XVI CONVEGNO NAZIONALE
REAZIONI PERICICLICHE
E SINTESI DI ETERO E CARBOCICLI

Matera, 26 e 27 giugno 2015

Aula Sassu, sede di San Rocco, Università degli Studi della Basilicata

Comitato Scientifico

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Maurizio D'Auria

Maria Funicello

Patrizia Scafato

Licia Viggiani

PROGRAMMA

Venerdì 26 giugno

12:30 Registrazione

13:00 Cocktail di benvenuto

14:30 Apertura dei lavori: Introduzione e saluti

Prima sessione: Presiedono i Professori: **Donato Pocar e Giuseppe Faita**

15:00 **PL1** **Paola Bonaccorsi** (Università degli Studi di Messina)

"*La Dolce Vita" of Sulfenic Acids*

15:30 **O1** **Stefano Menichetti** (Università degli Studi di Firenze)

New Potent Chain Breaking Antioxidants from 2,3-Dihydrobenzo[b][1,4]oxathiines to 7-Hydroxy-2,3-Dihydrobenzo[b]thiophenes Transposition

15:50 **O2** **Chiara Zagni** (Università degli Studi di Catania)

Synthesis of 4-{[(3R,3aR)-1,1-Dioxido-6-Oxohexahydro-2H-[1,2,5]Thiadiazolo [2,3-a]Pyrazin-3-yl]methoxy}-Butanhydroxamic Acids as Potential Histone Deacetylase Inhibitors

16:10 **O3** **Carla Sappino** (CNR – IBPM – Università della Sapienza di Roma)

Synthesis of Benzofuran Derivatives and Their Biological Evaluation

16:30 **Pausa caffè**

Seconda sessione: Presiedono i Professori: **Gianluigi Broggini e Francesco De Sarlo**

16:50 **O4** **Fabrizio Machetti** (CNR – Università degli Studi di Firenze)

Functionalisation of Fullerenes with Primary Nitro Compounds

17:10 **O5** **Iole Cerminara** (Università degli Studi della Basilicata)

The Aza-Wittig Electrocyclization Reaction in the Synthesis of Benzothieno[b]pyridines, New Anti-Alzheimer Small Molecules

17:30 **O6** **Antonella Bochicchio** (Università degli Studi della Basilicata)

[3,3]-Sigmatropic Claisen Rearrangement: a Rapid Access to Phenylpropenes and Lignan Structures

17:50 **O7** **Silvana Pedatella** (Università degli Studi Federico II di Napoli)

Microwave Assisted Synthesis of Pyridophenoxazinones, a Class of Powerful Antiproliferative Compounds

18:10 **O8** **Carolina Vurchio** (Università degli Studi di Firenze)

Isoxazolidines as Versatile Precursors of New Lentiginosine Derivatives

18:30 **Riunione consiglio scientifico CIRP**

20:30 **Cena sociale**

Sabato 27 giugno

Terza sessione: Presiedono i Professori: **Maria Chiara Aversa e Antonino Corsaro**

9:00 **PL2** **Maria Luisa Gelmi** (Università degli Studi di Milano)

Unusual Chemoselective Rh^{II}-Catalysed Transformations of α-Diazocarbonyl Piperidine Cores

9:30 **O9** **Francesca Cardona** (Università degli Studi di Firenze)

The Osmium-Catalyzed Tethered Aminohydroxylation of Glycals Allows a Stereodirected Access to 2- and 3-Aminosugars

9:50 **O10** **Tea Borelli** (Università degli Studi dell' Insubria)

Tunable Intramolecular Pd-Catalyzed Amination of Alkenes Depending on Hypervalent Iodine

10:10 **O11** **Andrea Temperini** (Università degli Studi di Perugia)

A New Metal-Free Multicomponent Approach to Biaryls

10:30 **Pausa caffè**

Quarta Sessione: Presiedono i Professori**: Maurizio D'Auria e Andrea Temperini**

11:00 **O12** **Beatrice Macchi** (Università degli Studi Tor Vergata di Roma)

Biological Effects of Heterocyclic and/or Carbocyclic Synthetic Compounds: Recent Results

11:20 **O13** **Alberto Mazza** (Università degli Studi di Milano)

Synthesis of a New Heteropolycyclic System as Topoisomerases I Inhibitor

11:40 **O14** **Sara Pellegrino** (Università degli Studi di Milano)

The Cycloaddition of Sulfonilazides with Enamines: an Evergreen Click Reaction on the Route of Flexible β-Amyloid Mimics

12:00 **O15** **Giorgia Regini** ((Università degli Studi di Trieste)

An Old Approach for New Inhibitors of BACE I: the Biginelli Reaction

12:20 **O16** **Rosalia Sferruzza** (Università degli Studi Federico II di Napoli)

Novel Approaches to Electron-Poor Trisubstituted Furans and Their Application in the Synthesis of Lignan-Like Compounds

12:40 **O17** **Stefano Tommasone** (Università degli Studi di Salerno)

Biomolecular Recognition Through Calixarene Cycloadducts

13:00 **O18** **Paolo Quadrelli** (Università degli Studi di Pavia)

Fluorescent Probes from Nitrile Oxides

13:20 **Chiusura dei lavori**

14:30 **Riunione Prin 2010 coordinatore Prof. Alberto Brandi**

"La Dolce Vita" of Sulfenic Acids

Maria Chiara Aversa, Anna Barattucci, Paola Bonaccorsi

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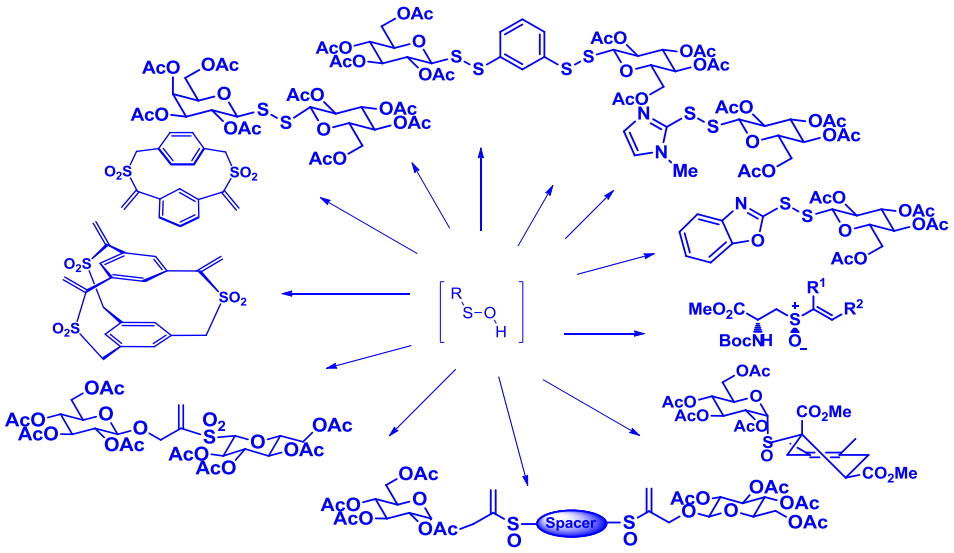
Sulfenic acids (R-SOH) frequently act as reactive intermediates in biological and synthetic chemistry. Among the numerous examples that Nature offers to our knowledge, cysteine-derived sulfenic acids are recognized as key intermediates in signal transduction, transcriptional regulation events, and oxidative stress response. They also play catalytic and structural roles in enzymes. Furthermore, the sulfenic function is involved in the biosynthesis of thiosulfinates that give the characteristic odor and flavor to the *Allium* species and in the lachrymatory process of cut onion (1). On the other hand, the electronic nature of their S–O bond and its involvement in various, often stereospecific, reactions have prompted many applications of sulfenic acids in organic synthesis, such as their use as key intermediates in the preparation of peculiar sulfoxides (2).
This communication aims at summarizing recent contributions on the generation and use of transient sulfenic acids in the stereocontrolled synthesis of sulfoxides and disulfides (3). These substrates offer a wide range of synthetic opportunities such as the synthesis of sulfinyl dienes to be involved in stereoselective DA reactions, the preparation of libraries of bioactive sulfurated molecules, the synthesis of unsymmetrical disulfides. Some of these synthetic routes will be shown and discussed.



