2ème Colloque Franco-Roumain de Chimie Médicinale, Iasi, Roumanie

03-05 Octobre 2012

Al 2-lea Colocviu Franco-Român de Chimie Medicală, Iaşi, România

03-05 Octombrie 2012

2nd French-Romanian Colloquium on Medicinal Chemistry, Iasi, Romania

October, 03-05 2012

Sponsors du 2ème Colloque Franco-Roumain de Chimie Médicinale
CoFrRoCM-2012

„ALEXANDRU IOAN CUZA" University of IAŞI

FACULTY OF CHEMISTRY

Bulevardul Carol I nr. 11, 700506

Iaşi, România

Ecole des Hautes Etudes d'Ingénieur
Lille, France

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Dr. Alina Ghinet - École des Hautes Etudes d'Ingénieur, Lille, France

Prof. dr. Elena Bîcu – Faculté de Chimie, Université « Al. I. Cuza », Iasi, Roumanie

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- **Conf. dr. Lucian Bîrsă** - Directeur Département Chimie, Université «Al. I. Cuza», Faculté de Chimie, Iasi, Roumanie

UNIVERSITATEA ALEXANDRU IOAN CUZA

Iaşi (Roumanie)

Ecole des Hautes Etudes d'Ingénieur
Lille (France)

2ÈME COLLOQUE FRANCO-ROUMAIN DE CHIMIE MEDICINALE

03-05 Octobre 2012

Iaşi, Roumanie

Programme du 03/10/2012

09h00: Accueil

10h00: Cérémonie d'ouverture :

Prof. Dr. Vasile IŞAN
(Recteur de l'Université « Al. I. Cuza », Iaşi, Roumanie)
Prof. Dr. Aurel Pui
(Vice-doyen de la Faculté de Chimie, Université « Al. I. Cuza », Iaşi, Roumanie)
Dr. Alina GHINET
(Organisatrice du colloque, Ecole des Hautes Etudes d'Ingénieur, EA 4481, Lille, France)

Session Chair: *Prof. Dr. Adam Daïch, Université Le Havre, France*

10h20: 1ère conférence

« New c-Src kinase inhibitors with a thieno-pyridine structure; Problems and Solutions »
Dr. Solo GOLDSTEIN *(Conseiller Scientifique Diversité Chimique, Servier, Croissy-sur-Seine, France)*

11h00: 2ème conférence

« Novel therapeutic approaches for the treatment of neurodegenerative diseases »
Prof. Dr. Patricia MELNYK *(Université Lille Nord de France, EA4481 "Groupe de Recherche Interdisciplinaire Innovation et Optimisation Thérapeutique", Faculté des Sciences Pharmaceutiques et Biologiques Lille, France)*

11h40: 1ère communication orale

« New synthetic scaffolds through unexpected 1,6-aza-Michael addition to chromone derivatives: Application in the synthesis of aromathecin analogues »
Cătălin PINTIALĂ (*Doctorant, URCOM, Université du Havre, Le Havre, France)*

12h00: 2ème communication orale

« Poly(carboxybetaines) derived from poly(*N*-vinylimidazole) as antibacterial agents. Physico-chemical properties of aqueous and salted solutions »
Dr. Anca Giorgiana GRIGORAŞ (*"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania)*

12h20-14h00: Pause déjeuner

Session Chair: *Prof. Dr. Benoît Rigo, Ecole des Hautes Etudes d'Ingénieur, France*

14h00: 3ème conférence

« Role of Catalysis in Pharmaceutical Chemistry »
Dr. Jolanta ROUSSEAU *(Maître de Conférence, Unité de Catalyse et chimie de Solide (UCCS - UMR 8181), IUT de Béthune Université d'Artois, Béthune, France)*

14h40: 4ème conférence

« **Influence of azole structures and substitutions on protein farnesyltransferase activity and on protozoan parasite proliferation** »

Dr. Joëlle DUBOIS *(Directeur Equipe de Recherche, Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, France)*

15h20-16h00: Pause café + posters

16h00: 3ème communication orale

« **Synthèse de nouvelles *iso*combrétastatines : un nouveau cas d'homologation de cétones** »

Vivien STOCKER (*Doctorant, Ecole des Hautes Etudes d'Ingénieur, EA 4481, Lille, France)*

16h20: 5ème conférence

« **Beyond visual range: a molecular modeler's eye view of predictions** »

Dr. Amaury FARCE *(Université Lille Nord de France, EA4481 "Groupe de Recherche Interdisciplinaire Innovation et Optimisation Thérapeutique", Institut de Chimie Pharmaceutique Albert Lespagnol, Lille, France)*

17h00: 6ème conférence

« **Time-lapse cell monitoring in drug activity assessment** »

Dr. Mircea LEABU (*Institut National de Pathologie "Victor Babes", Bucarest, Roumanie)*

Programme du 04/10/2012

Session Chair: *Dr. Solo Goldstein, Laboratoires Servier, France*

09h15: 7ème conférence

« **Hétérocyclisations de sels *N*-acyliminium via un hétéroatome : acétals mixtes fusionnés** »

Prof. Dr. Adam DAÏCH *(Laboratoire de Chimie, URCOM, Université du Havre, Le Havre, France)*

09h55: 4ème communication orale

« **New methods of synthesis of 1,3,5-triazine-2,4(1*H*,3*H*)-diones, 4-methoxy-1,3,5-triazin-2(1*H*)-ones and 1,3-dimethyl-1,3,5-triazine-2,4-diones** »

Liliana LUCESCU (*Doctorante, Faculté de Chimie, Université « Al. I. Cuza », Iaşi, Roumanie)*

10h15-11h00: Pause café + posters

11h00: 8ème conférence

« **Conception et synthèse d'inhibiteurs de topoisomérase I dérivés de la luotonine A** »

Prof. Dr. Benoît RIGO *(Responsable Pharmacochimie, Ecole des Hautes Etudes d'Ingénieur, EA 4481, Lille, France)*

11h40: 9ème conférence

« **Development of inhibitors targeting hypoxia cell signaling** »

Prof. Dr. Hiroyuki NAKAMURA *(Faculty of Science, Gakushuin University Mejiro, Tokyo, Japan)*

12h20-14h00: Pause déjeuner

Session Chair: *Prof. Dr. Patricia Melnyk, Faculté des Sciences Pharmaceutiques et Biologiques, France*

14h00: 10ème conférence

« **How important is the trimethoxy unit in the structure of tubulin polymerization inhibitors** »

Dr. Alina GHINET *(Chercheur, Ecole des Hautes Etudes d'Ingénieur, EA 4481, Lille, France)*

14h40: 11ème conférence

« **Dérivés carbazoliques pour l'élaboration des matériaux photosensibles** »

Prof. Dr. Galina DRAGALINA *(Université d'Etat de Moldavie, Chişinău, Moldavie)*

15h20-16h00: Pause café + posters

16h00: 12ème conférence

« **New therapeutic approaches in Inflammatory Bowel Disease** »

Prof. Dr. Régis MILLET *(Institut de Chimie Pharmaceutique Albert Lespagnol, EA 4481, Université de Lille 2, Lille, France)*

16h40: 5ème **communication orale**

« ***In vivo* and *in vitro* sustained release study of theophylline from biodegradable and biocompatible alginate/PNIPAAm hydrogels** »

Dr. Raluca Petronela DUMITRIU (*Institut de Chimie Macromoléculaire "Petru Poni", Iasi, Roumanie)*

17h00: 13ème **conférence**

« **Natural endiynes analogs** »

Dr. Mihail Lucian BÎRSĂ *(Directeur Département Chimie, Faculté de Chimie, Université « Al. I. Cuza », Iaşi, Roumanie)*

20h00: Repas de gala (restaurant Select)

Programme du 05/10/2012

Session Chair: *Dr. Alina Ghinet, Ecole des Hautes Etudes d'Ingénieur, France*

09h30: 6ème **communication orale**

« **Anhydride-modified collagen** »

Daniela PAMFIL (*Doctorante, Institut de Chimie Macromoléculaire "Petru Poni", Iasi, Roumanie)*

09h50: 7ème **communication orale**

« **Implication du récepteur $P2X_7$ dans l'inflammation** »

Davy BAUDELET (*Doctorant, Ecole des Hautes Etudes d'Ingénieur, EA 4481, Lille, France)*

10h10: Pause café + posters

10h50: 14ème **conférence**

« **Conception, synthèse et évaluation antitumorale de nouvelles indolizin-3-yl(aryl/hétéroaryl)méthanones** »

Prof. Dr. Elena BÎCU *(Faculté de Chimie, Université « Al. I. Cuza », Iaşi, Roumanie)*

11h30: 8ème **communication orale**

« **Chemical composition and antibacterial activity of the essential oil of *Cupressus semperverens* cone from Algeria** »

Dr. M'hamed NASRI *(Ecole Normale Supérieure, Laboratoire d'étude et de développement des techniques de traitement et d'épuration des eaux et de gestion environnementale, Alger, Algérie)*

11h50: Conclusions et clôture du colloque

12h00: Pause déjeuner + enlèvement posters

Les posters seront exposés pendant toute la durée du colloque (03-04-05 octobre 2012).

"Alexandru Ioan Cuza" University of Iasi, Romania

Short history

We take pride in being the first modern university of Romania, inheriting values, reputation and educational knowledge. Established in October 1860, Alexandru Ioan Cuza University of Iaşi is the oldest university in our country. Its history follows the patterns of the Romanian nation. The University of Iaşi, as it was initially named, was founded in 1860, only one year after the establishment of the Romanian state, and it was both a result and a catalyst of the rise of the Romanian national spirit. It was no historical accident that the city of Iaşi became the host of the most prominent institution in Romanian education: for ages, Iaşi had represented a privileged cultural area, preserving both the native and the European cultural spirit in a conquered territory. In the 17th century, the academy in Iaşi was already synchronized with the European spirit and model. Courses were taught in Greek, the language of culture in the European Orient.

The 19th century saw the rise of the nationalist spirit, Romanian language, culture and conscience. The solemn inauguration of the University of Iaşi, on October 26th 1860, was to mark a long evolution and it represented the first great step from medieval high school to modern higher education.

With only three faculties in the beginning - Law, Philosophy and Theology, the university developed into a truly European academic centre. The mobility of the teaching staff, students, books and ideas placed the University of Iaşi on a professional and scientific level that was widely recognized.

After World War II, the structural change of the political regime in Romania determined deep transformations in higher education policies, too. It also imposed a new ideological horizon, a dominant immobility and dogmatism that obstructed initiatives. Higher education was isolated while traditional relationships established with the great Western schools and trends became very difficult to maintain. In our university, the structure of faculties changed several times after 1948. The eight faculties (Mathematics - Mechanics, Physics, Chemistry, Biology - Geography, Law, Philology, History - Philosophy and Economics) ensured the training of specialists for fundamental education and research fields. It is important to underline that what was imposed in terms of dogmatism and ideology had only a formal official value, while most of the teaching staff continued to keep their dignity and academic status. Concessions were formal, not basic. It was a price that had to be paid for saving both academia and academics.

The falling of the totalitarian regime in December 1989 opened new perspectives for Romanian education. The reconstruction activity was spontaneous and radical, involving all fields: structure, curriculum, communication system, human resources. University autonomy, decentralization and freedom of decision lead Romanian higher education towards new horizons. Still in a difficult financial situation, it has been gradually regaining its place in the European community.

Alexandru Ioan Cuza University of Iaşi has the revelation of freedom of thought and of action. We feel it in the quality of teaching and research, in the determination and commitment to excellence.

The university today

Alexandru Ioan Cuza University of Iaşi (UAIC) is the first modern Romanian university and it has kept this privileged position not only for historical reasons. Nowadays, it ranks first at national level in terms of research, education and institutional transparency.

This university, which first opened its doors to only 70 students back in 1860, currently has more than 31.000 students, 15 faculties and almost 250 study programmes at Bachelor, Master and Doctoral level. Its educational offers are among the most diversified, including specializations taught in English and French (mostly at Master and Doctoral level), jointly achieved in collaboration with partner universities from abroad, as well as courses created in cooperation with the business sector, which offers employment to the best graduates.

The perfect way to get a better grasp of what *Alexandru Ioan Cuza* University means and represents is *Graduation Day* – an annual event in a unique concept for Romania – when about 6000 students celebrate their graduation by walking from the main university building to the city centre. This ceremony is living proof that the particular place Iaşi has gained in the history of Romanian higher education has been maintained. It testifies to the amazing capacity of this city – and of its higher education institution - to remain forever young and innovative in spirit. No wonder that the most performing system of e-learning – BlackBoard Academic Suite was implemented here, that the progressive assessment system is currently implemented and exceptional results have been obtained in the research field.

In 2011, Alexandru Ioan Cuza University has been classified by the Ministry of Education, Research, Youth and Sports as a "Ist category" university – the category available for advanced research and education universities.

Besides the international cooperation in research projects, *Alexandru Ioan Cuza* University has concluded partnerships with prestigious universities from all over the world. It is a member of the Coimbra Group, Utrecht Network, EUA (European University Association), IAU (International Association of Universities) and AUF (l'Agence Universitaire de la Francophonie).These dynamic international relations have made it possible for about 1500 students and academics from UAIC to benefit from study and teaching / research mobilities abroad every year and participate in various international workshops, seminars, conferences etc.

History, key dates and figures

1885: Founded

1935: Accredited by the "Commission des Titres d'Ingénieur": the French National body for Engineering
1968: Recognized by the State

15 000 Alumni
1 900 Current students
4 Research disciplines
10 Majors
170 Full-time teaching staff
350 Part-time teachers
72 Partner universities
260 Annual semester exchanges

Networks

HEI is a founding member of the largest private multidisciplinary university in France: Lille Catholic University, training some 22 000 students annually. In addition we are active within FESIC, the CGE, Campus France and N+i.

A five-year curriculum

- **The general cycle** (3 years - Bachelor's degree)

The first 2 years entail an integrated foundation of courses. During the 3rd year, students organize their time into 4 main activities in a holistic, multidisciplinary approach:
- Science and engineering techniques • Management and business environment
- General studies, ethics and communication • Personal development

- **The professional cycle (**2 years - Master's degree)

During the first year students pursue their 4 main activities and also choose one of 10 different concentrations:
Architectural Engineering / Banking, Finance and Insurance / Biomedical Engineering / Building and Civil Engineering / Chemistry and Chemical Engineering / Computer Science and Information Technology / Energy, Building and Environment / Energy, Electrical Systems and Control Systems / Industrial Management / Mechanical Design and Engineering / Technologies, Innovation, Textiles and International Management

Distinguishing Attributes

- **An accredited degree of acknowledged prestige**

Our graduates are renowned as HEI engineers throughout all areas of specialization, due to the reputation HEI carries with the leading companies in France and Worldwide.

HEI engineers are capable of efficiently resolving complex problems and are at ease in carrying out complex tasks in an efficacious systematic manner, within budget. They are also well versed in teamwork, organization and structure, leadership, and project management, with clear, precise communication skills. They are sought after for these competencies and also their humanistic and multi-cultural approach to project management and problem solving.

- **Immediate job placement in Top positions**

Our students are often recruited prior to finishing their studies. Some of the top companies which hire our students: Bouygues, Logica, Eiffage, Renaut, Alten, Altran, Cegelec, Sopra, Decathlon, EDF, SOGEA, Toyota, PSA Peugeot Citroen, Rabot Dutilleul, Areva, Total, L'Oreal, Coca Cola, Cap Gemini, Thompson, to name only a few.

- **Cooperation with the business community**

Industrial relations are in fact our driving force in every aspect of our activities: teaching and class work, various training periods, Eleven Week Projects, many forms of internships, industrial projects, industrial and private sector involvement on-campus and in our curricula as well as through recruitment fairs.

- **Work placement and international experience**

HEI engineers possess strong practical experience; all courses are highly industrial business world oriented. Students must spend three separate periods, during their studies in Gemini, Thompson, to name only a few.

- **Cooperation with the business community**

Industrial relations are in fact our driving force in every aspect of our activities: teaching and class work, various training periods, Eleven Week Projects, many forms of internships, industrial projects, industrial and private sector involvement on-campus and in our curricula as well as through recruitment fairs.

- **Work placement and international experience**

HEI engineers possess strong practical experience; all courses are highly industrial business world oriented. Students must spend three separate periods, during their studies in industry and must also undertake an industrial study/research project within a company or university research laboratory.
In addition all students undertake an international experience during their studies within this framework or within the context of an exchange programme.

- **Academic exchanges**

Academic exchanges take place during the 4th and 5th years of study for the student to study in a foreign school or university for one or two semesters. HEI maintains strong ties with 72 academic partners in 28 countries, actively pursuing a policy of establishing double-diplomas.

Close interaction with students, professional prospects

Each of our future engineers is accompanied throughout their personally developed training program. All students are advised on a one-to-one basis, allowing them to successfully complete the engineering program of their design, both in terms of polyvalence and practical specialization.
Successful engineers immediately take on management responsibilities within industry, or choose to further develop their skills in graduate school completing M.Sc. and/or PhD. training. All students, faculty members and post-doctoral staff contribute to an active international research program.

- **Research and development: a core activity**

R &D is organized into 4 areas of expertise on which HEI's reputation has been built:
- Electrical Power Networks and Intelligent Transport
- Innovative Materials
-Sustainable Health and Chemistry, and the transversal discipline
- Energies, Building and Environment.

CONFÉRENCES INVITÉES

C1. Nouveaux Inhibiteurs de Kinase c-Src à Noyau Thiéno-Pyridine ; Problèmes et Solutions

S. GOLDSTEIN
Consultant Indépendant Chimie Médicinale et Diversité Chimique
Servier, 125 Chemin de Ronde, 78290 Croissy-sur-Seine, France

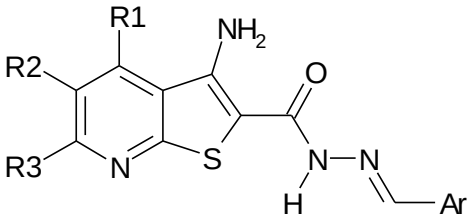
Parmi les cibles qui ont attiré l'intérêt des chercheurs aussi bien en milieu académique qu'industriel la tyrosine kinase c-Src occupe une place de choix.

En effet il a été démontré qu'une activité dérégulée de cette enzyme joue un rôle important dans la progression des tumeurs et que des inhibiteurs de c-Src ont un effet bénéfique dans plusieurs modèles pathologiques dans la thérapie du cancer.

La synthèse et le profile biologique d'une nouvelle classe d'inhibiteurs c-Src élaborée autour d'une 3-amino-thiéno[2,3-b]pyridine découverte lors d'une campagne de criblage de la base structurale Servier, seront présentés.

L'accent sera mis sur la démarche scientifique incluant les études de structure-activité, la modélisation moléculaire ainsi que la cristallographie aux Rayons X.

L'approche a permis l'obtention d'inhibiteurs actifs également au niveau cellulaire.



Correspondance. Tel + 33 1 55 72 25 99, solo.goldstein.part@fr.netgrs.com

C2. Novel therapeutic approaches for the treatment of neurodegenerative diseases

Patricia Melnyk[1,2*], ThiHuu Nguyen[1,2], Stéphane Burlet[3], Sabiha Eddarkaoui[1,4], David Blum[1,4], Cecilia Estrella[3], Luc Buée[1,4], Nicolas Sergeant[1,4], and Philippe Verwaerde[3]

[1] *Université Lille Nord de France, F-59000 Lille, France*
[2] *UDSL, EA 4481, UFR Pharmacie, F-59000 Lille, France*
[3] *AlzProtect, F-59000 Lille, France*
[4] *Inserm U837, Jean-Pierre Aubert Research Center, F-59000 Lille, France*

Alzheimer's disease (AD) is the most prevalent cause of dementia in adults aged of 65 and over and accounts for 60 to 80% percent of cases. Yet there are no curative drugs and treatments remain symptomatic. AD is a multifactorial slow and progressive dementing disease that combines two pathophysiological mechanisms: the amyloid pathology and the Tau pathology. The first one results from extraneuronal aggregation of Aβ peptides that derive from cleavages of a large transmembrane precursor named amyloid protein precursor. The second one corresponds to intraneuronal accumulation and aggregation of abnormally modified microtubule-associated tau proteins; to form the so-called neurofibrillary tangles. Most of the efforts have focused on one pathology, especially the amyloid pathology and yet, current clinical trials failed to succeed in phase III. Protein mis-folding, protein aggregation and prion-like diffusion of protein pathogens are mechanisms common to several neurodegenerative diseases including AD.

