Argomenti di Tesi e Tirocinio

Topics for Master and Bachelor Thesis

Dipartimento di Chimica
Università degli Studi di Milano

A.A. 2014/2015
Secondo Semestre

Preface

This volume collects up-to-date information on the research activity of the groups working at the Dipartimento di Chimica of the Università degli Studi di Milano (and at closely related Departments). It is meant to help those students who are about graduating, and are seeking an exciting topic to confront with during the final stage of their education. The collection is on a voluntary basis and, thus, by no means exhaustive of the opportunities that students may find in the Department. With the same token, only a short summary of the activities is provided, but the accompanying authors' contact information may help to obtain further details.

Contributions are grouped into areas of interest (Sections), according to the old italian Scientific Sectors ("Settori Scientifico-Disciplinari") of the contributing authors, to let the readers easily find the information they are looking for. Most often, though, such grouping is only indicative, since research activities may cross the boundaries of the traditional chemical disciplines or of chemistry itself. This explains why the reader will also find contributions from different Departments.

Within each Section, contributions are sorted in alphabetical order, according to the first corresponding author, if present, or to the first author otherwise. A list of all contributing authors is provided at the end of the volume.

Enjoy it!

Milano, Aprile 2015

Prof. Rocco Martinazzo
(Organizer)

Prof. Laura Raimondi
(Head of Collegio Didattico)

Prof. Francesco Demartin
(Head of Dipartimento di Chimica)

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Chimica Analitica

Instrumental chemical analysis for cultural heritage

S. Bruni and V. Guglielmi

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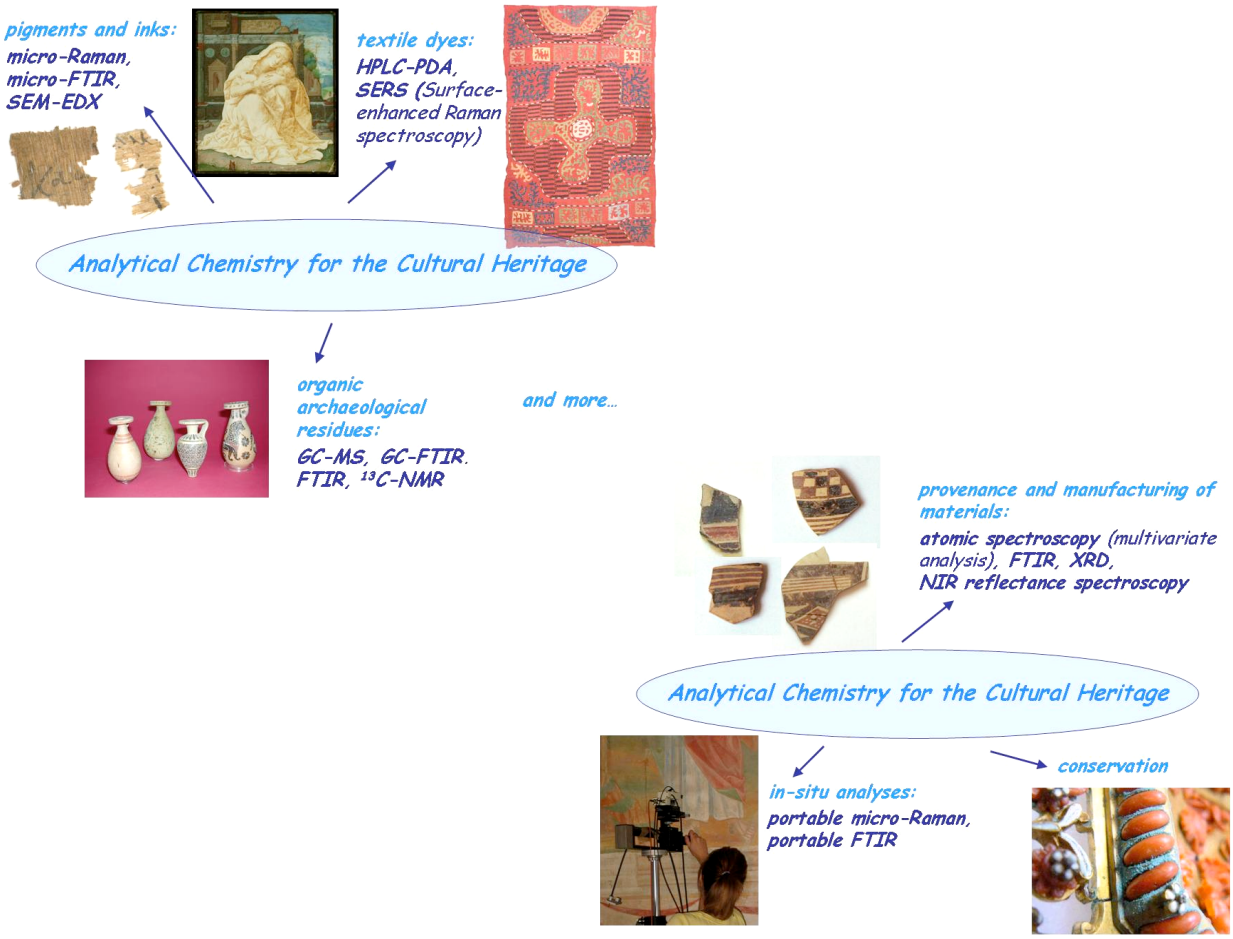
Our research activity is devoted to the application of spectroscopic (FTIR, Raman, UV-Vis-NIR, AAS, XRD, SEM-EDX) and chromatographic (GC, HPLC, GC-FTIR) techniques for *in-situ* and laboratory analysis of artistic and archaeological materials.
Our main goals are: (1) the solving of specific analytical problems by consolidated procedures; and (2) the development of new methods for frontier applications.
We offer the opportunity to get acquainted with a wide range of instrumental analytical methods, nowadays used besides in the field of cultural heritage also in forensic science, food analysis, characterization of modern industrial materials (ceramics, glasses, plastics, etc.) and others.
Our graduates are currently employed in many different industrial contexts, from pharmaceuticals and cosmetics to analysis laboratories and analytical instrumentation manufacturing. Some of them still work in the field of chemical analysis applied to works of art.
Subjects for traineeships and theses in our laboratory include:

- *pigments* and *binders* in ancient and contemporary painting
- *organic natural dyes* in historical textiles
- *archaeological pottery* (provenance and manufacturing technology)
- *organic archaeological materials* (perfumed resins, adhesives, food remains…)
- *environmental deterioration products* of stone and metal artefacts



Info at:
"Laboratorio di chimica analitica per i beni culturali" – Dipartimento di Chimica, corpo A, 1° piano

Electrochemistry for Modified Electrodes, Modified Electrodes for Electroanalysis

Luigi Falciola and Valentina Pifferi

ElectroANalytical Chemistry Group (ELAN)
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The ELectroANalytical Chemistry Group (ELAN) is devoted to the development, the characterization and application of chemical analytical methods, particularly based on electrochemical phenomena, and to the comprehension of the kinetics and mechanism of electrode processes, with special attention to the important roles of the electrode material and the solvent media.

The main scope of the Group is the **development of new electroanalytical methodologies** (particularly those based on voltammetric pulsed and stripping techniques) **and new electrode materials** (modified electrode and composites, ink-jet printed and screen-printed electrodes) to be used in laboratory or *on-site*, for different applications in the fields of sensors, the environmental analysis and of the quality control of different products (water, foodstuff, drugs, ...).

In this context, the group is continually producing **new electroanalytical sensors** based on **electrodes modified with nanostructured materials** (carbon nanotubes, graphene, metal or oxide nanoparticles) **and/or conducting or non-conducting polymers**, in order to improve their performances (limits of detection and quantification, sensibility, accuracy, selectivity and specificity) or to detect completely new analytes, such as compounds and pollutants of emerging concern. In particular, in the environmental field, the Group is focusing its attention on the study of different processes of wastewaters remediation from selected organic (furan, benzidine, toluidine, tolidine, ...) and inorganic (arsenic, chrome, ...) compounds also at trace levels.

Due to the strong interdisciplinary nature of the research topics and of the know-how acquired in the field of the analytical and physico-chemical characterization of materials, the Group collaborates with other Research Groups inside and outside the Chemistry Department of the Università degli Studi di Milano and with different industrial companies in order to solve different analytical problems, particularly using electrochemical techniques.

In this research fields, the ELAN Group offers the possibility of experimental Bachelor and Master Thesis on the following main Topics:

- characterization and use of new electrodic materials (nanotubes, graphene, nanoparticles, polymers,…) for modified electrode for the trace analysis of contaminants of emerging concern;
- innovative materials for enhancing the performances (sensibility, durability, self-cleaning) of modified electrodes;
- development of electroanalytical methodologies for the detection of organic and inorganic water pollutants;
- development of electroanalytical methodologies for the detection of contaminants in food and beverages;
- … YOUR IDEA COULD BE a NEW TOPIC!

Please, verify the availability of the topic of your interest directly with prof. Falciola.
For more information, visit the web page of the Group and/or come to visit us…

…you are welcome!

Our very recent papers:

[1] G. Soliveri, **V. Pifferi**, G. Panzarasa, S. Ardizzone, G. Cappelletti, D. Meroni, K. Sparnacci and **L. Falciola**, "Self-cleaning properties in engineered sensors for dopamine electroanalytical detection", Analyst, 140, 1486 – 1494 (2015).

[2] A. Mardegan, **V. Pifferi**, E. Pontoglio, **L. Falciola**, P. Scopece and L. M. Moretto, "Sprayed carbon nanotubes on Pyrolysed Photoresist Carbon Electrodes: Application to o-toluidine determination", *Electrochem. Comm.* 48, 13-16 (2014).

[3] **V. Pifferi**, G. Cappelletti, C. Di Bari, D. Meroni, F. Spadavecchia and **L. Falciola**, "Multi-Walled Carbon Nanotubes (MWCNTs) modified electrodes: Effect of purification and functionalization on the electroanalytical performances", Electrochimica Acta 146, 403-410 (2014).

Elettrochimica ed elettroanalisi di molecole e materiali molecolari per l'energetica, l'optoelettronica e la sensoristica, Elettrodi chirali ed elettroanalisi chirale applicata al campo farmaceutico, Liquidi ionici chirali ed elettroliti di supporto chirali, Elettroanalisi su elettrodi catalitici applicata al campo ambientale, Elettroanalisi per il controllo qualità degli alimenti

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A) ELETTRODI CHIRALI per la discriminazione e la valutazione dell'eccesso enantiomerico degli antipodi di molecole d'interesse farmaceutico e biologico. Abbiamo da poco presentato (*Angew. Chem.* 2014, *Chemistry* 2014, *Chemical Science* 2015) una rivoluzionaria famiglia di materiali molecolari chirali che permettono di ottenere per elettrodeposizione elettrodi perfettamente speculari, in grado per la prima volta di separare nettamente i segnali di antipodi di molecole chirali, permettendo di discriminarli e anche di stimare l'eccesso enantiomerico. La ricerca proposta consiste sia nella preparazione degli elettrodi enantiopuri per elettrooligomerizzazione o altre tecniche di deposizione disponibili nel nuovo laboratorio dipartimentale di caratterizzazione avanzata SmartMatLab) sia nella messa a punto di protocolli per la loro applicazione alla discriminazione degli enantiomeri di molecole d'interesse farmaceutico e biologico. (Coll. con F. Sannicolò, con diversi colleghi UNIMI e con Università dell'Insubria)

B) Elettroanalisi per la CARATTERIZZAZIONE DI MATERIALI AVANZATI per l'optoelettronica, il fotovoltaico e la sensoristica. Le tecniche elettroanalitiche, in particolare voltammetria, spettroscopia d'impedenza elettrochimica, microbilancia elettrochimica al quarzo, spettroelettrochimica, fotoelettrochimica... sono oggi fondamentali per la caratterizzazione e lo sviluppo di materiali molecolari avanzati per l'optoelettronica, il fotovoltaico, la sensoristica, etc, sia come singola molecola, sia come device da essa ricavato. Proponiamo in questo campo progetti in collaborazione con gruppi di ricerca di chimica organica e inorganica del nostro Dipartimento e di ISTM-CNR, su complessi luminescenti per OLED, complessi e molecole push-pull da usarsi come sensibilizzatori per celle solari organiche e semiconduttori e polimeri conduttori per il fotovoltaico e la sensoristica. Questi progetti potranno anche comprendere una interessante parte di implementazione dei materiali caratterizzati in forma di dispositivo, grazie alla disponibilità del nuovo laboratorio dipartimentale di caratterizzazione avanzata SmartMatLab.

C) Elettroanalisi per la caratterizzazione e lo sviluppo di LIQUIDI IONICI CHIRALI; Elettrochimica ed elettroanalisi in LIQUIDI IONICI I liquidi ionici sono sali organici liquidi a temperatura ambiente, che sono allo stesso tempo buoni solventi e buoni trasportatori di carica. Questo, unitamente alla bassa volatilità, li rende mezzi di reazione innovativi molto attraenti, per i processi chimici in generale, e in particolare per i processi elettrochimici dove essi fanno sia da solvente sia da elettrolita di trasporto, e hanno prestazioni eccellenti per es. nei processi di elettrodeposizione di materiali organici e inorganici. La chiralità li può rendere anche "intelligenti", in quanto capaci di distinguere molecole esistenti come immagini speculari, promuovendo processi enantioselettivi. Proponiamo lo studio elettroanalitico di innovativi liquidi ionici ed elettroliti di supporto "inerentemente chirali", nonché studi di importanti questioni relative all'impiego dei liquidi ionici (elettrodi di riferimento, conduttività, purificazione...) (Progetto finanziato da Fondazione Cariplo, in collaborazione con F.Sannicolò e con ISTM-CNR)

D) Elettroanalisi su elettrodi elettrocatalitici per la rilevazione e il monitoraggio di ALOGENURI ORGANICI (come ritardanti di fiamma *priority organic pollutants* nelle acque lombarde) Molti tra i *priority organic pollutants* presenti nelle acque lombarde, di cui occorre sviluppare protocolli di monitoraggio e abbattimento, sono alogenuri organici. Da anni studiamo le straordinarie proprietà catalitiche di elettrodi di metalli nobili quali Ag e Au per la elettroriduzione selettiva e in condizioni blande del legame carbonio alogeno. Proponiamo progetti di applicazione di tali elettrodi per la rilevazione e lo studio di nuove famiglie di alogenuri in nuove matrici, anche d'interesse ambientale, come ritardanti di fiamma *priority organic pollutants* nelle acque lombarde. (Coll. con Università di Padova)

E) Elettroanalisi per il CONTROLLO DI QUALITA' DEGLI ALIMENTI (Acqua, Latte, Pesce...). Le tecniche elettroanalitiche (conduttimetria, potenziometria, amperometria, voltammetria...) sono fondamentali per il controllo qualità e di processo in campo alimentare, offrendo la possibilità di monitorare un'ampia gamma di fondamentali parametri chimico fisici. In quest'ambito proponiamo progetti di sviluppo e applicazione di protocolli elettroanalitici per il controllo di qualità degli alimenti, insieme con il Dipartimento di Scienze Veterinarie per la Salute, la Produzione Animale e la Sicurezza Alimentare.

Phytochemical characterization of hops grown in Northern Italy

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Even if in Italy hop (*Humulus lupulus* L.) does not represent a traditional cultivation, it has been recently introduced as a small-scale production of excellence, though it uses essentially imported cultivars.
In our research, we evaluate the phytochemical profiles of different cultivated or spontaneous cultivars, grown in Northern Italy. The evaluation involves both phytochemical components of interest for brewing, such as bitter acid composition, and volatile organic fractions and polyphenols, which are of potential interest in the field of traditional medicine. It should thus be possible to highlight the original features of each cultivar, changes in qualitative and/or quantitative characterizing componentsfrom their comparison and, eventually, dependence on climatic factors and cultivation.

Female inflorescences of *H. lupulus*

Chimica Fisica

Chimica Teorica Quantistica e Semiclassica

M. Ceotto[1]

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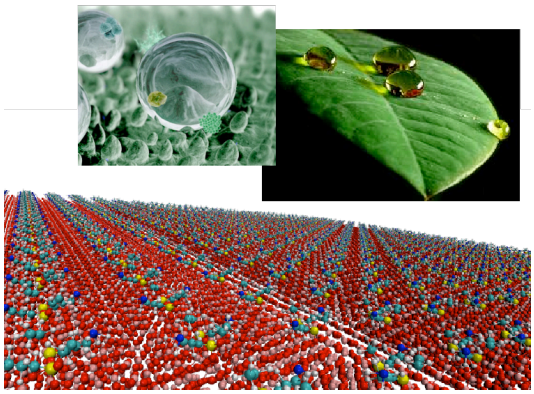
Nel mio gruppo di ricerca si affrontano le seguenti tematiche:

- Sviluppo di metodi quantistici teorici per lo studio delle reazioni chimiche in collaborazione con Prof. J. Schrier di Haveford College, Pennsylvania, USA (vedi articoli 1,2,3);
- Sviluppo di codici di dinamica molecolare semiclassica su schede grafiche (GPU) in collaborazione con Prof. D Tamascelli del Dipartimento di Fisica (vedi ad esempio articolo 4);
- Dinamica Molecolare accelerata da principi primi in collaborazione con Prof. W.L.Hase, Texas Tech University (USA) (vedi articoli 5,6);
- Dinamica Molecolare quantistica semiclassica in collaborazione con Prof. A. Aspuru-Guzik, Harvard University (USA) e Prof. F. Grossmann, Dresden Tech. Univ. (GER) (vedi ad esempio articolo 7);
- Simulazioni di nanostrutturati a base di TiO2 per la fotocatalisi in collaborazione con Prof.s S. Ardizzone, G. Cappelletti e L. Falciola (vedi articoli 8, 9)
- Calcoli quantistici da principi primi di semiconduttori dopati di seconda generazione (in collaborazione con Prof. L. Lo Presti (vedi ad esempio articolo 10).

Sono sempre a disposizione per ogni chiarimento su queste tematiche.



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[2] S. Mandrà, S. Valleau, **M. Ceotto***, "Deep Nuclear Resonant Tunneling Thermal Rate Constant Calculations", *Int. J. of Quantum Chemistry*, **113** (12), 1722-1734 (2013);
[3] **M. Ceotto***, "Vibration-assisted tunneling: a semiclassical instanton approach", *Mol. Phy.* **110** (9-19), Special Issue 547-559 (2011)
[4] D. Tamascelli, F.S. Dambrosio, R. Conte, **M. Ceotto***, "Graphics Processing Units Accelerated Semiclassical Initial Value Representation Molecular Dynamics", *J. Chem Phys.*, **140**, 174109 (2014);
[5] **M. Ceotto***, Y. Zhuang, W.L. Hase, "Accelerated direct semiclassical molecular dynamics using a compact finite difference Hessian scheme", *J. Chem. Phys.* **138**, 054116 (2013);
[6] Y. Zhuang*, M. R. Siebert, W.L. Hase, K.G. Kay, **M. Ceotto***, "Evaluating the Accuracy of Hessian Approximations for Direct Dynamics Simulations" *J. Chem. Theory and Computation*, **9** (1), 54-64 (2013);
[7] R. Conte, A. Aspuru-Guzik, **M. Ceotto***, "Reproducing Deep Tunneling Splittings, Resonances, and Quantum Frequencies in Vibrational Spectra From a Handful of Direct Ab Initio Semiclassical Trajectories", *J. Phys. Chem. Lett.*, **4**, 3407−3412 (2013);
[8] F. Spadavecchia*, G. Cappelletti, S. Ardizzone, **M. Ceotto**, M. S. Azzola, L. Lo Presti, G. Cerrato, L. Falciola, "Role of Pr on the Semiconductor Properties of Nanotitania. An Experimental and First-Principles Investigation", *J. Phys. Chem C* **116** (43), 23083-23093 (2012)
[9] **M. Ceotto***, L. Lo Presti*, G. Cappelletti, D. Meroni, F. Spadavecchia, R. Zecca, M. Leoni, P. Scardi, S. Ardizzone, "About the Nitrogen Location in Nanocrystalline N-Doped TiO2: Combined DFT and EXAFS Approach" *J. Chem. Phys. C* **116** (2), 1764-1771, (2012)
[10] L. Lo Presti*, **M. Ceotto**, F. Spadavecchia, G. Cappelletti, D. Meroni, R.A. Acres, S. Ardizzone, "Role of the Nitrogen Source in Determining Structure and Morphology of N-Doped Nanocrystalline TiO2", *J. Phys. Chem C*, **118**, 4797-4807 (2014);

Simulazione Quantistica di Nanomateriali Avanzati

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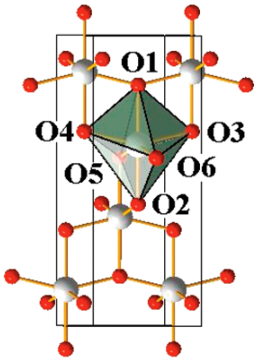
http://users.unimi.it/ceotto/index.html

Nei nostri gruppi di ricerca si offrono attività di tirocinio triennale e tesi magistrale inerenti alla simulazione quantistica e ab initio di sistemi modello per la comprensione e la progettazione di nanomateriali avanzati con applicazioni ambientali e industriali[1-6]. Le attività di ricerca sono svolte in collaborazione con gruppi sperimentali (prof. Ardizzone, prof. Falciola, Dr. Cappelletti) e possono comprendere esperimenti svolti presso facilities di luce di sincrotrone (Grenoble, FR e Trieste, IT).



[1] F. Spadavecchia*, **M. Ceotto**, **L. Lo Presti**, C. Aieta, I. Biraghi, D. Meroni, S. Ardizzone, G. Cappelletti, "Second Generation Nitrogen Doped Titania Nanoparticles: A Comprehensive Electronic and Microstructural Picture", Chi. J. of Chemistry, 32 (12), 1195-1293 (2014)
[2] C. Marchiori, G. Di Liberto, G. Soliveri, L. Loconte, L. **Lo Presti***, D. Meroni*, **M. Ceotto**, C. Oliva, S. Cappelli, G. Cappelletti, C. Aieta, S. Ardizzone, "Unraveling the Cooperative Mechanism of Visible-light Absorption in Bulk N, Nb Codoped TiO2 Powders of Nanomaterials", J. Phys. Chem C, 118, 24152-24164 (2014)
[3] **L. Lo Presti***, **M. Ceotto**, F. Spadavecchia, G. Cappelletti, D. Meroni, R.A. Acres, and S. Ardizzone, "Role of the Nitrogen Source in Determining Structure and Morphology of N-Doped Nanocrystalline TiO2", J. Phys. Chem C, 118, 4797-4807 (2014)
[4] F. Spadavecchia*, S. Ardizzone, G. Cappelletti, L. Falciola, **M. Ceotto**, and D. Lotti, "Investigation and optimization of photocurrent transient measurements on nano-TiO2", J. of Applied Electrochem. 43 (2), 217-225 (2013)
[5] F. Spadavecchia*, G. Cappelletti, S. Ardizzone, **M. Ceotto**, M. S. Azzola, **L. Lo Presti**, G. Cerrato, L. Falciola, "Role of Pr on the Semiconductor Properties of Nanotitania. An Experimental and First-Principles Investigation", J. Phys. Chem C 116 (43), 23083-23093 (2012)
[6] **M. Ceotto***, **L. Lo Presti***, G. Cappelletti, D. Meroni, F. Spadavecchia, R. Zecca, M. Leoni, P. Scardi, S. Ardizzone, "About the Nitrogen Location in Nanocrystalline N-Doped TiO2: Combined DFT and EXAFS Approach" J. Chem. Phys. C 116 (2), 1764-1771, (2012)

Teoria e simulazioni ab-initio delle proprietà di nuovi materiali

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Keywords: Ab-initio, DFT, dinamica molecolare, OLEDs, cemento, supercomputing, Quantum-Espresso

CV sintetico – Laurea in Scienza dei Materiali (MI-Bicocca 1999), Dottorato in Fisica della Materia Condensata (SISSA-Trieste 2002), esperienza pluriennale di ricerca (SISSA-Trieste, Rutgers University, MIT, Oxford University), dal 2010 ricercatore t.i. CNR-ISTM.

