light-driven hetero-[2+2]-cycloaddition (Paternò-Büchi) reaction. This procedure allows the one-step access to differently substituted tetrahydrooxeto-indoles **3** (Figure 1). Interestingly, these motifs are present in a large number of alkaloids and natural products.⁵ Adopting the MFP setup we demonstrate the generality of the light-driven method by evaluating a variety of indole silyl enol ethers **1** and carbonyl compounds **2**. Remarkably, the present method allows the construction of valuable all-carbon quaternary stereocenters with high regio- and stereocontrol.

References:

- [1] L. Dell'Amico, A. Vega-Peñaloza, S. Cuadros, P. Melchiorre, *Angew.Chem. Int. Ed.* **2016**, 55, 3313-3317.
- [2] D. M. Schultz, T. P. Yoon, *Science* **2014**, 343, 1239176.
- [3] R. C. McAtee, E. J. McClain, C. R. J. Stephenson, *Trends in Chemistry* **2019**, 1, 111-125.
- [4] J. Mateos, A. Cherubini-Celli, T. Carofiglio, M. Bonchio, N. Marino, X. Companyó, L. Dell'Amico, *Chem. Commun.*, **2018**, 54, 6820-6823.
- [5] M. Fréneau, N. Hoffmann, *J. Photochem. Photobiol. C: Photochemistry Reviews*, **2017**, 33, 83-108.

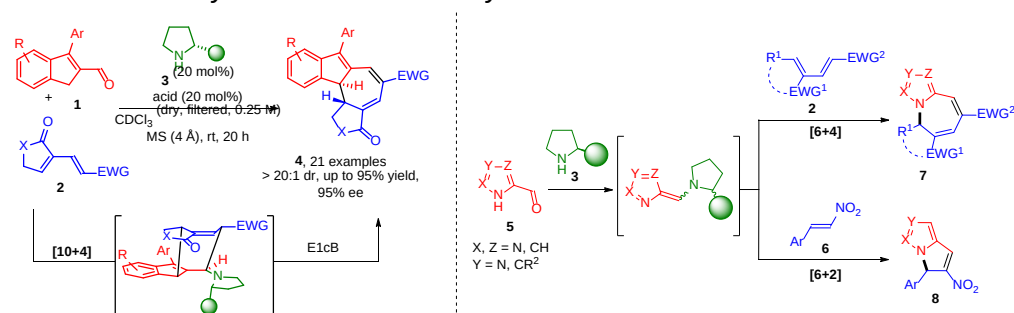
Higher order cycloadditions: from a stereoselective rediscovery to a computational fascination.

G. Bertuzzi,^{a,b} K.A. Jørgensen,^b K. N. Houk^c

^a Department of Industrial Chemistry "Toso Montanari" University of Bologna, Viale Risorgimento 4, Bologna.

^b Department of Chemistry Aarhus University, DK-8000 Aarhus C, Denmark; ^c Department of Chemistry and Biochemistry and Department of Chemical and Biomolecular Engineering, University of California, Los Angeles, California 90095, United States
giulio.bertuzzi2@unibo.it

Higher order cycloadditions (HOCs), i.e. cycloaddition reactions involving more than six π -electrons, became a popular research topic in organic chemistry, following the computational and experimental reports of Woodward, Hoffmann and Houk.¹ Organocatalysis was shown to be a competent strategy to induce enantioselectivity in HOCs, as demonstrated by a recent report by Jørgensen.² Following this principle, we developed a strategy to disclose the first catalytic stereoselective [10+4] cycloaddition. Amino isobenzofulvenes, generated *in situ* from aldehydes **1** and catalyst **3**, were reacted with dienes **2**, affording intriguing tetracyclic scaffolds **4**.³ Experimental and computational evidence suggest that the observed stereoselectivities arise from kinetically controlled amino isobenzofulvene formation. Moreover, we have developed a novel concept for the activation of heteroaromatic compounds, such as pyrrole-, imidazole- and pyrazole-carbaldehydes **5** by organocatalysis, generating electron-rich hetero-6 π -intermediates acting as nucleophiles.⁴ These react in a highly chemo-, regio- and stereoselective manner with various types of electron-deficient dienes **2** and olefins **6**, in [6+4] and [6+2] cycloaddition reactions, respectively. The methodology provided bio-attractive pyrrolo-azepine scaffolds **7** and pyrrolizidines alkaloid scaffolds **8**. As suggested by computational studies, stereocontrol occurs at the second C–C bond forming step, rather than the N–C bond forming transition state. Based on these two examples, this presentation will demonstrate that HOCs, besides being a powerful tool to construct complex and biologically relevant scaffolds, are extremely fascinating on the computational point of view, revealing peculiar features in reactivity and stereoselectivity.



Scheme 1. Organocatalytic enantioselective [10+4], [6+4] and [6+2] cycloadditions.

References:

- [1] a) R. Hoffmann, R. B. Woodward, *J. Am. Chem. Soc.* **1965**, 87, 2046-2048; b) K. N. Houk, R. B. Woodward, *J. Am. Chem. Soc.* **1970**, 92, 4143-4145.
- [2] R. Mose, G. Preegel, J. Larsen, S. Jakobsen, E. H. Iversen, K. A. Jørgensen, *Nat. Chem.* **2017**, 9, 487-492.
- [3] B. S. Donslund, N. I. Jessen, G. Bertuzzi, M. Giardinetti, T. Palazzo, M. L. Christensen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2018**, 57, 13182-13186.
- [4] G. Bertuzzi, M. K. Thøgersen, M. Giardinetti, A. Vidal-Albalat, A. Simon, K. Houk, K. A. Jørgensen, *J. Am. Chem. Soc.* **2019**, 141, 3288-3297.

Stereocontrolled synthesis of pyrrolidine iminosugars' lipophilic derivatives

M. De Angelis,^a L. Lanciotti,^a C. Lucarini,^a G. Forte,^a D. Odore,^a A. Ricelli,^b G. Righi^b

^aChemistry Department, University La Sapienza, Rome, Italy

^bCNR-IBPM, "Sapienza" University of Rome, Dep. Chemistry, P.le A. Moro 5 – 00185 Rome, Italy
m.deangelis@uniroma1.it

Iminosugars, carbohydrate analogues with a nitrogen atom in place of the endocyclic oxygen¹, turned out to be of great interest in their ability to inhibit important enzymes, such as glycosidase and glycosyltransferase². Thanks to this property, these alkaloids are considered a great target in treating a wide range of diseases like cancer, viral and bacterial infections, sphingolipid storage disorders³. The working group we refer to has already provided a synthetic strategy to obtain pyrrolidine iminosugars in a stereocontrolled way. According to several studies, the selectivity and power of these inhibitors significantly increase when lipophilic chains are introduced^{4,5,6,7,8}, allowing them to enter the cells' lipophilic double layer, reaching the central nervous system. From this perspective, we are focusing on functionalization of primary and secondary hydroxyl groups, introducing the alkyl chains in various steps of the synthetic pathway mentioned before.