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(2) a) Barattucci, A.; Di Gioia, M.L.; Leggio, A.; Minuti, L.; Papalia, T.; Siciliano, C.; Temperini, A.; Bonaccorsi, P. *Eur. J. Org. Chem.* **2014**, 2099–2104; b) Barattucci, A.; Bonaccorsi, P.; Papalia, T.; Manganaro, N.; Gattuso, G. *Tetrahedron Letters* **2014**, *55*, 5096–5100.
(3) Bonaccorsi, P.; Marino-Merlo, F.; Barattucci, A.; Battaglia, G.; Papaianni, E.; Papalia, T.; Aversa, M.C.; Mastino, A. *Bioorg. Med. Chem.* **2012**, *20*, 3186-3195.

Unusual Chemoselective Rh^{II}-Catalysed Transformations of α-Diazocarbonyl Piperidine Cores

Maria Luisa Gelmi, Egle Beccalli, Andrea Bonetti, Raffaella Bucci, Francesca Clerici, Sara Pellegrino

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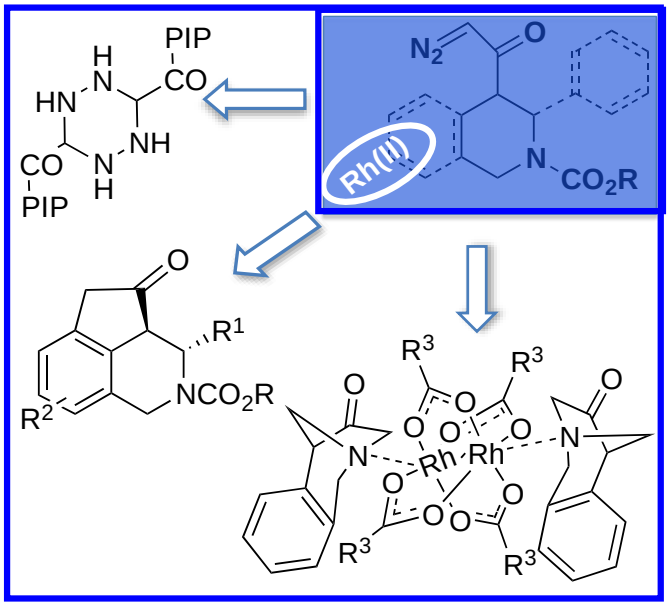
The binomium α-diazocarbonyl derivatives and Rh^{II}-catalysis represents a strong tool for the preparation of numerous carbocyclic and heterocyclic compounds, otherwise difficult to obtain.(1) The success of these approaches is related to the high level of regio- and stereo-control that, in general, is guaranteed by selection of the appropriate Rh^{II} catalyst from the available assortment.(2)
The reactivity of various α-diazocarbonyl piperidine scaffolds, characterised by an increased molecular complexity, was tested with various Rh^{II} catalysts.(3) The structure of the starting reagent is of relevance to the synthetic results. An unexpected dimerisation took place, starting from the simple piperidine scaffold, to give the hexahydrotetrazine ring system. Products derived from a nitrogen ylide intermediate or aromatic substitution (1,3,4,5-tetrahydro-2,5-methanobenzo[*c*]azepine and 1,2,3,3a-tetrahydrocyclopenta[*de*]isoquinolin-4(5^H)-one rings, respectively) were obtained from tetrahydroisoquinoline derivatives. The chemoselectivity of the reaction could be controlled by the choice of starting reagent, Rh^{II} catalyst and the reaction conditions. Finally, it was found that the azepino heterocycle could coordinate to the catalyst to give new Rh^{II} complexes.



(1) a) McKervey, A. *Chem. Rev.* **1994**, *94*, 1091-1160; b) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577-6605.
(2) a) Trindade, A.F.; Coelho, J. A. S.; Afonso, C. A. M.; Veiros, L. F.; Gois, P. M. P. *ACS Catal.* **2012**, *2*, 370-383; b) Padwa, A.; Austin, D. J. *Angew. Chem. Int. Ed. Eng.***1994**, *33*, 1797-1815.
(3) Bonetti, A.; Beccalli, E.; Caselli, A.; Clerici, F.; Pellegrino, S.; Gelmi, M. L. *Chem. Eur. J.* **2015**, *21*, 1692-1703.

New Potent Chain Breaking Antioxidants from 2,3-Dihydrobenzo[*b*][1,4]oxathiines to 7-Hydroxy-2,3-Dihydrobenzo[*b*]thiophenes Transposition

[1]Leonardo Di Pietro, [1]Caterina Viglianisi, [2]Riccardo Amorati, [1]Stefano Menichetti

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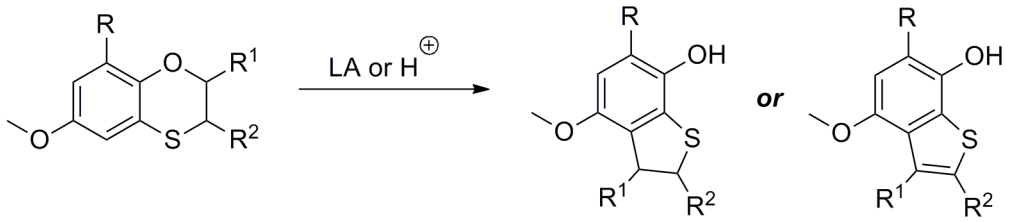
In this communication a new acid (Lewis or Brønsted) promoted transposition of 2,3-dihydrobenzo[*b*][1,4]oxathiines (1) to 7-hydroxy-2,3-dihydrobenzo[*b*]thiophenes will be presented and discussed in terms of mechanism, scope and limitation. A particular emphasis will be devoted to the role played by the sulfur atom in the mechanism of this new rearrangement leading , regio- and stereoselectively, to the formation of dihydrobenzo[*b*]thiophenes or benzo[*b*]thiophenes depending upon reaction conditions and stoichiometry.



Chain breaking antioxidant activity (2) of dihydrobenzo[*b*]thiophenes and benzo[*b*]thiophenes obtained through this rearrangement will be also discussed focussing the attention on the structure-activity relationship fine tuning achieved with these polyphenolic antioxidants containing a sulfur benzofused heterocycle system.

(1) Menichetti, S.; Viglianisi, C. *Cur. Med. Chem*. **2010**, *17*, 915-928
(2) a) Menichetti, S.; Aversa, M. C.; Cimino, F.; Contini, A.; Tomaino, A.; Viglianisi, C. *Org. Biomol. Chem*. **2005**, *3*, 3066-3072; b) Amorati, R.; Cavalli, A.; Fumo M. G:, Masetti, M.; Menichetti, S.; Pagliuca, C.; Pedulli, G. F.; Viglianisi, C. *Chem-Eur. J*., **2007**, *13*, 8223-8230; c) Amorati, R.; Catarzi, F.; Menichetti, S.; Pedulli, G. F.; Viglianisi, C. *J. Am. Chem. Soc*., **2008**, *130*, 237-244; d) Menichetti, S.; Amorati, R.; Pedulli, G. F.; Bartolozzi, M. G.; Viglianisi, C. *Chem-Eur. J*., **2011**, *17*, 12396-12404.