Attività di ricerca – Degradazione indotta da polaroni ed eccitoni in materiali OLED (progetto finanziato da Samsung), spettroscopie magnetiche (NMR, EPR, Mössbauer) computazionali, relazione fra composizione e proprietà meccaniche del cemento, transizioni di fase e nuovi materiali ad alte pressioni, isolanti topologici, crystal structure prediction (CSP), sviluppo di codici (http://www.quantum-espresso.org)

Collaborazioni – SAMSUNG Korea, M. Scavini, R. Martinazzo, L. Lo Presti (Unimi), M. Pavanello (Rutgers), M. Kiffner (Oxford-Singapore), E. Tosatti (SISSA), D. Scherlis (Buenos Aires), C. Gray (Cambridge), S. Leoni (Cardiff), N. Varini (EPFL-CSCS), F. Spiga (Cambridge), M. Bremholm (CMC-Aarhus)

Tesi supervisionate – Studio computazionale delle proprietà di trasporto elettronico in GeTe (L. Oggioni, 2013)

Sono disponibile a supervisionare tesi triennali e magistrali, sui seguenti argomenti. Sono inoltre disponibile a supervisionare tesi miste sperimentali/computazionali in collaborazione con i colleghi CNR-ISTM e del dipartimento di Chimica di Unimi.

- **Modeling e simulazioni per l'industria**
  - Degradazione indotta da polaroni ed eccitoni in materiali OLED (finanziato da Samsung)
  - Modeling della struttura e proprietà meccaniche del cemento
  - Calcolo del trasporto elettronico in Phase Change Materials (es. Ge2Sb2Te5) (in collab. con Micron-Agrate)
- **Relazioni struttura-proprietà** (in collaborazione con M. Scavini)
  - Dinamica molecolare e struttura di nanoparticelle di Fe2O3
  - Proprietà strutturali ed elettroniche di vetri Pb-GeO2
  - Struttura di nanoparticelle core-shell Au-Fe3O4
  - Analisi delle proprietà strutturali di leghe *BaZnGa*
- **Alte pressioni e polimorfismo**
  - Transizioni di fase e stabilità di LnN (Ln=lantanidi) ad alta pressione (in collab. con CMC)
  - Calcolo dell'invariante topologica Z2 in LnB (Ln=lantanidi) sotto pressione (in collab. con CMC)
  - Nuove materiali ad alta pressione: BiS2 e BiSe2 (in collab. con CMC)
  - Polimorfismo e transizioni elettroniche di BaBiO3 ad alta pressione (in collab. con E. Tosatti)
  - Esplorazione del polimorfismo del cioccolato
- **Sviluppo di metodi e codici**
  - Implementazione dei potenziali core-shell in LAMMPS
  - Implementazione della dinamica di momenti magnetici in LAMMPS, dinamica molecolare del ferro e acciaio nello stato paramagnetico
  - Porting e ottimizzazione dei codici QE-GIPAW e CE-TDDFT su GPU (in collaborazione con F. Spiga e N. Varini)
  - Implementazione di force-fields classici in Quantum-Espresso
  - Implementazione dei metodi Solid-State-NEB e Solid-State-Dimer per calcolare barriere di reazione in Quantum-Espresso
  -

Studi di nuovi materiali molecolari con metodi quanto-meccanici e sperimentali basati sulla diffrazione di raggi X

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Studio quanto-meccanico di materiali avanzati per l'optoelettronica, il fotovoltaico e la sensoristica

Accurati metodi quanto-meccanici vengono applicati alla progettazione e caratterizzazione, in collaborazione con gruppi sperimentali, di nuovi cromofori organici e metallorganici altamente
luminescenti per OLED, sistemi push-pull con incrementate proprietà ottiche non lineari, light-responsive materials. L'attività teorica consiste nella predizione delle proprietà geometriche, elettroniche ed ottiche dei sistemi investigati e di loro possibili aggregati, e nella razionalizzazione delle misure sperimentali (spettri di assorbimento ed emissione, misure di iperpolarizzabilità, determinazioni per via elettrochimica di HOMO-LUMO energy gap)

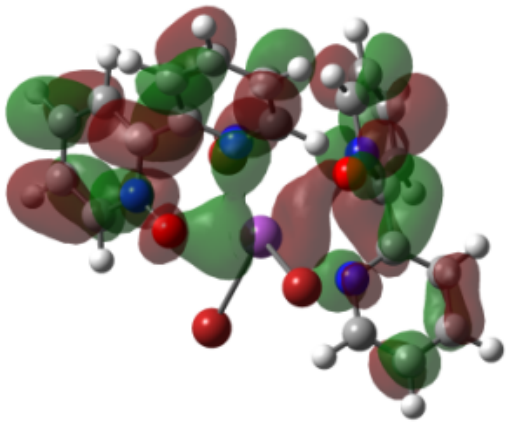


Figura 1 Plots of M062X/def2-SVP HOMO (left) and LUMO (right) of the optimized geometry of [BiB_3(*bp2mo*)]

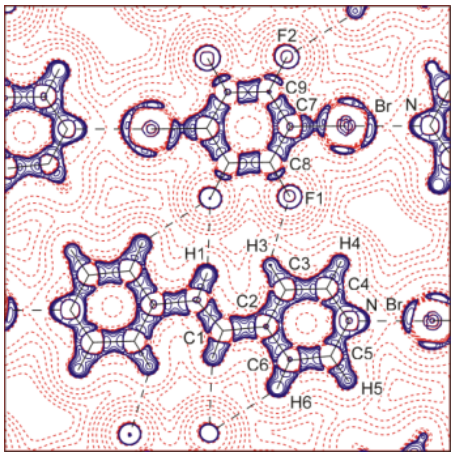
In collaborazione con: E. Cariati, M. Pizzotti (Unimi), C. Botta (CNR-ISMAC), P. Metrangolo (Polimi), D. Pasini (UniPV), N. Mercier (Université d'Angers, France), A. Priimagi (Tampere University of Technology, Finland

Determinazione della densità elettronica di sistemi molecolari tramite diffrazione di raggi X

I dati raccolti con un esperimento di raggi X a bassa temperatura consentono di determinare con grande accuratezza la densità elettronica $\rho(r)$ del sistema in esame e quindi tutte le sue proprietà monoelettroniche. L'analisi della topologia di $\rho(r)$ conduce direttamente alla definizione e caratterizzazione di concetti chimici quali atomi, molecole, strutture, legami, interazioni di non legame. Nel presente laboratorio sono stati condotti, in particolare, numerosi studi su sistemi assemblati tramite halogen bond (C–I···N, C–I···O, C–Br···N) e sono attualmente in corso studi su un sistema halogen-bonded perfluorurato che consente anche l'investigazione di interazioni deboli quali C–H···F e C–F···F–C. La ricerca prevede sia una parte prettamente sperimentale relativa alla conduzione dell'esperimento di raggi X (scelta e manipolazione dei cristalli, raccolta ed elaborazione dei dati), sia una parte di elaborazione teorica che include il raffinamento dati e l'analisi topologica. Lo studio è integrato inoltre da calcoli ab initio sugli stessi sistemi studiati sperimentalmente.

In collaborazione con: M. Sironi (Unimi), G. Resnati (Polimi)

Studio quanto-meccanico di interazioni di non legame



Si utilizzano tecniche altamente sofisticate (CCSD(T), MPx, DFT con appropriati funzionali) per la determinazione accurata delle proprietà geometriche ed energetiche di interazioni di non legame quali il legame ad alogeno, in particolare l'interazione C–X···π ed il legame ad alogeno debole (X=F, Cl) in idrocarburi polialogenati con implicazioni in chimica verde (clorofluorocarburi, idroclorofluorocarburi e idrofluorocarburi). I sistemi studiati vengono inoltre sottoposti all'analisi topologica della densità elettronica allo scopo di investigare la natura dell'interazione e all'analisi di decomposizione dell'energia allo scopo di determinare i contributi più significativi all'interazione (elettrostatico, dispersivo, …).

In collaborazione con: M. Sironi (Unimi), G. Resnati (Politecnico di Milano)

Processi reattivi catalitici: sviluppo di catalizzatori, studio delle loro caratteristiche chimico-fisiche e della loro attività in reazioni target di sfruttamento di biomassa

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I catalizzatori inorganici eterogenei sono solidi sulle cui superfici avvengono trasformazioni chimiche con formazione di nuovi prodotti. I catalizzatori solidi possono essere usati sia in processi gas-solido, sia liquido-solido, cioè i reagenti da trasformare possono essere presenti nella fase fluida gassosa o in fase liquida. I catalizzatori permettono alla reazione di procedere in modo selettivo con formazione dei prodotti desiderati.
L'identificazione di adeguati catalizzatori e lo sviluppo dei relativi processi catalitici in cui essi partecipano rappresentano un campo di ricerca di interesse culturale con associate importanti ricadute applicative in vari settori (chimica primaria, secondaria, farmaceutica, chimica di specialità, ecc.).

La natura e composizione del catalizzatore insieme alle condizioni sperimentali operative dirige il tipo di trasformazione che il reagente subisce per formare il prodotto. Vi sono diverse "famiglie" di catalizzatori: ossidi, metalli, zeoliti, fosfati, ecc., che sono usati per le molte reazioni che richiedono l'ausilio di un catalizzatore per migliorare la cinetica della reazione.

Un campo innovativo di ricerca connesso con l'esigenza di ottenere energia e *chemicals* è quello della valorizzazione della biomassa rinnovabile, in particolare quel tipo di biomassa che proviene dagli scarti agricoli e forestali. Lignina, cellulosa e inulina sono tre polimeri saccaridici naturali ottenibili dalla biomassa che costituiscono una fonte di partenza molto abbondante e facilmente disponibile. Sono necessarie alcune *azioni* (idrolisi, isomerizzazioni, disidratazioni) per aggredire tali polimeri prima di arrivare ai prodotti di interesse, tra cui si può citare l'idrossi-metilfurfurolo (HMF), il furfurale, l'acido levulinico.

Catalizzatori adatti per valorizzare la biomassa saccaridica sono quelli che presentano funzionalità acide o basiche sulla loro superficie (siti acidi di Brönsted e siti acidi di Lewis). I catalizzatori solidi acidi o basici sono in grado di sostituire gli acidi e le basi minerali liquide e gassose nei processi reattivi con vantaggi ecologici e di sicurezza dell'intero processo, di conseguenza il loro sviluppo e ottimizzazione è di grande interesse.

I laboratori di ricerca di A.G. e P.C. da sempre si occupano di temi che riguardano la catalisi eterogenea e la cinetica catalitica. Da molti anni, le ricerche sviluppate sono legate alla valorizzazione catalitica delle biomasse saccaridiche usando come substrati di partenza polimeri, disaccaridi e monosaccaridi col fine di ottenere prodotti che rappresentano i nuovi *building blocks* dell'industria chimica.

Le operazioni che tipicamente vengono eseguite nei laboratori sono legate *i*) alla preparazione dei catalizzatori solidi in forma massiva e supportata che sono ottenuti a partire da precursori molecolari (sali, complessi metallici, ecc.) con metodi di precipitazione, sol-gel, impregnazione, ecc.; *ii*) alla caratterizzazione chimico-fisica dei catalizzatori ottenuti utilizzando tecniche analitiche sviluppate nei propri laboratori e altre strumentazioni dipartimentali per determinare proprietà morfologiche, strutturali e superficiali, e *iii*) alla misura dell'attività catalitica utilizzando reattori *slurry* di tipo batch, e linee di reazione con reattore catalitici a letto fisso operanti a completo ricircolo e in flusso continuo.

Le ricerche sono svolte in collaborazione con ricercatori dell'ISTM-CNR e con altre Università e Centri di Ricerca italiani e esteri (Università di Napoli, Federico II, IRCELYON, Institut de Recherches sur la Catalyse et l'Environnement di Lyon, UPMC Sorbonne Université, Paris, Université de Lille-1, Lille, Universidad Autonoma de Madrid, Madrid, University of Nanjing, Nanjing, Cina).

I riferimenti di alcuni recenti articoli pubblicati sono qui di seguito riportati.

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Nanomaterials for environment, health and energy: synthesis and physico-chemical characterization of nanostructured materials for energetic applications

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Fuel cells for low temperature applications are the subject of intensive research because they could reduce consumption of primary fossil fuels and greenhouse gas emissions. Difficulties come from the sluggish kinetic behavior of cathodic oxygen reduction reaction (ORR). Platinum and Pt-alloys are currently the best catalysts for this reaction. Nevertheless, due to the natural scarcity and cost of platinum, finding alternative non-precious materials is a necessary and very attractive challenge. In the last years, many efforts have been devoted to demonstrate that nitrogen-doped carbon nanostructures, like graphene and nanotubes (N-CNTs), have great potential as Pt substitutes in ORR. Their specific electronic properties are extraordinarily improved by the presence of nitrogen species which disturb the uniform π-cloud and increase the localized density of states at the Fermi level. These modifications impart a n-type dopant activity and an enhancement of the electrocatalytic activity. Furthermore, many papers show that the ORR electroactivity can be modified by varying preparation method, precursor nature and composition of the catalyst used in the nanotube synthesis. Therefore the aim of our work is to synthesize innovative nanostructured electroactive materials (see Figure 1) and characterize them by physico-chemical methods. In order to study their electrocatalytic behavior towards ORR, polarization curves are recorded in acidic and alkaline solutions using a Rotating Disk Electrode (RDE) and Rotating Ring Disk Electrode (RRDE). X-ray Diffraction (XRD) and Photoelectron Spectroscopy (XPS) are used to investigate bulk and surface chemistry in combination with measurements using synchrotron light (in collaboration with Dr. Marco Scavini). Porosity and specific surface area are investigated by BET. Scanning and Transmission Electronic Microscopy (SEM and TEM) are used to study the materials morphology (in collaboration with Dr. Nadia Santo, CIMA). Magnetic measurements are performed in collaboration with Prof. Alessandro Lascialfari (Dip. Fisica, Unimi).

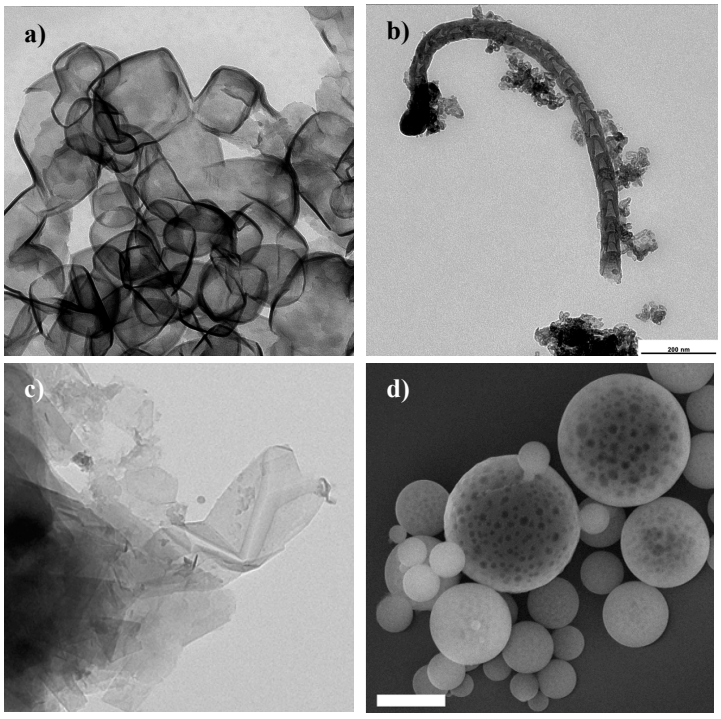

Figure 1. Nanostructured electroactive materials synthesized in our lab:
a) Nanocubes, b) Nanotubes, c) Graphene, d) Microspheres

Crystal Growth in Gelled Solutions: application to organic and inorganic compounds

Dott. Leonardo Lo Presti[1] and Prof.ssa Silvia Rizzato[1*]

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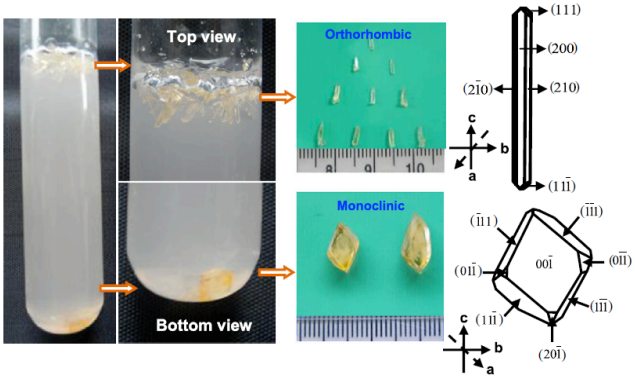
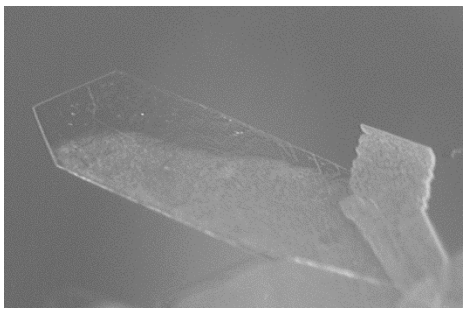
The use of gels (agarose, poly-methyl methacrylate gel, silica gel) or viscous materials (polyethylene oxide-PEO, polyvinyl chloride-PVC, polyvinylpyrrolidone-PVP, etc) as growth media in water or in organic solvents, for a wide range of compounds, including proteins and both inorganic and organic compounds has been reported in the literature. The presence of the gel is responsible for special features of nucleation and growth as the convection currents cannot occur; thus mass transport can occur only by diffusion. These conditions can lead to better crystal quality.[1]
We want to explore the possibility of using a variety of gel and resin-like systems as a dispersion matrixes to increase the size and quality of the crystals of organic and organometallic compounds, but also as a medium for stabilize the crystals, modify the crystal habit and controlling polymorph crystallization.[2]

CrystalLab **Crystal** growth and **Crystal**lographic **Lab**oratory





A novel method for the separation of mono and ortho polymorphs of paracetamol in gel matrix.[3a]

Diffraction quality and stability of the crystals improved by gel inclusion in coordination compounds.[3b]

[1] a) K.H. Henisch, Crystals in Gels and Liesegang Rings, Cambridge University Press, Cambridge, 1998; b) L. Carlucci, G. Ciani, J. M. Garcìa-Ruiz, M. Moret, D. M. Proserpio and S. Rizzato *Cryst. Growth Des.*, , **9**(*12*), 5024, (2009).
[2] R.I. Petrova and J.A. Swift *Crystal Growth & Design*, **2**(6), 573, (2002)
[3] a) C. Sudha, P. Parimaladevi and K. Srinivasan *Materials Science and Engineering*, **C47**, 150–155, (2015); b) S. Rizzato, M. Moret *unpublished results*.

Studio e progettazione di sistemi molecolari auto-assemblanti: verso una teoria unificata della cristallizzazione

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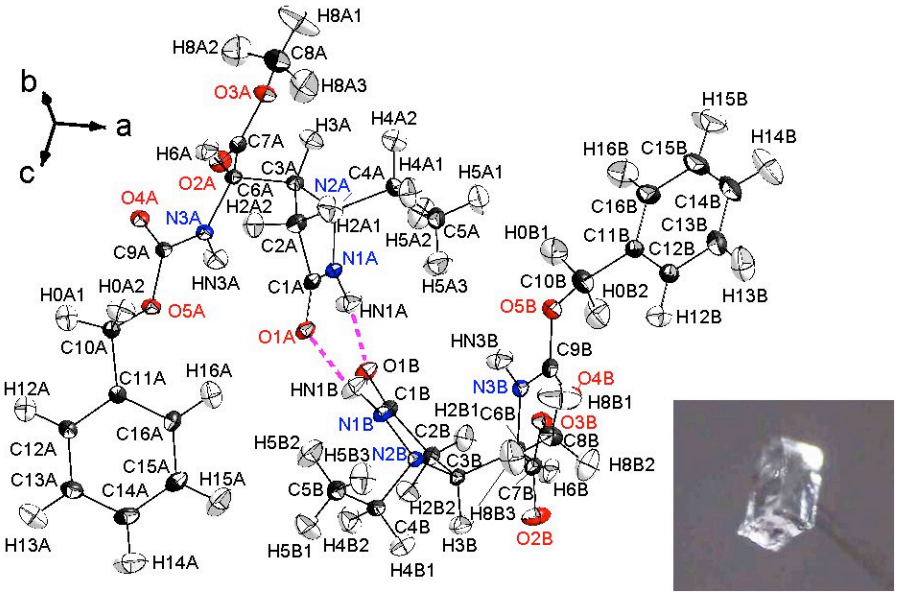
Comprendere il polimorfismo nei materiali cristallini rappresenta oggi una delle più affascinanti e complesse sfide della moderna ingegneria cristallina, con importanti applicazioni farmaceutiche ed industriali. Nei nostri gruppi di ricerca si offrono attività di tirocinio triennale e tesi magistrale inerenti ad esperimenti di cristallizzazione, diffrazione di raggi X e simulazioni quantomeccaniche nei solidi volti a studiare il riconoscimento molecolare e a correlarlo alle proprietà fisico-chimiche dei materiali.[1-3]



[1] **L. Lo Presti**, M. Sist, L. Loconte, A. Pinto, L. Tamborini, C. Gatti, *Rationalizing the Lacking of Inversion Symmetry in a Noncentrosymmetric Polar Racemate: An Experimental and Theoretical Study* Crystal Growth & Design 2014; 14(11). DOI: 10.1021/cg501074x

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Theoretical chemistry in the Chemical Dynamics Theory Group lab

Matteo Bonfanti[1], Gian Franco Tantardini[1,2] and Rocco Martinazzo[1,2,*]

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We work in the field of theoretical/computational chemistry. We develop theories, models and methods for addressing challenging physico-chemical quantum problems in realistic complex environments. Fields of application and inspiration comprise:

- **Materials science**, including graphene physics and chemistry (band-gap and strain engineering, substrate modulation, atomic-scaled resonant scatterers, charged impurities and topological defects), new carbon allotropes, novel Si-based 2D materials and semiconducting inherently chiral polymers, with applications in nanoelectronics, optoelectronics and spintronics [1].
- **Electron transport** through nanoscale systems and molecular junctions, of interest for nano-electronics and molecular electronics [2]
- **Quantum dynamics** of Excitation Energy- and Charge- Transfer in bulk heterojunctions, of interest for photovoltaics and quantum biology [3]
- Traditional **quantum chemical dynamics** in the gas-phase, in the condensed phase and at the gas-surface interface, with a focus on interstellar chemistry [4]

To address these problems we make profitably use of *state-of-the-art* methods: advanced quantum chemistry tools for the electronic structure problem (from highly accurate wavefunction-based methods for small systems, to density-functional-theory-based approaches for large-scale problems with up to several thousands of atoms), *first-principles* Non-Equilibrium Green's Function methods for electron dynamics and exact, time-dependent wavepacket methods for high-dimensional molecular (quantum) dynamics.