A future aim will include the immobilization of synthesized compounds on magnetic nanoparticles and silver nanoclusters in drug delivery applications.

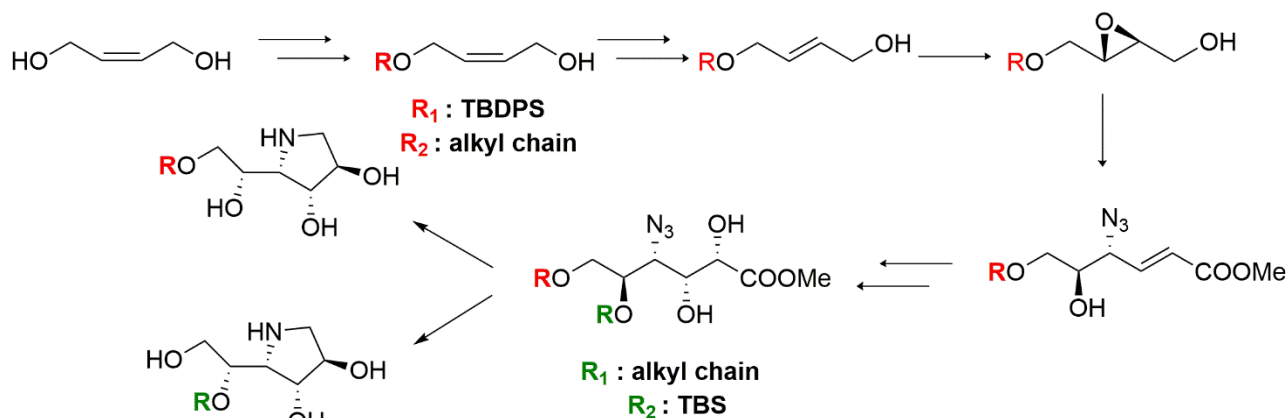


Figure 1: synthetic strategy of lipophilic derivatives

References:

- [1] G. Legler, *Adv. Carbohydr. Chem Biochem.* **1990**, 48, 319-384.
- [2] M. L. Sinnott, *Chem. Rev.* **1990**, 90, 1171-1202.
- [3] T. C. Wascher, I. Schmoelzer, A. Wiegratz, M. Stuehlinger, D. Mueller-Wieland, J. Kotzka, M. Enderle, *Eur. J. Clin. Invest.* **1994**, 24, 45-49.
- [4] H. S. Overkleeft, G. H. Renkema, J. Neele, P. Vianello, I. O. Hung, A. Strijland, A. van den Burg, G. J. Koomen, U. K. Pandit, J. M. F. G. Aerts, *J. Biol. Chem.* **1998**, 273, 26522-26527.
- [5] H. R. Mellor, F. M. Platt, R. A. Dwek, T. D. Butters, *Biochem. J.* **2003**, 374, 307-314.
- [6] H. R. Mellor, J. Nolan, L. Pickering, M. R. Wormald, F. M. Platt, R. A. Dwek, G. W.; Fleet, T. D. Butters, *Biochem. J.* **2002**, 366, 225-233.
- [7] A. Mehta, S. Ouzounov, R. Jordan, E. Simsek, X. Lu, R. M. Moriarty, G. Jacob, R. A. Dwek, T. M. Block, *Antivir. Chem. Chemother.* **2002**, 13, 299-304.
- [8] N. Asano, H. Kizu, K. Oseki, E. Tomioka, K. Matsui, M. Okamoto, M. Baba, *J. Med. Chem.* **1995**, 38, 2349-2356.

Synthesis of new 1,2-diaminic ligand for the asymmetric Henry reaction

L. Primitivo,^a F. Di Pietro,^a L. Bonanni,^a C. Sappino,^a L. Suber,^b G. Righi^c

^aChemistry Department, University La Sapienza, Rome, Italy

^bCNR-ISM, Monterotondo Scalo, Rome

^cCNR-IBPM Chemistry Department, University La Sapienza, Rome, Italy
ludovica.primitivo@uniroma1.it

Over the years, asymmetric catalysis has taken on increasingly central in enantioselective synthesis. Using chiral catalysts, both synthetic and of natural origin, optical active molecules can be obtained starting from prochiral molecules, with high yields and enantiomeric excesses.¹

Recently, we have developed a new ligand with an amino alcoholic structure, ligand **1** (Figure 1), which has proved to be an excellent chiral catalyst in the dialkylzinc addition reaction to aldehydes.²

Having found in literature significant advantages in the use of 1,2-diaminic ligands³ in asymmetric synthesis and in light of the good results obtained with **1**, the work we present concerns the synthesis and of a new chiral ligand with diaminic catalytic site, taking as model ligand **1**.

Once any attempt to transform the ligand **1** into the desired structure failed, it was decided to construct the new ligand by passing through the formation of an aziridine ring and the subsequent regioselective opening of the same (Figure 2). Currently, the synthetic strategy chosen to optimize ligand structure involves its application in the Henry reaction.⁴

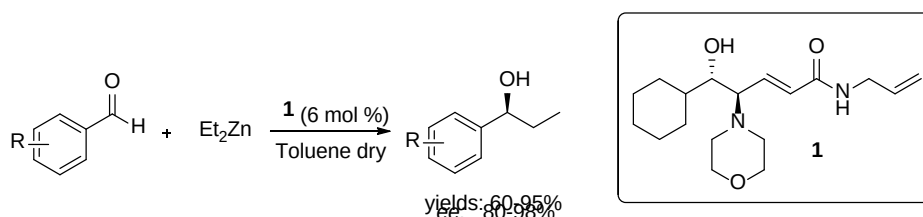


Figure 1 Catalytic efficiency of **1** in the asymmetric addition of diethylzinc to aldehydes **1**.