In a collaborative project targeting AD, several compounds families have been developed and one compound is ready to enter regulatory clinical phase I trials. This compound is to our knowledge the first compound acting on APP metabolism (increase in APP-CTFs and sAPPα, decrease in Aβ) and able to interfere with Tau pathology development *in vivo*. This compound is able to improve cognitive impairments in transgenic mice. The search for the molecular target of this compound leads us to identify a protein involved in the degradation of altered proteins.

The presentation will focus on main results obtained with this compound.

* Corresponding author, tel. +33 320964949, e-mail address patricia.melnyk@univ-lille2.fr (Patricia Melnyk)

C3. Role of catalysis in pharmaceutical chemistry

Jolanta Rousseau

Unité de Catalyse et Chimie de Solide (UCCS-UMR8181), Université d'Artois, Béthune)

Catalysis is a very wide field ranging from molecular chemistry to materials science. The catalysis has become increasingly important in the pharmaceutical industry. The use of catalytic processes could promote the reduction of energy consummation, accelerate reaction rate and increase selectivity by decreasing the formation of secondary products.

First we will review some classical examples of application of catalysis in medicinal chemistry and we will end by recent academic and also industrial developments.

Rôle de la catalyse en chimie pharmaceutique

La catalyse est un domaine très vaste allant de la chimie moléculaire à la science des matériaux. La catalyse est devenue de plus en plus importante en industrie pharmaceutique. L'utilisation des procédés catalytiques peut favoriser la réduction des consommations d'énergie, accélérer la vitesse de réactions ainsi qu'augmenter leur sélectivité en diminuant la formation de produits secondaires.

Tout d'abord nous passerons en revue des exemples classiques d'application de la catalyse en pharmacochimie et nous terminerons par des développements académiques et industriels récents.

* Author e-mail address: jolanta.rousseau@univ-artois.fr (Jolanta Rousseau)

C4. Influence of azole structures and substitutions on protein farnesyltransferase activity and protozoan parasite proliferation

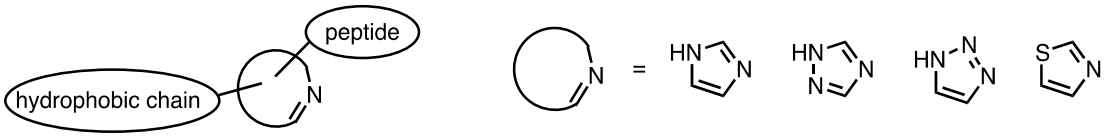
Guillaume Pousse[1], Stéphanie Duez[1], Philippe Grellier[2], and Joëlle Dubois[1,*]

[1]*Institut de Chimie des Substances Naturelles, CNRS UPR2301, avenue de la Terrasse, 91190 Gif sur Yvette, France*

[2]*Département RDDM, CP52, Muséum National d'Histoire Naturelle, UMR 7245 CNRS, 57 rue Cuvier, 75005 Paris, France*

Protein farnesyltransferase (FTase) catalyzes the farnesylation of many proteins in a critical post-translational step. This modification plays a crucial role in intracellular signal transduction, cell proliferation and apoptosis. Growth of protozoan parasites is severely impaired by inhibition of the prenylation pathways compared with mammalian cells and, consequently, FTase has appeared as a potential target for parasitic diseases such as malaria and African sleeping sickness.[1]

The imidazole ring is often a common moiety of potent protein farnesyltransferase inhibitors (FTIs). Other azole rings such as triazoles or thiazoles are also found in FTIs. As part of our search for new FTIs with antiparasitic activity, we developed different synthetic pathways to functionalize these azole rings with peptidic or/and hydrophobic moieties.[2] Series of azole-containing FTIs (**1**) have been synthesized where the peptide, its position and the azole ring have been varied.



1

Evaluation of their inhibitory activity on isolated FTase and parasitic growth showed that imidazole bearing the VFM tripeptide at position 5 is the best azole derivative. Introduction of the farnesyl moiety at position 1 greatly improved its antiparasitic activity.

References

1- Eastman, R. T.; Buckner, F. S.; Yokoyama, K.; Gelb, M. H.; Van Voorhis, W. C. *J. Lipid Res.* **2006,** *47*, 233-240.

2- (a) Marcia de Figueiredo, R.; Coudray, L.; Dubois, J. *Org. Biomol. Chem*. **2007**, *5*, 3299-3309. (b) Kerhervé, J.; Botuha, C.; Dubois J. *Org. Biomol. Chem*. **2009**, *7*, 2214-2222. (c) Duez, S.; Coudray, L.; Mouray, E.; Grellier, P.; Dubois, J. *Bioorg. Med. Chem.* **2010**, *18*, 543-556.

* Corresponding author, tel. 0033169823058, e-mail address: joelle.dubois@icsn.cnrs-gif.fr (Joëlle Dubois)

C5. Beyond visual range: a molecular modeler's eye view of predictions

Amaury Farce*, Nicolas Renault, Xavier Laurent and Philippe Chavatte

ICPAL, Université Lille Nord de France, BP83, 5006 Lille cedex

Drug Design depends largely on the capacity to understand the Structure-Affinity/Activity Relationships underlying the biological response of the compounds. Highly specialized tools have been developed to overcome the burden of manually describing each pharmacomodulation, from the first tentative mathematical depiction of cytotoxicity as a function of water solubility to modern self learning neural networks. This variety of tools is built on nearly as various technical approaches, ranging from linear regression of the root mean square of error prediction to the much more recent Support Vectors theory.

All these methods have the common goal of eventually predicting the activity of new compounds before their testing, rather than only describing more or less accurately the SAR of already tested molecules. Although each new method has brought large promise, none of the older methods have been abandoned, leaving a relatively large number of prediction methods, all with their own advantages and weaknesses. In many ways, there is not strictly a better method of prediction, as the perfect tool for a given subject is heavily dependent on the degree of information available on the target at a molecular level, on the compounds from a structural point of view, on the exact method of evaluation of their activity, on the mechanism of action and on the information needed to propel research in the field. Moreover, in a close parallel with aviation, whatever the tool may be, the user is also a major factor in the efficiency of the prediction.

Through a series of examples from our laboratory, we will try to outline the efficiency factors related to low dimensionality QSAR, 3D molecular fields QSAR, SVM and Bayesian networks, balancing the ease of use and the ease of results interpretation. The drawbacks and the traps awaiting the unwary as well as the power user will be sketched.

Overall, even if the technical methodologies for building a predictive model are numerous and different, it is the ultimate goal of prediction that really defines what can be called a good model, cutting through the apparent divergence of QSAR to keep the tool user humble (and most often anxiously waiting for biological testing). As they all have the same goal, all these methods share a common core of simple rules that help keep them useful for medicinal chemists and efficient from the modeler’s point of view.

C6. Time-lapse cell monitoring in drug activity assessment

Mircea Leabu

University of Medicine and Pharmacy Carol Davila, Bucharest, Romania
„Victor Babeş" National Institute of Pathology, Bucharest, Romania

Time-lapse investigation of cell behavior became a helpful manner to develop studies related to cellular events such as adherence, spreading, proliferation, migration or cell death as a result of handling the culture medium chemistry, including the addition of putative drugs. Two are the most useful procedures for real time cell monitoring: time-lapse videomicroscopy and cell layer impedance measurements, both of them supported by appropriate equipments. In our lab, two of the most competitive equipments available on the market do exist: Biostation IM (Nikon) for time-lapse videomicroscopy and xCELLigence System (Roche Diagnostics) for the measurement of changes in cell layer impedance as a result of variations in cell behavior under different experimental conditions. My talk will introduce to the audience the two new approaches allowing time-lapse cell monitoring and the two equipments in terms of advantages and limits for their use in the assessment of presumed drugs' effects on cell adherence, spreading, motility, proliferation and cell death. The complementariness of the results obtained by the two equipments and techniques will be discussed, considering various experimental conditions. The techniques presented proved to be useful in getting hypotheses and for designing experiments further, using standard biochemical and/or cell biology methods, in order to decipher details related to the molecular mechanisms of the studied compounds' effects, determining changes in the cell behavior.

In conclusion, two new approaches, that are helpful in the investigation of drugs' activity and effect on cell physiology and pathology, will be critically considered.

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* Author e-mail address: mircea.leabu@ivb.ro (Mircea Leabu)

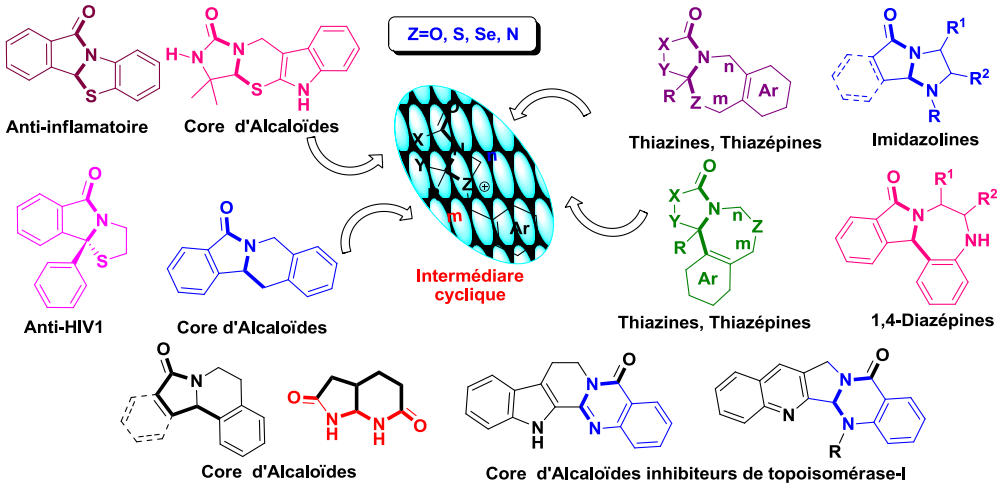
C7. Hétérocyclisations de sels *N*-acyliminiums via un hétéroatome: acétals mixtes fusionnés

Adam Daïch, Prof.

URCOM, INC3M FR-CNRS 3038, EA 3221, UFR des Sciences & Techniques de l'Université du Havre, 25 Rue Philippe Lebon, B.P 540, F-76058 Le Havre Cedex, France; ***adam.daich@univ-lehavre.fr***

Un de nos axes de recherche majeur consiste en le développement de nouvelles méthodologies de synthèse potentiellement utiles en chimie organique et bio-organique. Dans ce type d'activité, le hasard est omniprésent et les évènements, inattendus, apportent souvent des perspectives nouvelles.

Les méthodes de synthèse que nous développons dans notre groupe ont pour cœur la formation d'ions *N*-acyliminiums, généralement générés en milieu acide.[1] Ces intermédiaires cationiques, dérivés des imides chiraux ou non, sont piégés de façon intermoléculaire ou intramoléculaire par divers types de nucléophiles incluant des hétéroatomes (O, S, Se, N) pour conduire, après des aménagements fonctionnels, à des structures inédites selon des procédés nouveaux, simples et originaux.[2]



Notre démarche générale consiste à viser des charpentes molécules d'intérêt pharmaceutique judicieusement sélectionnées en vue leurs évaluation biologique. De plus le choix des molécules cibles est étroitement lié à celui des collaborateurs ou réciproquement selon les cas. Dans cette présentation, l'illustration de ces procédés se décline à travers quelques applications majeures que nous présenterons. De même les principaux facteurs déterminant lors de ces réactions ainsi que les aspects synthétiques et mécanistique seront présentés et discutés.

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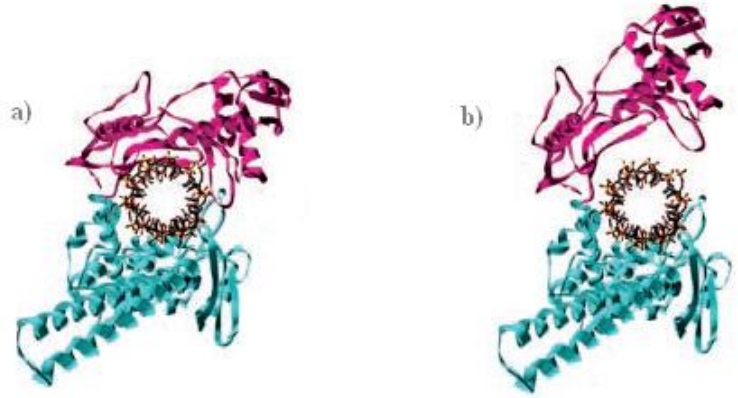
C8. Conception et synthèse d'inhibiteurs de topoisomérase I dérivés de la luotonine A

Benoît Rigo* et Thomas Boisse

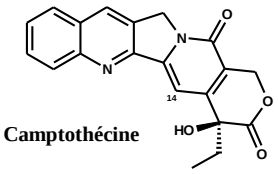
Laboratoire de Pharmacochimie, Hautes Etudes d'Ingénieur, 59046 Lille, France

La présentation décrit la conception et la synthèse de composés à visée antitumorale, capables d'inhiber la topoisomérase I, enzyme surexprimée dans de nombreux cancers.

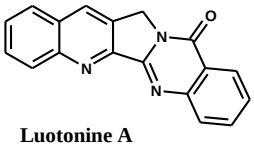


Représentation de la topoisomérase I et d'un fragment d'ADN à partir de sa structure cristalline (vue dans l'axe de l'ADN), en conformation ouverte (a) ou fermée (b).

Les inhibiteurs de topoisomérase I agissent pour la plupart en stabilisant réversiblement un complexe **binaire** ADN-Topoisomérase I. Un complexe **ternaire** est alors formé. La molécule vient se loger à l'interface de l'enzyme et d'une zone de coupure d'un brin de l'ADN. L'intercalation de l'inhibiteur dans le complexe binaire empêche la religation du brin ; l'enzyme est alors liée de façon covalente à l'ADN. La collision de la fourche de réplication avec le complexe ternaire génère des cassures d'ADN, létales pour la cellule qui finit par mourir par apoptose.



Camptothécine



Luotonine A

Le premier inhibiteur connu de la topoisomérase I est la camptothécine. Nous avons choisi comme hits la luotonine A qui est une molécule d'origine naturelle. Sa structure est proche de celle de la camptothécine, et la littérature décrit son inhibition de la topoisomérase I.

[1]Carey, J.F., Schultz, S.J., et al. *Proc. Natl. Acad. Sci. U. S. A.* **2003**, *100*, 5640.

Corresponding author e-mail:benoit.rigo@hei.fr (Benoît Rigo, tel. 0033-3 28 38 48 58)

C9. Development of Inhibitors Targeting Hypoxia Cell Signaling

Hiroyuki Nakamura*

Department of Chemistry, Faculty of Science, Gakushuin University, Tokyo 171-8588, Japan

The formation of new blood vessels sprouting from existing host capillaries (angiogenesis) is a necessary process for tumors to grow beyond a certain critical size. Specific inhibition of this tumor-induced angiogenesis prevents growth of many types of solid tumors and provides a novel approach for cancer treatment. Angiogenesis factors such as vascular endothelial growth factor (VEGF) and erythropoietin (EPO) are key growth factors in tumor angiogenesis. Hypoxia-inducible factors (HIF) are heterodimeric (α/β) transcriptional factors and major physiological stimuli for expression of angiogenesis factors. The levels of HIF-1α are low under normal oxygen conditions (normoxia) but increase in response to hypoxia. HIF-1α has been found in a wide variety of human primary tumors compared with corresponding normal tissue, thus considered to be a potential target for antineoplastic therapy [1].

We developed carborane-containing phenoxyacetanilides (**1**) as potent inhibitors of HIF-1α activation under hypoxic conditions [2]. Furthermore, we succeeded in the synthesis of multifunctional molecular probes of HIF-1 inhibitors (**2**) for combining photoaffinity labeling and click reaction moieties in the molecules in order to clarify the action mechanism of **1** against HIF inhibition. Using the probe molecules (**2**), we identified that HSP60 is the target protein of **1**, indicating that HSP60 might be a new molecular target for HIF inhibition [3,4].

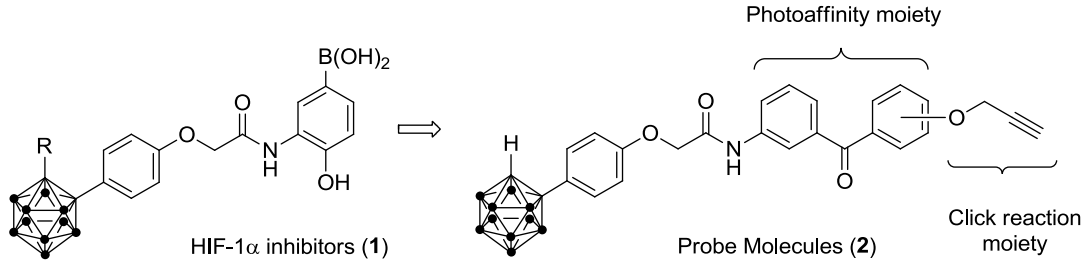


Figure 1. Design of Probe Molecules.

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[3] a) H. S. Ban, K. Shimizu, H. Minegishi, H. Nakamura, *J. Am. Chem. Soc.* **2010**, *132*, 11870. b) H. Nakamura, Y. Yasui, M. Maruyama, H. Minegishi, H. S. Ban, S. Sato, *submitted.*

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* Corresponding author, tel. +81 3 3986 0221, e-mail address hiroyuki.nakamura@gakushuin.ac.jp (Hiroyuki Nakamura)

C10. How important is the trimethoxy unit in the structure of tubulin polymerization inhibitors

Alina Ghinet[1, 2, 3,*]

[1]*Department of Organic Chemistry, 'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Bd. Carol I nr. 11, 700506 Iasi, Romania*
[2]*Univ Lille Nord de France, F-59000 Lille, France*
[3]*UCLille, EA 4481 (GRIIOT), Laboratoire de Pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France*

Tubulin is a heterodimer of closely related and tightly linked globular α- and β-tubulin proteins, capable to polymerize in hollow tubes called microtubules. The microtubule system is involved in many essential cell functions,[1] and their importance in cell division makes microtubules an important target for anticancer drugs. To date there are at least 28 compounds targeting tubulin in clinical development.[2] Combretastatin A-4 (CA-4) (**1**, Fig. 1), extracted from *Combretum caffrum* by Pettit *et al*,[3] depicts high affinity for the colchicine binding site, and is one of the most potent antimitotic agents. Research on combretastatin A-4 in order to improve its *in vivo* activity led to the discovery of phenstatin (**2**, Fig. 1).[4]

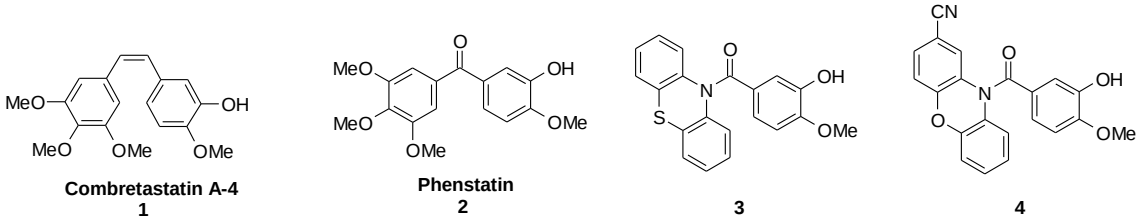
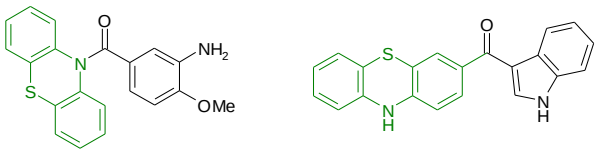


Figure 1. Structure of combretastatin A-4 (**1**), phenstatin (**2**), and of compounds **3** and **4**

We were puzzled by a recent report on the strong inhibition of tubulin polymerization and antiproliferative activities of phenoxazine and phenothiazine derivatives such as compounds **3** and **4** (Fig. 1).[5] In these products, the heterocycle system seems to correspond to the A ring of the standard tubulin polymerization agents. We decided to synthesize phenstatin analogs utilizing phenothiazine as an A ring (*e. g.* compounds **5** and **6**, Fig. 2) in order to explore some structure-activity relationships in this family of compounds.



5: GI_{50} (K-562) = 39.8 nM
GI_{50} (MDA-MB-435) = 29.2 nM

6: GI_{50} (K-562) = 395 nM
GI_{50} (MDA-MB-435) = 112 nM

Figure 2. Structure and biological activity of target compounds **5** and **6**

Acknowledgements: The author gratefully acknowledges the CommScie (project POSDRU/89/1.5/S/63663) for financial support.