Group members: Rocco Martinazzo, Gian Franco Tantardini, Matteo Bonfanti, Paolo Bonardi, Marta Pasquini, Mattia Peluchetti, Michele Pizzochero

On-site collaborations: Francesco Sannicolò, Patrizia Mussini, Mariangela Longhi, Davide Ceresoli
External collaborations: Irene Burghardt, Keith H. Hughes, Bret Jackson, Liv Hornekaer

Selected contributions:

[1] R. Martinazzo, "*Atomic-scale defects in graphene*", in Handbook of Graphene Science, CRC Press, in press; M. Casartelli, S. Casolo, G.F. Tantardini and R. Martinazzo, "*Structure and stability of hydrogenated carbon atom vacancies in graphene*", Carbon, **77** (2014) 165; F. Sannicolo, et al. "*Inherently Chiral Macrocyclic Oligothiophenes: Easily Accessible Electrosensitive Cavities with Outstanding Enantioselection Performances*", Chemistry, **20** (2014) 15298

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Modellistica Molecolare: l'approccio quantomeccanico

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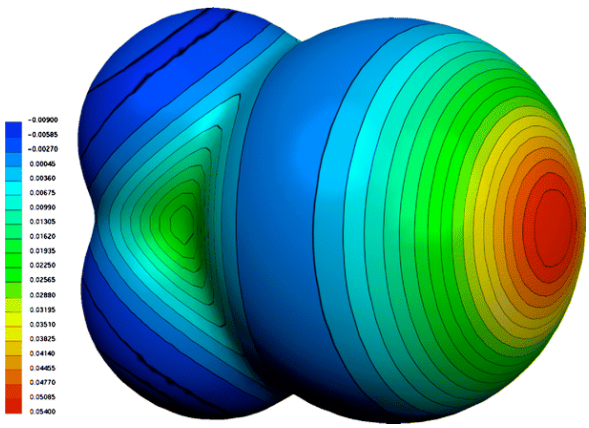
La Meccanica Quantistica permette in linea di principio il calcolo esatto ed ab-initio di tutte le proprieta' di un qualsiasi sistema atomico o molecolare. Per ottenere questo risultato si dovrebbe risolvere in modo esatto l'equazione di Schrodinger che invece, come ben noto, puo' essere risolta esattamente solo per pochi e semplicissimi sistemi chimici. E' pertanto di fondamentale importanza l'utilizzo di metodi approssimati ed attualmente sono a disposizione dei chimici teorici un gran numero di diversi approcci che si distinguono per il diverso peso computazionale: dai metodi semi-empirici caratterizzati da un basso costo computazionale ai sofisticati metodi CCSD(T) che permettono di ottenere risultati molto accurati ma che necessitano di una potenza di calcolo estremamente elevata. Fra questi due estremi esistono naturalmente una pletora di altri metodi con accuratezze e costi intermedi.
Nel nostro gruppo i principali metodi quantomeccanici oggi disponibili vengono impiegati per lo studio di diversi sistemi molecolari.
Recentemente una particolare attenzione e' stata dedicata allo studio del legame ad alogeno che presenta diverse analogie con il ben piu' noto legame ad idrogeno.
A prima vista il legame ad alogeno sembra violare i principi fisici fondamentali. Questo legame consiste infatti in una interazione di legame fra un atomo di alogeno, notoriamente caratterizzato da una carica negativa vista la sua elettronegativita', ed una fonte di elettroni quali un doppietto presente su un atomo di ossigeno o di azoto, od una nuvola pi-greco di un sistema aromatico.
Uno studio quantomeccanico sofisticato permette in realta' di evidenziare attorno all'atomo di alogeno una anisotropia del potenziale elettrostatico con la comparsa di una regione positiva, denominata sigma hole, che permette l'interazione con una regione ricca di elettroni.
Il legame ad alogeno sta trovando attualmente interessanti applicazioni nella scienza dei materiali, nella chimica supramolecolare e nel drug design.
E' pertanto di fondamentale importanza sia valutare l'accuratezza offerta dai diversi metodi di calcolo che la possibilita' di comprendere sempre meglio questo tipo di interazione.
Per raggiungere questo obiettivo nel nostro gruppo stiamo studiando il legame ad alogeno applicando diversi approcci computazionali. La densità alettronica ottenuta dai diversi calcoli viene poi analizzata utilizzando la tecnica di Bader (Atoms in Molecules) che permette di elucidare la natura delle interazioni.



Anisotropia del potenziale elettrostatico in una molecola alogenata. La regione in rosso evidenzia una regione di potenziale elettrostatico positivo denominata sigma hole. Tramite questa regione l'atomo di alogeno puo' interagire, ad esempio, con un doppietto elettronico.

Modellistica Molecolare: l'approccio della Dinamica molecolare

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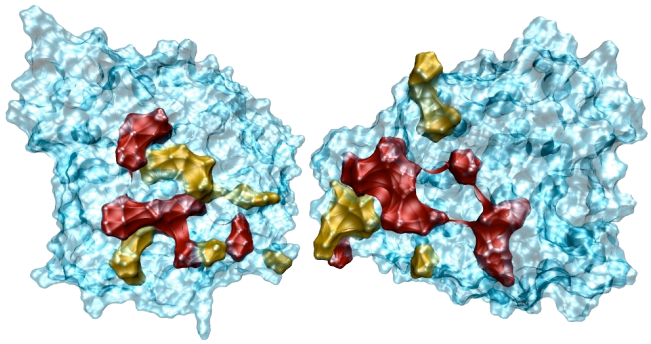
La Dinamica Molecolare permette lo studio di sistemi estremamente complessi quali le proteine o il DNA, sia isolati che in complesso con piccole molecole, altre proteine, membrane, ecc.
Il nostro Gruppo di Ricerca utilizza numerose tecniche basate sulla Dinamica Molecolare per lo studio di diverse problematiche:

A) Le interazioni proteina-proteina. Questo tipo di interazione sta attirando negli ultimi anni l'interesse di molti ricercatori poiche' si intravede nella possibilita' di modulare le interazioni fra proteine il punto di partenza per poter ottenere nuove classi di farmaci. Dal punto di vista modellistico e' possibile ottenere una mappatura a livello molecolare delle interazioni fra due proteine ed iniziare quindi a disegnare nuovi inibitori o promotori.
B) I chaperoni molecolari. Esistono alcune molecole organiche molto semplici che permettono di proteggere le proteine per esempio da stress termici. Queste molecole rivestono grande importanza nel proteggere specie vegetali da condizioni di siccita' e sono quindi un punto di partenza per lo sviluppo di nuove molecole di interesse agricolo e per la salvaguardia del patrimonio idrico del pianeta. La modellistica molecolare permette di indagare il meccanismo di protezione delle proteine al fine di avere una base razionale per lo sviluppo di nuovi chaperoni molecolari.
C) Sviluppo di campi di forze per lo studio di nuove interazioni. La Dinamica Molecolare utilizza delle forme funzionali parametrizzate in maniera opportuna per descrivere le principali interazioni intra ed intermolecolari. La conoscenza sempre piu' approfondita delle interazioni fra molecole puo' portare alla revisione delle parametrizzazioni attualmente impiegate. Ad esempio l'interazione con atomi di alogeni e' spesso caratterizzata da potenziali elettrostatici caratterizzati da anisotropie che devono essere descritte con degli sviluppi particolari dei parametri impiegati.



Interazione fra due proteine: la determinazione dei residui piu' importanti per l'interazione, evidenziati in giallo e rosso, tramite tecniche modellistiche, e' uno dei primi passi per il disegno razionale di nuove molecole che possono modulare l'interazione fra le proteine.

Ossidi Funzionali: ricercando il nesso tra struttura e proprietà fisiche

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Parole Chiave: Ossidi Funzionali; Conduttori Ionici; Materiali Multiferroici; Nanoparticelle; Proprietà Elettriche e Magnetiche; Diffrazione; Luce di Sincrotrone; Sorgenti di Neutroni; Spettroscopia EPR.

Attività di Ricerca: Il gruppo di ricerca studia la relazione tra la struttura, le proprietà fisiche e la termodinamica dei difetti in **ossidi cristallini funzionali**, ovvero "*materiali in grado di svolgere una funzione e di produrre un segnale in risposta a stimoli esterni*" (Enciclopedia Treccani), quali ad esempio:
- l'applicazione di un campo elettrico con risposte in termini di conducibilità (es **conduttori ionici e superconduttori**) e/o di para-, ferro- e antiferro-elettricità (es. **materiali ferroelettrici**);
- l'applicazione di un campo magnetico con conseguente para-, ferro-, ferri- e antiferro-magnetismo (es. **materiali ferromagnetici**).

Materiali che hanno risposte sia a stimoli elettrici che magnetici possono essere **magnetoresistenti**, **multiferroici**, etc.
In molte classi di materiali, l'insorgere delle proprietà sopra descritte è legato alla presenza di difetti e rotture di simmetria (ad esempio nelle soluzioni solide), che causano fluttuazioni composizionali e strutturali la cui coerenza spaziale può variare da qualche Ångstrom a diverse decine di nanometri.
Per comprendere le importanti proprietà fisiche di tali materiali è fondamentale descriverne la struttura a partire dall'intorno chimico degli atomi (corto raggio), passando per la scala nanometrica (medio raggio), fino all'ordine cristallino (lungo raggio).
Tale studio strutturale utilizza tecniche di indagine non convenzionali (**High-Resolution Powder Diffraction, Pair Distribution Function Analysis, Anomalous Scattering, EXAFS**), ottenibili solo presso grandi infrastrutture di ricerca europee, quali ESRF, ILL, ISIS, ALBA, ELETTRA e PSI. In tali ambiti il gruppo di ricerca vanta **oltre 50 esperimenti approvati** negli ultimi anni.
Le misure magnetiche vengono effettuate nel laboratorio di **Risonanza di Spin Elettronico**.
Oggetto di tali ricerche sono sistemi cristallini di interesse per la ricerca di base e/o per applicazioni tecnologiche. I materiali indagati sono in particolare:

- **elettroliti solidi per celle a combustibile;**
- **materiali multiferroici o magnetoresistenti;**
- **superconduttori;**
- **nanoparticelle e nanocompositi.**

Collaborazioni internazionali:
- Dr. Michela Brunelli, Dr. Claudio Ferrero, Dr. Gavin Vaughan, Dr. Giuseppe Portale (European Synchrotron Radiation Facility, Grenoble);
- Prof. Simon Billinge, Dr. Xiaohao Yang (Columbia University);
- Sabine Schlabach, Michael Hagelstein (Karlsruhe Institute of Technology);
- Claudio Mazzoli (Brookhaven National Laboratory);
- varie collaborazioni nel Dipartimento, con colleghi dell'ISTM-CNR e di altre Università italiane.

Descrizione dell'Internato di Tesi.
Nel corso del Tirocinio di Tesi lo studente:

- preparerà i propri campioni in forma di polveri **microcristalline** e/o **nanocristalline**;
- li caratterizzerà dal punto di vista strutturale e microstrutturale;
- **determinerà accuratamente la struttura a diverse lunghezze di scala** mediante **diffrattometria di raggi-X** da **Luce di Sincrotrone** (**www.esrf.eu**) o **di Neutroni** (**www.ill.fr**);
- determinerà le proprietà fisiche dei campioni (es. proprietà magnetiche con tecnica **EPR**).

Grazie alla stretta collaborazione con il **Dr. Ceresoli**, ricercatore del CNR, sarà possibile affiancare uno studio teorico all'indagine sperimentale sopra descritta.
È possibile scegliere una tesi incentrata sull'analisi dei dati raccolti negli scorsi anni dal gruppo di ricerca presso le grandi infrastrutture di ricerca europee sopra elencate.

Laboratory of Applied Electrochemistry

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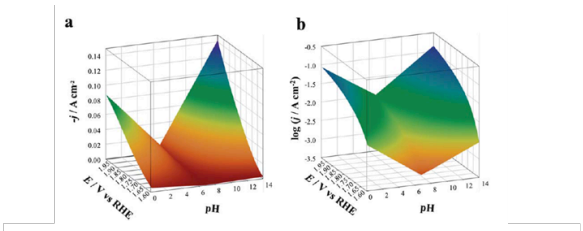
The Laboratory of Applied Electrochemistry offers the possibility of improving the knowledge on fundamental and applied aspects of chemistry of materials, while practicing and acquiring skills in highly interdisciplinary topics and applications, mainly centred on energy, environmental and biological issues. The proposed subjects cover (i) the preparation and characterisation of electrochemical cells (Li-based secondary cells, Zn-based primary cells, fuel cells) together with the preparation, characterisation and use of the relevant electrode and their electrocatalytic materials; (ii) the hydrogen production by water electrolysis and photoelectrolysis; (iii) the recovery of value added compounds by detoxification of wastes; (iv) the development of investigation tools and protocols for material characterisation and process control; (v) the development of in-situ and in-operando spectroelectrochemical techniques for the elucidation of reaction mechanisms; (vi) the use of microelectrodes in scanning electrochemical microscopy and for sensing.

The research activity is performed in collaboration with Italian (Università degli Studi di Milano: Department of Chemistry, Department of Physics, Department of pharmacological and biomolecular sciences, Università del Salento, Università di Pavia, C.N.R. - ISTM di Milano and IENI – Padova) and International Research Laboratories: Allen J. Bard (The University of Texas at Austin-USA), Joaquin Rodriguez-Lopez (The University of Illinois at Urbana-USA) Christian Amatore (Ecole National Superieure, Paris, France), Juan Feliu (University of Alicante, Spain).

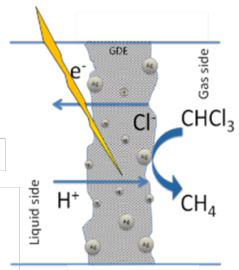
Recent research topics:

ENERGY: new cathodic nanocomposite materials for ORR and OER in aqueous and non aqueous matrices for different new generation batteries. Photoelectrochemical decomposition of water.

ENVIRONMENT: materials for electrochemical hydrodehalogenation of organic compounds in liquid and gas stream.

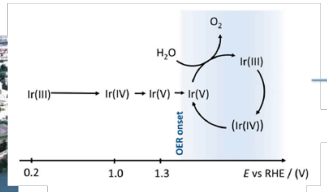


Energy Conversion and Storage: Batteries and H_2 production

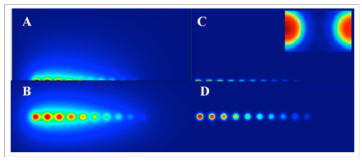


Environmental Electrochemistry

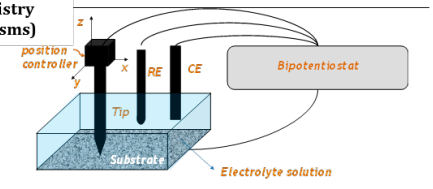
Electrochemistry and X-Ray Absorption Spectroscopies



Basic Electrochemistry (Reaction mechanisms)



Microelectrodes and Digital Simulation



Scanning Electrochemical Microscopy (SECM)

Chimica Generale ed Inorganica

Design, synthesis and characterization of porous Coordination Networks for gas storage and catalytic applications

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In the last twenty years the tools of **coordination chemistry** have been intensively used to construct extended structures known as **Coordination Networks (CNs)** and **Metal-Organic-Frameworks (MOFs).** The easy synthetic processes, the highly crystalline nature and the potential properties of these compounds have been the driving force for the exponential development of this new research area and of new functional materials. Many and diverse properties are shown by coordination networks, that are strongly dependent from the intrinsic porosity of the materials and that frequently act in a synergistic way. Among others, the adsorption and storage of energetically (H_2 and CH_4) and environmentally (CO_2) important gases and the catalytic applications are particularly attractive.
The research undertaken in Carlucci's lab is focused on this general research topic and, in particular, deals with **synthesis**, **structural** and **topological** characterization and **applications** of CNs.

Possible thesis topics are:

i) Design and synthesis of new chelate coordination complexes functionalized on the periphery with donor groups (Metalloligands) to be used for the step-wise building up of heterometallic porous CNs. ß-diketones functionalized with nitrile, pyridyl, tetrazole and carboxylic groups are used as chelating ligands (see ref. 3 and fig. 1).
ii) Development of new organic ligands with extended aromatic units to be used for the synthesis of new CNs with luminescent properties.
iii) Design and synthesis of robust and water resistant CNs to be applied under aqueous conditions (in collaboration with Torino, Firenze and Perugia Universities).
iv) Development of **graphene/MOF composites** for efficient **gas storage** applications (in collaboration with Nagano University - Japan).
v) Structural, topological and **entanglement** analyses on extended dataset of crystal structures by the use of the program TOPOS in collaboration with prof. Davide M. Proserpio (see ref. 1 and fig. 2).

Experimental procedures and methods include: synthesis of organic ligands, synthesis and crystallization of coordination complexes and networks, x-ray diffraction, thermal analyses, gas adsorption measurements.

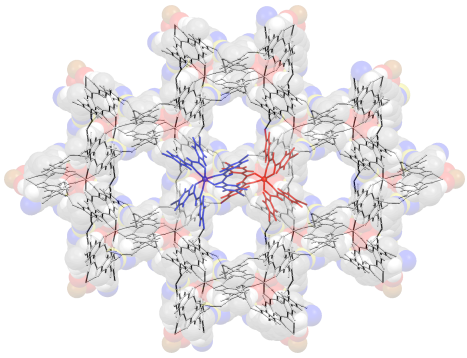

Figure 1: A porous heterometallic CN built up using tris-chelate ß-diketonate metalloligands

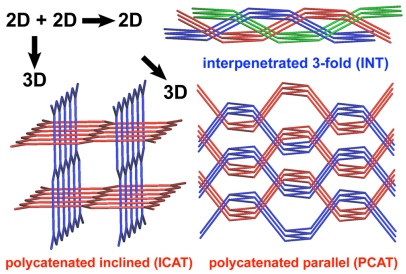

Figure 2: Entanglement in 2D CNs

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Bio-inspired ligands for the synthesis of chiral transition metal complexes: innovative catalysts for eco-friendly transformations

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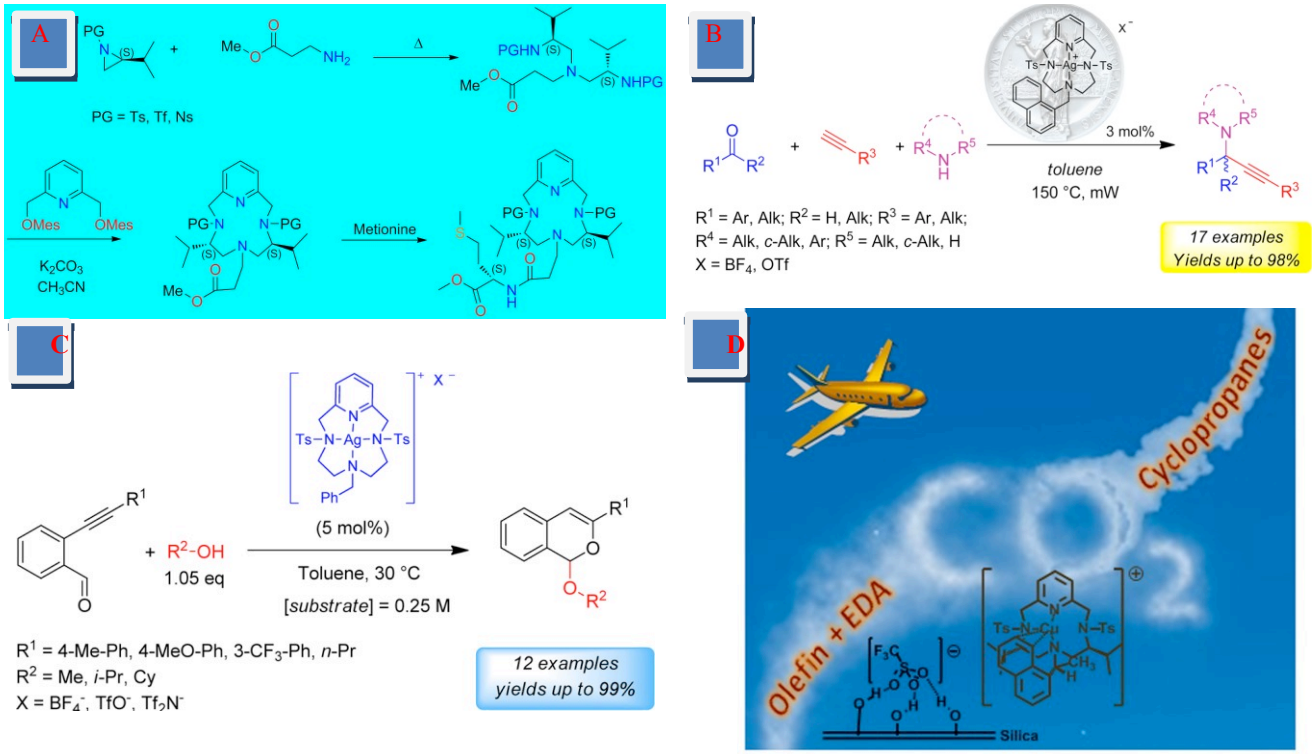
Research Interests: Homogeneous Catalysis, Heterogeneous Catalysis, Coordination Chemistry, Organometallic Chemistry, Mechanistic Studies, Asymmetric Synthesis, Bio-inspired Ligands.