Synthesis of 4-{[(3*R*,3a*R*)-1,1-Dioxido-6-Oxohexahydro-2*H*-[1,2,5]Thiadiazolo [2,3-*a*]pyrazin-3-yl]methoxy}-Butanhydroxamic Acids as Potential Histone Deacetylase Inhibitors.

[1]C. Zagni, [1]G. Floresta, [1]M. A. Chiacchio, [2]S.V. Giofrè, [2]R. Romeo, [3]G. Broggini

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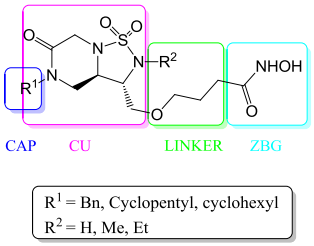
Oxidative metal catalysis for diamination of alkenes has recently emerged as a powerful tool for the synthesis of heterocycles that incorporate the vicinal diamine structural motif (1-4). Nitrogen heterocycles containing the vicinal diamine unit are ubiquitous in biologically active small molecules. Here we report the synthesis of 4-{[(3*R*,3a*R*)-1,1-dioxido-6-oxohexahydro-2*H*-[1,2,5]thiadiazolo[2,3-a]pyrazin-3-yl]methoxy}-butanhydroxamic acids as potential histone deacetylase inhibitors (HDACi).



Histone acetylation induced by histone acetyl transferases (HATs) is associated with gene transcription, while histone hypoacetylation induced by histone deacetylases (HDACs) activity mainly results in transcriptional repression. Altered expression of HDACs have been linked to tumor development. Thus, HDACs are among the most promising therapeutic targets for cancer treatment. Structurally, HDAC inhibitors are characterized by a cap group, a connecting unit (CU), a linker and a zinc chelator (ZBG) (6).
Using palladium or bromide catalyzed diamination we prepared a series of compounds bearing the hydroxamic portion as zinc binding group, a small spacer, a connective unit formed by 1,1-dioxido-6-oxohexahydro-2*H*-[1,2,5]thiadiazolo[2,3-*a*]pyrazin-2-yl) portion and a benzyl or cycloalkyl groups as capping. Preliminary docking studies show that the molecules are able to insert in the HDAC catalytic pocket and bind zinc ion, thus inhibiting the enzymatic activity.

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(2) G. Broggini, V. Barbera, E. M. Beccalli, U. Chiacchio, A. Fasana, S. Galli, S. Gazzola *Advanced Synthesis & Catalysis*, **2013**, *355*, 1640–1648.
(3) U. Chiacchio, V. Barbera, R. Bonfanti, G. Broggini, A. Campisi, S. Gazzola, R. Parenti, G.Romeo *Bioorg. Med. Chem.*, **2013**, *21*, 5748–5753.
(4) E. Beccalli, G. Broggini, S. Gazzola, A. Mazza *Org. Biomol. Chem.*, **2014**, *12*, 6767–6789.
(5) C. Zagni, U. Chiacchio, A. Rescifina, *Curr. Med. Chem.*, **2013**, *20,* 167–185.
(6) W. S. Xu, R. B. Parmigiani, P. A. Marks, *Oncogene* **2007**, *26*, 5541–5552.

Synthesis of Benzofuran Derivatives and Their Biological Evaluation

[1]Bovicelli Paolo, [2]Fabrizio Bottaro, [2]Carla Sappino, [2]Michela Tomei, [2]Emanuela Mandic', [1]Righi Giuliana, [3]Beatrice Macchi, [3]Caterina Frezza

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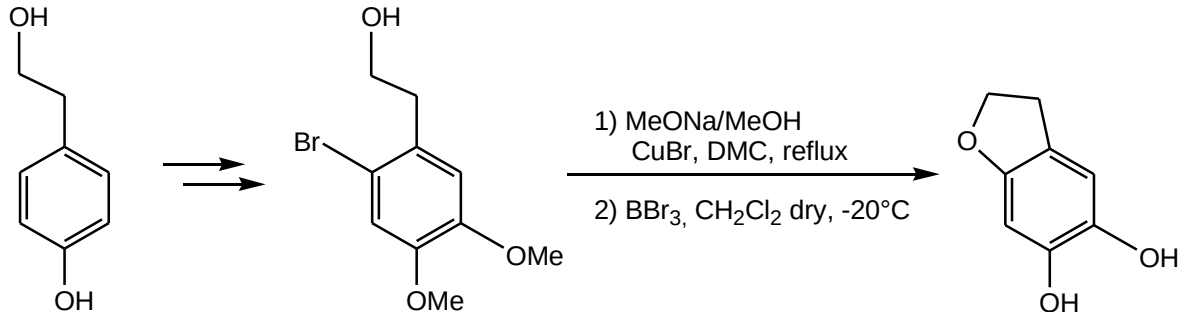
In the last years we largely investigated a method for oxy-functionalize the aromatic ring of natural occurring compounds, in order to enhance their biological activities (1).
The method involves a methanolysis of an aromatic bromide; the bromination of activated aromatic rings can be performed by a number of methods (2), but the most efficient and clean was that in which the electrophilic species is generated *in situ* by the oxidation of NaBr with oxone (3).
This bromination/methanolysis sequence was recently used also in the development of a synthetic strategy for the preparation of benzofuran and benzopyran derivatives, a group of biological active heterocycles extracted from different plants and used in traditional medicine of some countries. To synthesize 2,3-diidrobenzofuranes and benzofuranes scaffolds for the preparation of more complex molecules, we decided to start from tyrosol, a phenol largely present in olive oil production waste, with no biological importance.



The biological activity of some of the prepared compounds was assessed by measuring their ability to induce cytotoxicity by inhibiting cell metabolism and cell death by apoptosis in a monocytoid cell line U937.

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(2) Sternbach, L.H. *Prog. Drug Res.***1978**, *44*, 1340–1344. Goldberg, Y.; Alper, H. *J. Mol. Cat.***1994**, *88*, 377.Roy, S.C.; Guin, C.;Rana, K.K.;Maiti, G. *Tetrahedron Lett.* **2001**, *42*, 6941–6942.

Functionalisation of Fullerenes with Primary Nitro Compounds

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[1]Istituto di Chimica dei Composti Organo Metallici del Consiglio Nazionale delle Ricerche c/o Dipartimento di Chimica Ugo Schiff
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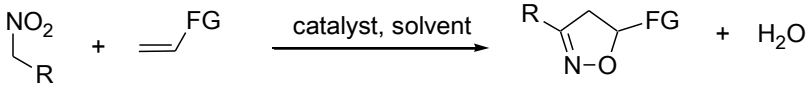
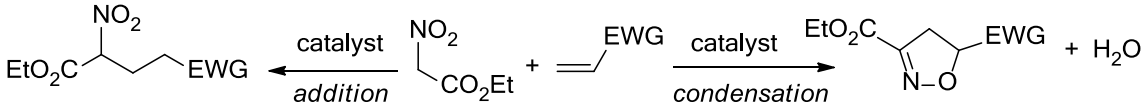
We have thoroughly investigated a new general procedure for the synthesis of 4,5-dihydroisoxazoles by catalysed cycloaddition-condensation of primary nitro compounds with olefins (Scheme 1).(1)



Scheme 1

This protocol, in one single pot, avoids the use of dehydrating reagents. These cycloadditions have been successfully carried out, using appropriate catalysts, either in chloroform or in ethanol (2a) or in water (2b,c). The reaction is applicable to a wide range of functionalised dipolarophiles in good to excellent yields. Reactions with electron-poor dipolarophiles lead to either condensation to isoxazolines or to conjugate addition products, depending on the nitro compound (*e.g.* ethyl nitroacetate) and catalyst: the presence of copper (II) in the catalytic system selectively favours condensation (Scheme 2).(3)



Scheme 2

The application of this protocol to a peculiar electron-poor dipolarophile such as [60]fullerene(4) as well as to single- or multiwalled carbon nanotubes, according to the reaction conditions, lead to usual condensation or to peculiar addition products (Figure 1).(5) These can be used either for functionalisation of [60]fullerene or carbon nanotubes.