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* Corresponding author, tel. +33 328 38 48 58, e-mail address alina.ghinet@hei.fr (Alina Ghinet)

C11. Dérivés carbazoliques pour l'élaboration des matériaux photosensibles

Dragalina Galina[1], Robu Ştefan[1], Popuşoi Ana[1], Culeac Ion[2]

[1]Université d'État du Moldova, [2]Academie de Science du Moldova

Dans le cadre de ce travail ont été étudiés les dérivés du carbazole, qui se montrent comme très prometteurs dans la préparation des produits polymériques photosensibles, utilisés dans l'enregistrement et la transmission d'information, pour la protection des documents, des produits industriels et alimentaires contre la falsification, le dépistage des défauts, pour la confection des objets holographiques, ainsi que pour la préparation des matériaux utilisés dans le stockage des données.

Les matériaux photosensibles à base du carbazole doivent correspondre à un ensemble d'exigences qui visent l'adhésivité au support, la transparence, les caractéristiques déformantes et thermo-mécaniques, la photosensibilité etc. Dans le but d'obtenir les produits avec les caractéristiques optimales, nous avons étudié la relation entre la structure chimique et les propriétés des polymères carbazoliques pour rendre possible la synthèse dirigée dans ce domaine. La variation de la structure a englobé les modifications sur le vertical (la distance entre le noyau du carbazole et la chaîne polymérique), sur l'horizontale (y compris la plastification avec les alkylméthacrylates) et la modification des substituants au niveau du noyau carbazolique (H, Br, NO_2).

L'étude a démontré que si le noyau carbazolique est situé près de la chaîne polymérique (le cas du polyvinylcarbazole), on obtient des produits très rigides. Ainsi, pour améliorer la mobilité des groupes carbazoliques et leurs propriétés mécaniques, nous avons obtenu et bien étudié les polymères à base de *N*-carbazolylméthyl(méth)acrylate, de *N*-carbazolyléthyl(méth)acrylate, epoxypropylcarbazole etc, qui ont été copolymérisés avec les monomères plastifiants.

Les produits des réactions ont été purifiés par des méthodes chromatographiques. A base des monomères obtenus, nous avons synthétisé, par voie radicalaire, les copolymères carbazoliques pour les systèmes photosensibles.

En fonction du but poursuivi, au niveau de l'étape de préparation des matériaux (pellicules), les copolymères carbazoliques ont été dopés avec des agents électronoaccepteurs (tétraiodométhane, trinitrofluorenone etc. pour augmenter la photoactivité et la photoluminescence), ou ils ont été liés chimiquement (au moyen de groupes fonctionnels) avec les produits médicinaux etc.

L'enregistrement des images a été effectué avec le laser *Argon* – la lumière verte (région 517 nm). Les réseaux obtenus ont une résolution R□2000 mm^{-1} et l'efficacité de diffraction 20-25%. Ces réseaux peuvent être utilisés en original ou pour l'obtention de la matrice métallique et des copies correspondantes, utilisées dans la protection des documents, des produits etc.

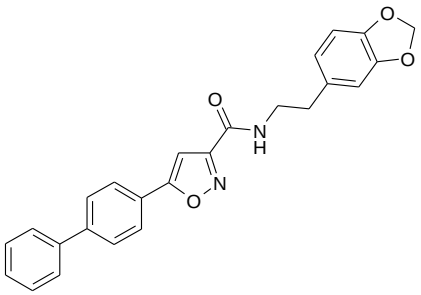
C12. New therapeutic approaches in Inflammatory Bowel Disease

Régis Millet
Université Lille Nord de France, ICPAL, EA 4481, IFR114,
3, rue du Professeur Laguesse, BP-83, F-59006, Lille, France

Endocannabinoids (ECs), including anandamide (AEA) and 2-arachidonoylglycerol (2-AG), are arachidonic acid derived bioactive lipids that are biosynthesized on demand, and which, following the activation of both cannabinoid receptors (CB1 and CB2) trigger a wide range of biological responses. These physiological effects are transient due to a rapid inactivation of ECs by specific enzymes such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL).[1]

In the gastrointestinal tract, these endogenous ligands control, notably *via* CB1 and/or CB2 receptor activation, many physiological functions including intestinal motility, secretion and inflammation.[2] Accordingly, stimulation of cannabinoid receptors directly or indirectly constitutes a promising strategy to treat several gastrointestinal pathologies, especially diseases wherein an inflammatory process is involved such as for example inflammatory bowel diseases. An approach consisting in raising anandamide levels has been successfully applied to reduce intestinal inflammation by using inhibitors of EC membrane transport (VDM11) or FAAH (URB597).[3]

In addition, targeting FAAH is of particular interest since it increases AEA, and related *N*-acylethanolamines, levels without triggering psychotropic effects associated with central CB1 receptor activation.[4] In this context, we undertook the development of a new series of FAAH inhibitors based on a 3-carboxamido-5-aryl-isoxazole scaffold.[5] Among them, compound **39** displayed significant inhibitory FAAH activity (IC_{50} = 0.088 μM) and reduced colitis induced by intrarectal administration of TNBS (2,4,6-trinitrobenzene sulfonic acid) in mice, showing evidence that FAAH is a promising target for the Inflammatory Bowel Disease (IBD) treatment.



39

IC_{50} (FAAH) = 88 nM

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[4] Cravatt, B. F. et al. *Curr. Opin. Chem. Biol.* **2003**, *7*, 469.
[5] Andrzejak, V. et al. *Bioorg. Med. Chem.* **2011**, *19*, 3777.

C13. Natural Endiynes Analogs

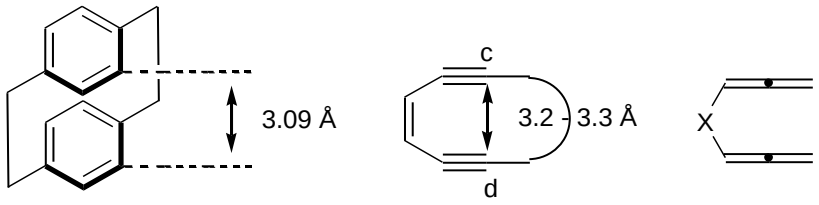
Mihail Lucian Birsa[1,*]

[1]*Department of Chemistry, Al. I. Cuza University of Iasi, 11 Carol I Bd., Iasi, Romania*

The so-called enediyne antibiotics, such as calicheamicin or esperamicin, are amongst the most potent antitumor agents known to date.[1-4] Formation of a diradical intermediate with accompanying cycloaromatization has been postulated as the key step in the DNA-cleavage activity of these natural products. However, because of the complexity, scarcity, and difficult synthesis of the natural enediynes, a variety of model enediynes have been prepared and tested for their biological activity during the last decade.

Because of the rigid molecular framework provided by the paracyclophane unit and its short interannular distance, functional groups in *pseudo-geminally* substituted [2.2]paracyclophanes are often held in such a position as to allow highly specific reactions to take place between them. Using *pseudo-geminally* substituted [2.2]paracyclophanes as spacers for bisallenic moieties, interesting starting materials for intra- or intermolecular reactions can be realized.

A rather interesting chemistry could arise from the combination of [2.2]paracyclophanes structures with acetylenic systems. It is known that in the crystal [2.2]paracyclophane the distance between *pseudo-geminal* carbons is 3.09 Å. On the other hand, Nicolaou postulated the critical upper limit for the *cd* distance required for cyclization of conjugated enediynes related to calicheamicins and esperamicins at a measurable rate at room temperature to be 3.2 - 3.3 Å.[5]



Following the idea to use [2.2]paracyclophane as spacer for model enediynes we decided to investigate the synthesis of heteroatom containing enediyne related structures. Thus, novel heteroatom containing bridges have been introduced in [2.2]paracyclophanes by the interaction of chalcogenide halides with *pseudo-geminal* triples bonds. The *anti*-addition with Markovnikov orientation of selenium halides to 4,15-bisethynyl[2.2]paracyclophane leads to the corresponding *E*-adducts.

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* Corresponding author, tel. +40 232 201349, e-mail address lbirsa@uaic.ro

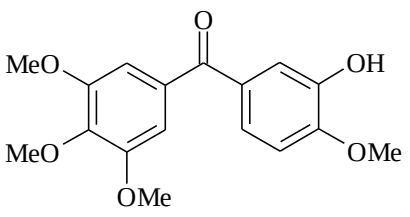
C14. Conception, synthèse et évaluation antitumorale de nouvelles indolizin-3-yl(aryl/hétéroaryl)méthanones

Elena Bîcu[1,*]

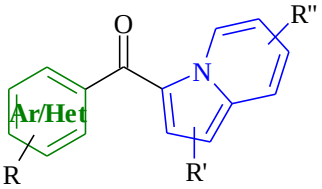
[1]*Department of Chemistry, Al. I. Cuza University of Iasi, 11 Carol I Bd., Iasi, Romania*

La tubuline est la cible de nombreuses petites molécules qui interfèrent avec sa dynamique de polymérisation. Les inhibiteurs de la polymérisation de la tubuline peuvent être classés en trois groupes différents en se basant sur leurs domaines de liaison avec la tubuline. On peut alors distinguer : les inhibiteurs du domaine Vinca, les inhibiteurs du site du taxol et les inhibiteurs du site de la colchicine (la colchicine et ses analogues, les combrétastatines, les phenstatines, les quinolones). Pour la conception de nos composés inhibiteurs potentiels de la polymérisation de la tubuline, nous nous sommes concentrés tout d'abord sur la structure d'un inhibiteur connu du site de la colchicine (SC) : la phenstatine.[1] De nombreuses modifications structurales de la phenstatine (Figure 1) ont été réalisées au niveau du cycle B.

Dans ce cadre, nous avons mis au point une synthèse d'analogues de la phenstatine comportant un nouveau noyau B de type indolizine différemment substitué (**Figure 1**). D'autre part, dans la série des dérivés de la phenstatine décrits dans la littérature, très peu de modifications structurales ont été effectuées au niveau du cycle A de type 3,4,5-triméthoxyphényle. Une partie de notre travail de recherche s'est focalisé sur la conception, la synthèse et l'évaluation pharmacologique de nouveaux analogues de la phenstatine comportant un cycle A de type phénothiazinique (**Figure 1**).



Phenstatine



Het: 10*H*-Phénothiazin-10-y

Figure 1. Structure de la phenstatine et des dérivés étudiés

Les dérivés synthétisés ont été évalués sur le panel de 60 lignées tumorales du NCI (National Cancer Institute) et les résultats obtenus confirment l'intérêt de tels composés.

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* Corresponding author, tel. +40 232 201347, e-mail address elena@uaic.ro

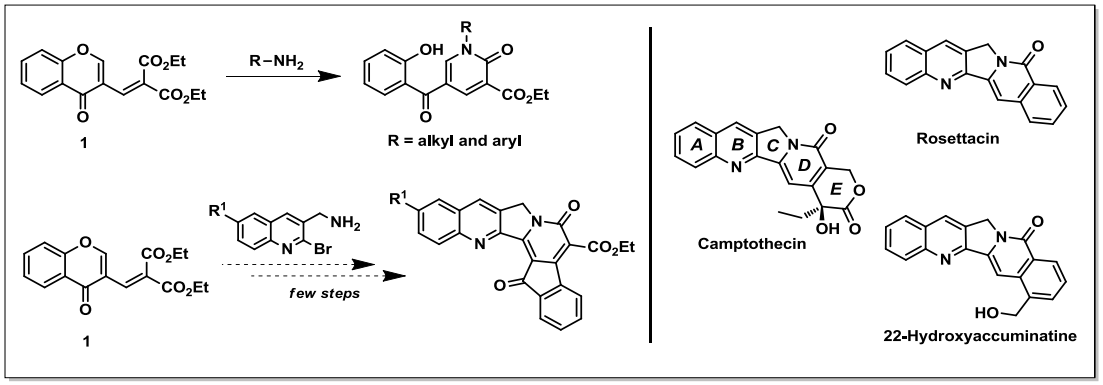
COMMUNICATIONS ORALES

CO1. New synthetic scaffolds through unexpected 1,6-aza-Michael addition to chromone derivatives: Application in the synthesis of aromathecin analogues

Catalin Pintiala, Ata Martin Lawson, Sébastien Comesse and Adam Daïch*

URCOM Laboratory, EA 3221, FR3038 Université du Havre,
25 rue Philippe Lebon, B.P. 540, 76058 ─ Le Havre Cedex, France
catalin.pintiala@univ-lehavre.fr

The *"aromathecin"* system represents a new class of topoisomerase-I (topo-I) inhibitor by acting in a similar way to camptothecin and the indenoisoquinolines. Camptothecin derivatives (topotecan and irinotecan, already marketed) are the only class of clinically approved topo-I inhibitors showing potent efficiency in anticancer therapy by intercalating into DNA-enzyme complex.[3] Several routes to aromathecin derivatives have been developed since many years in our laboratory.[4] In addition, one of our ongoing works is to develop a new synthetic route to aromathecin analogues using chromone derivatives as starting material due to their medicinal activities and their ability to be converted to a broad range of heterocyclic systems through reactions with various nucleophiles.[5]



The α,β-unsaturated Knoevenagel product **1** undergoes 1,6-aza-Michael nucleophilic addition of some primary amines following by chromone ring-opening and intramolecular cyclization in a domino process.[6] However, this type of chromone's reactivity is not widely described in literature and appears to be a convenient and efficient way to obtain many different systems bearing a pyridone scaffold of biological interest.

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CO2. Poly(carboxybetaines) derived from poly(N-vinylimidazole) as antibacterial agents. Physico-chemical properties of aqueous and salted solutions.

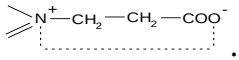
Anca Giorgiana Grigoras[*, 1, 2], and Vasile Cristian Grigoras[1]

[1]*Polymer Materials Physics, "Petru Poni" Institute of Macromolecular Chemistry, Aleea Grigore Ghica Voda, 41A, 7000487, Iasi, Romania*

[2]*Department of Biochemistry and Molecular Biology, Faculty of Biology,"Alexandru*

Poly(carboxybetaines) derived from poly(*N*-vinylimidazole) PNVI, and containing a methylene (B1), ethylene (B2), and propylene (B3) betaine groups, respectively, are analyzed from the physico-chemical and antibacterial points of views. The weight-average molecular weight $\overline{M}_w$, second virial coefficient A_2, Z-averaged root-mean-square radius of gyration R_g and hydrodynamic radius R_h of unfractionated probes are determined by MALLS (multiangle laser light scattering) and DLS (dynamic light scattering) measurements. All parameters vary in accordance with the type of solvent (pure water or 0.5M NaCl aqueous solutions).

The concave Zimm plot (Berry formalism) for all solutions, and predominantly larger values of $\overline{M}_w$ measured in pure water than in salted water (0.5M NaCl) confirm the associations of macromolecular chains by electrostatic interactions in the case of these polymeric quaternary ammonium betaines. Also, the positive A_2 values in pure water not seem too different from the values in salted aqueous solutions. DLS analysis reveals a predominantly bimodal distribution of the particle size corresponding to individual chains and aggregates, respectively, and an average value for R_h of about 30 nm depending on the solvent.

Some of poly(carboxybetaines) exhibit antimicrobial activity proved by Kirby-Bauer diffusion method. The *Escherichia coli* (ATCC 25922) cells are sensitive against poly(carboxybetaines) B1 (21.84 mg mL^{-1}) and B3 (28.2 mg mL^{-1}), but *Staphylococcus aureus* (ATCC 25923) cells are resistent to the tested poly(carboxybetaines). The absence of antimicrobial activity for the poly(carboxybetaine) B2 could be connected with the possibility of compensation of the opposite charges even into the same betaine group by formation of five-member rings like  .

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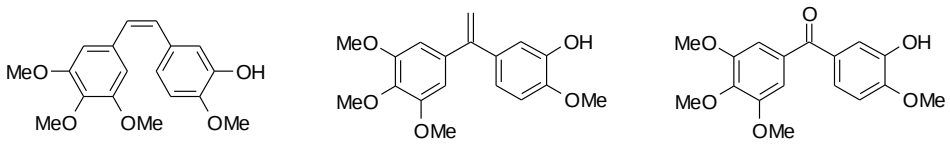
* Corresponding author, e-mail address: angrig@icmpp.ro (Anca Giorgiana Grigoras)

CO3. Synthesis of new *iso*combretastatins: a new case of ketone homologation

Vivien Stocker[1,2,*]

[1] *Univ Lille Nord de France, F-59000 Lille, France*
[2] *UCLille, EA GRIIOT (4481), Laboratoire de pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France*

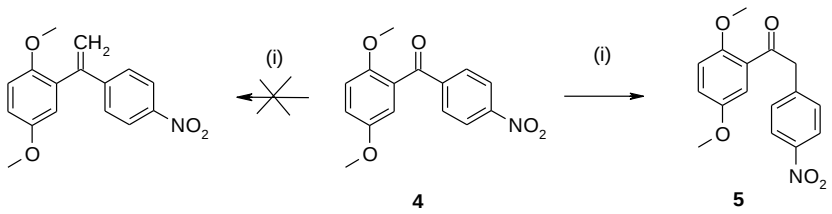
It has been recently described that a new family of substituted 1,1-diarylethylenes, called isocombretastatins, displays a biological activity similar to the one of their combretastatin or phenstatin homologues (Figure 1).



1 Combretastatin A-4 **2** *Iso*combretastatin A-4 **3** Phenstatin

Figure 1: Structure of combretastatin A-4 (1) and corresponding isocombretastatin A-4 (2) and phenstatin (3).

In order to synthesize novel isocombretastatins, numerous benzophenones were engaged into a Wittig reaction. We observed, in the case of ketone 4, that the corresponding 1,1-diarylethylene was not formed, instead ketone 5 was isolated (Figure 2).



4 **5**

Figure 2: (i) CH_3PPh_3Br (2 equiv.), tBuOK (5 equiv.), THF, rt, 18h.

A study of the influence of the aryl substituants on this ketone homologation was carried out, and a mechanism was proposed to explain the methylene insertion.

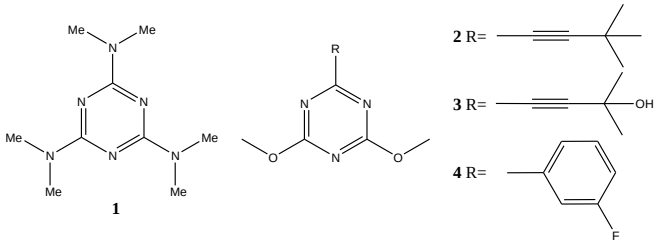
* Corresponding author,e-mail address vivien.stocker@hei.frb (Vivien Stocker)

CO4. New methods of synthesis of 1,3,5-triazine-2,4(1*H*,3*H*)-diones, 4-methoxy-1,3,5-triazin-2(1*H*)-ones and 1,3-dimethyl-1,3,5-triazine-2,4-diones

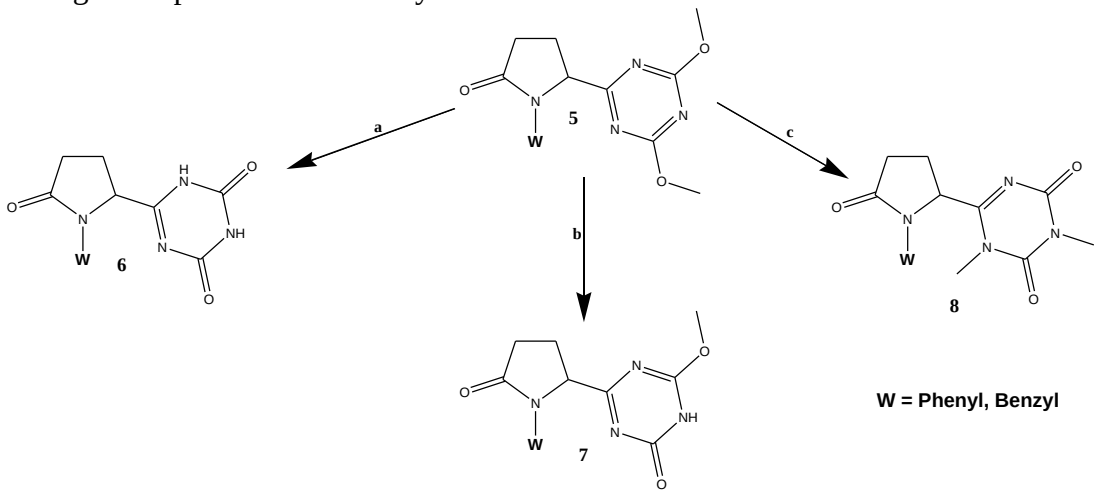
Liliana Lucescu[1], Souhila Oudir[2], Dalila Belei[1], Philippe Gautret[2], Benoît Rigo[2], Alina Ghinet[1,2]

[1] *Department of Organic Chemistry, 'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Bd. Carol I nr. 11, 700506 Iasi, Romania*
[2] *UCLille, EA 4481 (GRIIOT), Laboratoire de Pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France*

A series of 2,4,6-tris(*N*,*N*-dialkylamino)-1,3,5-triazines has been studied for their antitumoral activity[1-3]. Among these derivates, hexamethylmelamine (**1**), an alkylating agent, is very efficient against ovarian, breast, and lung cancers but it generates side effects limiting its use in clinic. Thereafter, similar compounds such as 2-alkyl-4,6-diheteroalkyl-1,3,5-triazines demonstrated a significant cytotoxicity towards various tumor cell lines *in vitro*.