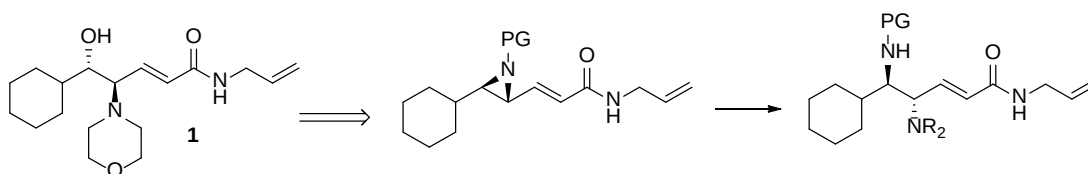


Figure 2 Developed synthetic strategy to obtain a chiral 1,2-diaminic ligand

References:

- [1] R. Noyori, *Angew. Chem. Int. Ed.* **2002**, *41*, 2008-2022.
- [2] C. Sappino, A. Mari, A. Mantineo, M. Moliterno, M. Palagri, C. Tatangelo, L. Suber, P. Bovicelli, A. Ricelli, G. Righi, *Org. Biomol. Chem.* **2018**, *16*, 1860-1870.
- [3] V. Bette, A. Mortreux, F. Ferioli, G. Martelli, D. Savoia, J. Carpentier, *Eur. J. Org. Chem.* **2004**, 3040-3045.
- [4] a) W. Jin, X. Li, B. Wan, *J. Org. Chem.* **2011**, *76*, 484-491; b) B. El-Asaad, E. Méta, I. Karamé, M. Lemaire, *Molecular Catalysis* **2017**, 435, 76-81.

Catalytic Asymmetric Oxidative γ -Coupling of α,β -unsaturated Aldehydes with Air as the Terminal Oxidant

A. V. Corti,^{a,b} B. L. Næsborg,^b C. L. A. Leth,^b D. P. H. Poulsen,^b K. A. Jørgensen,^{b,*}

^a Department of Industrial Chemistry "Toso Montanari", Alma Mater Studiorum - University of Bologna, V. Risorgimento 4, 40136 Bologna, Italy.

^b Department of Chemistry, Aarhus University Langelandsgade 140, 8000 Aarhus C, Denmark
vasco.corti2@unibo.it

Readily available chiral amines have been extensively used as catalysts for the activation of carbonyl compounds in the field of polar reactivity, which by reaction of electrophile and nucleophiles, provide products in a highly stereoselective manner.¹ In contrast, the involvement of short-lived open-shell species in asymmetric catalysis has remained relatively unexplored until recently, due to the inherent challenge of efficiently controlling the stereoselectivity of the product formation from high-energy intermediates.² The use of radicals in open-shell strategies can give access to different reactivity, for instance the coupling of two nucleophiles, which would not be feasible with polar reactivity.³ This communication presents the catalytic enantioselective coupling of two nucleophiles generated from α,β -unsaturated aldehydes via dienamine catalysis and a sub-stoichiometric amount of a single electron transfer-oxidant (SET-oxidant), that is reoxidized by air (Scheme 1). Merging organocatalysis with a transition metal featuring the appropriate redox properties provides the synergy necessary for the oxidation and subsequent radical coupling of the activated dienamine **I**. Air is used as the terminal oxidant of the process (Scheme 1).⁴

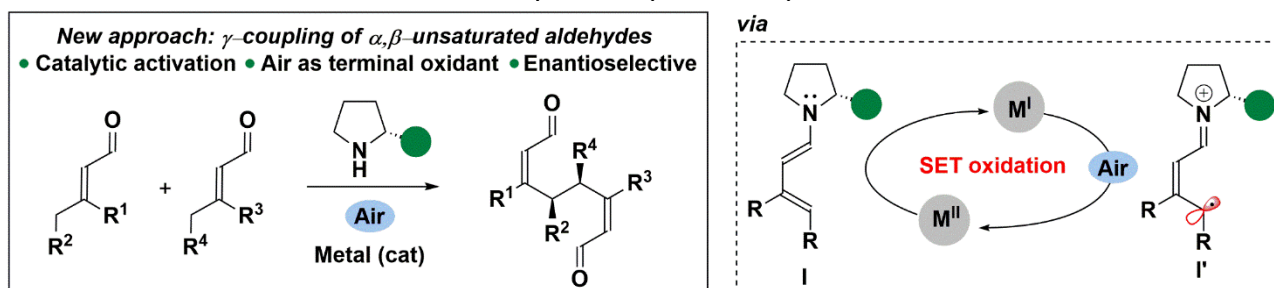


Figure 1

References:

- [1] a) B. List, *Asymmetric Organocatalysis*, Springer: Heidelberg, Germany, **2009**; b) D. W. C. MacMillan, *Nature* **2008**, 455, 304-308; c) B. S. Donslund, T. K. Johansen, P. H. Poulsen, K. S. Halskov, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2015**, 54, 13860-13874.
- [2] D. A. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, 316, 582-585.
- [3] a) T. Amaya, Y. Maegawa, T. Masuda, Y. Osafune, T. Hirao, *J. Am. Chem. Soc.* **2015**, 137, 10072-10075; b) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, 111, 1780-1824.
- [4] L. Næsborg, V. Corti, L. A. Leth, P. H. Poulsen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2018**, 57, 1606-1610.

Synthesis of α -Amido Silyl Enol Ethers via Silylative Ketene 3-Component Reactions: Synthetic Applications in Organic and Natural Products Synthesis

P. Capurro,^a C. Lambruschini,^a L. Moni,^a L. Banfi,^a R. Riva,^b A. Basso^a

^aUniversity of Genoa, Department of Chemistry and Industrial Chemistry, Via Dodecaneso 31, 16146 Genova

^bUniversity of Genoa, Department of Pharmacy, Via Dodecaneso 31, 16146 Genova
pietro.capurro@edu.unige.it

Silyl enol ether chemistry is nowadays well-grounded and established, as they proved to be invaluable intermediates in organic synthesis. However, despite the quantity of synthetic protocols that have been established over the years to achieve these useful molecules, the synthesis of silyl enol ethers from secondary α -ketoamides remained a challenge because of the presence of an acidic hydrogen on the amide group. Exploiting the experience of our group in photoinduced multicomponent reactions¹ and diazoketones reactivity,²⁻³ we designed a simple and straightforward reaction to access this virtually unexplored class of molecules.⁴

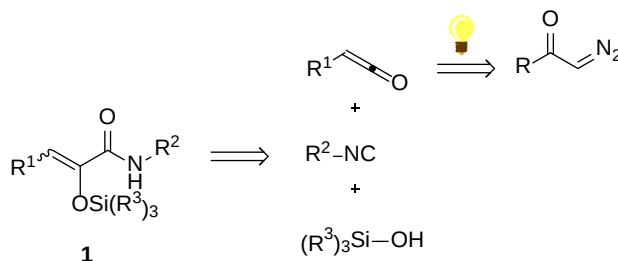


Figure 1: retrosynthetic approach for α -silyloxyarylamides of general structure 1

Silyl enol ethers of general structure **1** were achieved in high yield and in a stereoselective fashion, affording high percentages of Z isomer (generally > 95%) after an adequate screening and tuning of reaction conditions. We reported several synthetic applications for these molecules and paved the way for a straightforward synthesis of natural product analogues (Figure 2).