Currently, our research interest is focused on the employment in homogeneous catalysis of transition metal complexes with macrocyclic N-ligands, with special attention to the synthesis of new asymmetric ligands starting from easily available chiral pool (*i.e.* amino-acids or sugars), **A**, in order to produce cost-effective, energy-efficient and eco-friendly catalysts for use in production of chemicals. The target organic products are high added value fine chemicals **B** and/or structural units of biologically relevant compounds **C**. Particular emphasis is given to innovative technologies and to the mechanistic aspects of the catalytic reactions under study, in order to improve the catalyst design and performances. In recent projects, I moved my interests to the development of new methods which combine the ease of catalyst recovery of heterogeneous systems with the higher performances in terms of activity and selectivity obtained with homogeneous catalysts and to the use of continuous flow conditions **D**.



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[1] Castano, B.; Gallo, E.; Cole-Hamilton, D. J.; Dal Santo, V.; Psaro, R.; Caselli, A. *Green Chem.* **2014**, *16*, 3202. [2] Dell'Acqua, M.; Castano, B.; Cecchini, C.; Pedrazzini, T.; Pirovano, V.; Rossi, E.; Caselli, A.; Abbiati, G. *J. Org. Chem.* **2014**, *79*, 3494. [3] Trose, M.; Dell'Acqua, M.; Pedrazzini, T.; Pirovano, V.; Gallo, E.; Rossi, E.; Caselli, A.; Abbiati, G. *J. Org. Chem.* **2014**, *79*, 7311. [4] Castano, B.; Guidone, S.; Gallo, E.; Ragaini, F.; Casati, N.; Macchi, P.; Sisti, M.; Caselli, A. *Dalton Trans.* 2013, 42, 2451. [5] Castano, B.; Zardi, P.; Honemann, Y. C.; Galarneau, A.; Gallo, E.; Psaro, R.; Caselli, A.; Dal Santo, V. RSC Advances 2013, 3, 22199.

Push-pull meso- and ß-substitued ZnII-porphyrinates: from second-order nonlinear optics to dye sensitized solar cells

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During the last 15 years our work has been devoted to the synthesis of porphyrins and metalloporphyrins substituted in the *meso*, pyrrolic and axial positions, with the aim to introduce significant perturbations to the highly polarizable electronic system of porphyrin ring, which is characterized by a variety of low lying excited states. This feature has attracted a widespread interest for these molecules in the optical materials area and, in particular, we have investigated the second-order nonlinear optical (NLO) properties, determining the quadratic hyperpolarizability in solution, by the EFISH technique, of asymmetrically substituted *meso*- and β-pyrrolic tetraphenyl porphyrins, both with a push or pull substituent.[1]
Interestingly, the porphyrinic core has shown an ambivalent character as donor or acceptor, depending on the pull or push nature of the substituent respectively.[1]
Asymmetric arylethynyl push-pull porphyrinates were investigated, in order to evaluate the effect of different metals on the second-order NLO response, both theoretically[2] and experimentally.[3] Finally Zn^{II}-porphyrinates substituted in the axial position have shown to be less perturbed by the presence of the push or pull substituent.[1]
Also, the third-order nonlinear optical response has been investigated on some porphyrinic systems by means of two-photon absorption (TPA) measurements, for its possible applications based on optical limiting devices.[4]
More recently porphyrinic systems have shown all the characteristics to be very interesting dyes for applications in Dye Sensitized Solar Cells,[5] as confirmed by theoretical calculations, which have shown a well-defined localization, in the excited state, of the HOMO and the LUMO on the donor and acceptor moieties, respectively.[6]
Thus we have prepared some push-pull *meso*-substituted Zn^{II}-porphyrinates,[6,7] with a carboxylic group as acceptor/anchoring group, and a quite new series of Zn^{II}-tetraarylporphyrinates featured by sterically bulky *tert*-butyl groups, mono-substituted or push-pull di-substituted in *ß*-position by a straightforward and rapid method developed by our research group.[7]

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Magnetic Nanoparticles: Synthesis, Functionalization and Nanocharacterization

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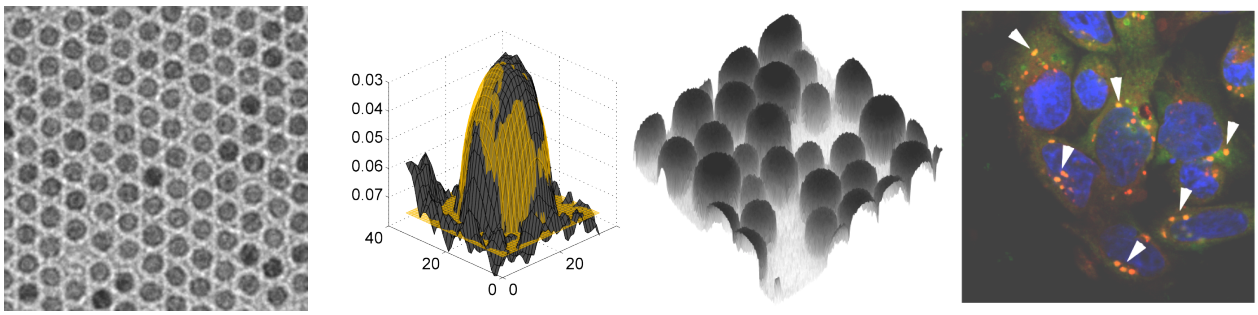
Research on magnetic nanoparticles (MNPs) is a very active field (about 5900 papers in 2014 only) as MNPs have exciting prospective applications in fields as diverse as ITC,[1] catalysis,[2] environmental remediation,[3] and biomedicine.[4] Our group design and synthesize MNPs tailored for specific applications but fundamental issues, such as MNP colloidal stability and magnetic phenomena, are always considered since successful applications require deep understanding of the underlying nanochemistry.

At present, we are mainly interested in the following applicative goals:

- Magnetic information storage: Heterostructured MNPs with enhanced magnetic stability
- Electromagnetic shielding: Composites of MNPs with conducting polymers
- Environmentally-friendly production of fine chemicals and polymers: MNP-based catalysts
- Water depuration: Composites of MNPs with antimicrobial/sequestrating polymers
- Theranostic agents for nanomedicine: MNPs functionalized with bioactive molecules

Our research work involves four main practical activities: (i) synthesis of size- and shape-controlled, homo- or hetero-structured inorganic nanoparticles; (ii) synthesis of active organic compounds (small molecules or polymers) and grafting on the MNPs; (iii) nanocharacterization of the MNPs by several techniques (TEM, FTIR, XRD, DLS, ICP, TGA, etc); (iv) functional characterization [e.g. magnetic properties, catalytic performance, biological assays (toxicity, immunogenicity, internalization, MRI)]. Activity (iv) is often carried out in collaboration with other laboratories (UniMi, CNR, UniFi, etc.).

We are a multi-disciplinary group where researchers with background in organic, inorganic, and physical chemistry closely collaborate and create fruitful research links with physicists, engineers, biologists, and pharmacologists.



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Nanostructured materials: synthesis, characterization and application in catalysis for fine chemicals and energy production

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Dr. D. Ferri - Paul Scherrer Institut (PSI) - Catalysis for Energy, Villigen – PSI, Switzerland
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Prof. J.M. López Nieto – Polytechnical University of Valencia,Institute of Chemical Technology(ITQ), Spain

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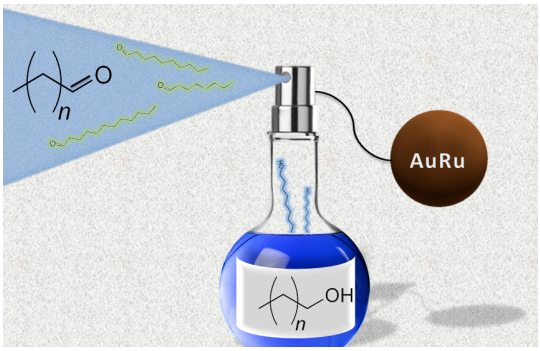
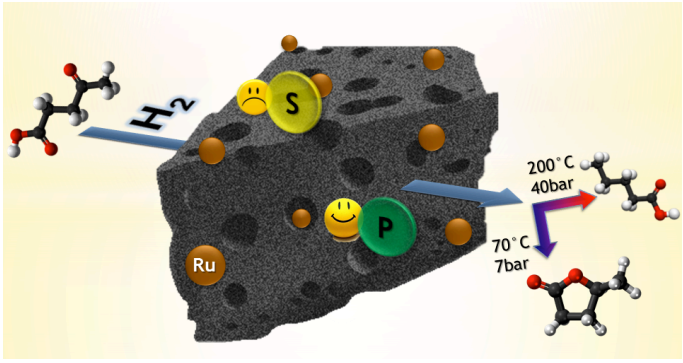
Catalysis is an essential core of the chemical industry and of particular interest in the fields of sustainable energy production and environmental protection. Therefore catalysis has been identified as a growth area. An important aim for catalysis is to tackle fundamental challenges such as design and improvement of catalysts and catalytic processes, understanding mechanisms for synthesis of novel materials and development of catalytic processes. Nanotechnology has introduced new opportunities into material science allowing a careful design of materials for each application upon controlling the size and, to some degree, the morphology and the surface properties of the nanoparticles produced. The controlled production of metal nanoparticle along with the use of advanced characterization methods is crucial in understanding catalytic processes and developing better catalysts in terms of higher activity, selectivity and durability. [1-8]





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[4] A. Villa, C. E. Chan-Thaw, M. L. Schiavoni, S. Campisi, D. Wang, and L. Prati, *Chinese Journal of Catalysis* **6** (2014) 35(6):945–951. DOI:10.1016/S1872-2067(14)60101-7
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Topological Crystal Chemistry

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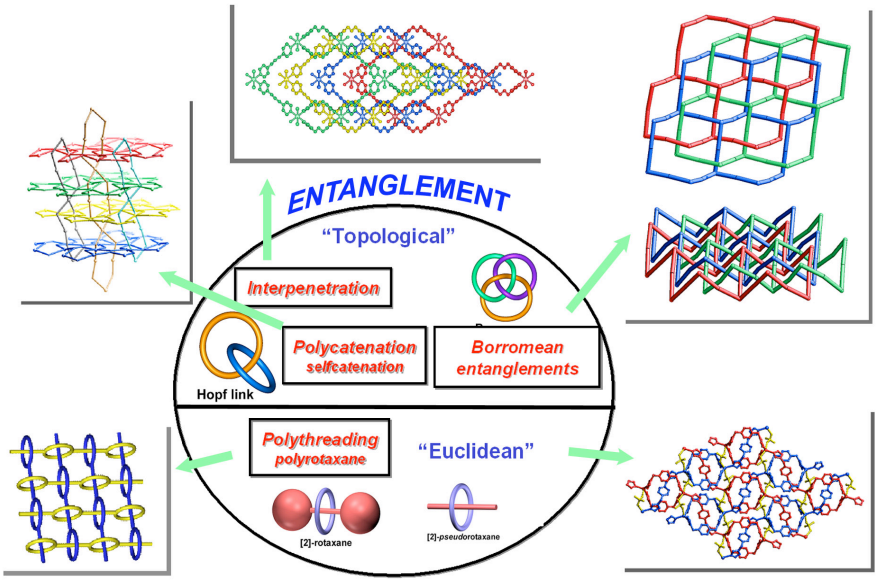
The design of new crystalline materials with extended framework structures such as Coordination Polymers, Metal Organic Frameworks and Supramolecular Networks, is of great interest due to their potential applications in different areas such as catalysis, gas uptake and ion exchange just to mention a few. The large variety of topologies shown by these extended architectures is also intriguing and the topological analysis of these structures has been the subject of numerous studies and different approaches have been devised for the rationalization and classification of these frameworks (in this regard we use the program TOPOS developed in collaboration with Prof. Blatov). Recently the role of the topology in crystal chemistry has been reviewed also in connection to properties: interpenetration in metal-organic frameworks can control gas uptake capabilities and catalysis; entanglement has been explored to tune magnetic properties; the role of minimal surfaces has been shown fundamental in the liquid crystal domains; tiling theory has been applied for zeolite prediction and properties.

Possible thesis topics are:

- underlying nets in coordination and supramolecular networks (hydrogen-bonds, halogen-bonds and others secondary interactions) (in collaboration with prof. Lucia Carlucci);
- entanglement in periodic structures (in collaboration with prof. Lucia Carlucci);
- interpenetration & properties (in collaboration with prof. Lucia Carlucci);
- structures as minimal surfaces;
- rod packings & nets;
- nanocluster and tillings in intermetallics and zeolites;
- cluster topology in polynuclear inorganic compounds.



Some recent literature:

- L. Carlucci, G. Ciani, D. M. Proserpio, T.G. Mitina, V. A. Blatov, "Entangled Two-Dimensional Coordination Networks: A General Survey." *Chem. Rev.***114,** 7557−7580 (2014).
- V. A. Blatov, A.P. Shevchenko, D. M. Proserpio "Applied topological analysis of crystal structures with the program package ToposPro." *Cryst. Growth Des.,* **14,** 3576-3586 (2014).
- E. V. Alexandrov, V. A. Blatov, A. V. Kochetkov, D. M. Proserpio "Underlying nets in three-periodic coordination polymers: topology, taxonomy and prediction from a computer-aided analysis of the Cambridge Structural Database" *CrystEngComm*, **13**, 3947-3958 (2011)

Coordination complexes for solar cells and electroluminescent devices

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One of the present technological main challenges is to address the problem of the increasing global energy demand in a clean and renewable manner by exploiting energy from Sun, thus avoiding issues related to fossil fuels such as pollution and finite available amounts. **Dye-sensitized solar cells** (DSSCs) are considered a realistic solution for harnessing the energy of the Sun and converting it into electrical energy. One of the most important components of DSSC is the photosensitizer, that is the dye which absorbs light from Sun and transfers an electron from its excited state to the conduction band of TiO_2. The most common sensitizers are Ru(II) complexes based on 2,2'-bipyridine ligands, such as *cis*-di(thiocyanato)bis(bpy-4,4'-dicarboxylate)ruthenium(II). However, a limitation of such Ru(II) complexes is the presence of thiocyanate, NCS, ancillary ligands.
In order to circumvent the issues related to the use of thiocyanate-based complexes, we synthetize and characterize organometallic and coordination Ru(II) compounds with chelating ligands (Fig 1a) [1].
Another important kind of devices are **organic light-emitting diodes** (OLEDs) in which an emissive electroluminescent layer containing a coordination complex emits light in response to an electric current.
To this respect we synthetize and characterize highly phosporescent coordination compounds such as terdentate cyclometallated Pt(II) complexes (Fig. 1b) [2]. In addition second-order nonlinear optical properties in solution and in thin films of various push-pull complexes are investigated [3].

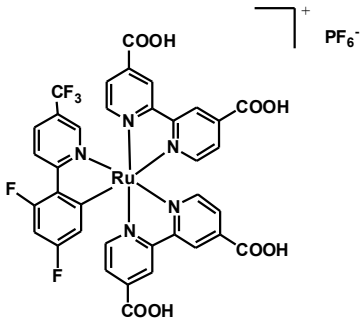

Fig. 1a

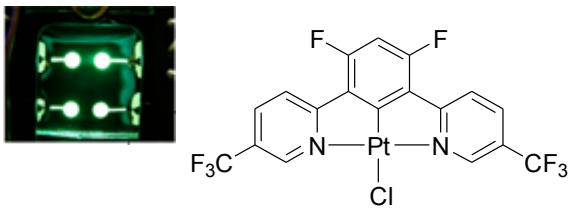

Fig 1b

[1] A. Abbotto, C. Coluccini, E. Dell'Orto, N. Manfredi, V. Trifiletti, M.M. Salamone, R. Ruffo, M. Acciarri, A. Colombo, C. Dragonetti, S. Ordanini, D. Roberto, A. Valore, *Dalton Trans.* **41**, 11731 (2012); A. Colombo, C. Dragonetti, A. Valore, C. Coluccini, N. Manfredi, A. Abbotto, *Polyhedron **82**,* 50 (2014).

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Application of Metal nanoparticles in nanomedicine

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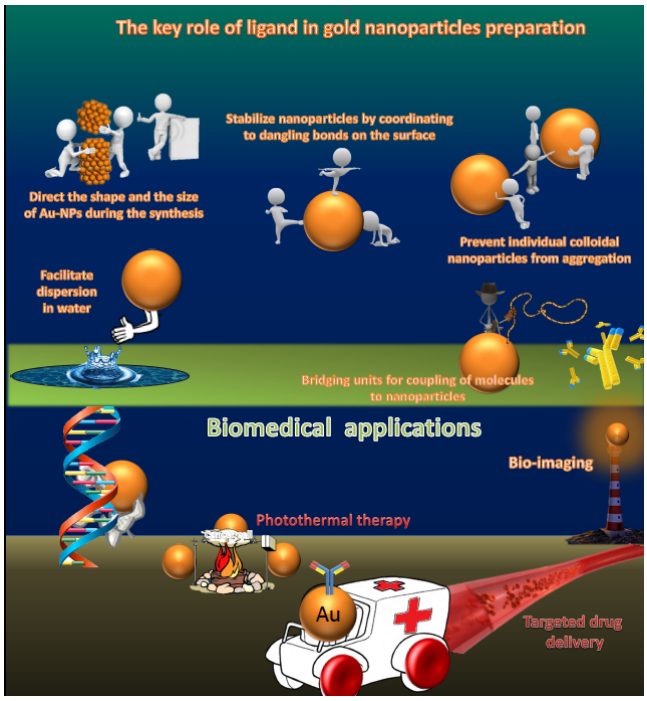
Nanotechnology is widely employed in biological systems and there are many examples in literature of studies on gold- or silver-bioconjugate systems and magnetic nanoparticles employed in nanomedicine (drug delivery, imaging, therapy,etc). Indeed the role played by nanoparticles can differ greatly from an active component to a blank transporter. Obviously the design of these nanoparticles differ depending on their own role and, for this purpose, nanotechnology plays a fundamental role. The functionalization of nanoparticle surface with targeting ligands, able to recognize specific markers, allows receptor-mediated endocytosis and nanoparticle internalization, thus, improving therapeutic efficacy for drugs or the targeted deposit or the nanoparticle itself.
The group recently developed metal sols stabilized by natural and non-toxic organic molecules, such as, amino acids, amino sugar or sugars, peptides able to negotiate intra- and intercellular membranes independently of receptors and temperature. Thus, taking advantage of this property and binding a therapeutic agent, the nanoconjugates could deliver the drug directly into the nucleus.
Presently the research has been switched toward the preparation of biocompatible and stable metal (Au, Ag) nanoparticles conjugated with proper, antibacterial stabilizer able to develop a synergetic effect with the metal nanoparticle.
Uv-vis spectroscopy and ζ-potential measurements provide information about the stability and size distribution of colloidal systems. The coordination of the studied ligands and drugs to the metal surface can be investigated through accurate ATR-FTIR and mono- and bidimensional NMR spectroscopy.
These researches are carried out in collaboration with the Bioscience Department of the University of Milan.



[1] F. Porta, Z. Krpetić, L. Prati, A. Gaiassi and G. Scarì, *Langmuir* **8** (2008) 24(14):7061-4. DOI:10.1021/la8008392
[2] S. Avvakumova, G. Scarì and F. Porta, *RSC Advances* **4** (2012); 2(9):3658-3661. DOI: 10.1039/C2RA20386C
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Chimica Industriale ed Impianti Chimici

Gruppo di processi e impianti per la chimica industriale

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Keywords: Fotocatalisi, biodiesel, biomasse, processo Fisher-Tropsch, processi di separazione e assorbimento, simulazione di processo e modelli, trattamenti superficiali.

ARGOMENTI DI TESI TRIENNALE E MAGISTRALE

FOTOCATALISI
- Sintesi e caratterizzazione di fotocatalizzatori a base di biossido di titanio nanometrico e micrometrico.
- Studio della fotodegradazione di inquinanti organici e inorganici, in fase liquida o gassosa, mediante l'utilizzo di reattori operanti in discontinuo o in continuo.

BIODIESEL
- Pretrattamento di oli vegetali e processo di transesterificazione per ottenere bio-carburanti.
- Sintesi di catalizzatori per i processi di transesterificazione e test in reattori batch e PFR.

PROCESSO di FISCHER-TROPSCH
- Studio della sintesi di Fischer-Tropsch in reattore a letto fisso in continuo.
- Preparazione di catalizzatori Fischer-Tropsch a base di Fe e Co attivato con Ru su diversi supporti

BIOMASSE
- Estrazione mediante ultrasuoni e purificazione di poliidrossialcanoati (PHA), ottenuti dal bio-trattamento di acque reflue.

BIOGAS
- Purificazione di biogas con acqua attraverso processi di assorbimento.

ARIA ARRICCHITA
- Produzione in batch e discontinuo di aria arricchita in O_2, attraverso assorbimento e desorbimento di aria in acqua, in condizioni di pressione e temperatura controllate.

SUPERFICI IDROFOBICHE
- Studio e formulazione di rivestimenti idrofobici a base di polimeri fluorurati.

SIMULAZIONE DI PROCESSO E MODELLI
- Determinazione dell'equilibrio liquido-vapore di miscele non ideali (cicloesanolo-cicloesanone) e simulazione (Simsci-Schneider Electrics, PROII).
- Regressione dei parametri cinetici di processi fotocatalitici e sintesi di bio-diesel per l'ottenimento delle costanti cinetiche.

Polimeri e materiali (LAMPO)

Ph.D. M. A. Ortenzi, Ph.D. H. Farina, Dott. G. Alberganti, Dott. S. Antenucci, Dott. V. Sabatini, Prof. G. Di Silvestro
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Catalytic processes for energy and environment

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The proposed projects are intended for both Bachelor and Master theses in Chemistry and Industrial Chemistry, as well as for PhD projects.
All the topics cover experimental activities and/or make use of specific software for kinetic modeling and process simulation. Currently, the main interest of the group is the development of innovative processes in the field of environmental catalysis and to exploit the potential of renewable energy sources. Attention is also devoted to the innovative design of existing industrial processes, aiming at their intensification and optimization. A non exhaustive list of proposals is reported in the following. Please ask for more details.

H_2 production from renewable sources

Hydrogen is an energy vector and industrial raw material of ever growing importance. Therefore, there is a strong interest in finding new routes to produce it sustainably and from renewable sources. We have considered in particular the adaptation of the well established steam reforming process to renewable raw materials: bioethanol, bioglycerol, biooil, biogas. Theses on this topic can be accounted for though experimental activity: catalysts preparation by means of innovative routes, catalyst characterization by means of various complementary techniques and most of all activity testing on a continuous micropilot plant. On the other side a demonstrative pilot plant is available for testing, including 6 reactors connected in series for hydrogen production and purification, and a fuel cell for the cogeneration of 5 kW electric + 5 kW thermal power (residential size). This latter experimentation aims at demonstrating the feasibility from the technical and economical point of view of the proposed strategy.
From the computational point of view theses are available on this and related topics making use of Athena Visual Studio for kinetic modeling and ASPEN ONE Engineering suite for process simulation. The latter tool allows to build a process scheme, imagine a proposed process feed and operating condition and simulate the possible products output. Suitable tools are available also for economic analysis of the full process. From this point of view fantasy has no limits and students may explore a full range of different processes, comparing them to find out the most feasible solution. The investigation can be extended also to other emerging technologies to exploit renewable sources (gasification, pyrolysis, etc.), depending on student's interest.