It was suggested that the antitumoral activity of some triazinic derivates is related to the fact that these compunds represented antimetabolites wich are able to accumulate in tumor cells. Currently, the chemical reactivity of these triazines attached in position 5 to *N*-benzylpyroglutamic or *N*-phenylpyroglutamic derivatives **5** has been explored under different conditions in order to access to new aza-analogs with potential bioactivity.



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Oudir S et al. Synthesis (2006).	

CO5. *In vivo* and *in vitro* sustained release study of theophylline from biodegradable and biocompatible alginate/PNIPAAm hydrogels

Raluca Petronela Dumitriu[1*], Ana-Maria Oprea[1], Catalina Natalia Cheaburu[1], Ovidiu Novac[2], Cristina Mihaela Ghiciuc[3], Lenuta Profire[3], and Cornelia Vasile[1]

[1] *"P. Poni" Institute of Macromolecular Chemistry, 41A Gr. Ghica Voda Alley, 700487, Iasi, Romania*
[2] *"Gh. Asachi" Technical University, Prof. dr. doc. Dimitrie Mangeron Str. No. 73, 700050Romania*
[3] *"Gr. T. Popa" University of Medicine and Pharmacy, University Str. No. 16, 700115, Iasi, Romania*

Theophylline-loaded mixed-interpenetrated polymeric networks based on poly(*N*-isopropylacryl amide) (PNIPAAm) and sodium alginate (ALG) covalently cross-linked with *N, N'*-methylenebisacrylamide according to the synthesis method previously reported [1-3] were investigated. The structural characteristics, thermal behavior and the presence of drug-matrix interactions were evidenced by FT-IR spectroscopy and by thermal analysis. The hydrogels loading degree with theophylline was evaluated by near infrared chemical imaging (NIR-CI) technique and confirmed also by FT-IR spectroscopy and microscopic examination; the drug loading was up to 73.2 % based on PLS-DA prediction (Partial least squares - Discriminate Analysis). The LD_{50} for hydrogels, after intraperitoneal administration as suspensions, is bigger than 3200 mg / kg. The LD_{50} obtained values demonstrated that the hydrogel compositions have a low toxicity.

Their biocompatibility was proved by the values obtained for the haematology and clinical biochemistry parameters, which lie in the accepted limits. Biodegradability of the alginate/PNIPAAm mixed-IPNs was evidenced by *in vitro* chemical and enzymatic degradation studies. The potential of the ALG/PNIPAAm hydrogels as sustained drug release formulations was revealed by the theophylline release studies performed both *in vitro* and *in vivo*.

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* Corresponding author, tel. +40232217454, e-mail address rdumi@icmpp.ro (Raluca Petronela Dumitriu)

CO6. Anhydride-modified collagen

Vasile Cornelia[1], Verestiuc Liliana[2], Nistor Manuela[1], and Pamfil Daniela[1,*]

[1]*Departament of Physical Chemistry of Polymers, "Petru Poni" Institute of Macromolecular Chemistry, 41A Gr. Ghica Voda Alley, 700487, Iasi, Romania*
[2]*Department of Biological Sciences,* .Gr. *T. Popa" University of Medicine and Pharmacy, Faculty of Medical Bioengineering, 9-13 Kogalniceanu Street, 700454, Iasi, Romania*

Chemical modification of polymers leads to obtain materials with improved and special properties and new applications. Collagen is widely used in the biomedical field and in tissue engineering owing to the low immunogenicity and toxicity and to its unique properties. Besides outstanding mechanical, haemostatic and cell-binding properties, collagen exhibits an excellent biocompatibility profile and predictable biodegradability. Porous acid-soluble collagen (type I and III) from bovine dermis was modified with vinyl groups by reaction with citraconic anhydride and dimethylmaleic anhydride. Some reactional parameters as mass ratio, pH and type of anhydride used for collagen modification were optimized in order to increase the substitution degree. A particular attention has been paid to the characterization of chemical modified collagen compared with unmodified collagen. The structure of modified collagen was assessed by FT-IR and 1H NMR spectral methods and by analytical determination of the amino groups in collagen using the TNBS assay. It has been established that anhydrides react with ε-amino groups of lysine and hydroxylysine, the positions of which in collagen molecules are determined by the primary structure of their molecular chains. The dependence of the viscosity of diluted collagen solutions on the concentration and temperature was followed to determine the denaturation transition. It was found that the transition temperature was significantly changed after chemical modification. Molecular weight, particle size analysis and zeta potential of the unmodified and modified collagen solutions proved that the modification took place because of increased average molecular weight, particle size and the second virial coefficient values. The obtained products have potential applications in tissue engineering and/or wound dressing.

* Corresponding author e-mail address: (Pamfil Daniela)

* Corresponding author, tel. +40232217454, e-mail address: pamfil.daniela@icmpp.ro (Pamfil Daniela)

CO7. Implication du récepteur $P2X_7$ dans l'inflammation

Davy Baudelet[1,2], Emmanuelle Lipka[1,3], Régis Millet[1,4], Philippe Gautret[1,2], and Benoît Rigo[1,2]

[1] *Univ Lille Nord de France, F-59000 Lille, France*
[2] *UCLille, EA GRIIOT (EA4481), Laboratoire de pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France*
[3] *Laboratoire de Chimie Analytique, Université de Lille 2, 3 rue du Professeur Laguesse, F-59046 Lille, France*
[4] *ICPAL, EA GRIIOT (EA4481), Université de Lille 2, 3 rue du Professeur Laguesse, F-59006 Lille, France*
davy.baudelet@hei.fr

Le récepteur $P2X_7$ est un récepteur canal qui appartient à la grande famille des récepteurs purinergiques. Ceux-ci sont sensibles aux nucléotides et nucléosides de structure purique et pyrimidique tels que l'adénosine, l'uridine triphosphate (UTP), l'adénosine diphosphate (ADP), et l'adénosine triphosphate (ATP). Ces récepteurs ont été classés en deux familles par Burnstock en 1978, avec d'une part les récepteurs P1 qui sont des récepteurs couplés aux protéines G (RCPG) sensibles à l'adénosine, et d'autre part les récepteurs P2 qui sont eux-mêmes subdivisés en deux sous familles. Avec d'un côté les récepteurs P2Y qui sont également des RCPG sensibles aux nucléotides (ATP, ADP, UTP…), et d'un autre la sous classe P2X qui compte sept récepteurs canaux, sensibles à l'ATP, identifiés à ce jour.

De nombreuses études ont été menées dans le but de mieux comprendre le rôle physiologique de ces différents récepteurs, notamment pour le récepteur $P2X_7$ qui est, depuis quelques années, l'un des plus étudiés du fait de ces caractéristiques particulières et de son implication potentielle dans différentes pathologies telles que l'inflammation.

Initialement dénommé P2Z, le récepteur $P2X_7$ avait été décrit à la surface des mastocytes en 1980. Cette protéine de 595 acides aminés a été clonée pour la première fois à partir de cerveaux de rats en 1996, puis à partir de monocytes humains en 1997. Ce récepteur est distribué dans une grande variété de types cellulaires. On le retrouve principalement au niveau des cellules d'origine hématopoïétique telles que les mastocytes, les monocytes, les macrophages, les lymphocytes, ainsi que sur d'autres tissus dont les fibroblastes, les cellules épithéliales et endothéliales, le système nerveux central et les cellules gliales du cerveau.

Ce récepteur présente une faible sensibilité à l'ATP (seul ligand endogène), et ne répond qu'à des concentrations supérieures à 100 µM. Lors d'un épisode inflammatoire ou d'un traumatisme, la concentration en ATP extracellulaire augmente et active le récepteur $P2X_7$. Ceci entraîne un efflux de potassium qui conduit à l'activation de la caspase-1 qui catalyse le clivage de la pro-IL-1β cytoplasmique en IL-1β mature. Puis, l'entrée de calcium dans la cellule conduit au relargage de cette cytokine pro-inflammatoire, et à l'activation de seconds messagers et cascades enzymatiques. L'implication du récepteur $P2X_7$ dans l'inflammation chronique a donc été évaluée et confirmée. Différentes équipes de recherche ont réalisé des études sur des souris invalidées pour le gène codant pour le récepteur $P2X_7$, ainsi que sur des souris sauvages traitées par des antagonistes de ce récepteur dans différents modèles d'inflammation chronique. Ces études révèlent que l'inhibition de l'activité de ce récepteur entraîne une amélioration de l'état des souris, par réduction de l'inflammation, faisant de ce récepteur une nouvelle cible potentielle dans le traitement de l'inflammation.

COMMUNICATIONS PAR AFFICHE

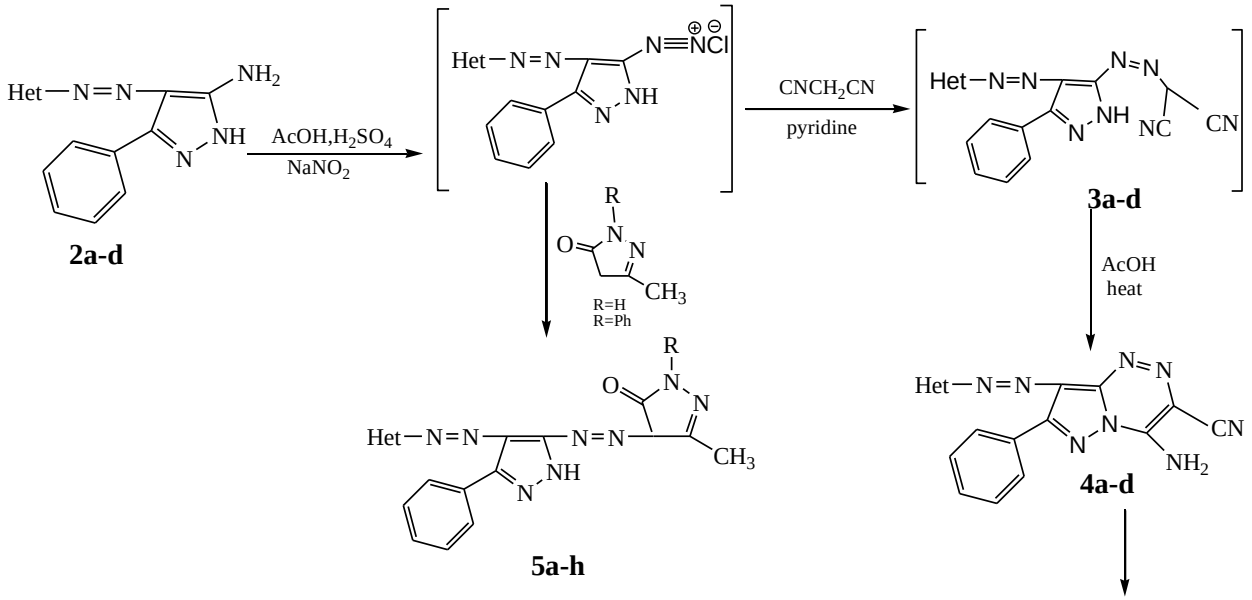
P1. Synthesis, antimicrobial activity and dying properties of some hetarylazopyrazolone and triazine dyes

Hala F. Rizk*, Seham A. Ibrahim, and Mohamed A. El-Borai.

Department of Chemistry, Faculty of Science, Tanta University, 31527 Tanta, Egypt

5-Amino-4-heterylazo-3-phenyl-1*H*-pyrazoles (**2a-d**) were diazotized and coupled with malonitrile and pyrazolone derivatives to give pyrazoloazo malononitrile (**3a-d**) and diazopyrazolylazo pyrazolone dyes (**5a-h**) respectively. Four novel pyrazolo[5,1-*c]*[1,2,4]triazine dyes (**4a-d**) were synthesized by heating pyrazoloazo malononitrile (**3a-d**) in glacial acetic acid. The structure of the synthesized dyes determined by elemental analysis and spectral data. All the synthesized dyes were screened for their antimicrobial activity against some Gram-positive bacteria, Gram-negative bacteria and antifungal. Also, the minimal inhibitory concentration (MIC) was studied.

In addition, the prepared dyes were applied to polyester fibers as disperse dyes. The fastness and colorimetric properties were measured. The results revealed that these dyes have good fastness and good affinity to polyester fabric.



a:Het. =pyrazine ring, R=H
b:Het. =imidazole ringe, R=H
c:Het. =thiazole ring, R=H
d:Het. = antipyrine ring, R=H
e;Het. =pyrazine ring, R=Ph
f:Het. =imidazole ring, R=Ph
g:Het. =thiazole ring, R=Ph
h:Het. =antipyrine ring, R=Ph

a: Het. =pyrazine ring
b : Het. = imidazole ring
c: Het. =thiazole ring
d: Het.= antipyrine ring

* Corresponding author: (Hala F. Rizk)

P2. Microwave-assisted synthesis of some new pyrazolopyrimidines and their antioxidant and antimicrobial activities. Part III

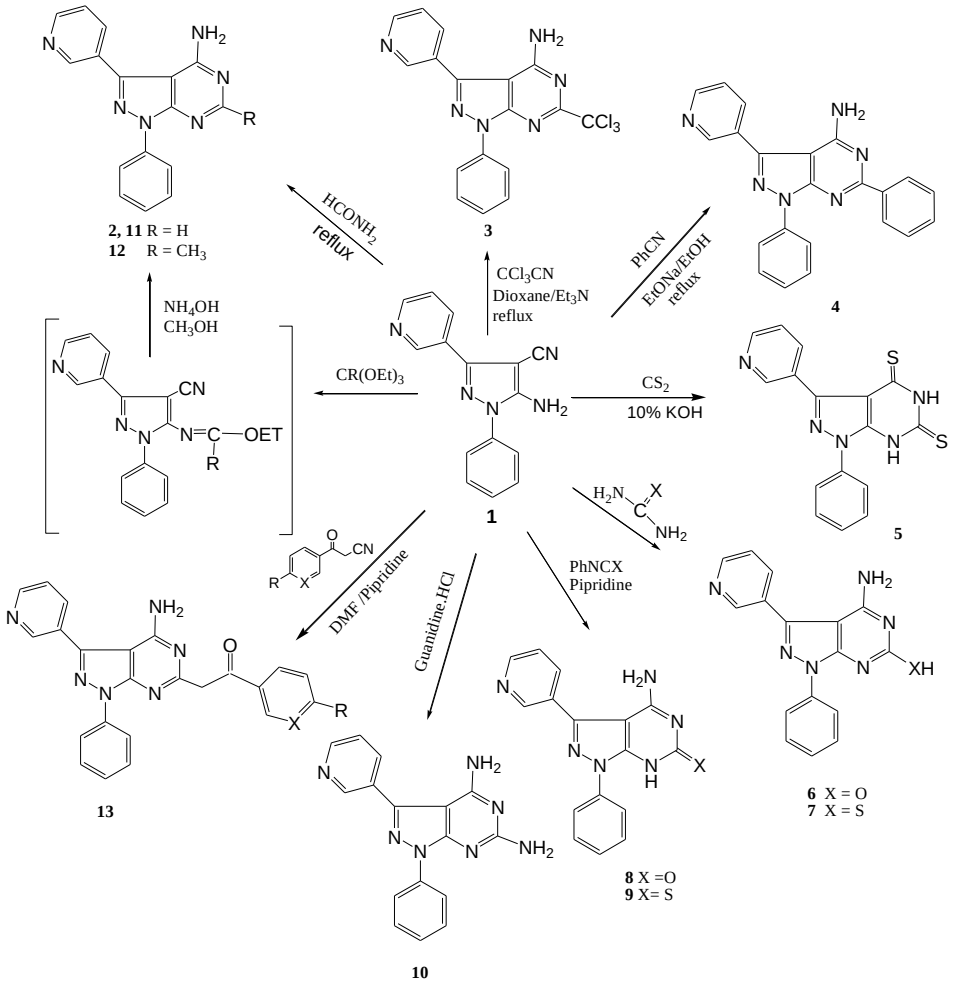
M.A. El-Borai*, H.F. Rizk, and I.Y. El-Deeb

Department of Chemistry, Faculty of Science, Tanta University, 31527 Tanta, Egypt

The preparation of the interesting compound (**1**) 5-amino-4-cyno-1-phenyl-3-(pyridin-3-yl)-1*H*-pyrazole was achieved by two routes. The reaction of (**1**) with different reagents as formamide, trichloroacetonitrile, benzonitrile, carbon disulphide, urea, thiourea, phenyl isocyanate, phenyl isothiocyanate, guanidine hydrochloride, triethyl orthoformate, triethyl orthoacetate and some *β*-ketonitriles was carried out under different experimental conditions. The products was in all cases the pyrazolo[3,4-*d*] pyrimidine derivatives.

Most of the reactions were done by conventional heating and microwave irradiation technique. The structure of the synthesized compounds was elucidated by spectroscopic methods. The antioxidant and antimicrobial activities of the synthesized compounds were studied.

Part [I] of the series M.A. El-Borai, H.F. Rizk, M.F. Abd-Aal, I.Y. El-Deeb, *Eur. J. Med. Chem.* 48 (**2012)** 92-96.
Part [2] Presented at the 4th EuCheMS Chemistry Congress (under publication)



* Corresponding author: (M.A. El-Borai)

P3. Poly(Lactic Acid) Synthesis: the Biotechnological Approach

Madalina Zanoaga,* and Fulga Tanasa

"Petru Poni" Institute of Macromolecular Chemistry, 41A Grigore Ghica Voda, Iasi, Romania

Lactic acid has a long history in human activities after its discovery in 1870. It is widely used in the healthcare, pharmaceutical, food, cosmetic and chemical industry and it is expected that lactic acid consumption in bio-chemical applications, which include poly(lactic acid) (PLA) and new "green" solvents, such as ethyl lactate, will increase with 19% per year.

There have been various attempts to produce lactic acid in an effective manner from inexpensive raw materials. It can be produced by either biotechnological fermentation of natural cheap raw materials, such as starchy and cellulosic materials, whey and molasses, or by chemical synthesis. Recently, the biotechnological approach has received considerable interest due to environmental concerns and the limited petrochemical feedstocks, although the cost of purification stages is a serious limitation.

The present work is a survey focused on lactic acid-producing microorganisms, natural cheap raw materials and fermentation pathways for lactic acid production.

* Corresponding author: (Madalina Zanoaga)

P4. Antimicrobial polymers for healthcare applications: structure design strategies and specific properties

Fulga Tanasa, and Madalina Zanoaga

"Petru Poni" Institute of Macromolecular Chemistry, 41A Grigore Ghica Voda, Iasi, Romania

Synthetic polymers have a significant place in the design of antimicrobial materials due to their distinct characteristics, such as specific macromolecular length, processability, low cost, tunable properties and diverse functionalities.

There are two major classes of antimicrobial polymers: biopassive and bioactive polymers. Biopassive polymers act towards reducing the proteins and bacteria adhesion to the surface without killing them. Bioactive polymers – containing immobilized antibiotics and antimicrobial agents - can destroy the pathogens on contact.

Generally, the objective of reducing protein adsorption, bacterial attachment and biofilm proliferation can be achieved through different approaches, which may include surface modification by hydrophilic polymers or block copolymers consisting of highly hydrated, flexible chains having low values of polymer–water interfacial forces. Surface hydration seems to be the most important factor in the case of short chain polymers, whereas for the long chain polymers it looks like the surface hydration and steric repulsion act synergistically.

This paper reviews some aspects concerning the development and future prospects in the field of antimicrobial polymers, as well as some limitations.