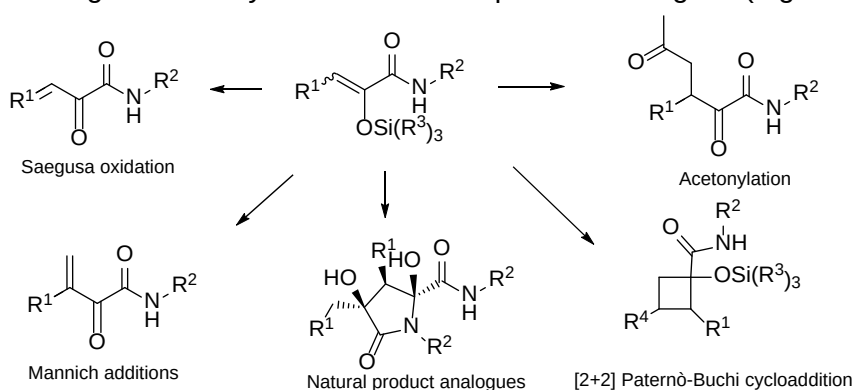


Figure 2: some synthetic applications of α -amido silyl enol ethers

References:

- [1] S. Garbarino, D. Ravelli, S. Protti, A. Basso, *Angew. Chem. Int. Ed.* **2016**, 55, 15476-15484.
- [2] A. Basso, L. Banfi, S. Garbarino, R. Riva, *Angew. Chem. Int. Ed.* **2013**, 52, 2096-2099.
- [3] S. Garbarino, L. Banfi, R. Riva, A. Basso, *J. Org. Chem.* **2014**, 79, 3615-3622.
- [4] F. Ibba, P. Capurro, S. Garbarino, M. Anselmo, L. Moni, A. Basso, *Org. Lett.* **2018**, 20, 1098-1101.

Elenco dei Partecipanti

ABBOTTO ALESSANDRO
Università degli Studi di Milano Bicocca
alessandro.abbotto@unimib.it

ALBANO GIANLUIGI
Università degli Studi di Pisa
gianluigi.albano@dcc.unipi.it

ALGIERI VINCENZO
Università degli Studi della Calabria
vincenzo.algieri@unical.it

ALLEGRINI PIETRO
Indena S.p.A.
pietro.allegri@indena.com

APPENDINO GIOVANNI
Università del Piemonte Orientale
giovanni.appendino@uniupo.it

ARNODO DAVIDE
Università degli Studi di Torino
davide.arnodo@edu.unito.it

AZZI EMANUELE
Università degli Studi di Torino
azzi.emanuele@gmail.com

BALDINO SALVATORE
Università degli Studi di Torino
salvatore.baldino@unito.it

BALLINI ROBERTO
Università degli Studi di Camerino
roberto.ballini@unicam.it

BANDINI MARCO
Università degli Studi di Bologna
marco.bandini@unibo.it

BARATTUCCI ANNA
Università di Messina
abarattucci@unime.it

BARBERO MARGHERITA
Università degli Studi di Torino
margherita.barbero@unito.it

BARRECA GIUSEPPE
CHEMESSENTIA srl
giuseppe.barreca@chemessentia.it

BASSO ANDREA
Università degli Studi di Genova
andrea.basso@unige.it

BECCALLI EGLE
Università degli Studi di Milano
egle.beccalli@unimi.it

BELLOMO CHIARA
Università degli Studi di Torino
chiara.bellomo@edu.unito.it

BENAGLIA MAURIZIO
Università degli Studi di Milano
maurizio.benaglia@unimi.it

BENASSI ALESSANDRA
Università degli Studi di Pavia
alessandra.benassi01@universitadipavia.it

BENZI ALICE
Università degli Studi di Genova
alice.benzi93@gmail.com

BERNARDI ANNA
Università degli Studi di Milano
anna.bernardi@unimi.it

BERTUZZI GIULIO
Università degli Studi di Bologna
giulio.bertuzzi2@unibo.it

BIAGIOTTI GIACOMO
Università degli Studi di Firenze
biagio2588@gmail.com

BIFULCO GIUSEPPE
Università degli Studi di Salerno
bifulco@unisa.it

BILLECI FLORIANA MARIA
Università degli Studi di Palermo
floriana.billeci@unipa.it

BLANGETTI MARCO
Università degli Studi di Torino
marco.blangetti@unito.it

BONCHIO MARCELLA
ITM-CNR, Università degli Studi di Padova
marcella.bonchio@unipd.it

BORBONE NICOLA
Università degli Studi di Napoli "Federico II"
nicola.borbone@unina.it

BORTOLINI OLGA
Università degli Studi di Ferrara
olga.bortolini@unife.it

BRANDI ALBERTO
Università degli Studi di Firenze
alberto.brandi@unifi.it

BRANDOLESE ARIANNA
Università degli Studi di Ferrara
arianna.brandolese@unife.it

BROGGINI GIANLUIGI
Università dell'Insubria
gianluigi.broggini@uninsubria.it

BRUNO INES
Università degli Studi di Salerno
brunoin@unisa.it

BRUNO GIACOMO
Olon Spa
GBruno@olonspa.it

BUCCI RAFFAELLA
Università degli Studi di Milano
raffaella.bucci@unimi.it

BUONSENSO FABIO
Università degli Studi di Roma "La Sapienza"
fabio.buonsenso@uniroma1.it

CAMPOFELICE AMBRA
Università degli Studi di Palermo
ambra.campofelice@unipa.it

CAMPOFELICE
Università degli Studi di Palermo
acampofelice@unipa.it

CAPACCHIONE CLOTILDE
Università degli Studi di Salerno
clcapacchione@unisa.it

CAPALDO LUCA
Università degli Studi di Pavia
luca.capaldo01@universitadipavia.it

CAPRIATI VITO
Università degli Studi di Bari "Aldo Moro"
vito.capriati@uniba.it

CAPRIOGLIO DIEGO
Università del Piemonte Orientale
diego.caprioglio@uniupo.it

CAPURRO PIETRO
Università degli Studi di Genova
pietro.capurro@edu.unige.it

CARCONI LUCA
CHEMESSENTIA srl
luca.carcone@chemessentia.it

CARDANO FRANCESCA
Istituto Italiano di Tecnologia/Università degli Studi di Genova
francesca.cardano@iit.it

CARDONA FRANCESCA
Università degli Studi di Firenze
francesca.cardona@unifi.it

CARDULLO NUNZIO
Università degli Studi di Catania
ncardullo@unict.it

CARLUCCI CLAUDIA
Università degli Studi di Bari "Aldo Moro"
claudia.carlucci@uniba.it