H_2 storage

Different materials have been proposed to safely and efficiently store hydrogen for application in the transportation sector. Unfortunately, the materials and technologies proposed are still far from optimization. Also in this case theses are offered including an experimental section and a simulation one. Experiments include materials preparation, characterization and testing by means of different equipment, in case operating up to 100 bar for a reliable estimation of the storage capacity in a real vehicle. Materials range from activated carbons to innovative metal alloys. Simulations are intended to find the optimal storage strategy, based on experimental data, and define the cost of a designed storage tank.

Re-design relevant industrial processes

As said above, during *in-silico* process design fantasy has no limits… Therefore, making use of the most reliable and industrially employed process design tool (ASPEN One), students will learn the basics of process design. Furthermore, ticks and trips for process integration and optimization will be applied to different industrial processes, in case proposed by the student based on his/her interest. This activity is in line with most industrial needs, giving the basis for process integration and optimization, dealing with economic comparison of different solutions.

Chimica Organica

A practical synthesis of morpholines and oxazepanes through Lewis base promoted halocyclization of hydroxyalkenes

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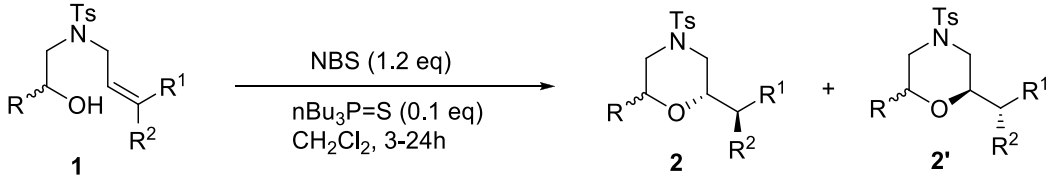
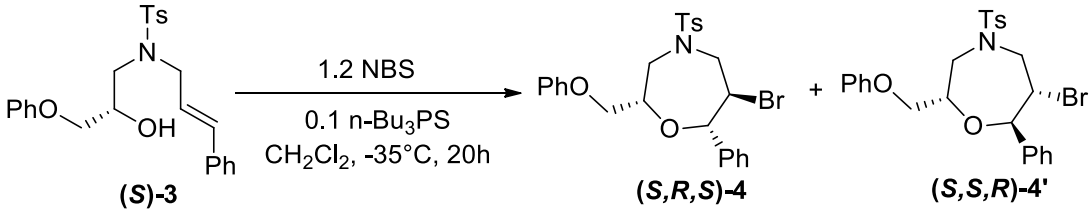
A concise synthesis of enantiomerically pure morpholines has been developed through the Lewis base promoted haloetherification of substituted hydroxyalkenes. A set of N-allyl-sulfonamides, bearing the nitrogen atom and the alkene required to generate the desired heterocycles, have been prepared with standard procedures and used as nucleophiles in the ring opening of epoxides under phase transfer catalysis conditions. Excellent yields of enantiomerically pure hydroxyalkenes **1** could thus be generated in a straightforward manner from the ring opening of easily available enantiopure epoxides.



The cyclization step has been carried out by reacting hydroxyalkenes **1** with *N*-bromosuccinimide in the presence of catalytic amounts of tributylphosphine sulphide as a soft Lewis base. The intermediate bromonium ion was thus smoothly converted without racemisation to a mixture of two diastereoisomeric compounds with good to excellent yields in a complete regioselective fashion.
The Lewis base is capable to inhibit racemisation of the bromonium intermediate thus enabling a stereoselective process leading to morpholines or oxazepane rings depending on the predominant cyclization mode. With all investigated enantiopure hydroxyalkenes **1** we could obtain good to excellent yields of two diastereoisomeric morpholines through 6-*exo* cyclization. The two diastereoisomers could be separated by chromatography or crystallization thus generating enantiomerically pure compounds.
However, in the case of phenyl substituted hydroxyalkene **3** (R^2 = Ph) the cyclization proceeded through a 7-*endo* cyclization mode thus generating a diastereoisomeric mixture (25% de) of oxazepanes **4**, which have been separated by crystallization. The structure of pure diastereoisomers thus obtained has been ascertained by X-ray diffraction analysis that allowed to assign the absolute configuration of the two newly generated stereocenters.
The diastereoisomeric excess could be increased to 35% in the presence of (*S*)-BINAPS as a chiral Lewis base. It is worth noting that the inversion of diastereoselectivity was observed by using better coordinating solvents such as acetonitrile.



[1] Tetrahedron Symposium 16-18 June 2015, Berlin.

A Practical Synthesis of Zosteric Acid: One Step Towards New Sustainable Antifouling Agent?

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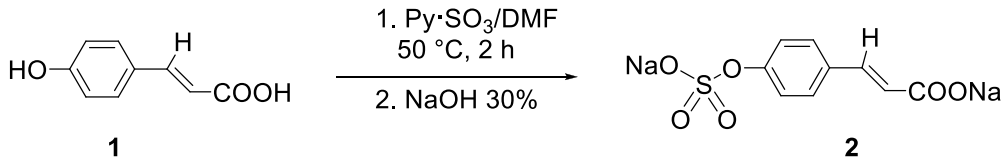
Zosteric acid is a secondary metabolite of the aquatic plant *Zostera Marina*, the most wide-ranging marine flowering plant in the Northern Hemisphere. In the last few years this compound stimulated a great deal of interest due to its demonstrated capability of hindering deleterious biofilm formation without exhibiting toxicity. Therefore zosteric acid represents a potential candidate for replacing toxic biocides employed in commercially available antifouling paints.
Zosteric acid has been isolated from natural sources through extraction with MeOH-H_2O mixtures or chemically synthesized from *p*-hydroxycinnamic acid (**1**). The extraction method affords only small amounts of the compound, whereas the chemical method suffers from limitations derived from the use of a corrosive reagent such as chlorosulfonic acid and toxic or dangerous solvents such as pyridine and diethyl ether. We recently developed a new practical method employing the complex Py·SO_3 as a solid, stable, sulfating agent (Scheme 1).



1 **2**

Scheme 1

The desired compound was isolated as sodium salt in nearly quantitative yields by neutralization of the reaction mixture with aqueous NaOH, followed by addition of methanol to remove sodium sulphate formed as byproduct. [1] Such a procedure can be easily scaled-up, thus providing a practical synthesis of sodium zosterate and zosteric acid derivatives [2] to be used as substitutes of toxic compound in the formulation of new environmentally friendly antifouling paints.

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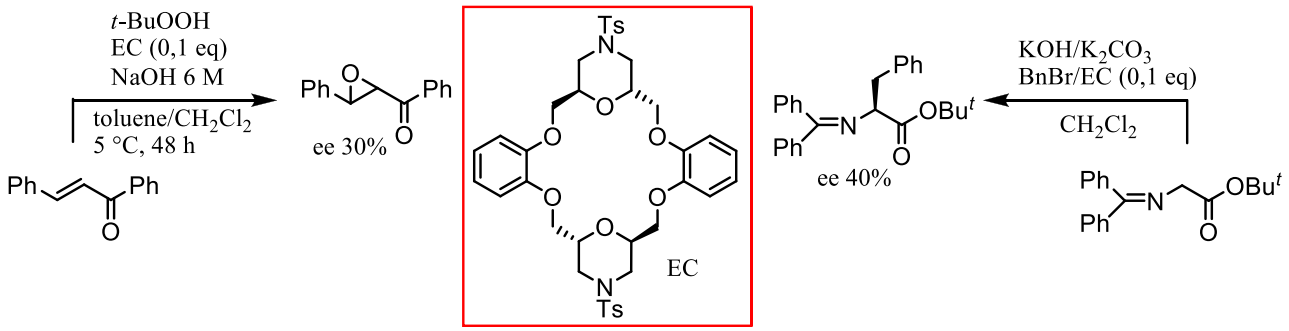
Nuovi processi a basso impatto ambientale

1. CATALISI PER TRASFERIMENTO DI FASE Domenico C. M. Albanese (domenico.albanese@unimi.it/Tel: 0250314165, 2° piano, corpo C, (ala nord)

Nel corso degli ultimi anni uno dei settori che ha suscitato maggiore interesse è quello della messa a punto di nuove reazioni più rispettose dell'ambiente. Questo sta avvenendo sia nel mondo accademico e sempre più anche nell'industria, sia per l'introduzione di nuove normative di protezione ambientale, almeno nel mondo occidentale, sia perché spesso un processo pulito è anche economicamente vantaggioso.
La catalisi per trasferimento di fase (CTF) rappresenta un utile strumento per la riduzione dell'impatto ambientale dei processi e spesso consente un vantaggio competitivo nei confronti dei prodotti provenienti dai paesi emergenti che sfruttano il basso costo del lavoro e la scarsità, quando non l'assenza, di norme ambientali sulle emissioni nell'ambiente dei processi industriali. Questa tecnica consente di condurre reazioni promosse da anioni tra due o più reagenti situati ciascuno in una fase distinta di un sistema eterogeneo. Le reazioni sarebbero inibite per l'impossibilità dei reagenti di entrare in contatto tra loro, ma con l'aggiunta di un opportuno catalizzatore (un sale quaternario di ammonio o fosfonio, oppure un polietere macrociclico o macrobiciclico), detto "trasferitore di fase", l'anione viene trasferito in fase organica sotto forma di coppia ionica altamente reattiva e la reazione può avere luogo, di solito in condizioni blande.
Il suo potenziale sintetico si è enormemente ampliato nel corso degli ultimi anni in seguito all'enorme sviluppo delle sue applicazioni anche in catalisi asimmetrica. La CTF è così diventata un utile strumento anche per la sintesi stereoselettiva. L'impiego di sali d'ammonio quaternari chirali ha infatti permesso di condurre in maniera stereoselettiva e con buone rese numerose reazioni attraverso l'attivazione stereoselettiva di diversi tipi di nucleofili.
Abbiamo iniziato un nuovo progetto di ricerca con l'obiettivo di sintetizzare nuovi eteri corona chirali a simmetria C_2. Il primo etere corona sintetizzato ha evidenziato una moderata capacità di controllare il decorso stereochimico delle due reazioni modello studiate (Schema 1), pertanto le ricerche sono attualmente indirizzate a modificare la struttura del catalizzatore per migliorarne l'efficienza.



Schema 1

2. BIOCATALISI Domenico C. M. Albanese (domenico.albanese@unimi.it/ Tel: 0250314165); Nicoletta Gaggero (nicoletta.gaggero@unimi.it- Tel: 0250314470)

Biocatalysts have many attractive features in the context of green chemistry: they are selective, highly efficient, biodegradable, work in mild reaction conditions (water as solvent, room temperature, neutral pH) affording cleaner reaction products. Furthermore, the use of biocatalysts get shorter synthesis avoiding the need of protection-deprotection steps and functional group activation.
In this regard, bovine serum albumin (BSA), a ubiquitous globular transport protein of biological systems, also catalyzes a number of organic reactions. Hydrophylic moieties are located on the protein surface, whereas hydrophobic residues are deeply buried in the interior of the molecule, creating suitable sites for reversible binding with endogenous and exogenous hydrophobic organic compounds.
We recently reported the use of BSA as a catalyst for stereoselective thio-Michael addition of aromatic and aliphatic thiols to chalcones.[1] In continuation of our interest on this subject, [2] we plan to investigate the BSA promoted Michael addition of *o*-aminothiophenols to chalcone in water in order to generate benzothiazepines, a very important class of compounds from the pharmaceutical point of view.

[1] N. Gaggero, D. C. M. Albanese *Tetrahedron* **2011**,
[2] N. Gaggero, D. C. M. Albanese *RSC Adv.* **2015**, *5*, 10588 (review).

Synthesis and Biological Evaluation of RGD Peptidomimetic-Paclitaxel Conjugates Bearing Lysosomally Cleavable Linkers

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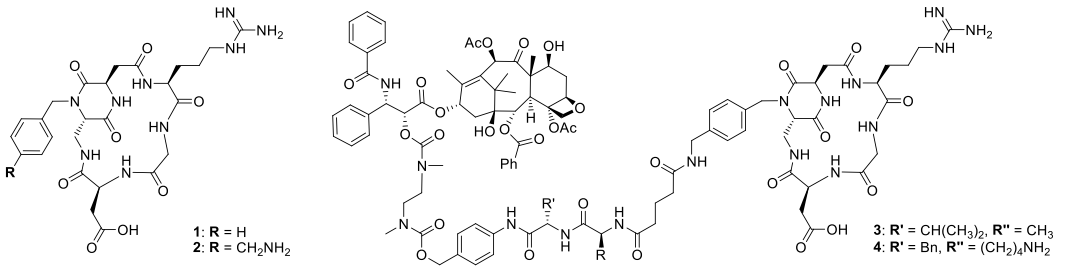
Integrins are a large family of heterodimeric transmembrane glycoprotein receptors, composed by two non-covalently-associated subunits (α and ß). Integrins $\alpha_V\beta_3$ and $\alpha_V\beta_5$ have been found to be overexpressed on blood vessels in human tumors, but not on vessels in normal human tissues. For this reason, these integrins have become attractive targets for pharmacological studies mainly in the oncology area. The Gennari and Piarulli group recently developed a peptidomimetic compound (**1**) containing the RGD (Arg-Gly-Asp) sequence and a diketopiperazine (DKP) scaffold as powerful $\alpha_V\beta_3$ integrin ligand.[1] A functionalized analogue of this ligand (**2**)[2] was linked to Paclitaxel through two lysosomally cleavable linkers (namely the Val-Ala and Phe-Lys peptide sequences).[3]



	IC_{50} (nM)		
Structure	CCRF-CEM ($\alpha_v\beta_3$ −)	CCRF-CEM $\alpha_v\beta_3$ ($\alpha_v\beta_3$ +)	Selectivity
Paclitaxel	155 ± 55	21 ± 2	7.4
RGD-Val-Ala-PTX (**3**)	5153 ± 977	77 ± 20	66.9
RGD-Phe-Lys-PTX (**4**)	535 ± 70	34 ± 2	15.7

Table 1: *Antiproliferative activity of* cyclo*[DKP-RGD] conjugates in CCRF-CEM and CCRF-CEM $\alpha_v\beta_3$ after 6 hour-treatment followed by compound washout and 138 hour-long growth in fresh medium.*

The resulting compounds **3** and **4** were subjected to stability assays in the presence of cathepsin B and lysosome extract, revealing that the free Paclitaxel is efficiently released under these conditions. The antiproliferative activities of the conjugates were evaluated against two isogenic cell lines expressing $\alpha_V\beta_3$ at different levels: the acute lymphoblastic leukemia cell line CCRF-CEM ($\alpha_V\beta_3$ −) and its subclone CCRF-CEM $\alpha_V\beta_3$ ($\alpha_V\beta_3$ +). A fairly effective integrin-targeting was displayed by conjugate **3**, which was found to inhibit cell proliferation with increased selectivity towards $\alpha_V\beta_3$-expressing cells compared to the free PTX (Table 1).

[1] Marchini, M.; Mingozzi, M.; Colombo, R.; Guzzetti, I.; Belvisi, L.; Vasile, F.; Potenza, D.; Piarulli, U.; Arosio, D.; Gennari, C. Chem. Eur. J. 2012, 18, 6195.
[2] Colombo, R.; Mingozzi, M.; Belvisi, L.; Arosio, D.; Piarulli, U.; Carenini, N.; Perego, P.; Zaffaroni, N.; De Cesare, M.; Castiglioni, V.; Scanziani, E.; Gennari, C. J. Med. Chem. 2012, 55, 10460.
[3] Dal Corso, A.; Caruso, M.; Belvisi, L.; Arosio, D.; Piarulli, U.; Albanese, C.; Gasparri, F.; Marsiglio, A.; Sola, F.; Troiani, S.; Valsasina, B.; Pignataro, L.; Donati, D.; Gennari, C. Chem. Eur. J. 2015, DOI: 10.1002/chem.201500158.

Acknowledgements: We gratefully acknowledge MIUR for financial support (PRIN project 2010NRREPL: Synthesis and Biomedical Applications of Tumor-Targeting Peptidomimetics).

Synthesis, characterization and biological evaluation of a dual action ligand targeting $\alpha_V\beta_3$ integrin and VEGF receptors

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Tumor angiogenesis is a crucial phenomenon for cancer development and metastasis, and is regulated by a number of cell surface receptors, such as integrin $\alpha_V\beta_3$ and VEGFRs, which are known to specifically interact (receptor-receptor "cross-talk").[1] A dual action ligand **1**, targeting both integrin $\alpha_V\beta_3$ and VEGFRs, was synthesized via conjugation of **3**, a functionalized analog of the potent peptidomimetic $\alpha_V\beta_3$ ligand **2**,[2] with the decapentapeptide **5**, a derivative acetylated at the Lys13 side chain of known peptide **4**, a VEGF receptor antagonist with anti-angiogenic activity.[3] Circular dichroism studies confirmed that both the RGD and VEGFR ligand portions of the dual action compound **1** substantially adopt the biologically active conformation. *In vitro* binding assays on isolated integrin $\alpha_V\beta_3$ and VEGFR-1 showed that the new conjugate **1** retains a good level of affinity for both its target receptors, although with one order of magnitude (10/20 times) reduction of potency. The dual action ligand **1** was able to strongly inhibit the VEGF-induced morphogenesis in HUVEC. Remarkably, its efficiency in preventing the formation of new blood vessels was similar to that of individual ligands **2** and **5**, despite the worse affinity towards integrin $\alpha_V\beta_3$ and VEGFR-1. This finding might be interpreted as the result of a synergy between the two covalently linked binding motifs.

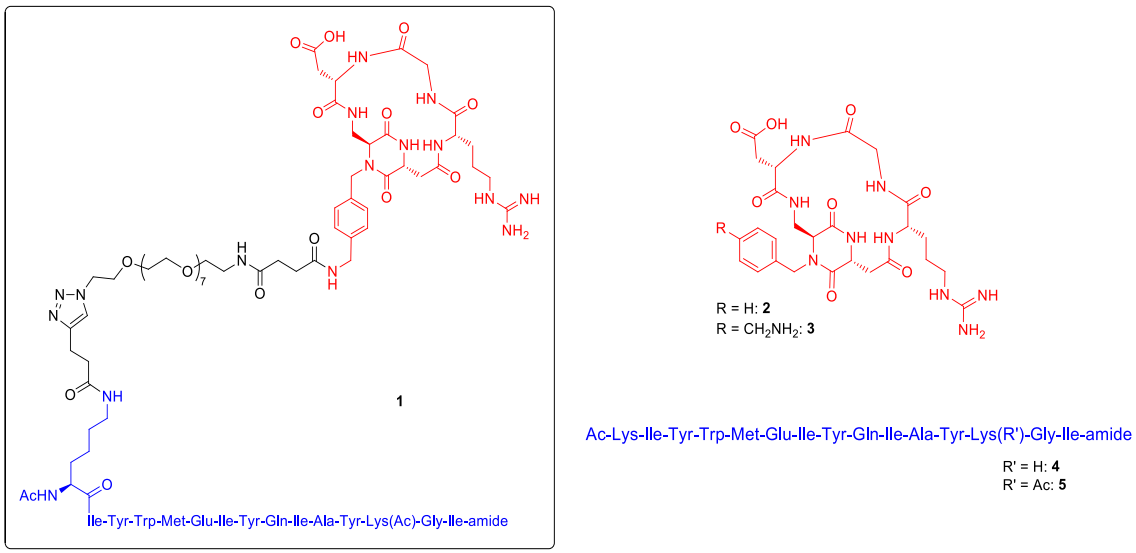

Figure 1. Dual action ligand **1** and its precursors.

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Acknowledgements: we gratefully acknowledge MIUR for financial support (PRIN project 2010NRREPL).

Cyclic isoDGR and RGD peptidomimetics: integrin antagonists and tumor-homing devices

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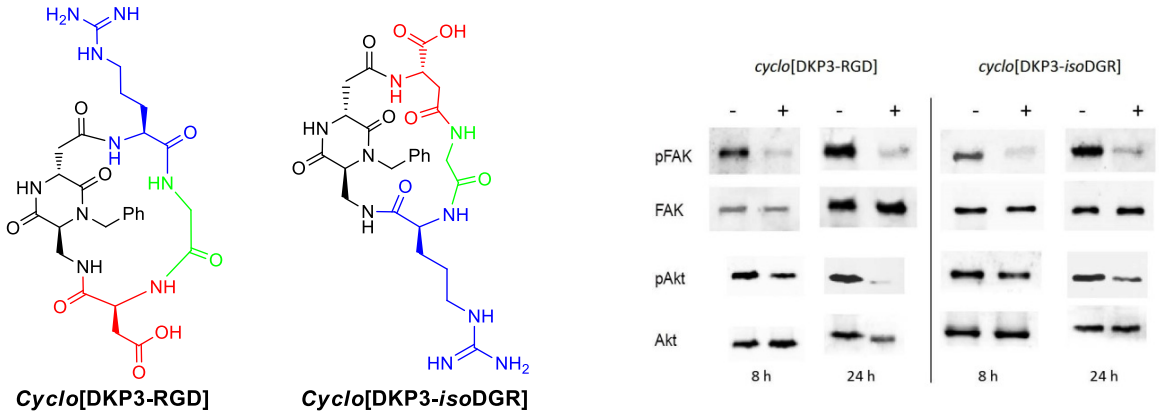
Integrins are a large family of cell adhesion receptors composed of two non-covalently bound α and ß transmembrane glycoproteins and are involved in physiological and pathological processes.[1] Several integrins, including $\alpha_V\beta_3$, $\alpha_V\beta_5$, $\alpha_5\beta_1$, and $\alpha_{IIb}\beta_3$, recognize endogenous ligands using the tripeptide sequence Arg-Gly-Asp (RGD) and its mimic *iso*Asp-Gly-Arg (*iso*DGR).[2] Four *cyclo*[DKP-*iso*DGR] integrin ligands have been synthesized and their ability to bind $\alpha_V\beta_3$ and $\alpha_V\beta_5$ integrins has been studied.[3] At least one low-nanomolar ligand was identified, namely *cyclo*[DKP3-*iso*DGR], which is, to the best of our knowledge, the most potent *iso*DGR $\alpha_V\beta_3$ integrin ligand reported so far (Figure 1). The biological activities of ligands *cyclo*[DKP3-RGD] and *cyclo*[DKP3-*iso*DGR], bearing the same bifunctional diketopiperazine (DKP) scaffold and showing similar $\alpha_V\beta_3$ integrin binding values, were compared in terms of their cellular effects in human U373 glioblastoma cells. They displayed overlapping inhibitory effects on the FAK/Akt integrin activated transduction pathway and on integrin mediated cell infiltration processes, and qualify therefore as integrin antagonists. With the aim of exploiting the tumor-homing potential[4] of *cyclo*[DKP3-*iso*DGR], a cyclic *iso*DGR peptidomimetic displaying a proper handle for conjugation to cytotoxic agents has been developed.