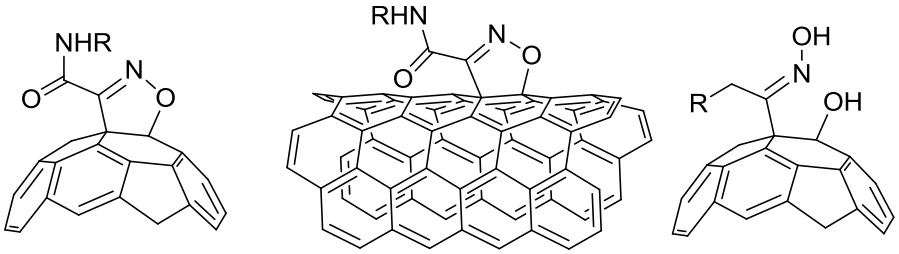


Figure 1

Acknowledgments: The authors thank the Ministero dell'Istruzione, Università e Ricerca (MIUR, Italy project FIRB 2011 – prot. RBAP11ETKA and MIUR, Italy project COFIN 2010-2011 – prot. 20109Z2XRJ).

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(3) Trogu, E.; De Sarlo, F.; Machetti, F. *Chem. Eur. J.* **2009**, *15*, 7940–7948.
(4) Biagiotti, G.; Cicchi, S.; De Sarlo, F.; Machetti, F. *Eur. J. Org. Chem.* **2014**, 7906–7915.
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The Aza-Wittig Electrocyclization Reaction in the Synthesis of Benzothieno[*b*]pyridines, New Anti-Alzheimer Small Molecules

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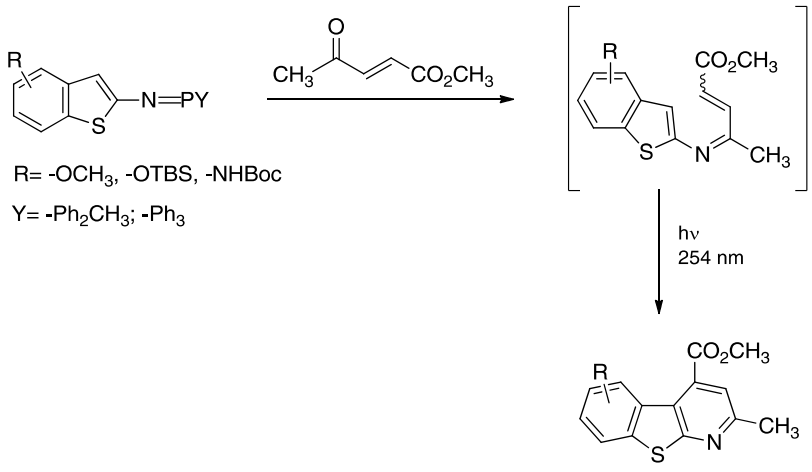
Similarly to the Wittig olefination, the Aza-Wittig reaction between an iminophosphorane and a carbonyl group allows to synthesize double bonds containing nitrogen (1). This reaction is used both for the synthesis of acyclic imines and for inserting of C=N double bonds in heterocyclic rings. Intermolecular Aza-Wittig consists in the formation of an imine that undergoes electrocyclization. As shown in next scheme, we used this effective reaction in the preparation of functionalized benzothieno[*b*]pyridines (2):



Several biological properties are already known for these small heterocyclic molecules but we investigated a new inhibitory activity against BACE1 enzyme. It's well known that BACE1 plays a key role in the development of Alzheimer's disease and its inhibition is a therapeutic target. Benzothieno[*b*]pyridines synthesized showed good inhibitory activity with IC_{50} values comparable to, in some cases better than, several BACE1 inhibitors reported in literature (3).

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(2) a) Cerminara, I.; Chiummiento, L.; Funicello, M.; Guarnaccio, A.; Lupattelli, P. *Pharmaceuticals* **2012**, *5*, 297-316; b) Bonini, C.; Chiummiento, L.; Funicello, M.; Spagnolo, P. *Tetrahedron* **2000,** *56*, 1517; c) Bonini, C.; D'Auria, M.; Funicello, M.; Romaniello, G. *Tetrahedron* **2002**, *58*, 3507; d) Bonini, C.; Funicello, M.; Scialpi R.; Spagnolo, P. *Tetrahedron* **2003**, *59*, 7515-7520.

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[3,3]-Sigmatropic Claisen Rearrangement: a Rapid Access to Phenylpropenes and Lignan Structures

Antonella Bochicchio, Lucia Chiummiento, Rossella Cefola, Maria Funicello, Paolo Lupattelli

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Phenylpropenes or allylbenzenes derivatives are the skeletons of many biologically important natural products as gingerol, eugenol, chavicol, safrole and estragole (1). They are also precursors of Lignans and Stegane structures which are studied for their important activities (2). (**Figure 1**)

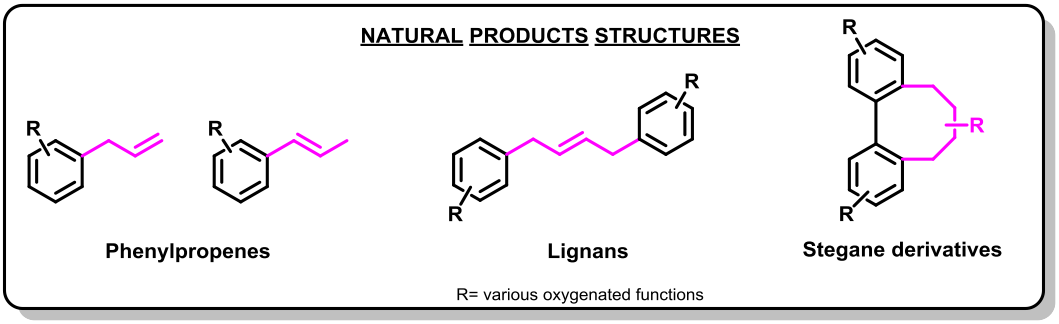

Figure 1

In this work we report a rapid and efficient methodology to obtain various phenylpropenes **1** performing a [3,3]-sigmatropic Claisen rearrangement of compounds **2** (3). The protected phenols could be easily prepared from substrates **3** with an allylation reaction on the corresponding free hydroxyl group. (**Figure 2**)

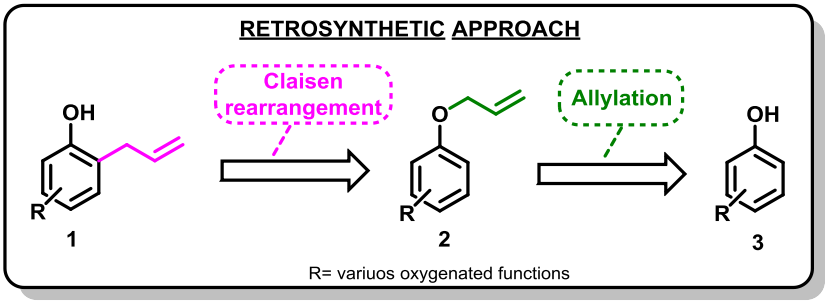

Figure 2

With this synthetical approach we are able to synthesize the 1,2,3,4-tetramethoxy-5-(2-propenil)benzene, an antibacterical natural product (4), in only 4 steps and 58% overall yield.