P5. Nouveaux inhibiteurs de la farnésyltransférase en série 1,2,3-triazoles-1,4-disubstitués

Carmen DUMEA[1], Simona ŞTEFANOVICI[1], Alina GHINEŢ[2], Joelle DUBOIS[3], Elena BÂCU[1], Dalila BELEI[1]

[1] *Department of Organic Chemistry, 'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Bd. Carol I nr. 11, 700506 Iasi, Romania*

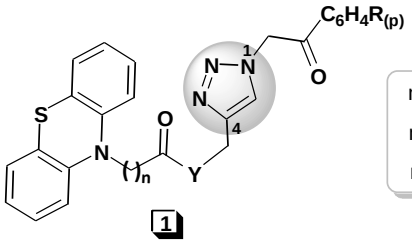
[2] *UCLille, EA 4481 (GRIIOT), Laboratoire de Pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France*

[3] *Institut de Chimie des Substances Naturelles, CNRS UPR2301, avenue de la Terrasse, 91190 Gif sur Yvette, France*

L'isoprénylation, ou encore appelée prénylation, est une modification post-traductionnelle qui consiste en l'ajout du groupement farnésyle du FPP (farnésyldiphosphate) ou géranylgéranyle du géranylgéranylpyrophosphate sur un résidu cystéine spécifique d'une protéine. Ce transfert se traduit par la formation d'une liaison covalente de type thioéther avec la cystéine en position carboxyterminale. Ce processus a été identifié sur les protéines Ras qui jouent un rôle fondamental dans la voie de signalisation qui permet la division cellulaire. En effet, empêcher le processus de farnésylation peut constituer une approche dans le traitement des cancers.[1]

Les recherches menées au sein de notre laboratoire ont été dirigées, ces dernières années, vers l'identification de tels inhibiteurs.

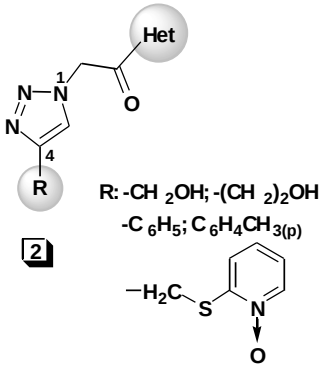
Nous avons récemment rapporté trois familles de nouveaux dérivés phenothiazin-triazoliques de structure générale **1**[2] comme inhibiteurs de la farnésyltransférase, certains présentant des valeurs de CI_{50} dans la gamme micromolaire.



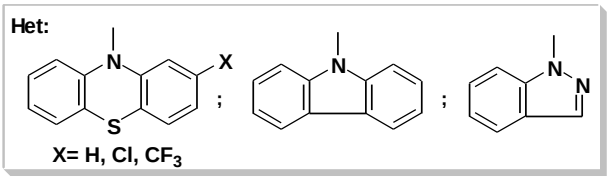
1

n= 2, Y= NH, R= Br	**IC_{50}(FTase)= 8.31±0.87 μM**
n= 2, Y= O, R= Br	**IC_{50}(FTase)= 1.3±0.28 μM**
n= 2, Y= NH, R= Br	**IC_{50}(FTase)= 24.31±4.97 μM**

Dans le but d'identifier de nouveaux dérivés 1,2,3-triazoliques, inhibiteurs potentiels de la farnésyltransférase, plusieurs modifications structurales ont été réalisées en positions 1 et 4 du noyau triazole et nous avons ainsi obtenu nouvelles séries de dérivés triazoliques, de structure générale **2**.



2



L'évaluation biologique de nouveaux dérivés synthétisés sur la farnésyltransférase humaine a montré que les hétérocycles volumineux en position 1 ainsi que la présence de chaînes alkyle en position 4 conduisent à l'amélioration des propriétés inhibitrices de la protéine.

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P6. Synthesis and pharmacological evaluation of tetrahydro-β-carboline derivatives displaying anti-tumoral activity

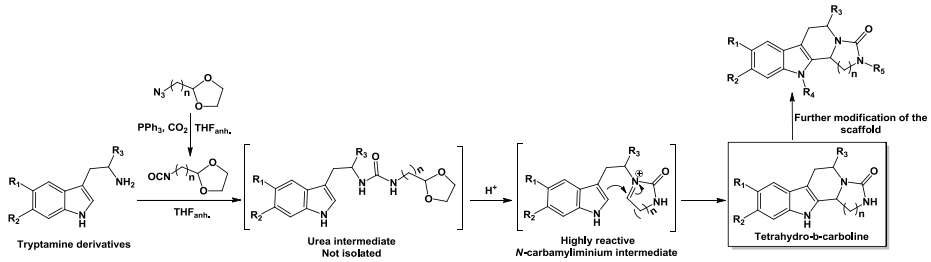
Alexandra Ionescu[1, 2], Sébastien Soriano[1], Damien Cornut[1], Robert Kiss[2], and Ivan Jabin[1*]

[1]*Laboratoire de Chimie Organique, Université Libre de Bruxelles, Av. F.D. Roosevelt 50, CP 160/06, 1050 Bruxelles, Belgium*

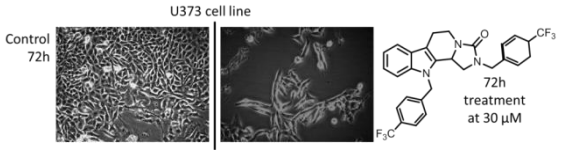
[2]*Service de Toxicologie, Université Libre de Bruxelles, Bv. du Triomphe 2, CP205/01, 1050 Bruxelles, Belgium*

Our strategy to bypass the resistance of several types of aggressive cancers[1] to apoptosis-inducing treatment is based on the synthesis of tetracyclic tetrahydro-β-carboline (THBC) derivatives containing an imidazolidin-2-one fused cycle. These structures are similar to harmine, the most selective and potent inhibitor[2] of DYRK1A kinase, that additionally displays antitumor properties.[3]

Based on previous results from the literature,[4,5] the present work describes a simple and effective "one-pot" methodology that leads to a new series of tetrahydro-β-carboline derivatives in excellent yields and purity. The process takes place via a Pictet-Spengler type reaction of an *N*-carbamyliminium ion generated in situ.



28 new compounds were synthesised and evaluated for their *in vitro* anticancer activity by means of the MTT colorimetric assay. These analyses show that several compounds inhibit cell proliferation *in vitro*, 3 of them emerging as hits. These 3 most efficient molecules display a cytostatic behaviour when assayed using quantitative videomicroscopy and a promising bioselectivity between cancerous and normal cell lines.



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* Corresponding author, tel. +32 2 650 3537, e-mail address ijabin@ulb.ac.be (Ivan Jabin)

P7. Synthesis of novel flavonoid-dithiocarbamic esthers and their corresponding 1,3-dithiolium salts

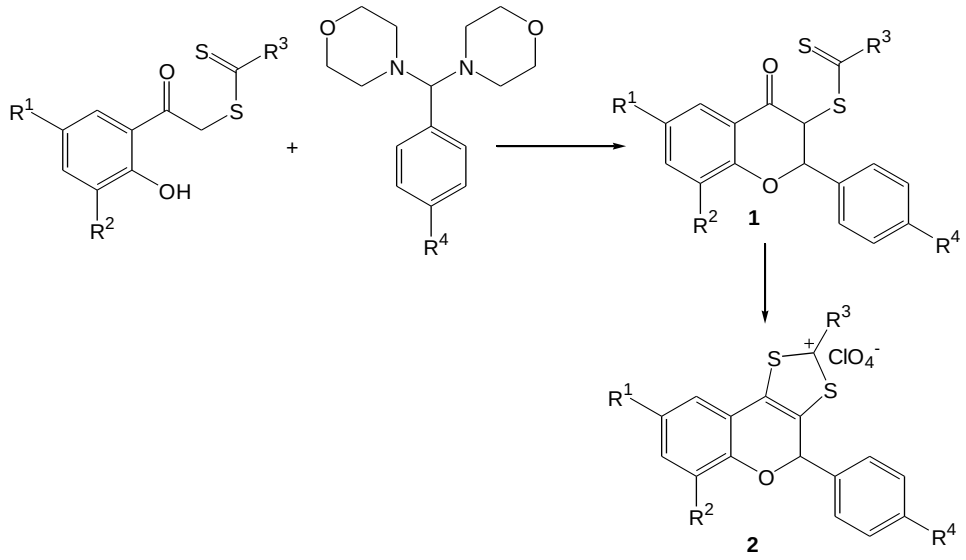
Mihail Lucian Birsa [1] and Lucian Gabriel Bahrin [1,*]

[1]*Department of Chemistry, "Alexandru Ioan Cuza" University, No. 11 "Carol I" Bld. 700506, Iasi, Romania*

The natural world represents a vast, untapped reservoir of medicinal compounds with the potential of treating numerous medical conditions of the modern world. For this reason, scientists often turn to nature in their search for new and better drugs that can address crucial issues like drug-resistant bacteria, or the prevention/treatment of cancer.

Flavonoids represent a widely-spread class of plant secondary metabolites that became known in the medical world for their antioxidant properties, making them ideal candidates in the search for new anti-cancer and anti-inflammatory drugs.

This communication presents the synthesis of novel flavanones (**1**) that contain a dithiocarbamic moiety in position 3, as well as their corresponding dithiolium derivatives (**2**) (Scheme 1).



Scheme 1

Dithiocarbamates (**1**) were obtained as a mixture of diastereomers. A major isomer was identified for all flavonoids. We therefore decided to investigate the structures of the two diastereoisomers, together with the influence of substituents on their ratio. In principle, the two isomers could have the hydrogen atoms at the 2 and 3 positions directed either to opposite sides or to the same side of the benzopyrane ring. The structural information provided by the NMR data has been unambiguously corroborated by X-ray analysis.

* Corresponding author, tel. +40 232 250277, e-mail address lucian.bahrin@chem.uaic.ro (Lucian Gabriel Bahrin)

P8. Composites ferrites – hydrogel avec potentielles utilisations en médecine

Anca Mihaela Dumitrescu[1], Alexandra Raluca Iordan[1,*]

and Mircea Nicolae Palamaru[1]

[1]*Faculté de Chimie, Université "Alexandru Ioan Cuza" Iaşi*
Bulevard Carol I nr. 11, 700506 Iaşi, Roumanie

Nos recherches portent sur la synthèse, la caractérisation et l'analyse microbiologique d'une ferrite de nickel nanostructurée et fonctionnalisée avec des hydrogels à base de polyacrylamide. La ferrite de nickel a été obtenue par le procédé sol-gel avec autocombustion en utilisant l'acide citrique comme agent chélatant / carburant. Les hydrogels et les composites ferrite - hydrogel ont été obtenues par un procédé original de polymérisation-réticulation simultanée en utilisant un agent de réticulation monofonctionnel. Les échantillons obtenus ont été caractérisés par spectroscopie IR, DRX, MEB. Les composites ont été utilisées pour la fixation d'un principe active (ampicilline). Les activités microbiologiques des systèmes composites - antibiotique sont déterminées sur une souche de test de *Staphylococcus aureus*.

L'antibiotique a été rendu dans le milieu progressif pour un long temps. Des résultats encourageants ont été obtenus sur des échantillons qui contiennent de la gélatine dans le système. La présence de la gélatine dans la matrice de polyacrylamide permet de réduire la toxicité des produits de dégradation et, par conséquent, d'accroître l'efficacité du médicament.

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* Auteur de correspondance, tel. +40 232 201348, e-mail : alexandra.iordan@uaic.ro

P9. 3-Carboxamido-5-aryl-isoxazole: From FAAH Inhibitors to Selective CB2 Cannabinoid Receptor Agonists in the Treatment of Inflammatory Bowel Diseases.

Aurelien Tourteau,[1] Virginie Lucas-Andrzejak,[1] Jamal El Bakali,[1] Mathilde Body-Malapel,[2] Nicolas Renault,[3] ,Amélie Lemoine,[1] Benoît Rigo,[4] Roxane Mansouri,[1] Christophe Furman,[1] Giulio G. Muccioli,[5,6] Didier M. Lambert,[6] Philippe Chavatte,[1,3] Pierre Desreumaux,[2] and Regis Millet.[1,*]

[1] *Université Lille Nord de France, ICPAL, EA 4481, IFR114, 3 rue du Professeur Laguesse, BP-83, F-59006, Lille, France.*

[2] *Université Lille Nord de France, INSERM U995, Faculté de Médecine, Amphi J & K, IFR114, Boulevard du Professeur Leclercq, F-59045 Lille, France.*

[3] *Université Lille Nord de France, Faculté des Sciences Pharmaceutiques et Biologiques, Laboratoire de Chimie Thérapeutique, EA 4481, IFR 114, 3 rue du Professeur Laguesse, BP-83, F-59006 Lille, France.*

[4] *UCLille, EA 4481, Laboratoire de Pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France*

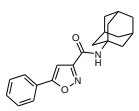
[5] *Bioanalysis and Pharmacology of Bioactive Lipids Laboratory, Louvain Drug Research Institute, Université catholique de Louvain, B-1200, Brussels, Belgium.*

[6] *Pharmaceutical Chemistry and Radiopharmacy Group, Louvain Drug Research Institute, Université catholique de Louvain, B-1200 Brussels, Belgium*

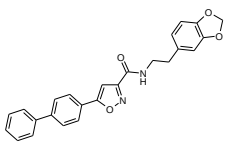
Crohn's disease and ulcerative colitis, known as inflammatory bowel diseases (IBD), are chronic inflammatory diseases of the digestive system. Both diseases are diagnosed in patients aged between 10 and 40 years and the current symptoms are abdominal pain, diarrhea, rectal bleeding, nausea and weight loss. According to the European Federation of Crohn's and ulcerative Colitis Associations (EFCCA), IBD affects over 2.2 million people in Europe. Despite investigations on these unbearable diseases, the causes of IBD are still unknown and no treatment is currently available.

Recently, several researches showed that the endocannabinoid system plays an autoprotective role in immunologically mediated disorders, making this endocannabinoid system an attractive therapeutic target for the treatment of IBD. Endocannabinoids (ECs), including anandamide (AEA) and 2-arachidonoylglycerol (2-AG), trigger a wide range of biological responses by activation of both cannabinoid receptors (CB1 and CB2). These physiological effects are transient because of a rapid inactivation of ECs by specific enzymes such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). Thereby, direct or indirect stimulation of cannabinoid receptors constitutes a promising strategy to treat numerous gastrointestinal pathologies, especially inflammatory diseases such as IBD. Indeed, the use of ECs membrane transport (VDM11) or FAAH (URB597) inhibitors in order to raise anandamide levels has been successfully applied to reduce intestinal inflammation.

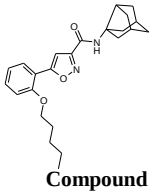
In this context, we focused on the molecular modeling associated conception and synthesis of 3-carboxamido-5-aryl isoxazole FAAH inhibitors. Encouraging preliminary results, compound 1 (IC50=500nM), support the molecular modeling and led us to carry out pharmacomodulations on this class of FAAH inhibitors. A library of 54 compounds was synthesized and evaluated for their biological activity leading to the discovery of compound 2. Andrzejak et al. described compound 2 with a great FAAH inhibition potential (IC_{50}=88nM), without affecting MAGL activity, and a colon inflammation decrease in a model of TNBS-induced colitis in mice. In parallel, our molecule library was evaluated in vitro for binding affinity on the CB2 receptor. Surprisingly, some compounds revealed a submicromolar full-agonist affinity for the CB2 receptor, without any cytotoxicity, as compound 3. Today, in vitro assays and in vivo assays are in progress in order to evaluate their anti-inflammatory effects, respectively on macrophages (LPS-stimulated TNF production) and on a model of TNBS-induced colitis in mice.



Compound 1
IC_{50} (FAAH) = 500 ± 62 nM



Compound 2
IC_{50} (FAAH) = 0.088 ± 0.004 µM



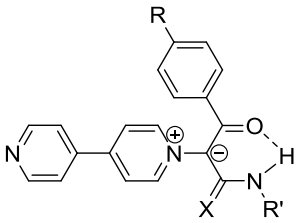
Compound 3
Ki (CB_2)= 9.0 ± 0.6 nM

P10. Biological activity for some palladium (II) complexes

Rodica Postolachi[1], Aurel Pui[1], Ramona Danac[1], Cristina Rambu[2] and Gabi Drochioiu[1]

[1]*Chemistry Department, "Al. I. Cuza" University of Iasi, 11 Carol I, Iasi 700506, Romania*
[2]*USAMV, "Ion Ionescu de la Brad" Iaşi*

Ylides are zwitterionic compounds in which carbanion is covalently bonded to a positively charged heteroatom as N, P, S, As, Sb [1]. Some of disubstituted *N*-ylides have proved to show biological activity [2] and some of it can coordinate metal ions forming complexes [3]. We report here the synthesis and complexation properties of new stable 4-(4'-pyridyl) pyridinium disubstituted monoylides with the general formula shown in the figure below:



R = -OCH_3, -CH_3
R' = α-naphthyl, -C_6H_4Br(p)
X = O, S

Physical methods (NMR, IR, UV-VIS, MS, XRD) were used for establishing the structures of new ylides ligands and their complexes with palladium (II) synthesized according to the method from literature [4]. The ligands 4-(4'-pyridyl) pyridinium disubstituted monoylides coordinate with palladium (II) through the nitrogen from amide group and oxygen from carbonyl group forming a six-membered chelate ring.

The antimicrobial activity for [Pd(II)$Y_{NIC}Cl_2$] complex was achieved through a qualitative type diffusion method. Insemination technique was to a standard strain of *Staphylococcus aureus* ATCC on solid culture medium. After 24 hours it was found the presence of inhibition zone about 20 mm for the salt and arround 7 mm for [Pd(II)$Y_{NIC}Cl_2$] complex, which means that the complex has a weak antimicrobial activity compared with it salt.

Another biological experiment for [Pd(II)$Y_{NIC}Cl_2$] complex was to determine the optimal capacity of wheat seeds Putna species germination in presence of palladium (II) complexes under ideal conditions. Palladium (II) complex contain bipiridinic nucleus which supposed to show the toxicity if it was involved in redox process. However, the palladium (II) complex was nontoxic (1,67; 0,67; 1< (3,10=D)), which allowed us to conclude for the first time that the toxicity effect is not due bipiridinic nucleus, but due to radicals with toxic properties.

Keywords: Palladium (II) complexes, Antimicrobial activity, Germination capacity

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P11. Synthesis and antiproliferative activity of 4-(2,4-dimethylphenyl)thiosemicarbazide and its azomethine derivatives

Aurelian Gulea[1], Artur Sargun[1,7], Alic Barba[2], Angela Jalba[1], Donald Poirier[3], Pyotr Petrenko[4], and Yuri Chumakov[4]

[1]*Department of Chemistry and Chemical Engineering, Moldova State University, 60 Mateevici street, Chisinau, Moldova*
[2]*Institute of Chemistry, Academy of Sciences of Moldova, 3 Academiei street, Chisinau, Moldova*
[3]*Oncology and Molecular Endocrinology Research Centre, CHUL Research Centre and Université Laval, 2705 Laurier boulevard, Québec City, Canada*
[4]*Institute of Applied Physics, Academy of Sciences of Moldova, 5 Academiei street, Chisinau, Moldova*

In order to develop novel antitumor medicines with improved clinical effectiveness, broadened spectrum of activity, and with reduced general toxicity 4-(2,4-dimethylphenyl)thiosemicarbazide and its five azomethine derivatives have been synthesised. The thiosemicarbazones **2-6** of 4-(2,4-dimethylphenyl)thiosemicarbazide **1** have been obtained by condensation of **1** with different aromatic carbonylic compounds: **2** 3-formylpyridine, **3** 4-formylpyridine, **4** 3-formylthiophene, **5** 2-formylquinoline, and **6** salicylaldehyde.

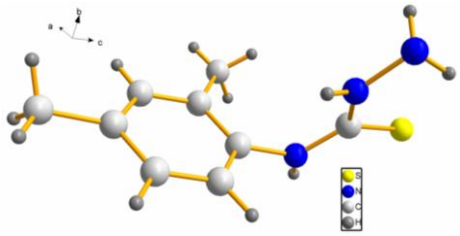
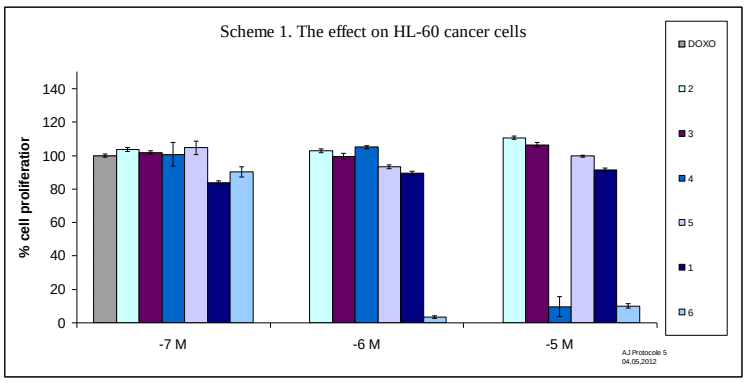


Fig. 1. Crystal structure of **1**

The composition and the structure of the synthesised substances have been determined by means of ^{1}H, ^{13}C NMR spectroscopy and X-ray diffraction (Fig. 1). All substances have been tested as inhibitors of human leukaemia (HL-60) cells growth (Scheme 1).