***Cyclo*[DKP3-RGD]** ***Cyclo*[DKP3-*iso*DGR]**

Figure 1. *Cyclo*[DKP3-RGD] and *cyclo*[DKP3-*iso*DGR] integrin ligands and inhibition of FAK/Akt phosphorylation in human U373 glioblastoma cells (western blot analysis).

Acknowledgements: we gratefully acknowledge Ministero dell'Università e della Ricerca for financial support (PRIN project 2010NRREPL).

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Computational modeling of peptidomimetics and glycomimetics targeting protein receptors

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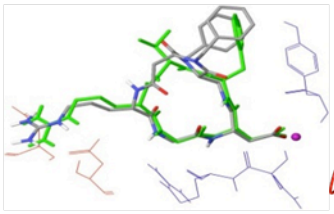
Keywords: computer-aided drug design, molecular recognition, molecular dynamics simulations, molecular docking, virtual screening

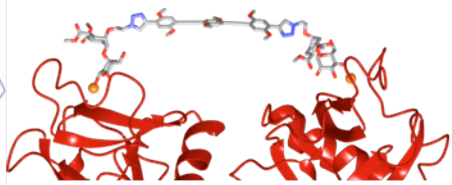
Computational modeling can provide insight at the atomic level into the recognition process of a peptide or sugar with its receptor and help to understand the requirements for binding. Our research is focused on the application of a broad range of computational techniques for the design and the study of structural and functional mimics of biomolecules, such as peptides and carbohydrates, which play a key role in the function of biological systems and in the etiology of many pathologic processes.
In particular, our activities are based on the combined use of molecular mechanics, computer simulations and docking calculations with available structural information (X-ray, NMR), and are aimed at defining structure and dynamics of peptidomimetics, glycomimetics and their complexes with the target protein.
Two main research projects are currently in progress.

The first project concerns the design and the study of **peptidomimetics** targeting protein-protein interactions of therapeutic relevance in cancer, such as the interactions involving cell adhesion molecules (integrins, cadherins) or other cell surface receptors (e.g. growth factor receptors) which play key roles in tumor angiogenesis, progression and metastasis. In this context, peptidomimetics mimicking the hot spots and the structural features of these protein interfaces represent a promising strategy for obtaining innovative drugs with an optimal pharmacological profile (see also the research lines of Prof. Gennari) [1].

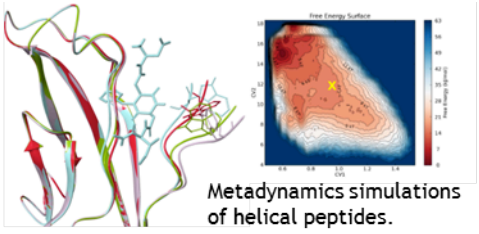
The second project is aimed at designing and studying **glycomimetics** as inhibitors of multivalent carbohydrate-protein interactions, which mediate viral and bacterial adhesion to host cells, such as the DC-SIGN-mediated adhesion in the initial steps of HIV infection (see also the research interests of Prof. Bernardi) [2].



Docking of a peptidomimetic ligand into $\alpha_v\beta_3$ integrin binding site.



Docking of a divalent ligand within two adjacent DC-SIGN binding sites.



Metadynamics simulations of helical peptides.

Molecular dynamics simulations of peptidomimetic ligand - cadherin complexes.

The strength of our research relies on the integration of different computational methodologies with experimental approaches to accomplish an interdisciplinary study, based on the interplay between computational, synthetic organic, structural chemistry and biology. In particular, our computational modeling activities are tightly interconnected with spectroscopic NMR studies performed by the group of Dr. Potenza [3], as shown in our posters 3 and 4.

[1] M. Mingozzi, A. Dal Corso, M. Marchini, I. Guzzetti, M. Civera, U. Piarulli, D. Arosio, L. Belvisi, D. Potenza, L. Pignataro and C. Gennari, *Chem. Eur. J.* **19**, 3563 (2013); F. Doro, C. Colombo, C. Alberti, D. Arosio, L. Belvisi, C. Casagrande, R. Fanelli, L. Manzoni, E. Parisini, U. Piarulli, E. Luison, M. Figini, A. Tomassetti and M. Civera, *Org. Biomol. Chem.* **13**, 2570 (2015); F. Doro, G. Saladino, L. Belvisi, M. Civera and F. L. Gervasio, *J. Chem. Theory Comput.*, Article ASAP (DOI: 10.1021/ct5010164)
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Targeting protein-protein interactions in cancer with peptidomimetics: insights into ligand conformation and ligand-receptor interactions

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The importance and specificity of protein associations in cellular events and in the development of many diseases make protein-protein interactions attractive targets for therapeutic intervention. In cancer, some specific cell surface receptors - e.g. the $\alpha_V\beta_3$, $\alpha_V\beta_5$ and $\alpha_5\beta_1$ integrins and several growth factor receptors - regulate diverse cell functions crucial to the initiation, progression and metastasis of tumors, through the formation of specific protein-protein complexes [1]. The demonstration that antibodies and peptidomimetic compounds designed from peptide sequences, can dissociate protein-protein interfaces involving these receptors or prevent protein complex formation suggests that this mechanism for inhibition of protein functions holds great promise as a novel therapeutic approach.
The poster will discuss the contribution of various computational techniques to the development of peptidomimetics capable of reproducing the Arg-Gly-Asp (RGD) tripeptide epitope that mediates the interaction between extracellular matrix proteins and integrins expressed on the membrane of cancer cells. In particular, the combined use of conformational analysis, molecular dynamics simulations and docking calculations with available structural information (x-ray, NMR) will be shown in defining the conformation of cyclic peptidomimetics containing rigid diketopiperazine (DKP) scaffolds, and the ligand-integrin interactions at a molecular level [2, 3]. The different stereochemistry and the different substitution of the scaffold, as well as the RGD or RGD-like recognition sequence, strongly influence the conformations adopted in the free-state and the binding mode of these ligands in the active site of $\alpha_V\beta_3$ and $\alpha_5\beta_1$ integrins. The results will be compared to the results of competitive receptor binding assays, of cell adhesion experiments and of NMR interaction studies of the peptidomimetic ligands with $\alpha_V\beta_3$ and $\alpha_5\beta_1$ integrin rich intact cancer cells [4].

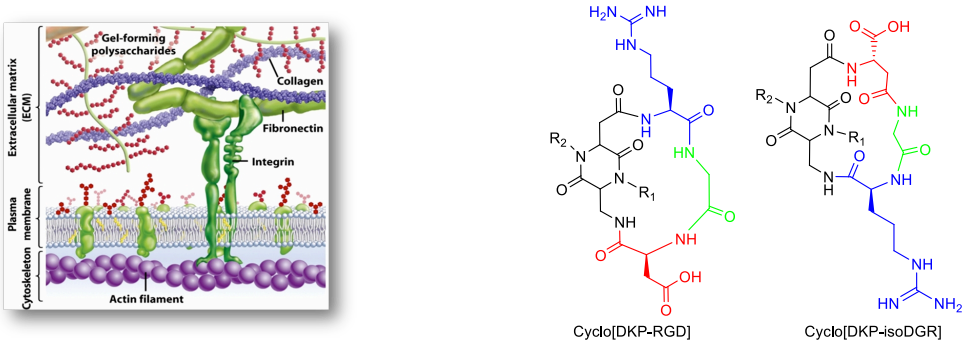

Figure 1. Integrins as transmembrane cell adhesion receptors (left). Cyclic peptidomimetic RGD and *iso*DGR integrin ligands (right).

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Flow chemistry - Catalytic reactors

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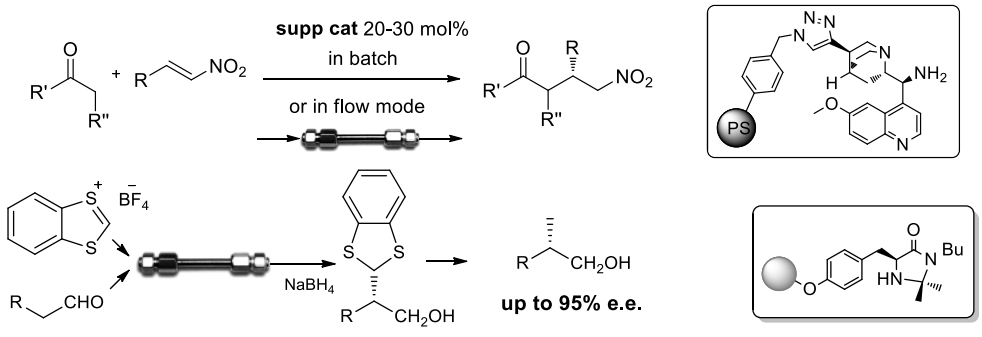
Over the last two decades *Green Chemistry* has become firmly established as an approach to designing new products and manufacturing processes in the pharmaceutical industry. To this end, the launch of a second generation process research program to develop environmentally favorable active pharmaceutical ingredients (APIs) manufacturing has now become a top-priority of major pharmaceutical companies. However, despite the impressive progress of the last years, the application of continuous-flow methodologies to the stereoselective synthesis of chiral multifunctional molecules is still underdeveloped. We reported for the first time the use of a bifunctional catalyst for the nucleophiles addition to nitrostyrene derivatives under continuous flow conditions; the potential of this flow chemistry approach was demonstrated by the successful synthesis of an advanced intermediate for the preparation of the GABA-B receptor agonist Baclofen and studies on other reactions are currently underway.[1]

In continuation of our works on immobilized catalysts the group is extending its activities into technological and engineering aspects. We focus on developing novel catalytic packed-bed and monolithic reactors,[2] exploiting the unique features of such devices in stereoselective transformations.[3]



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Organocatalysis – New catalytic synthetic methodologies

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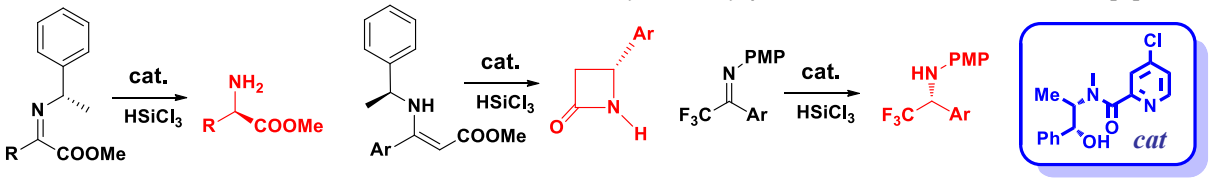
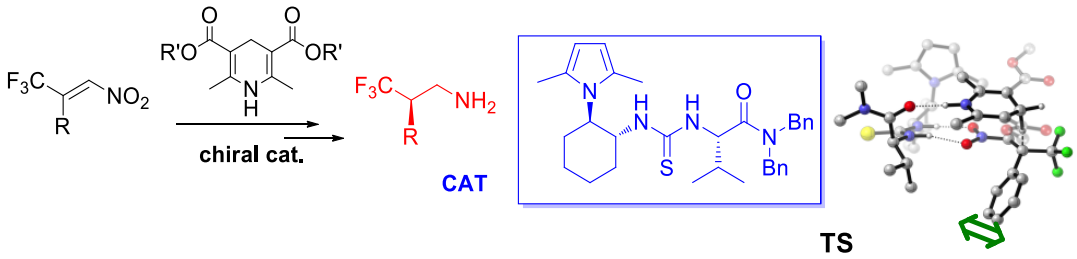
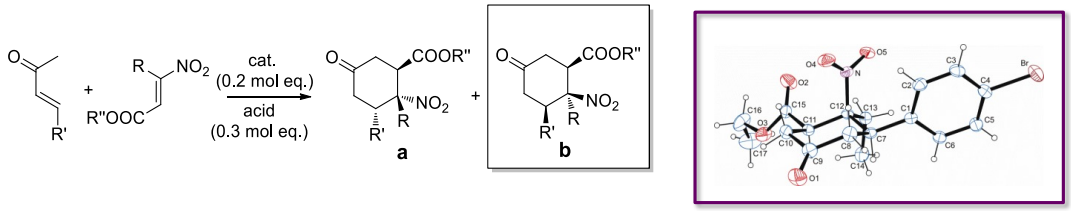
We are a very dynamic group interested in all aspects of **stereoselective synthesis**. Major efforts are dedicated to the development of novel synthetic methodologies and to the design, discovery and study of chiral catalysts; a special attention is devoted to the development of easily available, practical and widely applicable organocatalytic species. We are also starting new projects where we aim to take advantage of molecular recognition events to control (stereo)selectivity. In addition we use computational tools to investigate the transition structure geometries and to clarify the reaction mechanisms.
Despite the historical need of chiral amines, their synthesis remains challenging; the replacement of metal-based catalysts with equally efficient metal-free counterparts is very appealing in view of possible applications of non toxic, low cost, and environmentally friendly promoters on industrial scale.[1]



Three metal-free catalytic methodologies available for the reduction of carbon-nitrogen double bond are now available: i) binaphthol-derived phosphoric acids catalyzed reductions, with dihydropyridine-based compound as the reducing agent;[2] ii) trichlorosilane mediated reductions,[3] with chiral Lewis bases; iii) metal-free hydrogenation via FLP (Frustrated Lewis Pair) methodology.



New synthetic methods are explored: from (E)-ß-substituted-ß-nitroacrylates and α,β-unsaturated ketones, a stereoselective organocatalyzed one-pot methodology allowed to synthesize highly decorated chiral 2-nitro-cyclohexane carboxylic esters. The reaction is promoted by Cinchona alkaloids-derived primary amines in the presence of an acidic co-catalyst and affords two diastereoisomers, in good yields and high enantiomeric excess (often higher than 90% e.e.). By replacing conventional heating with microwave irradiation, cleaner reactions in short times (from 48 hours to 30 minutes) were obtained.[4]



The group is also interested in $SiCl_4$ mediated reactions; silicon tetrachloride is a weak Lewis acid with many attractive features: low cost, ready availability, favorable toxicity and safety profiles, possibility of multiple modes of activation. New metal-free methodologies have recently been developed to efficiently catalyze different reactions, where “hypervalent” silicon species are involved as intermediates.[5]

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Functionalized materials for imaging and supported chiral catalysts

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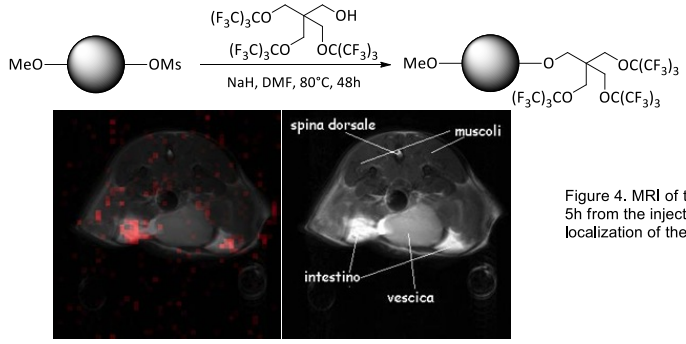
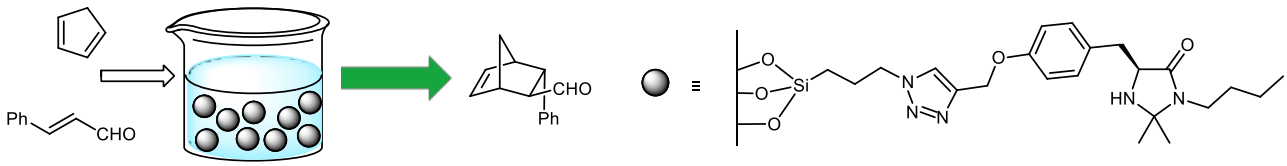
Recently we started a project aimed to the development of biodegradable polymers with controlled macromolecular architecture as **new polyfunctional agents for 19F MR imaging**. The research is highly multidisciplinary, related o organic, polymer, biological, and materials chemistry. Our target is the development of novel macromolecular materials bearing a fluorinated residue suitable for ^{19}F MRI, which may be further implemented with other functions, for example a diagnostic one or, in the future, even a therapeutic one. Because of the lack of any ^{19}F background in the body, observed signals originating from injected ^{19}F containing agent exhibit an excellent degree of specifity and merging of recorded ^{19}F images on ^{1}H images enables an exact anatomic localization of fluorinated substances as "hot spots" [1]



7	MW 5786	y = 80%	**%F = 9%**
8	MW 2786	y = 82%	**%F = 18.4%**
9	MW 1536	y = 68%	**%F = 33.4%**
10	MW 1336	y = nd	**%F = 38%**

Figure 4. MRI of the polymer 8 after 5h from the injection: in red the localization of the fluorine signal

The groups is interested in the immobilization of chiral catalysts onto different materials and exploit their physical-chemical properties to develop recoverable and recyclable catalysts. The synthesis of chiral imidazolidinones **on mesoporous silica nanoparticles**, exploiting different anchoring sites and different linkers was reported and fully characterized by solid-state NMR, N_2 physisorption, SEM, and TGA.[2]
The immobilization of an ad hoc designed organocatalyst on iron oxide **magnetic nanoparticles (MNPs)** allowed to develop a recovery of the chiral catalyst that has been successfully performed by simply applying an external magnet to achieve a perfect separation of the MNPs from the reaction mixtures.[3]
Recently, 9-Amino-9-deoxy-*epi*-quinine, properly modified by suitable linkers, was anchored on **highly cross-linked poly(styrene), poly(ethylenglycol) and silica.** The resulting species were characterized by NMR spectroscopy and tested as supported organocatalysts in the reaction between *i*-butyric aldehyde and nitrostyrene. PS- and PEG-supported catalysts outperformed their non-supported counterpart affording the desired product in high yield and ee (>90% ee).[4]
Other **chiral Hybrid Inorganic - Organic Materials** are currently under study.[5]



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Argomenti di Ricerca nel gruppo Bernardi

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Research Interests

Our group is interested in the design and synthesis of bioactive molecules that can be used as probes to interrogate biological systems.

In particular, we are currently focusing on two areas:

- antagonizing the action of sugar-binding protein (lectins) with ***glycomimetic*** structures
- controlling the activity of the heat-shock protein ***HSP90*** with chemical modulators.

Design and synthesis of glycomimetics

The interaction of sugars with proteins initiates many biological processes. We can achieve control of these processes using sugar-like structures to antagonize the natural ligands at the protein receptor level. Our group is using chemical knowledge and computational techniques to design and synthesize sugar mimics, based on known structural properties of bioactive oligosaccharides and of their protein complexes.

Our most recent results have been achieved with **DC-SIGN antagonists as inhibitors of viral infections.** DC-SIGN is a receptor of dendritic cells, involved in sexual transmission of HIV. Blocking DC-SIGN could allow to block viral entry at the mucosal level and represents a new opportunity for developing more effective antiviral drugs. Our *Poster 1* (MULTIVALENT DC-SIGN LIGANDS WITH A RIGID CORE OF CONTROLLED LENGTH) is dedicated to this topic.

Design and synthesis of Hsp90 allosteric modulators

Hsp90 is a molecular chaperone highly abundant in the whole cellular environment. It has different functions, and it is very important for the cell's response to stress, cell cycle control, cell survival and many signaling pathways. Recently it has become an important target for development of new drugs, in particular for cancer diseases and neurodegenerative disorders. Most of the known small-molecule inhibitors that have shown potent antitumor activity target the Hsp90 N-terminal domain and directly inhibit its ATPase activity.

In collaboration with Dr. Giorgio Colombo group at ICRM-CNR (Milan) we are rationally designing and synthesizing allosteric modulators (activators) of Hsp90 ATPase activity that retain antitumor activity. Our ***Poster 2*** (TOWARDS ALLOSTERIC MODULATORS OF HSP90) shows some of these interesting results.

Multivalent DC-Sign Ligands With a Rigid Core of Controlled Length

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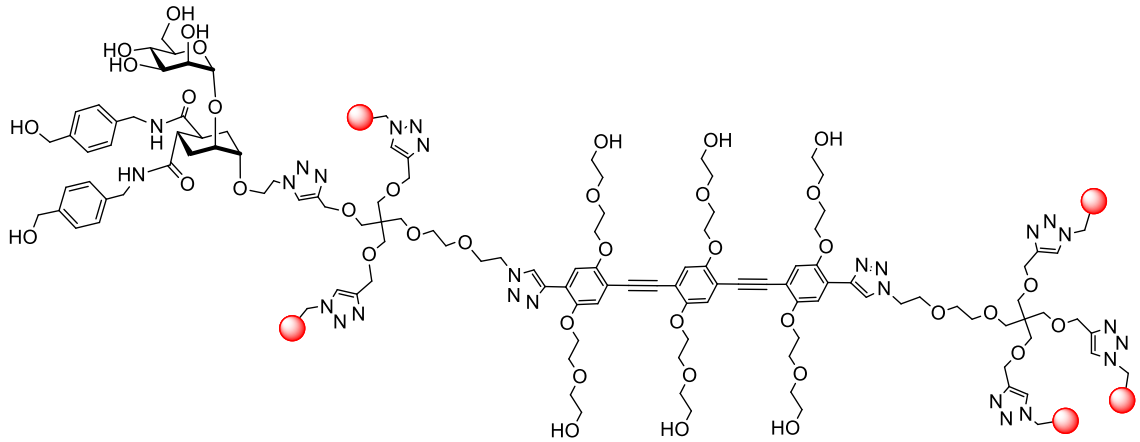
Human immunodeficiency virus (HIV) is still a major health problem, causing the death of over 1 million people per year. The search for HIV-entry inhibitors represents a promising challenge to prevent HIV infection. In this field, DC-SIGN, a receptor expressed at the surface of the mucosal dendritic cells and involved in the early stages of HIV infection, is an important cellular target.[1]
DC-SIGN is a calcium-dependent tetrameric lectin, which recognizes and binds high-mannose oligosaccharides displayed at the surface of HIV virus. The use of artificial molecules displaying multivalent carbohydrate moieties, able to interact with DC-SIGN with good affinity, should represent a therapeutic strategy in order to prevent HIV attachment to dendritic cells.