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Microwave Assisted Synthesis of Pyridophenoxazinones, a Class of Powerful Antiproliferative Compounds

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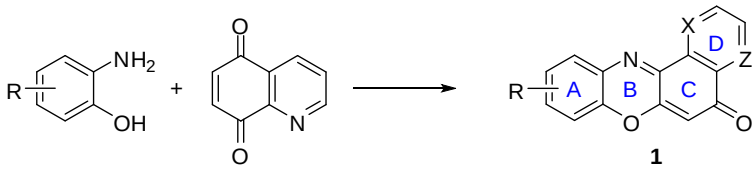
Chemotherapy is the most common treatment of cancer that consists of the use of antineoplastic drugs to destroy cancerous cells. Traditional drugs used in chemotherapy act especially on the cell duplication processes. They are non-specific and cause many undesired concurrent effects on the healthy cells. For this reason, during the last decade, the oncological research has focused on the multimodal therapy, a combination of anticancer treatments acting simultaneously on different biological domains, able to inhibit proliferation of tumor cells present in different phases of the cell cycle(1)**.** In order to obtain new antiproliferative compounds good for acting through the forementioned mechanisms, including DNA intercalation and topoisomerase inhibition, our attention was focused on the derivatives of pyridophenoxazinone (PPH, **1** R=H) system, an iminoquinone containing a planar tetracyclic system suitable for intercalating DNA G-C base pairs in a site specific mode(2).
Namely, we designed, after molecular modeling calculations, PPH carboxyamide derivatives holding at C-9 and C-10 positions an amino acidic chain or a sugar.
Unfortunately, the real obstacle to the availability of such molecule was represented by their synthesis. Therefore, in our opinion it seems to be worthwhile to report a new microwave (μW) assisted synthetic procedure to prepare PPH carboxyamides. In order to assess the validity of our method, we applied the procedure to the synthesis of variously substituted PPHs **1** and received evidence that microwave irradiation enables the preparation of those compounds in high yields and short reaction times.



1

X = N, Z = CH or X = CH, Z = N
R = H, CH_3, CO_2H, NO_2, Cl, Br, F

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Isoxazolidines as Versatile Precursors of New Lentiginosine Derivatives

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(+)-Lentiginosine **1** is a natural iminosugar with important inhibitory activity towards amyloglucosidases and Hsp90 (Heat Shock Protein 90).(1) Interestingly, it has been proven that the non natural enantiomer (–)-lentiginosine **2** and its 7-hydroxy derivative **3** display a potent proapoptotic activity against different cancer cell lines with a low toxicity towards healthy cells.(2) Recently, 7-substituted (–)-lentiginosines such as **4** have been synthesized and proved to the proapoptotic activity of the lead compounds **2** and **3** (Figure 1).(3)

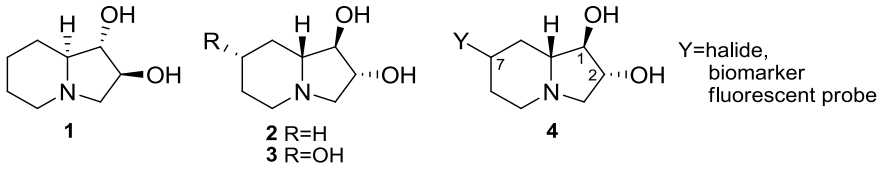
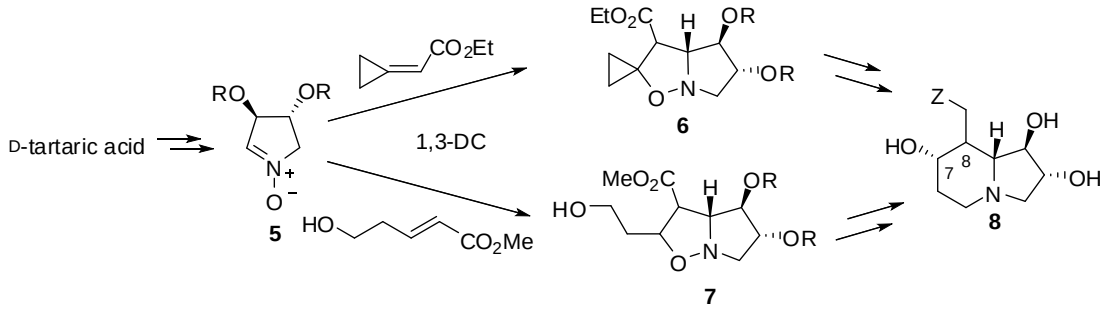


Figure 1.

The synthesis of new 7- and 8-substituted lentiginosines is currently underway. The synthetic strategy is based on 1,3-dipolar cycloaddition of enantiopure dihydroxylated pyrroline *N*-oxide **5** with different dipolarophiles. Adducts **6** and **7** are then converted into indolizidine derivatives **8** (Scheme 1).



Scheme 1.

The strained intermediate **6** is elaborated through a thermal rearrangement to give an indolizidinone structure. The intermediate **8** is elaborated through a sequential cyclization /reductive ring-opening. In this communication the synthesis and peculiar reactivity of hydroxy polycyclic isoxazolidines will be discussed.

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The osmium-catalyzed tethered aminohydroxylation of glycals allows a stereodirected access to 2- and 3-aminosugars

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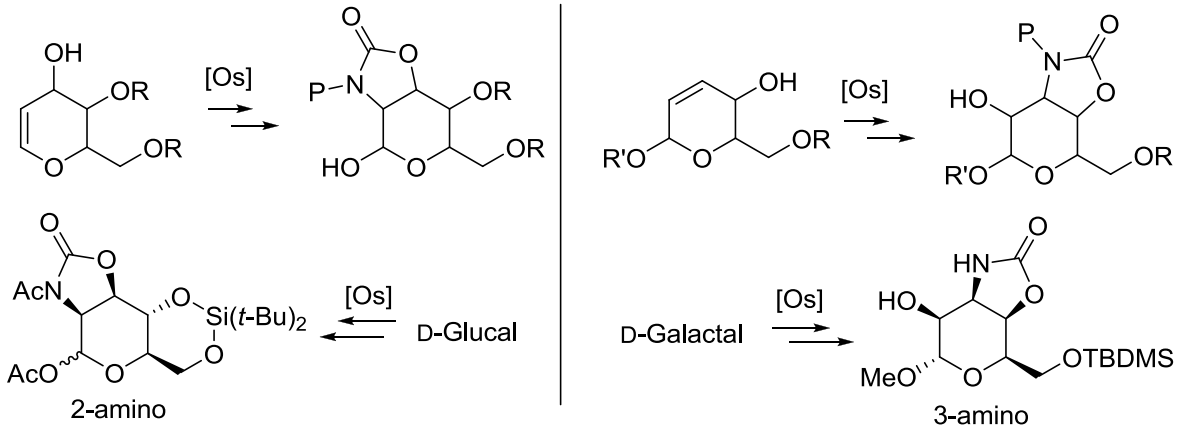
Amino sugars are key constituents of a wide variety of natural products and bioactive compounds such as, among the glycoconjugates, some natural occurring antibiotics (1). To circumvent the problems of low regio- and stereoselectivity often observed in the oxidation of olefins using the Sharpless aminohydroxylation methodology, Donohoe and co-workers introduced in 2001 a variation in the procedure that took advantage of tethering the nitrogen source to the allyl alcohol moiety (the "Tethered Aminohydroxylation" (TA)), which afforded excellent results with chiral allylic substrates (2). We envisaged that the double bond of glycals bearing a free OH group in allylic position could be exploited for this aim, and we describe herein our results on the osmium-catalyzed aminohydroxylation on glycals and derivatives. We found that glucals and galactals show complementary reactivity in dependence of the stage at which the reaction is performed, i.e., directly or after a double-bond shift consequent to a Ferrier rearrangement. This allowed access to both classes of 2-amino and 3-amino sugar derivatives, respectively, through hydrolysis of the oxazolidinone intermediates (3).