Antileukaemia bioassays have shown that antiproliferative activity of the synthesised compounds is manifested mainly within the concentrations 10 μM and 1 μM, and increases in the following series: **2** ≤ **3** < **5** < **1** < **4** < **6**. Therefore, the most active compounds **4** and **6** should be further studied as potential alternatives to traditional antileukaemia medicines. Also, from this study we have inferred that in order to obtain highly antiproliferative active azomethines from 4-(2,4-dimethylphenyl)thiosemicarbazide, it should be condensed with aromatic carbocyclic or heterocyclic aldehydes or ketones, which contain donor atoms (such as O or N) in the *ortho* position to the carbonyl group (e.g. salicylaldehyde, etc.).



This work has been performed with the financial support of the International Bilateral Project 10.820.09.10/RoA and Institutional Project 11.817.08.48A.

[7] Corresponding author, tel. +373 22 577 540, e-mail address: artur1809@gmail.com (Artur Sargun)

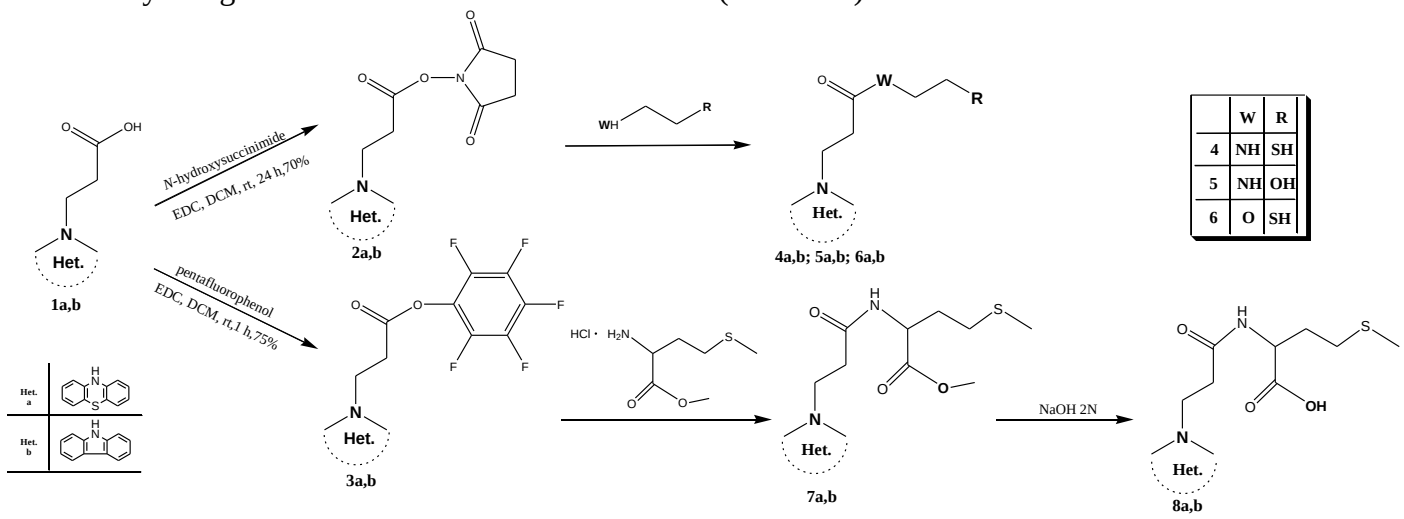
P12. Synthesis and biological evaluation of new phenothiazine and carbazole derivatives as inhibitors of human farnesyltransferase

Gina-Mirabela Dumitriu[1], Dalila Belei[1], Elena Bîcu[1], Joëlle Dubois[2], Benoît Rigo[3], Philippe Gautret[3], and Alina Ghinet[1,3,*]

[1]*Department of Organic Chemistry, 'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Bd. Carol I nr. 11, 700506 Iasi, Romania*
[2]*Institut de Chimie des Substances Naturelles, UPR2301 CNRS, Centre de Recherche de Gif, Avenue de la Terrasse, F-91198 Gif-sur-Yvette Cedex, France*
[3]*UCLille, EA 4481 (GRIIOT), Laboratoire de Pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France*

Many biological properties have already been described for phenothiazine and carbazole derivatives.[1] Some phenothiazine derivatives display anthelmintic activities,[2] and others are (reversible) inhibitors of trypanothione reductase,[3] inhibit lipid peroxidation[4] or tubulin polymerization[5], and some carbazole derivatives are inhibitors of human adipocyte fatty acid-binding protein.[6]

Compounds with the phenothiazine moiety were reported by our research group in the field of inhibitors of human farnesyltransferase.[7] We have now modified the carbazole and phenothiazine scaffolds by using chains often encountered in the field (Scheme 1).



Scheme 1. Synthesis of new phenothiazine and carbazole derivatives, inhibitors of farnesyltransferase

The biological activity of all the synthesized derivatives was evaluated on human FTase and the results obtained were in micromole fields. These results allow us to establish structure-activity relationships and targeting research to improve biological activity.

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* Corresponding author, e-mail address: alina.ghinet@hei.fr (Alina Ghinet)

P13. Chemical analysis and *in vivo* acute toxicity evaluation of two *Bidens tripartita* extracts

Raoul Bogdan Sandu[1*], Liliana Tarțău[2], Anca Miron[3], Marin Zagnat[4], Cristina Mihaela Ghiciuc[2], and Cătălina-Elena Lupuşoru[2]

1. PhD Student "Gr. T. Popa" University of Medicine and Pharmacy, Iasi, Romania
2. Department of Pharmacology, Faculty of Medicine, "Gr. T. Popa" University of Medicine and Pharmacy, Iasi, Romania
3. Faculty de Pharmacy, University of Medicine and Pharmacy, Iasi, Romania,
4. Faculty of Medical Bioengineering, University of Medicine and Pharmacy, Iasi, Romania

Abstract: The active substances found in some plants appear to increase the body's capacity to adapt to stress and changing situations. Adaptogens are naturally occurring substances with potent antioxidant properties having the ability to improve endurance, enhance physical performances and to produce effects associated with stress reduction. *Bidens tripartita* from family Asteraceae, commonly named Burr marigold or threelobe beggarticks is an annual plant, with yellow flowers, used in oriental medicine for its anti-inflammatory, diaphoretic and diuretic effects. Review of literature till date, showed that *Bidens tripartita* plant possesses various bioactive compounds such as: flavonoids, xanthophylls, volatile oil, acetylene and polyacetylene, sterols, aurones, chalcones, caffeine and tannins. The present study is **aimed** to investigate literature data regarding *Bidens tripartita* plant and to evaluate *in vivo* acute toxicity of alcoholic and aqueous extracts of it after intraperitoneal administration in mice. **Material and method:** The material plant for the study was represented by ethanolic and aqueous extracts from *Bidens tripartita,* plant collected during the flowering stage, from the zone Ciric, district of Iasi. Phyto-chemical analysis of the vegetable extracts of *Bidens tripartita* consisted of performing simple chemical tests. The acute toxicity of the these two extracts of *Bidens tripartita* was assessed on the basis of median lethal dose (LD50), minimum lethal dose (LD01 - no toxicity dose) and lethal dose 99 (LD99 - sure toxicity dose) calculation and was evaluated by different characteristic behavioral manifestations for the mouse, which can be retained as toxicity elements for the extract (lack of appetite, depression, immobility, respiratory distress, death). Experimental protocols were implemented according to recommendations of the "Gr. T. Popa" University Committee for Research and Ethical Issues. Data were statistically analyzed with SPSS software for Windows version 17.0 and ANOVA one-way method. **Results**: Phytochemical analysis of the vegetable extracts of *Bidens tripartita* detected the presence of different active principles, especially tannins, anthracene derivatives, and triterpenes in alcoholic extract and of anthracene derivatives, antocianosides, flavonosides, cumarines, saponosides, tannins, proteic compounds, polysaccharides in aqueous extract. The calculated value of LD50 allowed to find out the level of toxicity of vegetable products on the standardized toxicity scale WHO/IPCS. A lethal dose was determined at a rate of 4038mg of corporal weight for alcoholic extract and at a rate more than 5000mg of corporal weight for aqueous extract in mice. No macroscopic changes and histo-pathological lesions were observed in the organs of mice that died following the two extracts administration. **Conclusions**: The acute toxicity evaluation results showed that, both alcoholic and aqueous extracts of *Bidens tripartita* are included in the group with low slightly toxic products, being relatively safe toxicologically when administered intraperitoneally in mice. **Keywords**: alcoholic extract, aqueous extract, *Bidens tripartita*, lethal dose 50, mice.

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P14. Effect of cyclodextrin on the solubility of an anti-arrhythmic drug

Oana Maria Păduraru[1*], Andreea Bosînceanu[2], Gladiola Țântaru[2], and Cornelia Vasile[1]

[1]*Romanian Academy, "Petru Poni" Institute of Macromolecular Chemistry, 41A Grigore Ghica Voda Alley, 700487, Iasi, Romania*
[2]*"Gr. T. Popa" University of Medicine and Pharmacy, Faculty of Pharmacy, 16 University Str., 700115 Iasi, Romania*

Amiodarone, one of the most powerful anti-arrhythmic drugs is being used for the treatment of a wide variety of cardiac arrhythmias. The main problem with amiodarone is its very low water solubility (0.7 mg/ml), associated with low bioavailability. Complexation of this molecule with HP-β-CD offers the possibility to increase its aqueous solubility without the modification of its original structure.

Hydroxypropyl-β-cyclodextrin (HP-β-CD) is a derivative of β-cyclodextrin which is widely used for drug encapsulation due to its ability to form inclusion complexes, but also due to its high water solubility. Moreover, toxicological studies revealed that this derivative is well tolerated by the human body.

The aim of this work was to synthesize HP-β-CD/amiodarone inclusion complex by freeze-drying, in order to improve the solubility and the bioavailability of this active agent.

The complexation was evaluated using solubility studies, scanning electron microscopy (SEM), X-ray diffraction measurements (XRD) and differential scanning calorimetry (DSC). The solubility studies allowed the determination of the apparent stability constant of the complex and it was observed that the solubility in water increased, which indicates an increase in the amiodarone release.

Acknowledgments:
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P15. Coordination Compounds of Copper (II) as Regulators of Productivity and Biosynthesis of Cyanobacterium *Spirulina Platensis*

Valeriu Rudic[1,*], Ludmila Batir[1], Aurelian Gulea[2], and Victor Tsapkov[2]

[1]*Institute of Microbiology and Biotechnology, Academy of Sciences of Moldova, Chisinau, 2028, 1 Academiei Str. Republic of Moldova*
[2]*Coordination Chemistry Department, Moldova State University, Chisinau, 2009, 60 Mateevici Str. Republic of Moldova*

Investigation of non-traditional sources of bioactive substances is one of the current directions of biotechnology development. Cyanobacterium *Spirulina platensis* is widely explored and used in recent decades as a source of important bioactive substances. An important direction in biotechnology research is obtaining of spirulina biomass fortified with important micronutrients. In last decades action of coordination compounds of Zn(II), Co(II), Fe(III), Mn(II), Se(IV), Cr(III) on the growth and biochemical composition of cyanobacteria and microalgae has been extensively studied. New procedures for obtaining biomass with high content of bioactive substances were used as a basis for developing new technologies for obtaining biomedical and nutraceutical remedies.

Recent researches have demonstrated pronounced biological activity of coordination compounds of copper (II) that have antimicrobial, antifungal, anti-inflammatory, and anticancer activity. In order to reduce copper toxicity cyanobacterium *Spirulina platensis* can be cultivated in presence of coordination compounds of Cu(II) that lead to obtaining biomass with high content of copper and other bioactive substances with antimicrobial effect.

The purpose of the research was the study of copper bioaccumulation in spirulina biomass and its distribution in various fractions extracted from biomass.

Research subject served cyanobacterium *Spirulina platensis CNM-CB-02*. As regulators of copper content in biomass were used coordination compounds of Cu (II) acetato-N-[2-(2-hidroxietilamino)-ethyl]-salicilidenimino(1-)copper ([Cu(L-H)(CH_3COO)]) and bromo-{3-[(2-hydroxy-5-nitro-benzylidene)-amino]-propane-1,2-diolo}(1-)copper ([Cu(L-H)Br]).

As a result of the research two procedures of cultivation of spirulina in the presence of new coordination compounds of Cu(II) were developed. These procedures of cultivation lead to obtaining biomass with high content of copper bound with organic compounds of biomass (proteins, oligopeptides, amino acids, lipids, carbohydrates). Cultivation of spirulina in the presence of the compounds [Cu(L-H)(CH_3COO)] and [Cu(L-H)Br] at a concentration of 2,0 and 6,0 mg/L leads to reduction of productivity (1,02 and 0.92 g/L), but at the same time copper content accumulated in biomass reaches values of 10,63 and 11,14 mg%, respectively. Using fractionation of spirulina biomass it was determined that the largest growth of copper content is in carbohydrate fraction (28% and 31%). About 30% and 27% of the total amount of copper accumulated is bound to amino acids and oligopeptides. Processes of obtaining biomass of *Spirulina platensis* enriched with copper bound to organic compounds could be applied to develop new technologies for obtaining copper components preparations with antimicrobial, anti-inflammatory, and anticancer activities.

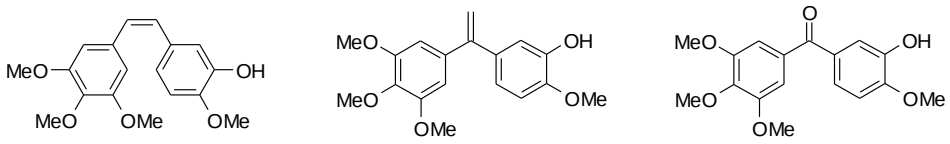
* Corresponding author: e-mail address:, tel. +373 22739878, e-mail: acadrudic@yahoo.com (Valeriu Rudic)

P16. An unexpected carbon insertion during a Wittig reaction attempt

Vivien Stocker,[1,2,*] Alina Ghinet,[1,2] Marie Leman, Benoît Rigo,[1,2] Régis Millet,[1,3] and Philippe Gautret.[1,2]

[1] *Univ Lille Nord de France, F-59000 Lille, France*
[2] *UCLille, EA GRIIOT (4481), Laboratoire de pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France*
[3] *Institut de Chimie Pharmaceutique Albert Lespagnol, Université de Lille 2, 3 rue du Professeur Laguesse, F-59006 Lille, France*

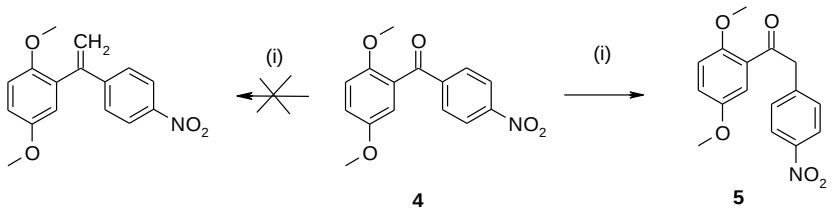
It has been recently described that a new family of substituted 1,1-diarylethylenes, called isocombretastatins, displays a biological activity similar to the one of their combretastatin or phenstatin homologues[8] (Figure 1).



1 Combretastatin A-4 **2** *Iso*combretastatin A-4 **3** Phenstatin

Figure 1: Structure of combretastatin A-4 (1) and corresponding isocombretastatin A-4 (2) and phenstatin (3).

In order to synthesize novel isocombretastatins, numerous benzophenones were engaged into a Wittig reaction. We observed, in the case of ketone 4, that the corresponding 1,1-diarylethylene was not formed, instead ketone 5 was isolated (Figure 2).



4 **5**

Figure 2: (i) CH_3PPh_3Br (2 equiv.), t-BuOK (5 equiv.), THF, rt, 18h.

A study of the influence of the aryl substituants on this ketone homologation was carried out, and a mechanism was proposed to explain the methylene insertion.

* Corresponding author,e-mail address vivien.stocker@hei.fr (Vivien Stocker)

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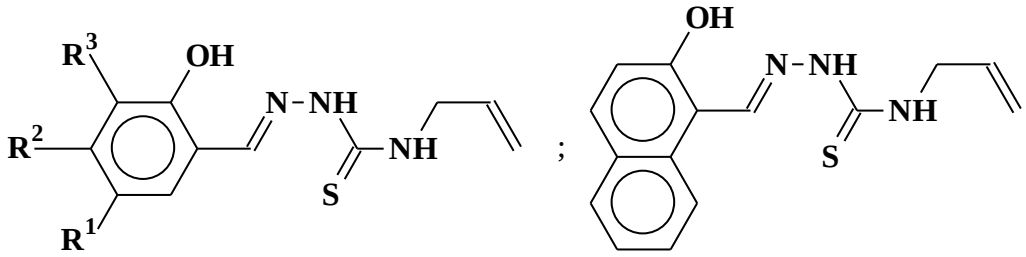
P17. Synthesis, Antitumor, and Antimicrobial Activity of Some 3d-Metal Complexes with 4-Allylthiosemicarbazones of Salicylaldehyde and Its Derivatives

Aurelian Gulea[1], Vasilii Graur[1,9], Elena Zariciuc[2], Angela Jalba[1], Victor Tsapkov[1], Larisa Sofroni[3], and Valeriu Rudic[2]

[1]*Coordination Chemistry Department, Moldova State University, Chisinau, 2009, 60 Mateevici Str. Republic of Moldova*
[2]*State University of Medicine and Pharmacy „N. Testemitanu", Chisinau, 2004, 165, bd. Stefan cel Mare si Sfant, Republic of Moldova*
[3]*Oncological Institute of Moldova, MD 2008, 30, Testemitanu str., Chisinau, Republic of Moldova*

The aim of this work is the synthesis, determination of the composition, structure, antimicrobial and antitumor activity of the coordination compounds of cobalt, nickel, copper, and zinc with 4-allylthiosemicarbazones (HL^{1-8}) of salicylaldehyde (HL^1), 5-bromo-(HL^2), 5-nitro-(HL^3), 3-methoxy-(HL^4), 3,5-dibromosalicylaldehyde (HL^5), 2,3-(HL^6), 2,4-dihydroxybenzaldehyde(HL^7), and 2-hydroxy-1-naphthaldehyde (HL^8).



HL^{1-7} **HL^8**

R^1= H, Br, NO_2; R^2 = H, OH; R^3 = H, OH, CH_3O, Br.

Salts of stated above metals react with thiosemicarbazones HL^{1-8} forming coordination compounds with composition $Co(L^{1-8})_2X$ and $M(L^{1-8})X$ (M = Cu, Ni, Zn; X = Cl, NO_3). Composition and structure of these compounds were determined on the basis of data from elemental analysis, X-ray analysis, magnetochemical research, IR spectroscopy, NMR spectroscopy (^1H and ^{13}C), and thermogravimetric analysis.

4-Allylthiosemicarbazones of the substituted salicylaldehydes and coordination compounds with them selectively inhibit the human promyelocytic leukemia HL-60 cells growth in the concentration 10^{-5}-10^{-6}M. In many cases synthesized coordination compounds have better activity than corresponding thiosemicarbazones. Coordination compound $Cu(L^6)NO_3$ inhibit growth of 100% of HL-60 cells growth in the concentration 10^{-5}-10^{-6} M. The synthesized complexes also display selective bacteriostatic and bactericidal activity towards a series of standard stems of *Staphylococcus aureus*, *Escherichia coli*, and *Candida Albicans* in the concentration range 0.7-120 μg/mL. The copper (II) coordination compounds show the highest activity.