Here we present a library of multivalent glycomimetic compounds potentially able to bind simultaneously two binding sites on DC-SIGN, thus exploiting the chelating binding mode to enhance their affinity for the target. Compounds were synthesised by varying the length of a rigid aromatic scaffold and the nature as well as the valency of the sugar moieties at each end of the central core. Every synthesised compound has been tested as HIV inhibitor through Surface Plasmon Resonance (SPR) inhibition assays.
Some of the synthesised compounds were tested for the ability to inhibit HIV transmission in an in vitro trans infection assay, revealing a high activity that seems depend on scaffold length. Tests were performed by Dr Angela Berzi, in the laboratories of Prof. Mario Clerici (University of Milan).
Synthetic pathways and biological tests will be presented, together with preliminary evaluation of compounds morphological behaviour in aqueous solution.[2]



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Insights into molecular bases of cadherin – small ligands interaction by STD - NMR

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Cadherins are calcium-dependent adhesive membrane proteins involved in intercellular junctions and overexpressed in several solid tumors [1]. Classical cadherins are characterized by a N-terminal extracellular domain, constituted by five EC1-EC5 domains rigidified at the interface by calcium ions, by a single pass transmembrane region and by a conserved C-terminal cytoplasmic tail. They mediate cell-cell adhesion by forming homophilic dimers between the N-terminal extracellular domains of two cadherins localized on adjacent cells. Cadherins are known to play a major role in physiological and pathological processes such as tissue morphogenesis and stability, as well as in the immune system regulation [2]. Cadherins' dysregulation has been shown to contribute to different aspects of tumor progression [3]. Thus, cadherins are becoming valuable diagnostic and prognostic indicators, as well as potential therapeutic targets. Despite a growing interest in the field, the rational design of small ligands targeting cadherins protein – protein interactions is still in its infancy. So far, only a N (neuronal subtype) – cadherin antagonist cyclic peptide, ADH-1, has entered clinical trials as a systemic anticancer agent [4]. Our group designed and synthesized a small library of peptidomimetics based on the tetrapeptide sequence Asp1 – Trp2 – Val3 – Ile4 (DWVI) of the N-terminal "adhesive arm" (identified by the crystallographic structures) of cadherins [5]. These compounds were obtained by replacing the central dipeptide Trp2 – Val3 unit of the DWVI adhesive motif with several scaffolds developed in our laboratories. Critical aspects concerning the initial recognition process of cadherins and complete adhesion mechanisms as well as structural and in silico studies of small molecule – cadherin interactions need to be fully investigated. So, we began structural investigation by NMR of the interaction between cadherins' constructs and some peptidomimetics.
NMR techniques, tr – NOESY and STD [6], are being applied in order to detect and study the binding epitopes of these compounds with the EC1 – EC2 construct of the epithelial subtype E – cadherin. NMR and X-ray experiments are being used to obtain insights into peptidomimetics – cadherin interactions at a molecular level, providing information on the ligand epitope as well as on the receptor - bound conformation.

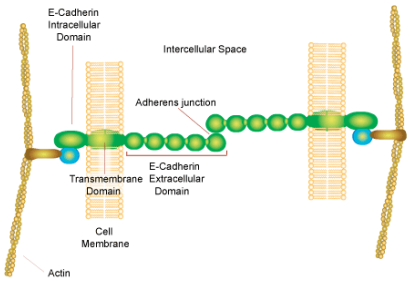

Figure 1. Cadherins as transmembrane cell adhesion receptors.

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For your thesis… Just a spoonful of sugar!

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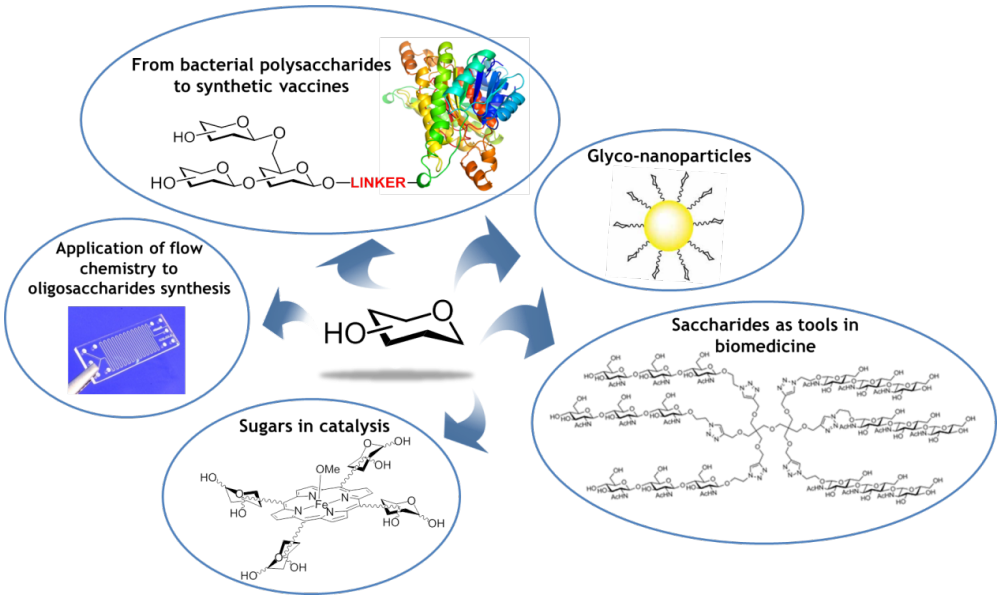
Our ongoing projects are focused on the synthesis of fragments of selected saccharide antigenic structures and their structural analogues (such as carba-analogues, C-glycosides and zwitterionic derivatives). Besides standard batch procedures, microfluidic technique is also applied to the synthesis of valuable intermediates.[1] The overall goal is the construction of multivalent systems by their conjugation to carrier proteins or nanoparticles, and the subsequent investigation of the biological and immunological properties of the resulting conjugates in pursuit of the rational design of new carbohydrate-based vaccines.[2-5]
We are also interested in the application of saccharides in biomedicine, as potential inhibitors of some key receptors involved in relevant diseases. For example, dendrimers and dendrons glycosylated with oligomers of *N*-acetyl glucosamine that are able to inhibit the activity of Mannose Binding Lectin (MBL) in brain tissue affected by ischemia. Another target are molecular chimeras containing two chemical entities with distinct structures and functions: one unit is a potential inhibitor of caspases (a class of proteins highly involved in apoptosis). The second entity is constituted by a saccharide unit potentially able to inhibit the activity of the enzyme *O*-glucosaminidase (OGA) and hence to inhibit, in an indirect way, the hyperphosphorylation of TAU protein that, according to recent studies, appears to be a major cause of degenerative diseases of the central nervous system, in particular Alzheimer's disease.
We are also interested in the synthesis of glycoporphyrins by the conjugation of saccharide units with a biocompatible porphyrin scaffold. These compounds have several biological applications due to the crucial role of carbohydrates in vital ligand-receptor interaction and recognition phenomena. In addition, since metallo-porphyrins are active in promoting nitrene and carbene transfer reactions, glycoporphyrin complexes with transition metal can be a new class of catalysts. Taking advantage of the chiral and hydrophilic nature of saccharide units, this class of compounds can be used either for asymmetric synthesis or to develop new sustainable water-soluble catalysts.



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Handling nano-objects: engineered metal-based nanoparticles for diagnostic and therapeutic applications

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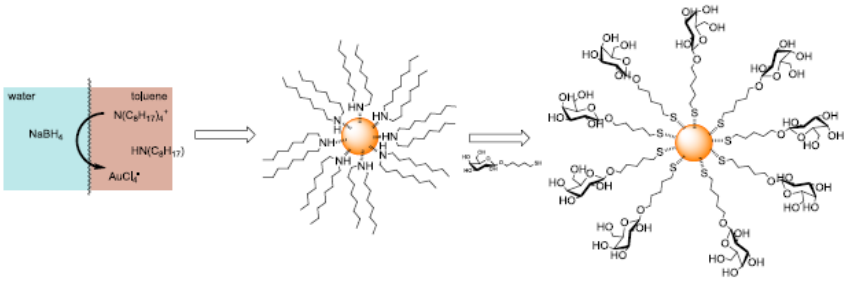
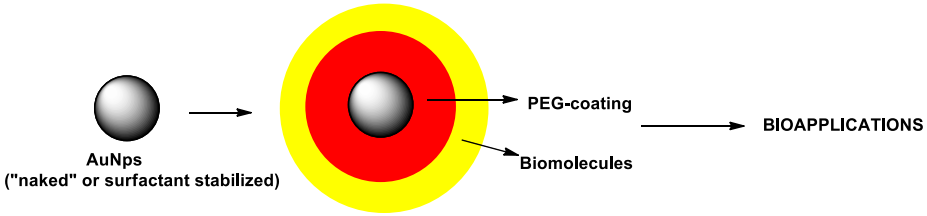
Among different polyvalent scaffolds capable to display multivalent interactions, gold nanoparticles (Au-NPs) have enormous potential applications in biology and medicine. Au-NPs can be coated with a strongly grafted monolayer of organic molecules (usually thiols) which can bear several biorecognition units. The ease of preparation, reproducibility and self-organized nature make Au-NP an ideal multivalent system for biological applications. Therefore, grafting synthetic saccharide fragments on gold nanoparticles would allow to compensate for their inherent poor immunogenicity, exploiting the property of multivalency to enhance the interaction of these nanosystems with specific antibodies, in pursuit of the rational design of novel carbohydrate-based vaccines.



In addition, stabilized gold nanoparticles show interesting behaviour as computed tomography (CT) contrast agents owing to their high X-ray absorption coefficient, low toxicity and high biocompatibility. The performance of these materials, in terms of prolonged circulation time, biodistribution, enhanced renal clearance and little accumulation in reticuloendothelial system (RES) organs strongly depends on their particle size, shapes and the nature of stabilizing ligands. The elucidation of these main factors is crucial in order to obtain effective and reliable contrast agents at the nano-size.



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Research activity of Prof. Giordano Lesma[1] and Dr.ssa Alessandra Silvani[2]

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- **Sintesi di composti antitumorali analoghi di prodotti naturali, potenzialmente in grado di aggirare il fenomeno della multidrug resistance.**
  Natural products are excellent sources for drug discovery and development. For cancer therapy, many antitumor agents used in the clinic are either ***natural products themselves or derivatives*** *from natural sources including plants, animals and microorganisms (also of marine origin). Because of numerous adverse effects and limitations in use, new drugs with better properties are needed.*
  Our current project regards the synthesis of analogues of natural products (**hemiasterlin, phenylahistine**), which are not substrates for efflux pumps (P-glycoproteins, multidrug resistance-associated proteins) or which are inhibitors for such proteins (**ecdysteroids**). **Pubblicazione più recente:** "Hemiasterlin analogues incorporating an aromatic, and heterocyclic type C-terminus: design, synthesis and biological evaluation" Lesma, G.; Silvani, A.; et al. *Molecular Diversity* **2014**, 18, 357-373. DOI 10.1007/s11030-014-9507-9

- **Progettazione, sintesi e valutazione conformazionale di nuove strutture peptidomimetiche potenzialmente attive nei processi d'interazione peptide-recettore o proteina-proteina**
  Peptide chemistry is at the core of cell signaling processes and accounts for many targets in medicine. Peptides often show high biological activities, but just partly fulfil the criteria of orally bioavailability, receptor selectivity and high stability towards enzymatic degradation, which would be amenable for pharmaceutical purposes. One strategy to overcome such drawbacks is the use of ***peptidomimetics****.*
  Our current project regards the design and synthesis of **minimalist peptidomimetics** by means of **multicomponent reactions (MCRs)/cyclization strategies**. In minimalist peptidomimetics, the scaffold can be every organic fragment, including heterocycles. MCRs have emerged as a powerful tool in synthetic organic chemistry aimed to 'atom economy', due to their valued features to maximize structural complexity and convergence. **Pubblicazione più recente:** "Application of the Ugi reaction with multiple amino acids-derived components: synthesis and conformational evaluation of piperazine-based minimalist peptidomimetics" Lesma, G.; Silvani, A. et al. *Org. Biomol. Chem.* **2015**, *Accepted,* DOI 10.1039/C5OB00218D.

- **Sviluppo di nuove metodologie di sintesi asimmetrica, per la medicinal chemistry.**
  The stereoselective formation of ***carbon–carbon and carbon–nitrogen bonds*** *has emerged as one of the most important topics in organic chemistry. In particular, the* ***metal-free asymmetric induction*** *by means of small organic molecules, so-called* ***organocatalysis****, has become a rapidly growing area of research as it offers mild reaction conditions and is environmentally benign.*
  Our current project regards the synthesis of **new chiral oxindole derivatives** by means of nucleophilic addition to carbon–nitrogen double bonds or by MCRs reactions. Among the procedures for organocatalysis reported to date, we focuse on **chiral Brønsted acid catalysis**, through the use of chiral phosphoric acids. **Pubblicazione più recente:** "Asymmetric Ugi 3CR on isatin-derived ketimine: synthesis of chiral 3,3-disubstituted 3-aminooxindole derivatives" Lesma, G.; Silvani, A. et al. *Beilstein J. Org. Chem.* **2014,** *10,* 1383-1389.

- **Valorizzazione degli scarti vegetali.**
  Waste valorization is the process of ***converting waste materials into more useful products*** *including chemicals, materials, and fuels.*
  Our current project regards an integrated valorization of the **rice productive chain** residues, with particular reference to isolation and structural characterization of high value **phytosterols**, assessment of their biological properties and possible chemical derivatization. **Pubblicazione più recente:** "Cannabinoid-free Cannabis sativa L. grown in the Po valley: evaluation of fatty acid profile, antioxidant capacity and metabolic content" Lesma, G.; Silvani, A. et al. *Natural Product Research* **2014**, DOI: 10.1080/14786419.2014.926354.

Tetrathia[7]helicene Derivatives: an Eclectic Class of Chiral Molecules to use in Asymmetric Catalysis and as DNA Intercalators

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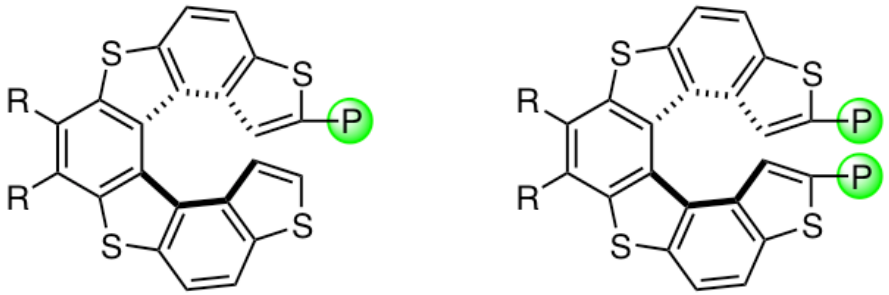
Tetrathia[7]helicenes (7-TH) are polyconjugated π-systems, in which four thiophene rings are orthofused to alternating arene rings to generate a non planar, chiral, stable helix which allows the existence of *M* and *P* enantiomers. The 7-TH systems are very interesting structures even because they can be easily and selectively functionalized in the alpha positions of the terminal thiophene rings, making it possible the introduction of appropriate substituents [1].
In this context, our studies are aimed to set up novel 7-TH phosphorus derivatives as potential chiral ligands to use both in asymmetric organometallic [2] and organocatalysis [3].



P : PR_2, $P(O)R_2$, $PR_2[BH_3]$, $P(O)(OEt)_2$

Moreover, we are also studying novel nanosystems for cell delivery of 7-TH derivatives as potential helical DNA intercalators [4].

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Peptide Nucleic Acids as Tools for Diagnostics and Therapy

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PNA are a remarkable example of a simple, neutral structure able to act as a perfect mimic of native nucleic acid structures in terms of molecular recognition properties. PNA are made of a pseudopeptide backbone, in which the ribose phosphodiester backbone of DNA and RNA is replaced by units of *N*-(2-aminoethyl)glycine, on which the nucleobases are inserted (Figure 1). Therefore, they can bind to target natural DNA or RNA with high sequence specificity and affinity and are excellent candidates in diagnostics and biodrug therapy.
Our studies on this research topic are aimed to tailor the structure of selected sequences of PNA to specific objectives with unconventional functionalities such as luminescent di-rhenium complexes or magnetic nanoparticles (MNPs).
The insertion of the luminescent rhenium complexes has a twofold aim: allowing the traceability of PNAs within the organism by optical imaging, and facilitating cell penetration [1]. The conjugation of PNA to MNPs can be exploited both as contrast agents for magnetic resonance imaging (MRI) and as sources of local overheating for hyperthermia treatment [2]. The study of these modified PNAs for the microRNA recognition in antisense strategy, both in vitro and in vivo, are currently in progress in our laboratory.

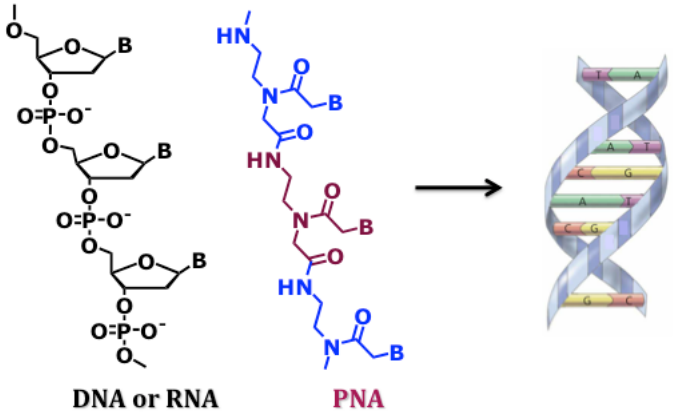

Figure 1.

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Silver(I) oxide nanoparticles as a catalyst in the azide-alkyne cycloaddition

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Metal oxide inorganic nanoparticles (NPs) have recently emerged as effective catalysts in a number of synthetically useful transformations, including 1,3-dipolar cycloadditions[1]. Such a reaction between arylzides and monosubstituted acetylenes[2] have been carried out for the first time in the presence of catalytic amounts of silver(I) oxide nanoparticles.

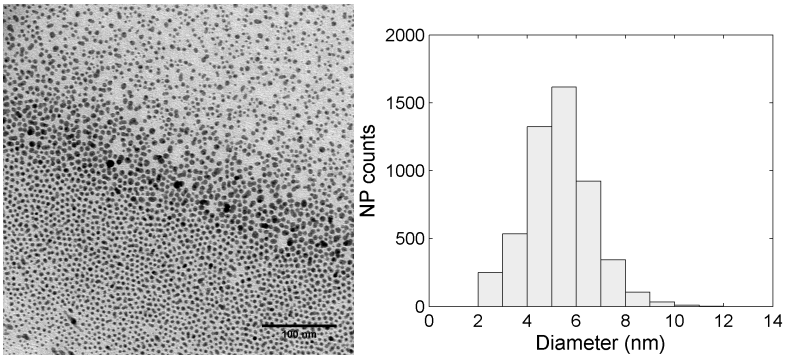
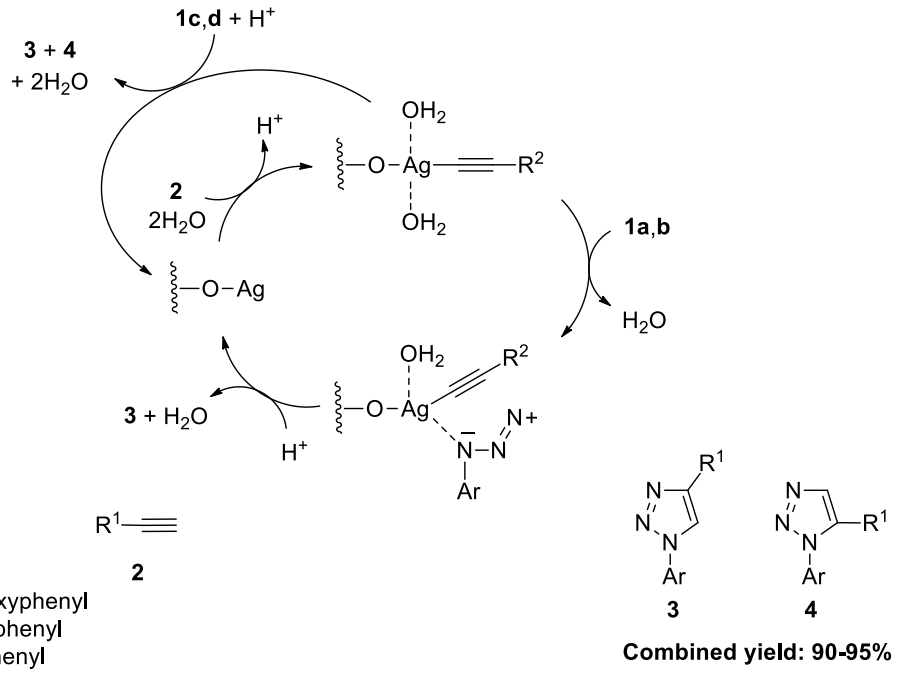


Figure. TEM image of as-synthesized Ag2O NPs (left) and the corresponding size distribution (right).

4-Substituted 1,2,3-triazoles **3** were usually the only products according to the usual "click" behaviour[1], while the presence of electron-withdrawing groups onto the azide moiety caused a loss of regioselectivity giving mixtures of 4- and 5-substituted 1,2,3-triazoles. The following novel catalytic cycle has been proposed to rationalise this latter "non-click" behaviour.



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Synthesis of new potential anticancer compounds

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Research in the Passarella group is centered on the chemical synthesis of new pharmaceutically active compounds. The strategies and approaches used are:

- Functionalization of known active compounds[1]
- Synthesis of analogues of active compounds[2]
- *Ex novo* synthesis supported by modeling studies
- Functionalization of known active compounds to induce the formation of nanoparticles by self- assembling[3]
- Optimization of the industrial synthesis of APIs (Active Pharmaceutical Ingredient)

A large number of collaborations with national and international research groups, involved in the fields of biology, biomedicine and computational chemistry, have been started because of the interdisciplinary nature of these projects.

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Use of chiral supramolecular ligands in Pd-catalysed enantioselective allylic substitution reactions

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The use of noncovalent supramolecular ligand-ligand and ligand-substrate interactions in transition metal-catalysed transformations is a rapidly emerging area of research. Non-covalent interactions between monodentate ligands (e.g., hydrogen bonding or coordinative bonding) have been shown to impart higher activity and chemo- regio- and stereoselectivity to the corresponding transition metal complexes in a number of catalytic applications. Analogously, supramolecular ligand-substrate interactions, and particularly hydrogen bonding, have been used to direct the regio- and stereochemistry of several metal-catalysed reactions. Moreover, the catalytic systems relying on supramolecular interactions are generally capable of self-assembling from simpler components in the environment where catalysis is to take place, and are therefore very well-suited for combinatorial catalyst discovery strategies and high-throughput screening. This research line aims at applying the concepts of supramolecular catalysis to Pd-catalysed asymmetric allylic substitution (AAS) reactions,[1] in order to achieve good activity and enantioselectivity employing monodentate ligands of simple preparation. This goal will be pursued exploiting two classes of chiral supramolecular ligands, PhthalaPhos[2] and BenzaPhos,[3] recently developed by the Gennari group and successfully applied in the Rh-catalyzed asymmetric hydrogenation of olefins. A further goal of the project will be, owing to the supramolecular properties of the ligands, to investigate the possibility of expanding the reaction scope to substrates possessing poor leaving groups (e.g. allylic alcohols), thus improving the atom economy of the process.