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Tunable intramolecular Pd-catalyzed amination of alkenes depending on hypervalent iodine

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Palladium(II)-catalyzed oxidative additions of nucleophiles to olefins have a prominent role in the literature of the last years, as they represent a smart tool for the synthesis of various organic compounds.(1) Among the parameters for the development of these reactions, the presence of an oxidizing agent is essential. Although different oxidants have been used to this purpose, the attention was recently directed toward hypervalent iodine reagents.

In this field, $PhI(OAc)_2$ has been efficiently used as a strong oxidant to promote 1,2-aminoacetoxylations of unsaturated amine derivatives. From the mechanistic viewpoint, first activation of the unsaturation by the Pd(II) catalyst triggers a rapid aminopalladation, leading to a σ-alkyl-palladium intermediate. Subsequent interaction with $PhI(OAc)_2$ generates the aminoacetoxylated product through a Pd(IV) intermediate. Some examples of inter- or intramolecular reactions which involve $PhI(OAc)_2$ as terminal oxidant have thus been reported in the literature.(2)

In the present work, we focus our attention toward the cyclization of various aminoalkenes in the presence of different hypervalent iodine reagents, such as $PhI(OAc)_2$ and $PhI(OCOCF_3)_2$ (Figure 1). While the former led aminopalladation/acetoxylation or aminopalladation/dehydropalladation processes, depending on the structure of olefin (terminal or internal, respectively), the latter provided only allylic amination products. It is worthwhile mentioning that the behaviour of $PhI(OCOCF_3)_2$ as promoter of a direct allylic aminations is so far unknown.

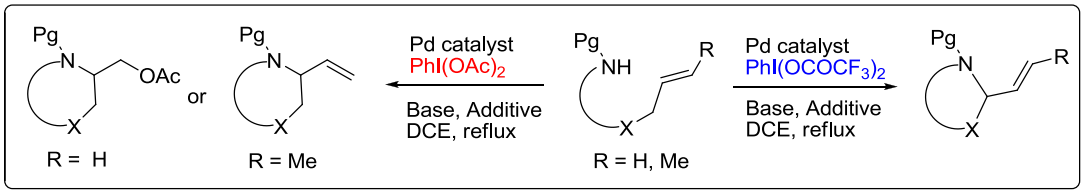

Figure 1

These results highlighted the potential of hypervalent iodine reagents as oxidants in palladium-catalyzed reactions, as they made possible aminoacetoxylation, amination or allylic amination reactions depending either on their counterions or on the structure of the substrate.

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A New Metal-Free Multicomponent Approach to Biaryls

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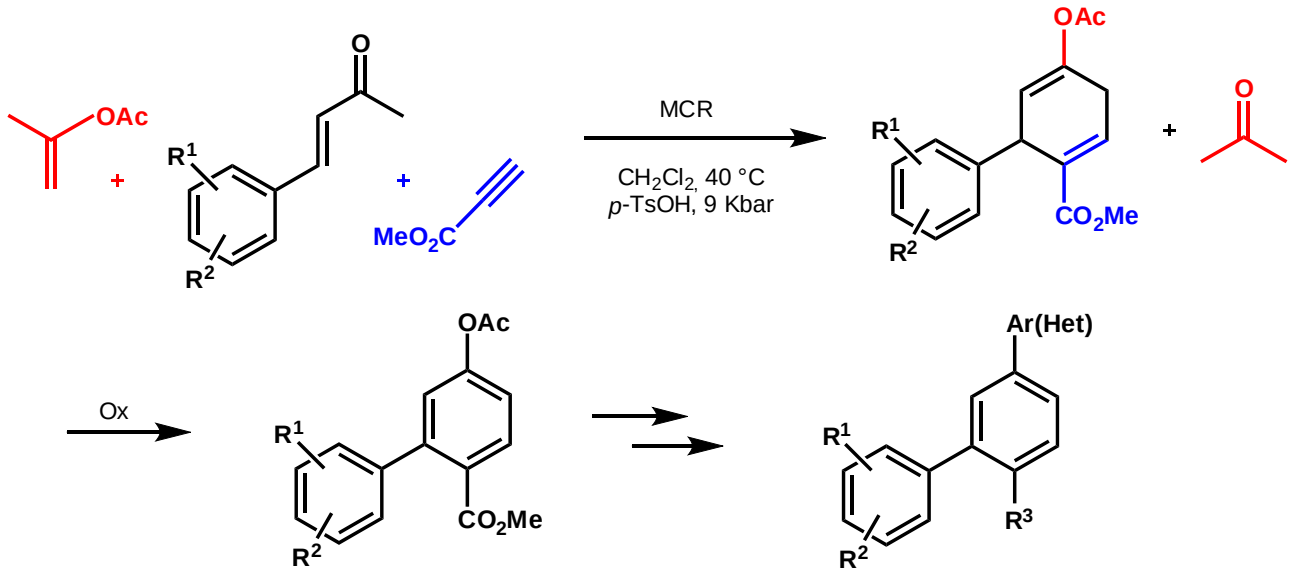
Multicomponent reactions (MCRs) are highly valuable transformations due to their ability to incorporate three or more substrates into a single target in one operation offering opportunities for diversity-oriented synthesis. As part of our studies on the synthesis of biologically active biaryls via a high-pressure Diels-Alder reaction (1,2), we present a new, metal-free, reaction of 4-arylsubstituted-but-3-ene-2-ones with isopropenyl acetate and methyl propiolate under high-pressure conditions (9 Kbar) in dichloromethane at 40 °C and in the presence of catalytic *p*-toluenesulfonic acid. Under these conditions, a new tandem enol acetylation of enones and sequential Diels-Alder cyclization occurred to give aryl-cycloexadiene intermediates which, after aromatization, afforded functionalized biaryls.



One particular attraction to this strategy is the ability to construct biaryl compounds possessing diverse functionalities on the aryl units that are not readily accessible from the traditional palladium-catalyzed cross-coupling reactions. This chemistry can be applied to the synthesis of biaryls which are interesting molecules in biology (3), pharmaceutical- and material-chemistry (4).