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* Corresponding author tel. +373 22 577689; e-mail address: vgraur@gmail.com (Vasilii Graur)

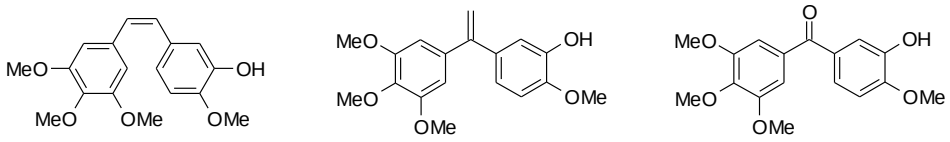
P18. Synthesis and biological evaluation of novel *iso*CA-4 derivatives

Vivien Stocker, [1,2,*] Philippe Gautret,[1,2] Benoît Rigo,[1,2] Régis Millet,[1,3] Amaury Farce,[1,4] Joëlle Dubois,[5] and Alina Ghinet.[1,2]

[1] *Univ Lille Nord de France, F-59000 Lille, France*
[2] *UCLille, EA GRIIOT (4481), Laboratoire de pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France*
[3] *Institut de Chimie Pharmaceutique Albert Lespagnol, Université de Lille 2, 3 rue du Professeur Laguesse, F-59006 Lille, France*
[4] *Institut de Chimie Pharmaceutique Albert Lespagnol, EA 4481, IFR114, 3 rue du Professeur Laguesse, 59006 Lille, France*
[5] *Institut de Chimie des Substances Naturelles, UPR2301 CNRS, Centre de Recherches de Gif, Avenue de la Terrasse, F-91198 Gif-sur-Yvette Cedex, France*

Among the large class of products known as tubulin inhibitors, the combretastatin family, and notably the combretastatin A-4 (Figure 1), exhibits a strong cytotoxicity and an antitubulin activity. But, despite their therapeutic interests, these compounds are prone to double-bond isomerization leading to E-isomer which decreases dramatically the activities.[10]

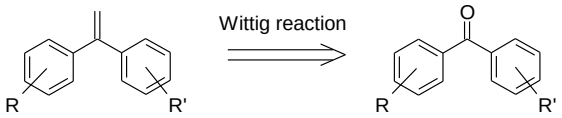
It has been recently described a new family of substituted 1,1-diarylethylenes called isocombretastatins.[11] These compounds display an activity similar to the one of their combretastatin homologues as inhibitors of tubulin polymerization and cytotoxic compounds.[11,12,13] Moreover, these products does not suffer any isomerization of the double bond.



1 Combretastatin A-4 **2a** *Iso*combretastatin A-4 **3a** Phenstatin

Figure 1: Structure of combretastatin A-4 (1) and corresponding isocombretastatin A-4 (2a) and phenstatin (3a).

These derivatives were easily prepared from phenstatin analogues by Wittig reaction (Figure 2).[13]



2 **3**

Figure 2: Synthesis of isocombretastatins derivatives by Wittig reaction.

We have synthesized a wide family of diversely substituted *iso*combretastatins by this method. Their cytotoxic activities were evaluated by the National Cancer Institute, and the results are presented here.

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P19. SIGMA-1 RECEPTOR AGONISTS AS POTENTIAL TREATMENT OF MULTIPLE SCLEROSIS

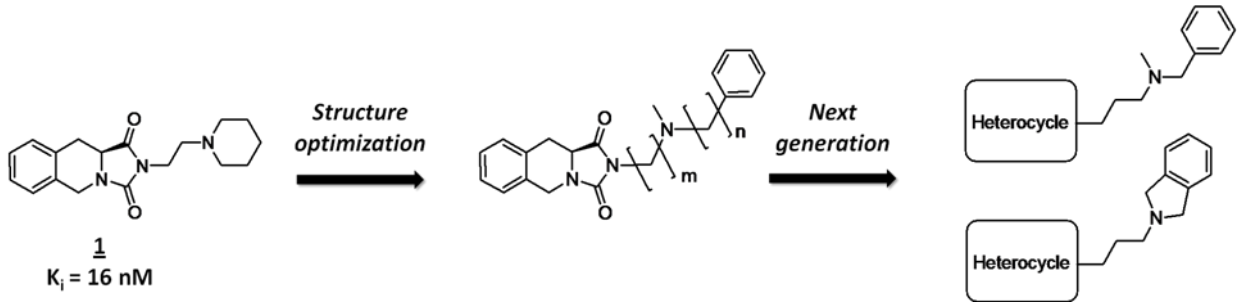
Marion Donnier-Maréchal[1,2], Pascal Carato[1,2], Bénédicte Vanteghem-Oxombre[1,3], Patrick Vermersch [1,3], and Patricia Melnyk [1,2]

[1] *Université Lille Nord de France, F-59000 Lille, France*
[2] *UDSL, EA 4481, UFR Pharmacie, F-59000 Lille, France*
[3] *UDSL, EA 2686, UFR Médecine, F-59000 Lille, France*

Multiple sclerosis (MS) is the most common disease of the central nervous system and affects more than 2.5 million people worldwide. This chronic inflammatory disease is characterized by the presence of multiple demyelinating lesions disseminated in the brain and spinal cord. Diagnosed mainly between 20 and 40, MS is the leading cause of nontraumatic disability among young people.

σ_1 receptors represent a structurally unique class of transmembrane receptors of the endoplasmic reticulum. Expressed in the central nervous system and especially in neurons, lymphocytes and oligodendrocytes, these receptors are known to be involved in the regulation of numerous neurotransmitters. Some σ_1 ligands showed high anti-inflammatory and neuroprotective properties. Thus, it is in this context that our interest is focused on validation of new σ_1 receptor ligands for the treatment of MS.

Substituted hydantoins have been widely used in biological screenings resulting in numerous pharmaceutical applications. Fused and optimized tetrahydroquinoline-hydantoin derivatives designed in our laboratory showed nanomolar σ_1 affinity, σ_2 /σ_1 selectivity around 75, very low cytotoxicity and ADME properties compatible with therapeutic development [1]. Binding of these compounds at the σ_1 receptors could be explained by the association of an aromatic moiety and a nitrogen atom previously proved to be a pharmacophoric element in a series of phenylalkylpiperidines and phenylalkylpiperazines [2]. Evaluated in EAE (Experimental Autoimmune Encephalomyelitis) model, the lead compound led to the development of less severe pathology. These promising results could be explained by an anti-inflammatory activity associated with a neuroprotective action of our ligands. The synthesis of next generation of ligands and biological results will be presented.



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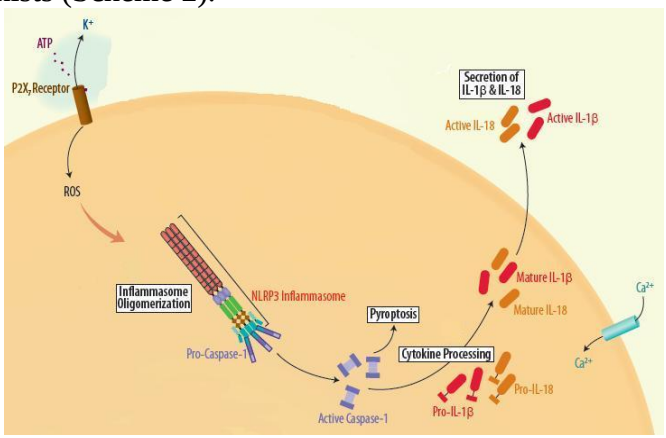
P20. Involvment of the Purinoreceptor P2X$_7$ In Inflammation and Cancer

Davy Baudelet[1,2], Emmanuelle Lipka[1,3], Régis Millet[1,4], Philippe GAUTRET[1,2], Benoît Rigo[1,2].

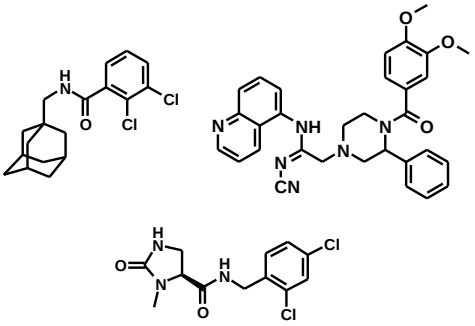
[1] *Univ Lille Nord de France, F-59000 Lille, France*
[2] *UCLille, EA GRIIOT (EA4481), Laboratoire de pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France*
[3] *Laboratoire de Chimie Analytique, Université de Lille 2, 3 rue du Professeur Laguesse, F-59046 Lille, France*
[4] *ICPAL, EA GRIIOT (EA4481), Université de Lille 2, 3 rue du Professeur Laguesse, F-59006 Lille, France*
davy.baudelet@hei.fr

The purinergic P2X$_7$ receptor (P2X$_7$R) is a ligand-gated ion channel which belongs to the family of ATP-sensitive receptors. P2X$_7$R is present in a variety of cell types, like haematopoietic cells, immune cells, microglia and astrocytes.[14] This receptor is implicated in numerous diseases including pain, neurodegeneration, inflammation and cancer.[15] Thus, this ionotropic receptor makes a new interest target to a novel therapeutic approach to the treatment of these diseases.

In lymphocytes and macrophages, P2X$_7$R activation results in the activation of phospholipase D and, in human macrophages, it elicits the release of the inflammatory cytokine IL-1β via activation of caspase-1 (Scheme 1).[14] This pro-inflammatory activity can be decreased by using P2X$_7$R selective antagonists (Scheme 2). [16,17,18]



Scheme 1 : Release of pro-inflammatory cytokines by P2X$_7$R activation



Scheme 2 : Examples of selective P2X$_7$R antagonists[16,17,18]

- It has been reported that the activation of P2X$_7$R by using agonists, can lead to an anti-tumoral activity.[19]
- However, in some different types of cancer, the opposite situation occurs, and the P2X$_7$ antagonists have benefic effects,[20] due to their capacity to inhibit multiple pro-tumoral cell signaling pathways.

Thus, taking these facts in consideration, we decided to study new selective P2X$_7$ antagonists in order to increase their anti-inflammatory and anti-tumoral activities.

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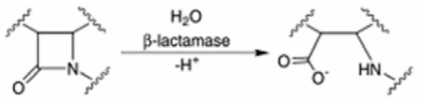
P21. KINETIC ACTION OF A PENICILLINASE WITH ATTENUATED ACTIVITY ON AN AQUEOUS SOLUTION OF PENICILLIN G

N. C. LUNGU, Maria ALEXANDROAEI, R. GRĂDINARU, I. V. ASAFTEI
Address: "Al. I. Cuza" University, Faculty of Chemistry, 11, Carol I Bd., 700506, Iaşi, Romania
e-mail addess: lungu@uaic.ro

The *β*-lactam antibiotics represent an antibiotic family like penicillins, cephalosporins, cephamycins and carbapenems widely used due to a remarkable tolerance, their comparatively high effectiveness, low cost, ease of delivery and minimal side effects. The instability of *β*-lactam antibiotics in aqueous solution is a hurdle in their useful and in the tests of evaluation of their pharmacokinetic properties and adverse reactions.

The *β*-lactamases confer significant resistance to these antibiotics through a hydrolyze process of the amide bond of the four-membered *β*-lactam ring leading in final to biologic inactive products.



The study of these enzymes has become an important focus of research because most bacteria produce *β*-lactamases. The ability or inability of a *β*-lactamase to confer resistance depends on its nature, kinetics and quantity.

The *β*-lactamases produced by gram-positive species are largely extracellular. By contrast, the *β*-lactamases of gram-negative species are largely periplasmic. The activity of most *β*-lactamases against most substrates can be described by the Michaelis-Menten equation: $v = V_{max}S/(K_m + S)$ where v is the hydrolysis rate, S is the *β*-lactam concentration, and V_{max} and K_m are the kinetic constants. A low K_m reflects high affinity and may be as critical to resistance as a high V_{max}. Higher levels of enzyme can cause greater resistance.

In the present work we determined the constants of the Michaelis-Menten's model in the case of action of a penicillinase with attenuated activity on a substrate of penicillin G in an aqueous solution. Kinetic results led us to the hypothesis that there is a hydrolytic - enzymatic degradation of penicillin G when there is a higher concentration and a chemical degradation when the substrate concentration significantly decreases. The resulted values were compared with those obtained in the absence of penicillinase.

Keywords: *β*-lactam antibiotics, penicillinase, Michaelis-Menten's model

P22. Acylic microparticles for the release of biologically active molecules

Maria-Andreea Lungan[1,*], Stefania Racovita[2], Silvia Vasiliu[2], and Marcel Popa[1]

[1]*"Gheorghe Asachi" Technical University of Iaşi, Faculty of Chemical Engineering and Environmental Protection Department of Natural and Synthetic Polymers, Prof. dr. docent Dimitrie Mangeron Str.,no. 73, 700050, Iaşi, Romania*

[2]*"Petru Poni" Institute of Macromolecular Chemistry, Gr. Ghica Voda Alley no. 41A, 700487, Iasi, Romania*

Within the last decade the progress in polymer science and engineering has led to the creation of new polymeric materials that have been used in many fields, especially in medical and pharmaceutical field [1-3]. In this context, entrapping of drug molecules in a macromolecular support obtained by a combination between natural and synthetic polymers is a helpful strategy for protecting drugs against chemical and enzymatic degradation, reducing dissolution rate, enhancing aqueous solubility of drug and/or targeting drug release. Among the synthetic polymers, ion exchange resins have received considerable attention for a broad spectrum of applications. The concept of using ion-exchange resins for controlled release of drugs has been introduced for more than 50 years. Also, the ion exchange resins have been suggested for uses in control of gastric acidity, treatment of cardiac edema or as taste-masking agents. The aim of this study was to develop a new drug delivery system for sustained release of cefotaxime sodium salt (CF) based on a complex of xanthan or gellan gum and an acrylic ion exchanger. CF is a third-generation cephalosporin antibiotic and it is used for infections of the respiratory tract, skin, bones, joints, urogenital system, meningitis and septicemia. The acrylic microparticles were obtained by the aminolysis-hydrolysis reaction of ternary copolymer (ethyl acrylate-acrylonitrile-divynilbenzene) with ethylenediamine. To increase the biocompatibility of the microparticles, two polysaccharides (gellan and xanthan gum) were selected to cover the surface of these acrylic beads. The microparticles based on this complex have been characterized by FT-IR spectroscopy, SEM microscopy and thermogravimetric analysis. The sorption equilibrium and the mechanism of CF release onto/from complex microparticles were also investigated. A higher capacity of drug loading on the complex microparticles was observed in comparison to the capacity of drug loading on the ion exchange microparticles. Also, the susceptibility of certain strains of bacterium towards cefotaxime and the new drug delivery systems was judged by measuring the size of inhibition diameter.

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* Corresponding author, tel. +40 741593790, e-mail address maria_andreea.lungan@yahoo.com (Maria-Andreea Lungan)

P23. Organic synthesis of iron chelators and characterization.

S. Abdelsayed[1*], T. Ha Duong[1], M. Hémadi[1], J. Hénault[1], J.-M. El Hage Chahine[1], P. Verbeke[2], C.-Z. Dong[1], N. Serradji[1*].

[1]*Univ Paris Diderot, Sorbonne Paris Cité, ITODYS-UMR CNRS 7086, 13 rue Jean-Antoine de Baïf, 75205 Paris cedex 13, France.*

[2]*Univ Paris Diderot, Sorbonne Paris Cité, Institut Jacques Monod-UMR CNRS 7592, 15 rue Hélène Brion,75205 Paris cedex 13, France.*

Iron is essential for the proper functioning of all living cells, however it is toxic when present in excess. Disorders of its homeostasis, of its bioavailability or toxicity caused by its excess are responsible for a large number of human diseases (hemochromatosis, β-Thalassemia…). Thus, using iron chelators as therapeutic agents, namely chelation therapy, has received increasing attention.

We describe, in this work, the synthesis of two iron chelators and illustrate the chelation properties of one of them.

*Correspondance : sy.abdelsayed@gmail.com; serradji@univ-paris-diderot.fr

P24. New polymeric materials with therapeutic applications

Maria-Andreea Lungan[1,*], Silvia Vasiliu[2], Stefania Racovita[2], Ioan Plesca[2], and Marcel Popa[1]

[1]*"Gheorghe Asachi" Technical University of Iaşi, Faculty of Chemical Engineering and Environmental Protection Department of Natural and Synthetic Polymers, Prof. dr. docent Dimitrie Mangeron Str.,no. 73, 700050, Iaşi, Romania*

[2]*"Petru Poni" Institute of Macromolecular Chemistry, Gr. Ghica Voda Alley no. 41A, 700487, Iasi, Romania*

Progress in polymer science and engineering led to the creation of new polymeric materials which represents one of the driving forces for the evolution of fundamental knowledge and development in various domains, especially in medical and pharmaceutical field [1-4]. In modern medicine, natural and synthetic polymeric materials with various architectures have been developed to achieve two main objectives: (1) to optimize the drug therapeutics and (2) to improve patient compliance. A combination between synthetic and natural polymers could lead to new polymeric materials with specific properties for delivery of low and high molecular weight drugs. Among these materials, the porous adsorbents have capture attention as macromolecular supports for immobilization of various biologically active molecules.

The purpose of this study was to investigate the use of new microparticles based on glycidyl methacrylate (GMA) and xanthan (XAN) as drug carriers for some hydrophilic drugs. The microparticles were obtained by suspension polymerization technique. Crosslinking is a very important process in the formation of the adsorbents structure. Using the suspension polymerization technique it is possible to obtain porous beads, which could have an optimal morphological structure. The properties of the porous crosslinked copolymers were influenced by synthesis parameters such as: the nature of the porogenic agent and the crosslinked agent, the crosslinking degree and the monomers ratio. Morphological characteristics such as: specific surface, skeletal and apparent densities, volume pore and porosity were investigated. The crosslinked copolymers were also characterized by ESEM/EDAX microscopy and FT-IR spectroscopy. Drug (cefotaxime sodium salts and augmentin) loading in microparticles was performed through diffusion process after the formation of the microparticles. The amounts of retained and released drug were determined spectrometrically at 236 nm for cefotaxime and 272 nm for augmentin.

Based on the drug release profiles the new synthesized microparticles could be considered suitable for use as oral drug delivery systems.

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* Corresponding author, tel. +40 7415937907, e-mail address: maria_andreea.lungan@yahoo.com (Maria-Andreea Lungan)

P25. Virtual Screening of CB_2 Receptor Agonists from Bayesian Network and High-Throughput Docking: Structural Insights into Agonist-Modulated GPCR Features

Nicolas Renault [1], Xavier Laurent [1], Amaury Farce [1,2*], Jamal El Bakali [2], Roxane Mansouri [3], Philippe Gervois [3], Régis Millet [2], Pierre Desreumaux [4], Christophe Furman [3], Philippe Chavatte [1,2]

[1] Laboratoire de Chimie Thérapeutique, Faculté des Sciences Pharmaceutiques et Biologiques, Université Lille-Nord de France, EA 4481, 3 rue du Professeur Laguesse, BP 83, 59006 Lille Cedex, France

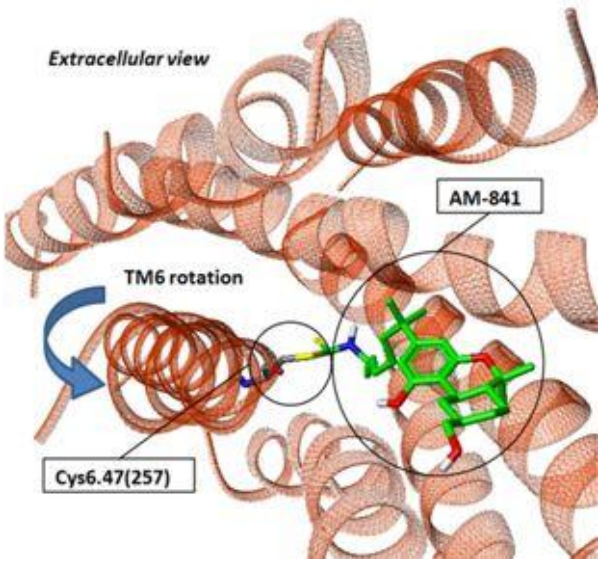
[2] Institut de Chimie Pharmaceutique Albert Lespagnol, Université Lille-Nord de France, EA 4481, 3 rue du Professeur Laguesse, BP 83, 59006 Lille Cedex, France.

[3] Institut de Chimie Pharmaceutique Albert Lespagnol, Université Lille-Nord de France, Plate-forme de binding et biologie moléculaire, EA 4481, 3 rue du Professeur Laguesse, BP 83, 59006 Lille Cedex, France.

[4] Université Lille-Nord de France, Faculté de Médecine, Amphis J et K, INSERM U995, Boulevard du Professeur Jules Leclerc, 59045 Lille Cedex, France.

The relevance of CB_2-mediated therapeutics is well established in the treatment of pain, neurodegenerative and gastrointestinal disorders. Recent works such as the crystallization of class-A GPCRs in a range of active states and the identification of specific anchoring sites for CB_2 agonists challenged us to design a reliable agonist-bound homology model of CB_2 receptor.

A virtual screening protocol was employed to discover new potential CB_2 agonists. First, the initial commercial library was focused by a 2D ligand-based Bayesian network built around known agonists. This focused database was then submitted to a 3D high throughput docking run against a homology model of CB_2. This model has been previously carefully adjusted to render a putative agonist-bound state and therefore offer the best accuracy for the key interaction points of agonists.



This protocol led to a 140-compound database, which was tested *in vitro* for their affinity. 13 molecules were in the micromolar range and were further tested for their functional activity. Most of them behaved as CB_2 agonists, among which two novel full agonists emerged.

The exclusive discovery of agonists illustrates the reliability of the agonist-bound state model and the ability to use homology modeling as a reliable starting point for GPCR agonists design.