CASAPULLO AGOSTINO
Università degli Studi di Salerno
casapullo@unisa.it

CASERTANO MARCELLO
Università degli Studi di Napoli "Federico II"
marcello.casertano@unina.it

CASNATI ALESSANDRO
Università degli Studi di Parma
alessandro.casnati@unipr.it

CASTAGNOLO DANIELE
King's College London
daniele.castagnolo@kcl.ac.uk

CATALANI MARIA PIA
EVOTEC
maria.catalani@aptuit.com

CAUTERUCCIO SILVIA
Università degli Studi di Milano
silvia.cauteruccio@unimi.it

CECCARELLI JACOPO
Università degli Studi di Firenze
jacopoceccarelli@hotmail.it

CELAJ ODETA
Università degli Studi della Campania "Luigi Vanvitelli"
odetacelaj92@gmail.com

CERVERI ALESSANDRO
Università degli Studi di Bologna
alessandro.cerveri2@unibo.it

CEVASCO GIORGIO
Università degli Studi di Genova
giorgio.cevasco@unige.it

CHINI MARIA GIOVANNA
Università degli Studi di Salerno
mchini@unisa.it

CHIURCHIU ELENA
Università degli Studi di Camerino
elena.chiurchiu@unicam.it

CHRISTODOULOU MICHAEL
Università degli Studi di Milano
michael.christodoulou@unimi.it

CINA' VALERIO
Università degli Studi di Palermo
valerio.cina@unipa.it

CIPOLLA LAURA
Università degli Studi di Milano Bicocca
laura.cipolla@unimib.it

CIRILLO MARTINA
Università degli Studi di Bologna
martina.cirillo3@unibo.it

CITARELLA ANDREA
Università degli Studi di Messina
andrea.cita93@hotmail.it

CLEMENTE FRANCESCA
Università degli Studi di Firenze
francesca.clemente@unifi.it

COLARUSSO ESTER
Università degli Studi di Salerno
ecolarusso@unisa.it

COLELLA MARCO
Università degli Studi di Bari "Aldo Moro"
marco.colella@uniba.it

CONTE VALERIA
Università degli Studi di Roma "Tor Vergata"
valeria.conte@uniroma2.it

COPPOLA CARMEN
Università degli Studi di Siena
carmencoppola19@gmail.com

CORDARO MASSIMILIANO
Università degli Studi di Messina
mcordaro@unime.it

CORRADINI ROBERTO
Università degli Studi di Parma
roberto.corradin@unipr.it

CORTI VASCO
Università degli Studi di Bologna
vasco.corti@hotmail.it

COSTANTINO VALERIA
Università degli Studi di Napoli "Federico II"
valeria.costantino@unina.it

CRAMAROSSA MARIA RITA
Università degli Studi di Modena e Reggio Emilia
mariarita.cramarossa@unimore.it

CRINGOLI MARIA CRISTINA
Università degli Studi di Trieste
cringolimcr@gmail.com

CRISTOFORI VIRGINIA
Università degli Studi di Ferrara
virgicristofori@gmail.com

DAL CORSO ALBERTO
Università degli Studi di Milano
alberto.dalcorso@unimi.it

DALLA CORT ANTONELLA
Università degli Studi di Roma "La Sapienza"
antonella.dallacort@uniroma1.it

D'AMATO ASSUNTA
Università degli Studi di Salerno
asdamato@unisa.it

D'ANNA FRANCESCA
Università degli Studi di Palermo
francesca.danna@unipa.it

DA PIAN MARTA
Università degli Studi di Padova
marta.dapian@unipd.it

D'AURIA MARIA VALERIA
Università degli Studi di Napoli "Federico II"
mariavaleria.dauria@unina.it

DEAGOSTINO ANNAMARIA
Università di Torino
annamaria.deagostino@unito.it

DE ANGELIS MARTINA
Università degli Studi di Roma "La Sapienza"
m.deangelis@uniroma1.it

DE ANGELIS FRANCESCO
Università degli Studi dell'Aquila
francesco.deangelis@univaq.it

DE CASTRO CRISTINA
Università degli Studi di Napoli "Federico II"
decastro@unina.it

DE COMBARIEU ERIC
Indena SpA
eric.decombarieu@indena.com

DE LUCA LIDIA VERA GIOVANNA
Università degli Studi di Sassari
ldeluca@uniss.it

DE MARINO SIMONA
Università degli Studi di Napoli "Federico II"
simona.demarino@unina.it

DE VITA SIMONA
Università degli Studi di Salerno
sdevita@unisa.it

DECAVOLI CRISTINA
Università degli Studi di Milano Bicocca
c.decavoli@campus.unimib.it

DEL PLATO CRISTINA
IIT Istituto Italiano di Tecnologia - Roma
cristina.delplato@uniroma1.it

DELL'AMICO LUCA
Università degli Studi di Padova
luca.dellamico@nemo.unipr.it

DESOKY MOHAMED MAGDY HASSAN
Università degli Studi di Torino
mohmed.desoky@gmail.com

DESSI' ALESSIO
ICCOM – CNR- Firenze e Università degli Studi di Siena
a.dessi@iccom.cnr.it

DI BARI LORENZO
Università degli Studi di Pisa
lorenzo.dibari@unipi.it

DI FABIO GIOVANNI
Università degli Studi di Napoli "Federico II"
difabio@unina.it

DI LECCE ROBERTA
Università degli Studi di Napoli "Federico II"
roberta.dilecce@unina.it

DI STEFANO STEFANO
Università degli Studi di Roma "La Sapienza"
stefano.distefano@uniroma1.it

d'ISCHIA MARCO
Università degli Studi di Napoli "Federico II"
dischia@unina.it

D'ORSI ROSARITA
Università degli Studi della Basilicata
rosarita.dorsi@gmail.com

DORIA FILIPPO
Università degli Studi di Pavia
filippo.doria@unipv.it

DOSSENA ARNALDO
Università degli Studi di Parma
arnaldo.dossena@unipr.it

DUGHERA STEFANO
Università degli Studi di Torino
stefano.dughera@unito.it

ESPOSITO ANNA
Università degli Studi di Napoli "Federico II"
anna.esposito5@unina.it

EVIDENTE ANTONIO
Università degli Studi di Napoli "Federico II"
evidente@unina.it

FALANGA ANDREA PATRIZIA
Università degli Studi di Napoli "Federico II"
and.falanga@gmail.com

FANTINATI ANNA
Università degli Studi di Ferrara
anna.fantinati@unife.it

FARINOLA GIANLUCA MARIA
Università degli Studi di Bari "Aldo Moro"
gianluca maria.farinola@uniba.it