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Biological Effects of Heterocyclic and/or Carbocyclic Synthetic Compounds: Recent Results

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The biological activity of some, newly synthesized heterocyclic and carbocyclic compounds has been recently investigated by us to determine their antiviral and/or antitumor potential. Regarding to candidate antiviral compounds, we focused our attention in setting up novel and effective assays to investigate the specific activity of nucleoside/non-nucleoside reverse transcriptase inhibitors (NRTI/NNRTI). New compounds as well as reference drugs were investigated for their anti-HTLV-1/anti-HIV potential by assessing their capability to inhibit in vitro both viral replication and the reverse transcriptase activity in a cell-free system. In addition, since one of the drawback of the antiretroviral therapy is toxicity toward uninfected cells, the compounds under study were tested to define their ability to inhibit cell proliferation or to induce apoptotic cell death in uninfected cells. During these studies, phosphonated-N,O-nucleosides have been identified as a novel class of antiretrovirals, showing to inhibit HTLV-1 infection while exhibiting low toxicity toward uninfected cells. These results allowed us to consider them as prototypes for future antiretroviral candidates. Regarding to candidate antitumor compounds, some iminosugars were found to be endowed with anti-proliferative and pro-apoptotic activity towards a number of tumor cell lines. D(-) lentiginosine, a non-natural compound, was the most effective agent in specifically inducing apoptosis, causing cell death and activation of caspase 3. Conversely, L(+)lentiginosine, the natural enantiomer, induced apoptosis at concentrations 5 times higher. Further studies revealed that very likely D(-)lentiginosine-induced cell death involves the mitochondrial signaling. More recent data show that D(-)lentiginosine is able to interfere with glucose and energetic metabolism of cancer cells. The low level of glucose uptake induced by this compound could be related to induction of autophagy in CAL-27 adherent tumor cells.

Synthesis of a New Heteropolycyclic System as Topoisomerases I Inhibitor

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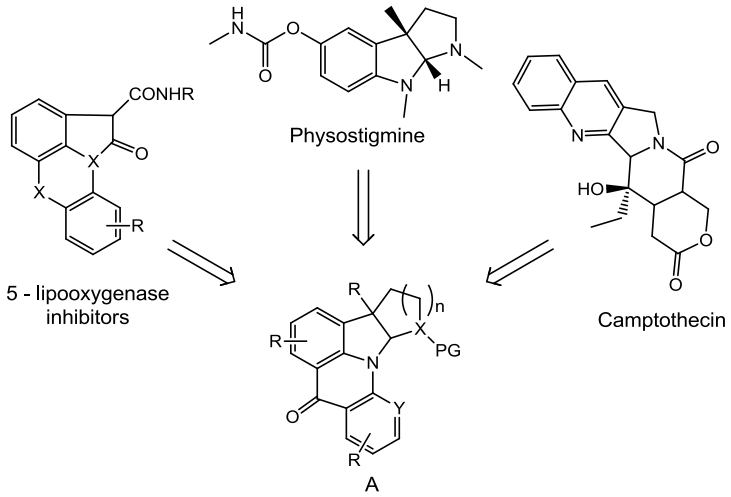
The DNA Topoisomerases are nuclear enzymes essential for vital cellular processes involved in different DNA activities: replication, transcription, recombination. (1) Topoisomerases I and Topoisomerases II act in a different way, involving single or double cleavage of the DNA strands. Inhibition of Topo I activities is lethal and leads to cell death, thus establishing topo I as a promising target for cancer treatment. Camptothecin (CPT), a natural alkaloid first isolated from extracts of *Camptotheca acuminata*, from which the potent anticancer agents irinotecan and topotecan are derived selectively, poison Topo I and exhibit strong antineoplastic activity against colorectal, breast, lung and ovarian cancers. (2) Several limitations of CPT and its analogs such as solubility, toxicity, resistance and above all the unstability under physiological conditions have encouraged the development of new CPT analogues. Considering some structural analogies between the physostigmine alkaloids (3), the 5-lipooxygenase inhibitors (4) and the camptothecin derivatives, new structures corresponding to compounds of general formula A, were designed by the way of molecular modeling and synthesized exploiting as a key step a palladium-catalyzed amination reaction. (5)



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The cycloaddition of Sulfonilazides with Enamines: an Evergreen Click Reaction on the Route of Flexible β-Amyloid Mimics

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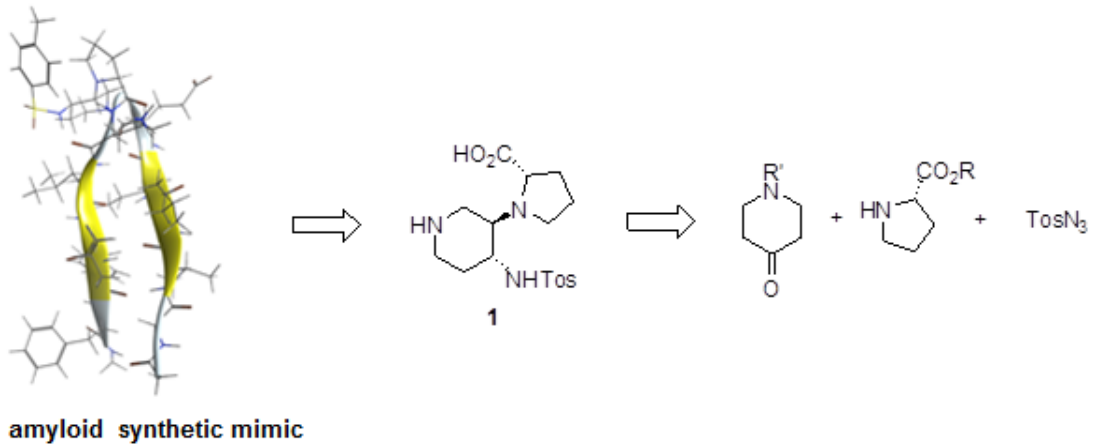
It is more than fifty years ago since the cycloaddition of sulfonyl azides with enamines was proposed.(1) This click reaction yields an unstable dihydrotriazole cycloadduct that undergoes a spontaneous rearrangement to 2-alkyl-sulfonylamidine and to sulfonylformamidine depending on the nature of the starting carbonyl reactant. In particular, when cyclic ketones are employed the main obtained products are azacycloalkene monosulfonyl diamines that are interesting syntons for heterocycle synthesis.(2)
Here we present the preparation of flexible β-amyloid synthetic mimics built on the piperidine-pyrrolidine semi-rigid scaffold **1** obtained through the above mentioned cycloaddition reaction.
Starting from commercially available and unexpensive reagents, *i. e. N*-benzyl piperidone, tosyl azide and proline methyl ester, the dipeptide mimetic **1** was prepared in multigram scale and in enantiopure form.(3) This compound was found really effective in stabilizing β-turn conformation in model peptides and it was used in the design of supramolecular inhibitors of amyloid aggregation. These constructs, containing sequences from neurotoxic $A\beta_{1-42}$ peptide, are able to greatly delay the kinetic of aggregation process and represent promising compounds for future investigation on Alzheimer's disease.



amyloid synthetic mimic

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An Old Approach for New Inhibitors of BACE I: the Biginelli Reaction.

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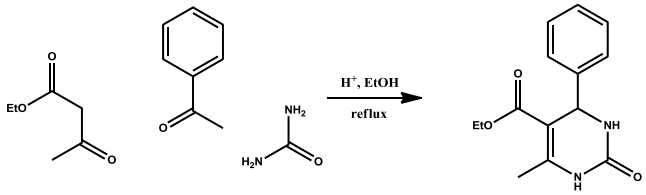
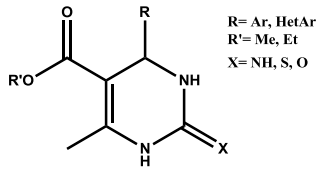
In 1893 Pietro Biginelli reported a simple one-pot cyclocondensation reaction of an aromatic aldehyde, urea and ethylacetoacetate in ethanol solution. (1)



Since then, a wide range of dihydropyrimidines have been synthetized with this multicomponent reaction, possessing different biological activities, including calcium channel blockers, antibacterial, antitumor, anti-inflammatory, antihypertensive and antiviral compounds. (2)
In this communication we will report on the development of BACE I inhibitors using this convenient synthetic approach. BACE I is an aspartic protease involved in the formation of amyloid plaques, which leads to the neurodegeneration typical of Alzheimer's disease and is currently one of the more promising targets to combat the desease. (3)
By combining urea, thiourea and guanidine as nucleophilic partners, different aromatic and heteroaromatic aldehydes, and a β-ketoester, we have synthesized a small library of dihydropyrimidines, some of which have shown excellent inhibition of BACE I, with IC_{50} in the micromolar and sub-micromolar range.