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* Phone: +33 3 20 96 40 20.E-mail: amaury.farce-2@univ-lille2.fr

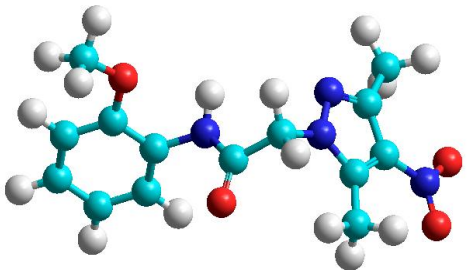
P26. Structure-Reactivity Relationship on Some New 2-(1H-Pyrazol-1-yl)-acetanilides with Local Anesthetic and Antiarrythmic Activities

Christina Zălaru[1*], Maria Marinescu[1], Mircea Iovu[2], Florea Dumitrașcu[3], Constantin Drăghici[3], Petre Ioniță[1] and Irina Zarafu[1]

[1]*University of Bucharest, Faculty of Chemistry, Department of Organic Chemistry, Biochemistry and Catalysys, Bucharest, 90-92 Road Panduri, Romania;*
[2]*University of Medicine and Pharmaceutics "Carol Davila", Center Research Synthesis and Organic Chemistry, 6-Traian Vuia St., Bucharest, Romania;*
[3]*Institute of Organic Chemistry C.D. Nenitescu, Romanian Academy 202 B, Spl. Independentei, Bucharest, Romania;*

Eight new substituted 2-(1H-Pyrazol-1-yl)-acetanilides were synthesized by N-alkylation of pyrazoles with 2-iodoacetanilides. The new compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, IR, UV-Vis, MS spectra and elemental analysis. Acute toxicity, local anesthetic and antiarrythmic activities were assesed for compounds using established protocols.

The structures of the synthesized compounds were optimized by AM1 semiempirical method. The calculated HOMO and LUMO energy difference gap were correlated with the dipole moment of each compound and with the therapeutically activity of the tested compounds.



2-(3,5-Dimethyl-4-nitro-pyrazol-1-yl)-2'-methoxyacetanilide

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*Christina Zalaru, 0744296197, e-mail address: chmzalaru@yahoo.com

P27. Targeting A_{2A} receptor to treat Alzheimer's disease: design, synthesis and evaluation of antagonists.

V. Moas, N. Renault, P. Chavatte, D. Blum, L. Buée, P. Melnyk, and L. Agouridas

A_{2A} antagonists appeared to be very promising pharmacological targets, especially in Parkinson's disease (PD) through their psychomotor and neuroprotective effects for which 5 compounds have reached clinical phases. Furthermore, an increasing number of studies suggest that pharmacological or genetic blockade of A_{2A} receptors ($A_{2A}R$) might be of great interest in Alzheimer's disease as it reduces □-amyloid deposits, Tau-phosphorylation and neurodegeneration. Although many efforts have been conducted for the identification of potent antagonist compounds, there is still a need for improving their affinity and selectivity towards other adenosine receptors as well as their ADME properties.

$A_{2A}R$ belongs to the family of G-protein coupled receptors. Based on the recently published crystalline structure of the A_{2A} receptor complexed with ZM241385, a selective and high-affinity antagonist[1] and on a pharmacophoric model,[2] we have designed new ligands using *in silico* docking studies starting from antagonists that we recently identified in our group. Then, best compounds identified from SAR and ADME studies (PRIM, Lille) will be tested in animal models for neurodegenerative diseases, in collaboration with Dr. L. Buée and Dr. D. Blum from U387 (JPARC, Lille).

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P28. Pyrite oxidation in acidic media

Cristina A. Constantin[1], Paul Chiriță[1], Mircea Preda[1,*]

[1]*Department of Chemistry, University of Craiova, Calea Bucuresti 107I, Craiova, Romania*

Oxidation of pyrite (the most abundant iron sulfide mineral) produces sulfuric acid and ferric iron, which favor the release of toxic metals (Pb, Cd, Cu, Hg, Zn) and arsenic. These elements can cause serious diseases like Arsenicosis (arsenic intoxication), Itai-Itai (cadmium intoxication) and Minamata disease (mercury intoxication). The main natural oxidants of pyrite are: molecular oxygen (O_2), ferric iron (Fe^{3+}) and hydrogen peroxide (H_2O_2).

The pyrite oxidation in the presence of O_2, Fe^{3+} and H_2O_2 was investigated at pH 2.5 and 25°C by potentiodynamic method. The corrosion currents (i_{corr}) were determined by Tafel method. i_{corr} increases from 1.83 µA cm^{-2}, in the case of O_2, up to 146 µA cm^{-2}, in the case of H_2O_2. An intermediary value of i_{corr}=80.1 µA cm^{-2} was obtained when the oxidant was Fe^{3+}.

These finding indicate that, although O_2 is the main natural acceptor of electrons from pyrite, the mineral oxidation by H_2O_2 and Fe^{3+} can't be neglected when models of environmental contamination with toxic elements are proposed.

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**Emails: cristina.a.constantin@gmail.com; paulxchirita@gmail.com, mpredachim@yahoo.com;*

LISTE DES PARTICIPANTS CoFrRoCM-2012

1. Sylvie Abdelsayed, *Université Paris Diderot, Sorbonne Paris Cité, Paris, France*
2. Hocine Abderrahim, *Ecole Normale Supérieure, Kouba, Algérie*
3. **Cristina Maria Abuhaie**, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
4. Maria Alexandroaei, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
5. I. V. Asaftei, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
6. Lavinia Baciu-Atudosie, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
7. Lucian Gabriel Bahrin, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
8. Alic Barba, *Institute of Chemistry, Academy of Sciences of Moldova, Chisinau, Republic of Moldova*
9. Ludmila Batir, *Institute of Microbiology and Biotechnology, Academy of Sciences of Moldova, Chisinau, Republic of Moldova*
10. Davy Baudelet, *Ecole des Hautes Etudes d'Ingénieur, Lille, France*
11. Dalila Belei, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
12. A. Bensoltane, *Centre Universitaire Bordj Bou Arreridj, Algérie*
13. Elena Bîcu, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
14. Maria Bîrcă, *Moldova State University, Chisinau, Republic of Moldova*
15. Mihail Lucian Bîrsă, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
16. David Blum, *Université Lille Nord de France, Inserm U837, Jean-Pierre Aubert Research Center, Lille, France*
17. Mathilde Body-Malapel, *Université Lille Nord de France, Faculté de Médecine, Lille, France*
18. Thomas Boisse, *Ecole des Hautes Etudes d'Ingénieur, Lille, France*
19. Andreea Bosînceanu, *"Gr. T. Popa" University of Medicine and Pharmacy, Faculty of Pharmacy, Iasi, Romania*
20. Messaoud Boudjeniba, *Ecole Normale Supérieure, Kouba, Algérie*
21. Mohamed Boussaid, *National Institute of Applied Sciences and Technology, Tunis, Tunisia*
22. A. Bouzitouna, *Department of biochemistry, Badji Mokhtar Annaba University, Algeria*
23. Luc Buée, *Université Lille Nord de France, Inserm U837, Jean-Pierre Aubert Research Center, Lille, France*
24. Stéphane Burlet, *AlzProtect, Lille, France*
25. Pascal Carato, *Université Lille Nord de France, UDSL, UFR Pharmacie, Lille, France*
26. Tatiana Căpățînă, *Moldova State University, Chisinau, Republic of Moldova*
27. Philippe Chavatte, *Institut de Chimie Pharmaceutique Albert Lespagnol, Lille, France*
28. Catalina Natalia Cheaburu, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
29. Paul Chiriță, *Department of Chemistry, University of Craiova, Craiova, Romania*
30. Yuri Chumakov, *Institute of Applied Physics, Academy of Sciences of Moldova, Chisinau, Republic of Moldova*
31. Cristina A. Constantin, *Department of Chemistry, University of Craiova, Craiova, Romania*
32. Sébastien Comesse, *UFR des Sciences & Techniques de l'Université du Havre, Le Havre, France*
33. Damien Cornut, *Université Libre de Bruxelles, Bruxelles, Belgium*
34. Ion Culeac, *Académie des Sciences, Chisinau, Republique Moldavie*
35. Adam Daïch, *UFR des Sciences & Techniques de l'Université du Havre, Le Havre, France*
36. Ramona Danac, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
37. N. Deramchia, *Centre Universitaire Bordj Bou Arreridj, Algérie*
38. W. Derdoukh, *Centre Universitaire Bordj Bou Arreridj, Algérie*
39. Pierre Desreumaux, *Université Lille Nord de France, Faculté de Médecine, Lille, France*
40. C. Z Dong, *Université Paris Diderot, Sorbonne Paris Cité, Paris, France*
41. Marion Donnier-Maréchal, *Université Lille Nord de France, UDSL, UFR Pharmacie, Lille, France*
42. Galina Dragalina, *Moldova State University, Chisinau, Republic of Moldova*
43. Constantin Drăghici, *Institute of Organic Chemistry C. D. Nenitescu, Bucharest, Romania*
44. Gabi Drochioiu, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
45. Joëlle Dubois, *Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, France*
46. Stéphanie Duez, *Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, France*
47. Carmen Dumea, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
48. Florea Dumitraşcu, *Institute of Organic Chemistry C. D. Nenitescu, Bucharest, Romania*
49. Anca Mihaela Dumitrescu, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
50. Gina-Mirabela Dumitriu, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
51. Raluca Petronela Dumitriu, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
52. T. Ha Duong, *Université Paris Diderot, Sorbonne Paris Cité, Paris, France*
53. Sabiha Eddarkaoui, *Université Lille Nord de France, Inserm U837, Jean-Pierre Aubert Research Center, Lille, France*
54. Jamal El Bakali, *Institut de Chimie Pharmaceutique Albert Lespagnol, Lille, France*
55. Mohamed A. El-Borai, *Faculty of Science, Tanta University, Tanta, Egypt*
56. I. Y. El-Deeb, *Faculty of Science, Tanta University, Tanta, Egypt*
57. J. M. El Hage Chahine, *Université Paris Diderot, Sorbonne Paris Cité, Paris, France*
58. Ali El Khorchani, *National Institute for Researches on Rural Engineering, Water and Forests, Tunisia*
59. Amaury Farce, *Institut de Chimie Pharmaceutique Albert Lespagnol, Lille, France*
60. Christophe Furman, *Institut de Chimie Pharmaceutique Albert Lespagnol, Lille, France*

61. Philippe Gautret, *Ecole des Hautes Etudes d'Ingénieur, Lille, France*
62. Ali Gemeay, *Higher Institute of Medical Technology, Misurata, Libya*
63. Philippe Gervois, *Institut de Chimie Pharmaceutique Albert Lespagnol, Lille, France*
64. Cristina Mihaela Ghiciuc, *"Gr. T. Popa" University of Medicine and Pharmacy, Department of Pharmacology, Faculty of Medicine, Iasi, Romania*
65. Alina Ghinet, *Ecole des Hautes Etudes d'Ingénieur, Lille, France*
66. Solo Goldstein, *Consultant Indépendant Chimie Médicinale et Diversité Chimique, Servier, Croissy-sur-Seine, France*
67. Vasilii Graur, *Moldova State University, Chisinau, Republic of Moldova*
68. R. Grădinaru, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
69. Philippe Grellier, *Département RDDM, Muséum National d'Histoire Naturelle, Paris, France*
70. Anca Giorgiana Grigoraş, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
71. Vasile Cristian Grigoraş, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
72. Aurelian Gulea, *Moldova State University, Chisinau, Republic of Moldova*
73. M. Hémadi, *Université Paris Diderot, Sorbonne Paris Cité, Paris, France*
74. J. Hénault, *Université Paris Diderot, Sorbonne Paris Cité, Paris, France*
75. Seham A. Ibrahim, *Faculty of Science, Tanta University, Tanta, Egypt*
76. Alexandra Ionescu, *Université Libre de Bruxelles, Bruxelles, Belgium*
77. Petre Ioniță, *University of Bucharest, Faculty of Chemistry, Bucharest, Romania*
78. Alexandra Raluca Iordan, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
79. Mircea Iovu, *University of Medecine and Pharmaceutics "Carol Davila", Bucharest, Romania*
80. Ivan Jabin, *Université Libre de Bruxelles, Bruxelles, Belgium*
81. Angela Jalba, *Moldova State University, Chisinau, Republic of Moldova*
82. Abdelhamid Khaldi, *National Institute for Researches on Rural Engineering, Water and Forests, Tunisia*
83. Robert Kiss, *Université Libre de Bruxelles, Bruxelles, Belgium*
84. Mohamed Kouidri, *Faculty of Science, University Hassiba Benbouali Chlef, Algeria*
85. Taoues Lakki, *Ecole Normale Supérieure, Kouba, Algérie*
86. Didier Lambert, *Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium*
87. Mohamed Larbi Khouja, *National Institute for Researches on Rural Engineering, Water and Forests, Tunisia*
88. Xavier Laurent, *Université Lille Nord de France, Faculté des Sciences Pharmaceutiques et Biologiques, Lille, France*
89. Ata Martin Lawson, *UFR des Sciences & Techniques de l'Université du Havre, Le Havre, France*
90. Mircea Leabu, *University of Medecine and Pharmacy Carol Davila, « Victor Babes » National Institute of Pathology, Bucharest, Romania*
91. Marie Leman, *Ecole des Hautes Etudes d'Ingénieur, Lille, France*
92. Amélie Lemoine, *Institut de Chimie Pharmaceutique Albert Lespagnol, Lille, France*
93. Emmanuelle Lipka, *Université Lille Nord de France, Laboratoire de Chimie Analytique, Lille, France*
94. Virginie Lucas-Andrzejak, *Institut de Chimie Pharmaceutique Albert Lespagnol, Lille, France*
95. Liliana Lucescu, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
96. Maria-Andreea Lungan, *"Gheorghe Asachi" Technical University of Iaşi, Faculty of Chemical Engineering and Environmental Protection, Iaşi, Romania*
97. N. C. Lungu, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
98. Cătălina-Elena Lupuşoru, *"Gr. T. Popa" University of Medicine and Pharmacy, Department of Pharmacology, Faculty of Medicine, Iasi, Romania*
99. Roxane Mansouri, *Institut de Chimie Pharmaceutique Albert Lespagnol, Lille, France*
100. Maria Marinescu, *University of Bucharest, Faculty of Chemistry, Bucharest, Romania*
101. Patricia Melnyk, *Université Lille Nord de France, UDSL, UFR Pharmacie, Lille, France*
102. Meribai, *Université Es'Senia, Orna, Algérie*
103. Faten Mezni, *National Institute for Researches on Rural Engineering, Water and Forests, Tunisia*
104. Régis Millet, *Institut de Chimie Pharmaceutique Albert Lespagnol, Lille, France*
105. Anca Miron, *"Gr. T. Popa" University of Medicine and Pharmacy, Faculty of Pharmacy, Iasi, Romania*
106. V. Moas, *Université Lille Nord de France, UDSL, UFR Pharmacie, Lille, France*
107. D. Mouatssem, *Centre Universitaire Bordj Bou Arreridj, Algérie*
108. Giulio G. Muccioli, *Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium*
109. Boubakeur Nadjemi, *Ecole Normale Supérieure, Kouba, Algérie*
110. Hiroyuki Nakamura, *Department of Chemistry, Faculty of Science, Gakushuin University, Tokyo, Japan*
111. M'hamed Nasri, *Ecole Normale Supérieure, Kouba, Algérie*
112. ThiHuu Nguyen, *Université Lille Nord de France, UDSL, UFR Pharmacie, Lille, France*
113. Manuela Nistor, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
114. Abdallah Noui, *Institute of Agricultural Sciences, University Hassiba Benbouali Chlef, Algeria*
115. Ovidiu Novac, *"Gh. Asachi" Technical University, Iasi, Romania*
116. Ana-Maria Oprea, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
117. K. Ouali, *Department of biology, Badji Mokhtar Annaba University, Algeria*
118. Souhila Oudir, *Ecole des Hautes Etudes d'Ingénieur, Lille, France*
119. Mircea Nicolae Palamaru, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*

120. Daniela Pamfil, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
121. Oana Maria Păduraru, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
122. Pyotr Petrenko, *Institute of Applied Physics, Academy of Sciences of Moldova, Chisinau, Republic of Moldova*
123. Catalin Pintiala, *UFR des Sciences & Techniques de l'Université du Havre, Le Havre, France*
124. Ioan Plesca, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
125. Donald Poirier, *Oncology and Molecular Endocrinology Research Centre, CHUL Research Centre and Université Laval, Québec City, Canada*
126. Marcel Popa, *"Gheorghe Asachi" Technical University of Iaşi, Faculty of Chemical Engineering and Environmental Protection, Iaşi, Romania*
127. Lenuta Porfire, *"Gr. T. Popa" University of Medicine and Pharmacy, Iasi, Romania*
128. Guillaume Pousse, *Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette, France*
129. Popuşoi Ana, *Moldova State University, Chisinau, Republic of Moldova*
130. Rodica Postolachi, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
131. Mircea Preda, *Department of Chemistry, University of Craiova, Craiova, Romania*
132. Aurel Pui, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
133. Stefania Racovita, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
134. Cristina Rambu, *'USAMV, "Ion Ionescu de la Brad", Iasi, Romania*
135. Nicolas Renault, *Université Lille Nord de France, Faculté des Sciences Pharmaceutiques et Biologiques, Lille, France*
136. Benoît Rigo, *Ecole des Hautes Etudes d'Ingénieur, Lille, France*
137. Hala F. Rizk, *Faculty of Science, Tanta University, Tanta, Egypt*
138. N. Serradji, *Université Paris Diderot, Sorbonne Paris Cité, Paris, France*
139. Robu Stefan, *Moldova State University, Chisinau, Republic of Moldova*
140. Jolanta Rousseau, *Unité de Catalyse et Chimie de Solide, Université d'Artois, Béthune, France*
141. Valeriu Rudic, *State University of Medicine and Pharmacy „N. Testemitanu", Chisinau, Republic of Moldova*
142. Abdelkader Saadi, *Faculty of Science, University Hassiba Benbouali Chlef, Algeria*
143. Raoul Bogdan Sandu, *"Gr. T. Popa" University of Medicine and Pharmacy, Iasi, Romania*
144. Artur Sargun, *Moldova State University, Chisinau, Republic of Moldova*
145. Nicolas Sergeant, *Université Lille Nord de France, Inserm U837, Jean-Pierre Aubert Research Center, Lille, France*
146. Larisa Sofroni, *Oncological Institute of Moldova, Chisinau, Republic of Moldova*
147. Sébastien Soriano, *Université Libre de Bruxelles, Bruxelles, Belgium*
148. Vivien Stocker, *Ecole des Hautes Etudes d'Ingénieur, Lille, France*
149. Simona Ştefanovici, *'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Iasi, Romania*
150. Ismail Muftah Taban, *Faculty of Pharmacy, Seventh October University, Misurata, Libya*
151. Fulga Tanasa, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
152. Liliana Tarțău, *"Gr. T. Popa" University of Medicine and Pharmacy, Department of Pharmacology, Faculty of Medicine, Iasi, Romania*
153. Aurélien Tourteau, *Institut de Chimie Pharmaceutique Albert Lespagnol, Lille, France*
154. Victor Tsapkov, *Moldova State University, Chisinau, Republic of Moldova*
155. Gladiola Țântaru, *"Gr. T. Popa" University of Medicine and Pharmacy, Faculty of Pharmacy, Iasi, Romania*
156. Bénédicte Vanteghem-Oxombre, *Université Lille Nord de France, UDSL, UFR Médecine, Lille, France*
157. Cornelia Vasile, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
158. Silvia Vasiliu, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
159. P. Verbeke, *Université Paris Diderot, Sorbonne Paris Cité, Paris, France*
160. Liliana Verestiuc, *"Gr. T. Popa" University of Medicine and Pharmacy, Faculty of Medical Bioengineering, Iasi, Romania*
161. Patrick Vermersch, *Université Lille Nord de France, UDSL, UFR Médecine, Lille, France*
162. Philippe Verwaerde, *AlzProtect, Lille, France*
163. Marin Zagnat, *Faculty of Medical Bioengineering, University of Medicine and Pharmacy, Iasi, Romania*
164. Madalina Zanoaga, *"Petru Poni" Institute of Macromolecular Chemistry, Iasi, Romania*
165. Irina Zarafu, *University of Bucharest, Faculty of Chemistry, Bucharest, Romania*
166. Elena Zariciuc, *State University of Medicine and Pharmacy „N. Testemitanu", Chisinau, Republic of Moldova*
167. Christina Zălaru, *University of Bucharest, Faculty of Chemistry, Bucharest, Romania*
168. Nafila Zouaghi, *Ecole Normale Supérieure, Kouba, Algérie*