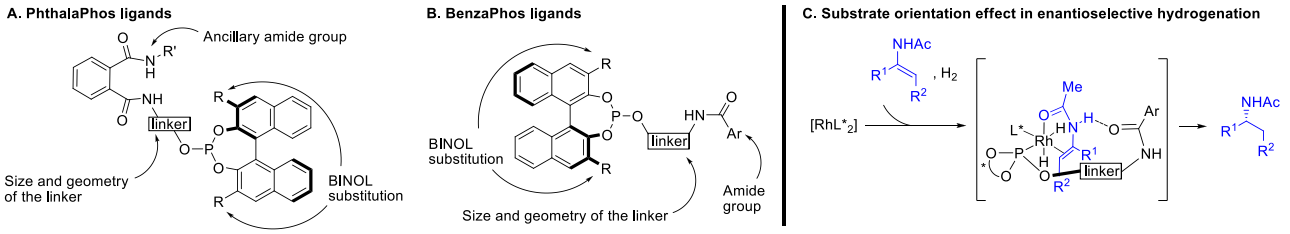

Figure 1. Modular structure of PhthalaPhos (A) and BenzaPhos ligands (B), and substrate orientation effect in Rh-catalysed hydrogenation.

Very recently, the Gennari group has also reported the first application of the PhthalaPhos ligands to AAS, and in particular to the synthesis of 1-vinyltetrahydroisoquinolines, key-precursors of several pharmacologically active molecules.[4]

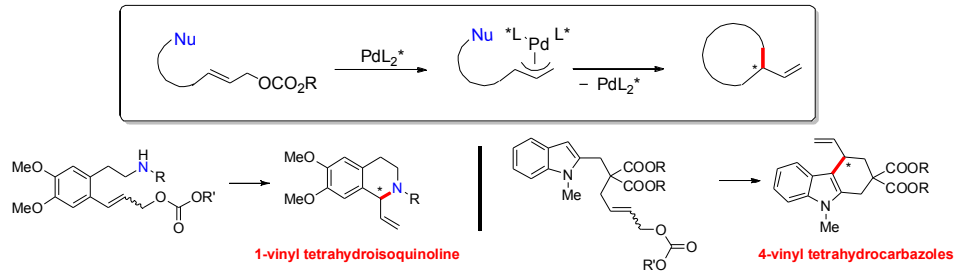

Figure 2. Heterocycle synthetic strategy: stereoselective Tsuji-Trost-type allylic substitution with chiral ligands L*.

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Acknowledgements: We thank the European Commission [EID-ITN Network 'REDUCTO', contract n. PITN-GA-2012-316371] and Consiglio Nazionale delle Ricerche (CNR) for financial support. L.P. thanks the Dipartimento di Chimica, Università di Milano, for financial support (Piano di sviluppo dell'Ateneo—anno 2014—Linea B.1—grants for young researchers).

New chiral Fe-cyclopentadienone complexes as pre-catalysts for asymmetric hydrogenation

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In recent years, Fe-cyclopentadienone complexes (1 in Figure 1)[1] have become a hot research topic for a series of reasons: A) Firstly, they are a demonstration of how a 'non-innocent ligand' can influence and modify the reactivity of a metal: analogously to what reported for the Shvo's Ru complexes,[2] their ligand, swinging between the cyclopentadienone (2) and the hydroxycyclopentadienyl form (3), enables a Fe(0)/Fe(II) catalytic cycle which does not belong to the typical reactivity of Fe-complexes. In this way, after activation by creation of a vacant coordination site, Fe-cyclopentadienone complexes are able to split H_2, and thus catalyze both the hydrogenation of carbonyl compounds and the de-hydrogenation of alcohols according to a concerted outer-sphere mechanism where, again, the ligand is actively involved with its OH group (Figure 1).[3] B) Secondly, they rely on a cheap, relatively non-toxic and environmentally benign metal such as Fe, which is nowadays increasingly considered for developing sustainable catalysts.[4] C) Last but not least, they are perfectly stable to air, moisture and even chromatography, which simplifies their isolation and purification. Activation (by creation of a vacant coordination site) may be performed in situ, i.e. where catalysis is to take place. As efficient chiral Fe-cyclopentadienones for enantioselective reductions are currently missing, we recently developed a new class of (R)-BINOL-derived complexes (Figure 2).[5] Considering the previously reported BINOL-derived catalysts and the above-mentioned mechanism,[3] we envisioned that 3,3'-substituents on the binaphthyl moiety would be needed to ensure an efficient transfer of stereochemical information from the catalyst's stereoaxis to the substrate. We thus prepared the complexes CK1, CK2 and CK3 (Figure 2), which were screened in the asymmetric hydrogenation (AH) of ketones after in situ activation (vide supra) by reaction with Me_3NO. As expected, complex CK2, bearing the biggest 3,3'-substituents on the binaphthyl system, allowed to obtain the best enantiomeric excess with acetophenone (50% e.e.) and was thus screened on a series of other ketones reaching up to 77% e.e.. Starting from 3,3'-dihydroxysubstituted complex CK3, the synthesis of new complexes bearing bulkier 3,3'-substituents (esters, ethers, aryl rings) has been undertaken. The obtained second-generation pre-catalysts will be tested in the AH of ketones and imines, as well as in hydrogen borrowing processes.

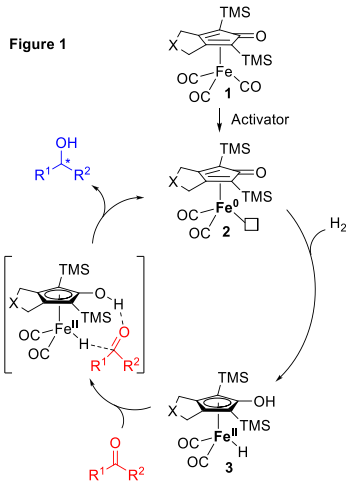

Figure 1

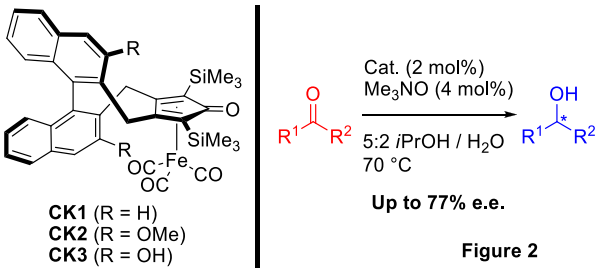

Figure 2

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Acknowledgements: This work was funded by the European Commission [EID-ITN Network 'REDUCTO', contract n. PITN-GA-2012-316371]. L.P. thanks the Dipartimento di Chimica, Università di Milano, for financial support (Piano di sviluppo dell'Ateneo—anno 2014—Linea B.1—grants for young researchers).

Application of advanced NMR techniques to ligand-target interaction

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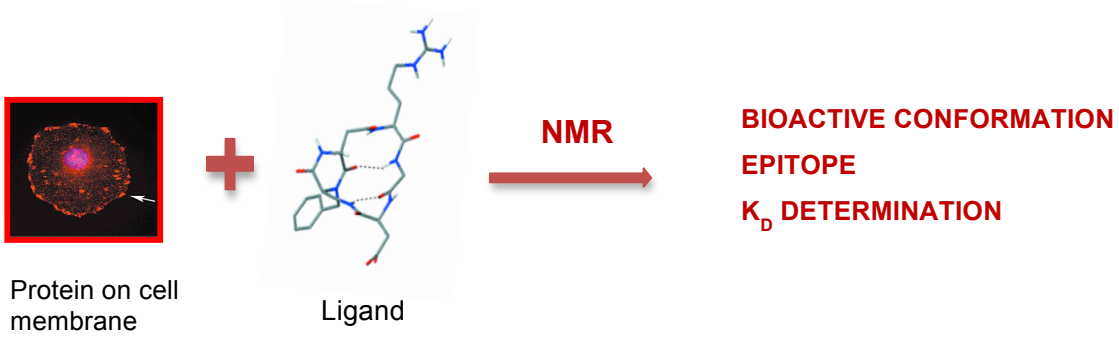
Keywords: NMR spectroscopy, conformational analysis, ligand-protein interaction, structure-activity relationships.

NMR spectroscopy is often valued for its ability to shed light on molecular structure, but probably, its greatest potential lies in the information that it can reveal about molecular interaction at the atomic level. The interactions of receptors with small molecules are key factors in many biomedical processes and the understanding, at the atomic or molecular level, of the diverse mechanisms by which this molecules are recognized, is the new frontier of chemical and biomedical discoveries. Bioaffinity NMR techniques enable the identification of high affinity ligands for a given protein target and result very powerful in target validation, lead discovery and protein-membrane interaction studies.
The object of the NMR observation might be (a) the ligand or (b) the receptor (protein or nuclei acid).

(a) The **ligand-based NMR techniques** focus on the NMR signals of the ligand and utilize NOE effects between protein and ligand. These techniques offer easy detection of binding events, additionally producing information on the bound conformation of the ligands and can be used as an epitope mapping device to describe the target-ligand interactions [1a].

(b) In **target-observed screening**, one is focused on measuring and mapping the perturbations in the resonances associated with the protein target upon ligand binding. A simple technique that exploits differences in chemical shift between free and bound protein targets is based on the detection of such changes in 15N/1H and/or 13C/1H correlation spectra of a protein upon titration of a ligand. Chemical shift mapping can provide structural information on the site of binding [1b]. As starting point for this experiment, it is essential to have an exhaustive assignment of the protein of interest and, if possible, to carry out in advance the determination of protein structure.



We are currently focusing on the identification of high affinity ligands (glycomimetics or peptidomimetics) for protein targets which are involved in disparate biological processes. In particular, we apply **ligand-based NMR techniques** to the study of the ligand-protein interactions for different targets:

- cadherins and HSP90 as isolated protein,
- integrins expressed and analyzed directly on intact cells [2,3],
- hemoagglutinin of influenza virus on transfected cells,
- RNA construct [4].

These research activities are conducted combining NMR data with computational studies performed by Prof. L. Belvisi group (see posters 3 and 4).
Our projects are also in collaboration with: Prof. A Bernardi and Prof. C. Gennari
Prof. A. Siccardi, Università Vita e Salute, San Raffaele Milano
Prof. U. Piarulli, Università dell'Insubria
Dott. E. Parisini, IIT Milano

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Towards Allosteric Modulators of HSP90

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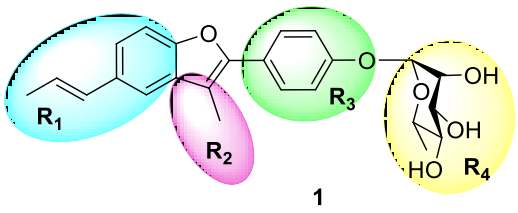
Hsp90 is an established anti-apoptotic target in cancer therapy.[1] Most of the known small-molecule inhibitors that have shown potent antitumor activity target the Hsp90 N-terminal domain and directly inhibit its ATPase activity.[2] However, many of these molecules display important secondary effects. A different approach to Hsp90 inhibition consists of targeting the protein C-terminal domain (CTD) and modulating its chaperone activity through allosteric effects. Using an original computational approach, allosteric hot-spots in the CTD have been recently identified that control interdomain communication.[3] A combination of virtual and experimental screening enabled identification of **1** (*Eupomatenoid-2*, Figure 1) as a lead for further development.[3] Four diversification areas have been identified (R_1-R_4, Figure 1).

Chemical approaches to the (glyco)diversification at R_4 will be presented,[4] along with alternative synthetic pathways for the synthesis of the 2-phenyl-benzofuran core and its diversification at R_1.

Preliminary results indicate that the compounds obtained so far are CTD ligands and are able to modulate Hsp90 activity.



1

Figure 1: Lead compound 1 (*Eupomatenoid*-2) and the four diversification areas (R_1-R_4) identified.

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Research activty of Prof. G. Speranza and Dr. C. F. Morelli

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Our current research projects are provided below:

CHEMISTRY OF NATURAL ORGANIC COMPOUNDS:

- isolation
- structural elucidation
- synthesis of bioactive secondary metabolites

BIOORGANIC CHEMISTRY AND BIOCATALYSIS:

- study of reactions catalyzed by γ-glutamyltransferase (γ-GGT) and their application to the synthesis of compounds of applicative interest as flavor enhancers (kokumi substances)
- chemoenzymatic synthesis of nucleosides catalyzed by purine nucleoside phosphorylase (PNP)

STUDIES ON CHEMORECEPTION OF THE UMAMI FLAVOR:

- synthesis of polypeptides, modified nucleosides and “hybrid” compounds

PEPTIDE SYNTHESIS:

- synthesis of peptides aimed at the conjugation with natural polymers for drug delivery processes

BIOREFINERY:

- valorization of agricultural and food industry waste
- study of the proteic fraction of the flax and hemp heel cake
- isolation and characterization of bioactive peptides and flavor enhancers

POLY-γ-GLUTAMIC ACID AS A NEW MATERIAL OF NATURAL ORIGINS:

- structural modifications aimed at drug delivery processes and nanoparticles preparation
- conformational studies
- study of biosynthesis and degradation

Residues of medicinal plants fermentation as source of active ingredients of innovative biopolymer-based formulations for health products

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Fermentation of plants of nutritional and medicinal value organically cultivated in Valtellina is the input to an innovative and sustainable project. The fermentation process produces "wines" in which the active principles of the plants are concentrated and transformed by the yeasts. At the end of the process consistent amounts of unrecyclable residues that still contain active principles are also obtained. In this project we plan to investigate the chemical content and evaluate the biological activity of these wastes from fermentation, and to develop methodologies to incorporate them into tailor-made biopolymers with the aim to prepare innovative formulations.
The plants selected in this project are known to contain polyphenols and flavonoids as main bioactive compounds. They are known to act as chemopreventive agents due to their antioxidant, anti-inflammatory actions and presently constitute the active principles in many nutraceutical formulations, both as pure components or in complex extracts [1].
On the other hand, it is known that polymeric biomaterials are largely used to vehiculate and slowly release to the sites of action the active principles.
The wastes from the fermentation of selected plants (pomegranate, cynara sp., opuntia sp., citrus sp.) from the agro-company cultivations are extracted to give materials that will be compared with the extracts of the fresh plants and the wine. Marker polyphenols will be used to standardize the extracts and the final bio-formulations. The chemical and biological studies of the materials extracted from the fermentation provide appropriate products that are eventually formulated in tailor made biopolymers to warrant the correct "release" and bioavailability of the active principles, while preserving their bioactivity. The controlled release of the bioactive natural products in the formulation will improve their efficacy and the maintenance of the biological properties will be assessed by cellular assays.
Lactic acid, lactide and glycerol and its oligomers, are used for the synthesis of biopolymers which are suitable for delivery formulations as they are bioavailable, biodegradable and food grade.
All the materials (extracts and formulations) are preliminarily evaluated for the antioxidant activity and tested in "*in vitro*" biological assays on selected cells expressing genes responsible for inflammation, to assess their potentialities for future "*in vivo*" tests. The kinetics of the release of the active ingredients from the formulations are determined by chromatographic analysis under different physiologically relevant conditions including gastrointestinal digestion to assess the potential adsorption in the gut or the plasma.
The project offers advances on the current state of the art in exploiting the residues of fermentation of medicinal plants as low cost and enriched source of polyphenols together with (poly)lactic acid, polyglycerols or polysaccharides appropriately prepared to exhibit a suitable macromolecular architecture to modulate their functionality. The results may find application in the fields of nutraceuticals and cosmeceuticals, depending on the delivery system.
The final aim is to promote the utilization of each step of processing, from the original plant to the waste products, to implement the chance to find new bio-products, with an accurate view to sustainable development.

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Biochimica

Recognition of Smac-mimetic compounds by the BIR domain of cIAP1

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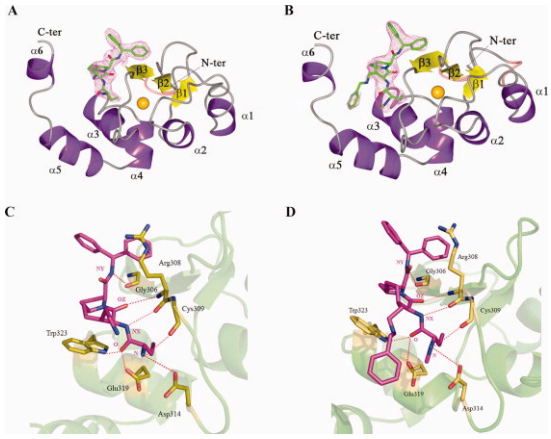
Inhibitor of apoptosis proteins (IAPs) are negative regulators of apoptosis. As IAPs are overexpressed in many tumors, where they confer chemoresistance, small molecules inactivating IAPs have been proposed as anticancer agents. Accordingly, a number of IAP-binding pro-apoptotic compounds that mimic the sequence corresponding to the N-terminal tetrapeptide of Smac/DIABLO, the natural endogenous IAPs inhibitor, have been developed. Here, we report the crystal structures of the BIR3 domain of cIAP1 in complex with Smac037, a Smac-mimetic known to bind potently to the XIAP-BIR3 domain and to induce degradation of cIAP1, and in complex with the novel Smac-mimetic compound Smac066. Thermal stability and fluorescence polarization assays show the stabilizing effect and the high affinity of both Smac037 and Smac066 for cIAP1- and cIAP2-BIR3 domains.



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Structure-function studies of medically relevant flavoenzymes

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Flavoenzymes catalyze a broad range of reactions thanks to the versatility of the flavin coenzymes (flavin adenine dinucleotide (FAD) and flavin adenine mononucleotide (FMN), both derivatives of vitamin b2), which can exist in the oxidized, 1-electron-reduced semiquinone and 2-electron-reduced hydroquinone states. The redox properties of the coenzyme, which are finely tuned by the protein environment, make flavoenzymes able to act as electron transferases, dehydrogenases, mono- and dioxygenases. Flavoenzymes are located at strategic points in metabolism where they act as switches between single electron donors and acceptors of electron pairs. They are involved in primary energy metabolism, in the synthesis of secondary metabolites, and also (e.g.) bioluminescence, DNA repair, control of gene expression and protein folding [1,2].

For these reasons understanding the structure-function relations of these enzymes is important to understand how enzymes achieve their enormous catalytic power, to extend their use in industrial and agro-food biotechnologies and, with reference to human health, to understand some fundamental biological processes and the molecular basis of some diseases, as well as to identify novel drug targets.

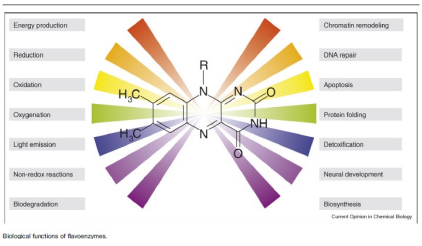
Our laboratory is currently interested in the characterization of several flavoenzymes, among which are:

- glutamate synthase (GltS), which is a complex iron-sulfur flavoenzyme essential for ammonia assimilation in bacteria and plants. Its essentiality in pathogens makes it of interest as a novel drug (antibiotic) target [3];

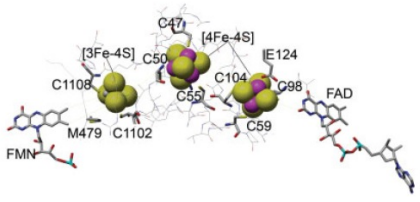
- human MICAL, a cytoplasmic multidomain enzyme responsible of the control of cytoskeleton dynamics through a so far unique - and still poorly understood - F-actin depolymerization reaction. Since (actin) cytoskeleton dynamics controls, among others, axon growth, cell-cell contacts, cell duplication, differentiation and migration, intracellular trafficking and gene transcription, a better understanding of MICAL's molecular properties will lead to a better understanding of these processes and, possibly, to novel ways to control them in pathological conditions [4].

- Human dimethyglycine dehydrogenase, a mitochondrial enzyme of the folate cycle, whose defects are associated with neurological disorders and, perhaps, mitochondrial diseases [5].

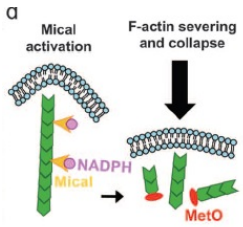
We use microbiology and molecular biology techniques to overproduce our wild-type or engineered proteins in bacterial hosts, and a range of chromatographic and basic biochemistry techniques for protein purification and initial characterization. With the wild-type and engineered forms obtained by site-directed mutagenesis, we mainly use absorbance and fluorescence spectroscopies under time-resolved (kinetic) or equilibrium conditions to determine how the enzyme catalyzes its corresponding reaction and how the reaction is modulated by ligands (including interacting proteins, potential active site and allosteric inhibitors or, in the case of glutamate synthase, the substrate themselves) or protein domains other than the catalytic one (in the case of MICAL). In each case, we aim to complement our functional studies with structural work done in collaboration with experts in the respective fields in Italy and abroad.



Role and distribution of flavoenzymes, [1]



The GltS flavin and Fe/S clusters forming an intramolecular electron transfer chain, [3]



Proposed MICAL's actin depolymerization reaction.

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Fisica Teorica, Modelli e Metodi Matematici

Infos about the Quantum Technology Lab

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INTRO: Devices that exploit quantum phenomena such as coherence, superposition and entanglement have the potential to enable radically new technologies. Several promising directions are now well known, for instance in quantum computation and simulation, quantum communication, quantum metrology and sensing. On the other hand, overcoming basic scientific questions as well as bridging from the scientific results to concrete engineering technologies is a challenging endeavour. In the Quantum Technology Lab we perform theoretical and experimental research to develop new solutions using quantum technologies that will ultimately address real world problem, with a potential for disruptive change. QTL aims contributing to solve problems in fundamental and applied science by using new tools based on quantum physics and quantum technologies, and by building-up core competences for the wider exploitation of quantum science and technologies in mainstream engineering, chemistry, and biology.

KEYWORDS: **Quantum information** (entanglement, superadditivity, communication). **Quantum metrology** (calibration, interferometry, nanopositioning). Quantum imaging (ghost imaging and diffraction, quantum litography). **Quantum computing** (NMR systems, superconducting circuits). **Quantum Biology** (open quantum systems, coherent transport). **Quantum Mechanics** (exotic potentials and atoms, nonclassical states).

TOPICS for MASTER THESIS**: Open quantum systems**: modelling and characterization of quantum and classical noise, non Markovianity random telegraph noise and colored spectra. **Quantum biology**: coherent energy transport, light harvesting systems. **Quantum computing**: NMR systems, superconducting circuits. **Quantum technology**: anharmonic oscillators, non Gaussianity, stochastic Schroedinger equations, statistical modelling of magnetic systems.

PEOPLE (staff): Matteo Paris (coordinator), Simone Cialdi, Stefano Olivares, Fabrizio Castelli, Bassano Vacchini, Nicola Piovella, Dario Tamascelli, see more at http://users.unimi.it/aqm/?page_id=2

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