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Novel Approaches to Electron-Poor Trisubstituted Furans and Their Application in the Synthesis of Lignan-Like Compounds

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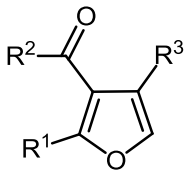
Furans, due to their easy preparation and great synthetic versatility, are important building blocks in the preparation of a wide number of natural and synthetic compounds of biological interest and are widely used as intermediates in organic synthesis (1). These properties encourage to research novel preparation methods, and to explore new applications of this system. Furans are easily reduced to dihydro- and tetrahydrofuran structures through the classic metal-catalyzed reactions, but are also easily oxidated to enediones, useful synthons, or butenolides, whose structural motif is present in bioactive natural products as well as in synthetic products, with a wide range of activities such as antibiotic, antifungal and anticancer agents (1). Among oxidation procedures the dye-sensitized photooxygenation is one of the most used for the mild reaction conditions and efficiency (2).
In this communication we describe the synthesis of trisubstituted furans via novel procedures of Friedel-Crafts (FC) reactions. The strategy is based on the use of Tf_2O (3) as promoter with reduction of steps and without the use of acid catalysts. We have used these furans as starting material and the reaction with singlet oxygen, generated by dye-sensitized photooxygenation, as key step in the synthesis of functionalized lignan-like compounds.



R^1 = Ar, cyclohexyl
R^2 = OMe, Ar
R^3 = CO_2Me,COAr, CH_2Ar

Lignans are widespread plant secondary metabolites holding a large series of bioactivities (4). Their isolation from plant materials is a laborious and expensive process and yields are generally low. For this over the years diverse synthetic approaches have been proposed (5).

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Biomolecular Recognition Through Calixarene Cycloadducts

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Most of the DNA interacting agents possess polycyclic aromatic hydrocarbons (PAH) which bind reversibly to the DNA by intercalation of their flat aromatic systems between base pairs (1). We have designed and synthesized calix[4]arene/pyrenylisoxazolidine conjugates as DNA intercalating agents (**Figure 1**) (2). One of them showed an IC_{50} of 95 nM toward follicular thyroid carcinoma. These derivatives were obtained by esterification of a calix[4]arene-dicarboxylic acid with both *trans*- and *cis*-pyrenylisoxazolidinyl alcohols, prepared by a 1,3-dipolar cycloaddition reaction (3).

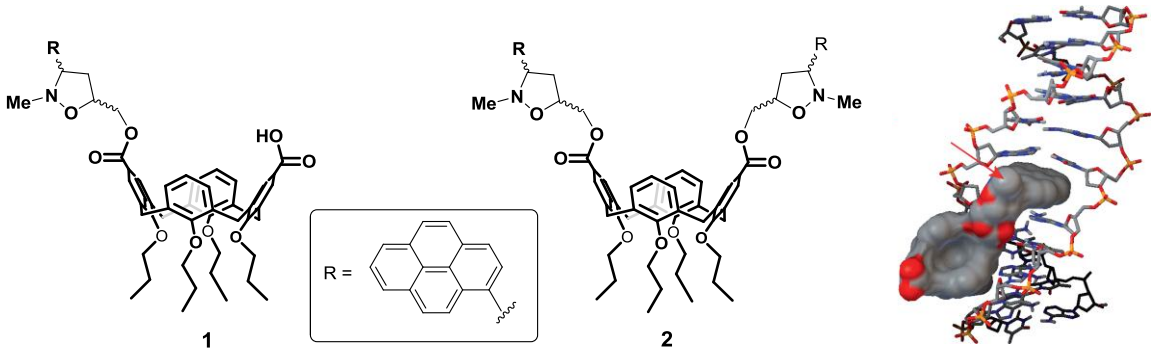

Figure 1

Following these results, we designed a second generation of conjugates in which the pyrenylisoxazolidine moieties can be directly introduced by a 1,3-dipolar cycloaddition on a calix[4]arene scaffold properly functionalized with terminal double bonds at the *exo* rim (**Figure 2**). These conjugates are less sensitive to hydrolysis than the previously described esters. Finally their biomolecular recognition abilities and cytotoxic activities will be evaluated.

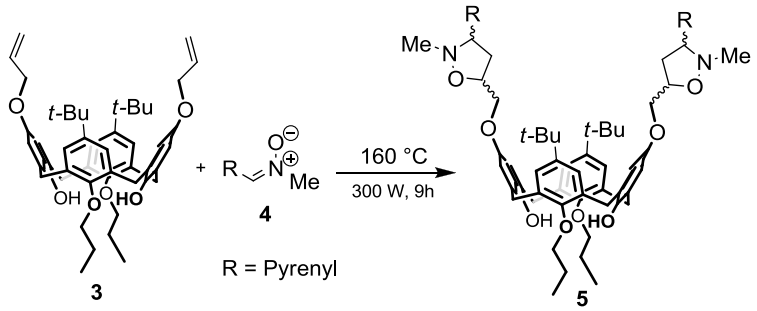

Figure 2

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Fluorescent Probes from Nitrile Oxides

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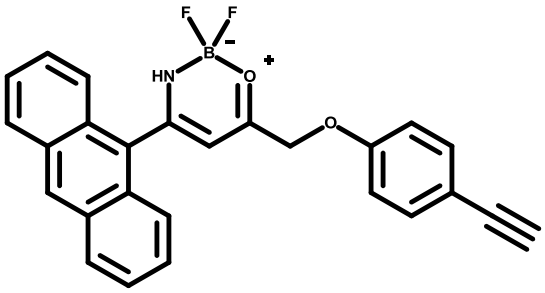
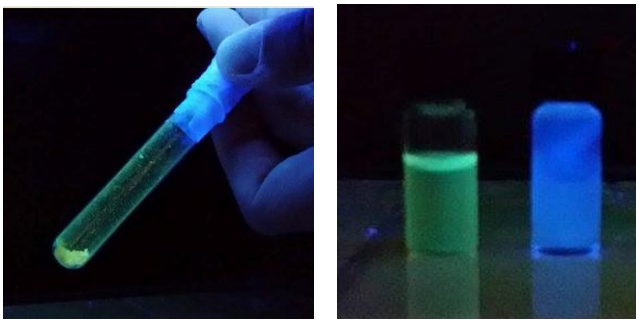
Bio-orthogonal chemistry provides an absolutely remarkable method for biomolecular studies of proteins, glycans, lipids in living systems without interfering with natural biochemical processes (1). From the chemical point of view, the development of bioorthogonal reactions imposes special and restrictive conditions, such as selectivity, biological inertness, strong covalent bonds, high reaction rates and biocompatibility of the chemical reactions (2).

The classical methodologies to perform a reliable chemical ligation are the well-documented Staudinger ligation (3), the Huisgen 1,3-dipolar cycloaddition of azides (Click Reactions) (4) as well as the Diels-Alder (DA) reactions of suitably design diene systems (5).

The use of reduced molecular weight organic molecules as chemical probes represents an outbreaking task in modern organic chemistry research (6). Typically, these molecules are analogues of the bio-interacting substrate containing a fluorescent tag for imaging analysis (7).





In the search of novel synthetic approaches to be applied at Activity-Based Protein Profiling (ABPP) (8), we describe here the rapid and selective synthesis of some new fluorescent compounds obtained from the chemistry of suitable nitrile oxides.

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