FERLIN FRANCESCO
Università degli Studi di Perugia
ferlin.francesco@gmail.com

FIAMMENGO ROBERTO
IIT Istituto Italiano di Tecnologia - Lecce
roberto.fiammengo@iit.it

FIDECKA KATARZYNA
Università degli Studi di Milano
kasia.fidecka@wp.pl

FILIPPINI GIACOMO
Università degli Studi di Trieste
giacomo.filippini.1989@gmail.com

FINAMORE CLAUDIA
Università degli Studi di Napoli "Federico II"
claudia.finamore@unina.it

FIORANI GIULIA
Università degli Studi di Venezia
giulia.fiorani@unive.it

FIORETTOLAURA
Università degli Studi di Napoli "Federico II"
laura.fioretto@unina.it

FONTANA ANTONELLA
Università degli Studi di Chieti "G. D'Annunzio"
fontana@unich.it

FORGIONE ROSA ESTER
Università degli Studi di Napoli "Federico II"
rosa-lie@live.it

FORMAGGIO FERNANDO
Università degli Studi di Padova
fernando.formaggio@unipd.it

FORTI GIACOMO
Università degli Studi di Pavia
giacomino.forti@gmail.com

FOSCHI FRANCESCA
Università degli Studi dell'Insubria
francesca.foschi@uninsubria.it

FRANCESCONI OSCAR
Università degli Studi di Firenze
oscar.francesconi@unifi.it

FRANCHI DANIELE
KTH | Royal Institute of Technology (Sweden)
danielef@kth.se

FRANCO FRANCESCA
Università degli Studi di Salerno
ffranco@unisa.it

FUNICELLO MARIA
Università degli Studi della Basilicata
maria.funicello@unibas.it

GALEOTTI MARCO
Università degli Studi di Roma "Tor Vergata"
marco.galeotti@uniroma2.it

GALLONI PIERLUCA
Università degli Studi di Roma "Tor Vergata"
galloni@scienze.uniroma2.it

GARLASCHELLI LUIGI
Università di Pavia
luigi.garlaschelli@unipv.it

GASTALDI MATTEO
Università degli Studi di Torino
matteo.gastaldi93@gmail.com

GELAIN ARIANNA
Università degli Studi Milano
arianna.gelain@unimi.it

GELMI MARIA LUISA
Università degli Studi Milano
marialuisa.gelmi@unimi.it

GENTILE DAVIDE
Università degli Studi di Catania
davide.gentile@unict.it

GENTILI DARIO
Università degli Studi di Camerino
dario.f.d.gentili@gmail.com

GHIGO GIOVANNI
Università degli Studi di Torino
giovanni.ghigo@unito.it

GHINATO SIMONE
Università degli Studi di Torino
simone.ghinato@unito.it

GIACALONE FRANCESCO
Università degli Studi di Palermo
francesco.giacalone@unipa.it

GIOFRE' SALVATORE VINCENZO
Università degli Studi di Messina
sgiofre@unime.it

GIOFRE' SABRINA
Università degli Studi di Milano
sabrina.giofre@unimi.it

GIORDANO ASSUNTA
CNR -Napoli
susigi@libero.it

GOTI ANDREA
Università degli Studi di Firenze
andrea.goti@unifi.it

GUALANDI ANDREA
Università degli Studi di Bologna
andrea.gualandi10@unibo.it

GUAZZELLI LORENZO
Università degli Studi di Pisa
lorenzo.guazzelli@unipi.it

HAWALA IVAN
Università degli Studi di Torino
ivan.hawala@gmail.com

LA FERLA BARBARA
Università degli Studi di Milano Bicocca
barbara.laferla@unimib.it

LA MANNA PELLEGRINO
Università degli Studi di Salerno
plamanna@unisa.it

LANZALUNGA OSVALDO
Università degli Studi di Roma "La Sapienza"
osvaldo.lanzalunga@uniroma1.it

LAURITA TERESA
Università degli Studi della Basilicata
teresalaurita89@gmail.com

LAURO GIANLUIGI
Università degli Studi di Salerno
glauro@unisa.it

LEGGIO ANTONELLA
Università degli Studi della Calabria
antonella.leggio@unical.it

LENCI ELENA
Università degli Studi di Firenze
elena.lenci@unifi.it

LEONE LOREDANA
Università del Piemonte Orientale
loredana.leone@uniupo.it

LICANDRO EMANUELA
Università degli Studi di Milano
emanuela.licandro@unimi.it

LICINI GIULIA
Università degli Studi di Padova
giulia.licini@unipd.it

LIGI MARIA CRISTINA
Università degli Studi di Firenze
mariacristina.ligi@unifi.it

LIGUORI ANGELO
Università degli Studi della Calabria
angelo.liguori@unical.it

LOCATELLI ERICA
Università degli Studi di Bologna
erica.locatelli2@unibo.it

LOMBARDO ALESSANDRO
Dipharma Francis
alessandro.lombardo@dipharma.com

LUCARINI MARCO
Università degli Studi di Bologna
marco.lucarini@unibo.it

LUPIDI GABRIELE
Università degli Studi di Camerino
gabriele.lupidi@unicam.it

MAGGINI MICHELE
Università degli Studi di Padova
michele.maggini@unipd.it

MAGLI SOFIA
Università degli Studi di Milano Bicocca
s.magli1@campus.unimib.it

MAIUOLO LOREDANA
Università degli Studi della Calabria
maiuolo@unical.it

MALVALDI MARCO

MANCUSO RAFFAELLA
Università degli Studi della Calabria
raffaella.mancuso@unical.it

MANCUSO AURORA
Università degli Studi di Messina
mancusoaurora@gmail.com

MANGONI ALFONSO
Università degli Studi di Napoli "Federico II"
alfonso.mangoni@unina.it

MARAFON GIULIA
Università degli Studi di Padova
giulia.marafon@gmail.com

MARANZANA ANDREA
Università degli Studi di Torino
andrea.maranzana@unito.it

MARCANTONI ENRICO
Università degli Studi di Camerino
enrico.marcantoni@unicam.it

MARCHESAN SILVIA
Università degli Studi di Trieste
smarchesan@units.it

MARSICANO VINCENZO
Università degli Studi dell'Aquila
vincenzo.marsicano@graduate.univaq.it

MARSICO GIULIA
Università degli Studi della Basilicata
giuliamar86@hotmail.it

MARTIN TEO
Università degli Studi di Roma "Tor Vergata"
teo.martin@uniroma2.it

MARTINA KATIA
Università degli Studi di Torino
katia.martina@unito.it

MARTINELLI JONATHAN
Università del Piemonte Orientale
jonathan.martinelli@uniupo.it

MARULLO SALVATORE
Università degli Studi di Palermo
salvatore.marullo@unipa.it

MARZANO MARIA
Università degli Studi di Napoli "Federico II"
maria.marzano@unina.it

MASI MARCO
Università degli Studi di Napoli "Federico II"
marco.masi@unina.it

MASSARO MARINA
Università degli Studi di Palermo
massaromarina@msn.com

MASSI ALESSANDRO
Università degli Studi di Ferrara
alessandro.massi@unife.it

MASSOLO ELISABETTA
Università degli Studi di Milano
elisabetta.massolo@gmail.com

MATASSINI CAMILLA
Università degli Studi di Firenze
camilla.matassini@unifi.it

MATEOS JAVIER
Università degli Studi di Padova
javier.mateoslopez@phd.unipd.it

MATTOTEIA DAIANA
Università del Piemonte Orientale
daiana.mattoteia@gmail.com

MAYOL LUCIANO
Università degli Studi di Napoli "Federico II"
mayoll@unina.it

MAZZANTI ANDREA
Università degli Studi di Bologna
andrea.mazzanti@unibo.it

MELUCCI MANUELA
ISOF - CNR - Bologna
manuela.melucci@isof.cnr.it

MENDUTI LUIGI
Università degli Studi di Milano
luigi.menduti@studenti.unimi.it

MENICHETTI ANDREA
Università degli Studi di Pisa
a.menichetti90@gmail.com

MENICHETTI STEFANO
Università degli Studi di Firenze
stefano.menichetti@unifi.it

MEZZINA ELISABETTA
Università degli Studi di Bologna
elisabetta.mezzina@unibo.it

MIGLIORINI FRANCESCA
Università degli Studi di Siena
migliorinifrancesca3@gmail.com

MINASSI ALBERTO
Università del Piemonte Orientale
alberto.minassi@uniupo.it

NOVARA FRANCESCA
Wiley
frnovara@wiley.com

MISITI DOMENICO
Università degli Studi di Roma "La Sapienza"
domenico.misiti@uniroma1.it

NOVELLO MARIANGELA
Università degli Studi della Calabria
novello.mariangela@gmail.com

MOLINARO ANTONIO
Università degli Studi di Napoli "Federico II"
molinaro@unina.it

OCCHIATO ERNESTO
Università degli Studi di Firenze
ernesto.occhiato@unifi.it

MONTESARCHIO DANIELA
Università degli Studi di Napoli "Federico II"
montesar@unina.it

OLIVIERO GIORGIA
Università degli Studi di Napoli "Federico II"
golivier@unina.it

MORAN PLATA MARIA JESUS
Università degli Studi di Torino
mjmoranpl@gmail.com

OSTHOFF CLAUDIA S.

MORDINI ALESSANDRO
ICCOM – CNR - Firenze
alessandro.mordini@unifi.it

PACE ANDREA
Università degli Studi di Palermo
andrea.pace@unipa.it

MUSCI PANTALEO
Università degli Studi di Bari "Aldo Moro"
pantaleo.musci@uniba.it

PACE VITTORIO
University of Wien
vittorio.pace@univie.ac.at

MUSUMARRA GIUSEPPE
Università degli Studi di Catania
gmusumarra@unict.it

PAGANO ANGELA
Università degli Studi di Genova
angela_pagano@alice.it

NATIVI CRISTINA
Università degli Studi di Firenze
cristina.nativi@unifi.it

PALMIERI ALESSANDRO
Università degli Studi di Camerino
alessandro.palmieri@unicam.it

NAVAZIO FEDERICA
Università degli Studi di Camerino
federica.navazio@unicam.it

PALUMBO PICCIONELLO ANTONIO
Università degli Studi di Palermo
antonio.palumbopiccionello@unipa.it

NEJROTTI STEFANO
Università degli Studi di Torino
stefano.nejrotti@unito.it

PASTORE GENNY
Università degli Studi di Camerino
genny.pastore@unicam.it

NICOTRA FRANCESCO
Università degli Studi di Milano
francesco.nicotra@unimib.it

PATAMIA VINCENZO
Università degli Studi di Catania
vincenzo.patamia@unict.it

NITTI ANDREA
Università degli Studi di Pavia
andrea.nitti01@universitadipavia.it

PELLACANI LUCIO
Università degli Studi di Roma "La Sapienza"
lucio.pellacani@uniroma1.it

NOTO RENATO
Università degli Studi di Palermo
renato.noto@unipa.it

PELLEGRINO SARA
Università degli Studi di Milano
sara.pellegrino@unimi.it

PELLICCIOLI VALENTINA
Università degli Studi di Milano
valentina.pelliccioli@studenti.unimi.it

PERI FRANCESCO
Università degli Studi di Milano Bicocca
francesco.peri@unimib.it

PETRICCI ELENA
Università degli Studi di Siena
petricci@unisi.it

PETRINI MARINO
Università degli Studi di Camerino
marino.petrini@unicam.it

PEZZELLA ALESSANDRO
Università degli Studi di Napoli "Federico II"
alessandro.pezzella@unina.it

PIBIRI IVANA
Università degli Studi di Palermo
ivana.pibiri@unipa.it

PICCIALI VINCENZO
Università degli Studi di Napoli "Federico II"
vinpicci@unina.it

PICCIALI GENNARO
Università degli Studi di Napoli "Federico II"
piccial@unina.it

PIERINI MARCO
Università degli Studi di Roma "La Sapienza"
marco.pierini@uniroma1.it

PINESCHI MAURO
Università degli Studi di Pisa
pineschi@farm.unipi.it

PINNA ALESSANDRO
Università degli Studi di Genova
alessandro92.pinna@gmail.com

PIPERNO ANNA
Università degli Studi di Messina
apiperno@unime.it

PLATELLA CHIARA
Università degli Studi di Napoli "Federico II"
chiara.platella@unina.it

PODERI CECILIA
Università degli Studi di Bologna
cecilia.poderi2@unibo.it

POLLASTRO FEDERICA
Università degli Studi del Piemonte Orientale
federica.pollastro@uniupo.it

POMELLI CHRISTIAN SILVIO
Università degli Studi di Pisa
christian.pomelli@unipi.it

PORCHEDDU ANDREA
Università degli Studi di Cagliari
porcheddu@unica.it

POTENZA MARIANNA
Università degli Studi di Salerno
mpotenza@unisa.it

PRANDI CRISTINA
Università degli Studi di Torino
cristina.prandi@unito.it

PRATO MAURIZIO
Università degli Studi di Trieste
prato@units.it

PRIMITIVO LUDOVICA
Università degli Studi di Roma "La Sapienza"
ludovica.primitivo@uniroma1.it

QUAGLIOTTO PIERLUIGI
Università degli Studi di Torino
pierluigi.quagliotto@unito.it

RAGAZZON GIULIO
Università degli Studi di Trieste
gragazzon@units.it

RAGLIONE VENANZIO
Università degli Studi di Roma "La Sapienza"
venanzio.raglione@uniroma1.it

RAZZETTI GABRIELE
Dipharma Francis
gabriele.razzetti@dipharma.com

RAVELLI DAVIDE
Università degli Studi di Pavia
davide.ravelli@gmail.com

REGINATO GIANNA
ICCOM - CNR Firenze
gianna.reginato@iccom.cnr.it

RICCIO RAFFAELE
Università degli Studi di Salerno
raffaele.riccio@soc.chim.it

RIELA SERENA
Università degli Studi di Palermo
serena.riela@unipa.it

RINALDI ANTONIA
Università degli Studi di Firenze
antonia.rinaldi@unifi.it

RISI CATERINA
Università degli Studi di Siena
risi@student.unisi.it

RIZZO SIMONA
ISTM-CNR Milano
simona.rizzo@istm.cnr.it

RIZZO CARLA
Università degli Studi di Palermo
carla.rizzo03@unipa.it

RODRIGUEZ DEL RIO CARLOS
Elsevier
c.rodriguezdelrio@elsevier.com

ROLETTO JACOPO
PROCOS S.P.A.
roletto@procos.it

ROMEO ROBERTO
Università degli Studi di Messina
robromeo@unime.it

ROSSI SERGIO
Università degli Studi di Milano
sergio.rossi@unimi.it

ROVIELLO GIOVANNI NICOLA
Università degli Studi di Napoli "Federico II"
giroviell@unina.it

RUSSO LAURA
Università degli Studi di Milano Bicocca
laura.russo@unimib.it

RUSSO PATRIZIO
Università degli Studi della Calabria
russopatrizio@outlook.it

SABUZI FEDERICA
Università degli Studi di Roma "Tor Vergata"
federica.sabuzi@uniroma2.it

SACCO MIRKO
Università degli Studi di Torino
mirko.sacco@unito.it

SALAMONE MICHELA
Università degli Studi di Roma "Tor Vergata"
michela.salamone@uniroma2.it

SAMBRI LETIZIA
Università degli Studi di Bologna
letizia.sambri@unibo.it

SANNICOLO' FRANCESCO
LABORATORI ALCHEMIA SRL
francesco.sannicolo@unimi.it

SARTORI ANDREA
Università degli Studi di Parma
andrea.sartori@unipr.it

SCALA ANGELA
Università degli Studi di Messina
ascale@unime.it

SCHETTINI ROSARIA
Università degli Studi di Salerno
rschettini@unisa.it

SCRIMIN PAOLO
Università degli Studi di Padova
paolo.scrimin@unipd.it

SIANI GABRIELLA
Università degli Studi di Chieti "G. D'Annunzio"
siani@unich.it

SILIPO ALBA
Università degli Studi di Napoli "Federico II"
silipo@unina.it

STEFANIA RACHELE
Università degli Studi di Torino
rachele.stefania@unito.it

TADDEI MAURIZIO
Università degli Studi di Siena
maurizio.taddei@unisi.it

TALLARICO SOFIA
Università degli Studi della Magna Graecia
sofia.tallarico@outlook.it

TANINI DAMIANO
Università degli Studi di Firenze
damiano.tanini@unifi.it

TEDESCHI TULLIA
Università degli Studi di Parma
tullia.tedeschi@unipr.it

TERRACCIANO STEFANIA
Università degli Studi di Salerno
sterracciano@unisa.it

VIGLIANISI CATERINA
Università degli Studi di Firenze
caterina.viglianisi@unifi.it

TETA ROBERTA
Università degli Studi di Napoli "Federico II"
roberta.teta@unina.it

VILLANI CLAUDIO
Università degli Studi di Roma "La Sapienza"
claudio.villani@uniroma1.it

TIECCO MATTEO
Università degli Studi di Perugia
matteotiecco@gmail.com

VISCARDI GUIDO
Università degli Studi di Torino
guido.viscardi@unito.it

TONIOLO GIANLUCA
Università degli Studi di Firenze
gianluca.toniolo@unifi.it

VOLPE CHIARA
Università degli Studi di Salerno
cvolpe@unisa.it

TRAPANI FEDERICA
Università degli Studi di Palermo
fed.trapani@gmail.com

WELTON THOMAS
Imperial College of London
t.welton@imperial.ac.uk

TRAPELLA CLAUDIO
Università degli Studi di Ferrara
trap@unife.it

YILDIRIM ONUR
Università degli Studi di Torino
onur.yildirim@unito.it

TROMBINI CLAUDIO
Università degli Studi di Bologna
claudio.trombini@unibo.it

ZAMPELLA ANGELA
Università degli Studi di Napoli "Federico II"
angela.zampella@unina.it

TURRIN GIULIA
Università degli Studi di Ferrara
giulia.turrin@student.unife.it

ZAPPIMBULSO NICOLA
Università degli Studi di Bari "Aldo Moro"
nicola.zappi@hotmail.com

VAGNONI MARTINA
Università degli Studi di Bologna
martina.vagnoni3@unibo.it

ZARRELLI ARMANDO
Università degli Studi di Napoli "Federico II"
zarrelli@unina.it

VALENTINI FRANCESCA
Università degli Studi di Roma "Tor Vergata"
valentini.francesca6@gmail.com

ZATOUT ROUKIA
Università degli Studi di Napoli "Federico II"
zatout.roukia@unina.it

VALGIMIGLI LUCA
Università degli Studi di Bologna
luca.valgimigli@unibo.it

ZICCARELLI IDA
Università degli Studi della Calabria
idaziccarelli@gmail.com

VEGA PENALOZA ALBERTO
Università degli Studi di Padova
alberto.vegapenaloza@unipd.it

ZINNA FRANCESCO
Università degli Studi di Pisa
francesco.zinna@unipi.it

VELTRI LUCIA
Università degli Studi della Calabria
lucia.veltri@unical.it

ZONGO LUC
Università degli Studi di Roma "Tor Vergata"
luc.zongo@uniroma2.it

Sponsor Istituzionali



UNIVERSITÀ
DEGLI STUDI
DI TORINO



CAMERA DI COMMERCIO
INDUSTRIA ARTIGIANATO E AGRICOLTURA
DI TORINO



UNIVERSITÀ DEL PIEMONTE ORIENTALE



Sponsor Gold



Sponsor Silver



Sponsor Bronze



Sostenitori

