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Abstracts

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- **Prof. dr. Benoît Rigo** - Responsable Pharmacochimie, École des Hautes Etudes d'Ingénieur, Lille, FR

C1. From microtubule-interacting agents to dual molecules acting on proteins farnesyltransferase and tubulin

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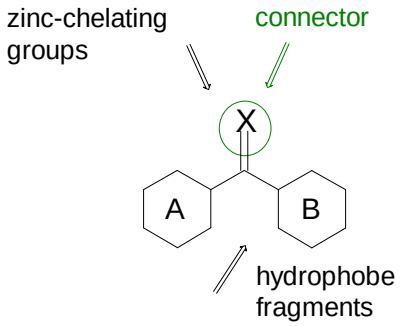
After cardiovascular diseases, cancer is the second cause of mortality in the world. Thus, it is necessary to study this disease and discover new anticancer drugs. Among others, we are principally interested in melanoma treatment.

We have just developed several new dual inhibitors, drug-hybrids FTis / MTis, active molecules on farnesyltransferase (FTase) and on tubulin polymerization (Figure 1). Their biological potential on both interest proteins (FTase and tubulin), on 60-cell line panel and on hybrid endothelial cells has already been confirmed. It is now necessary to deepen the knowledge of concerned chemical families and consequently, the project is focalized first on the design, the synthesis, the biological evaluation of new drug-hybrids FTis / MTis, and then the selection of the most interesting dual inhibitors in order to investigate their antitumor activity in vivo, their antivascular potential, and their ADME-Tox properties.



Structure of new mixtes inhibitors FTI / MTI currently developped

Figure 1.

Acknowledgements: This work was supported by a grant of the Romanian Ministry of Education, CNCS-UEFISCDI, project number PN-II-RU-PD-2012-3-0426. We gratefully acknowledge the National Cancer Institute (NCI) for biological evaluation of compounds on their 60-cell panel.

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C2. Tandem/Domino Processes Involving Simple Cationic Species which Target the Heterocyclic Diversity with Great Biological Potential

Adam Daïch, Prof.

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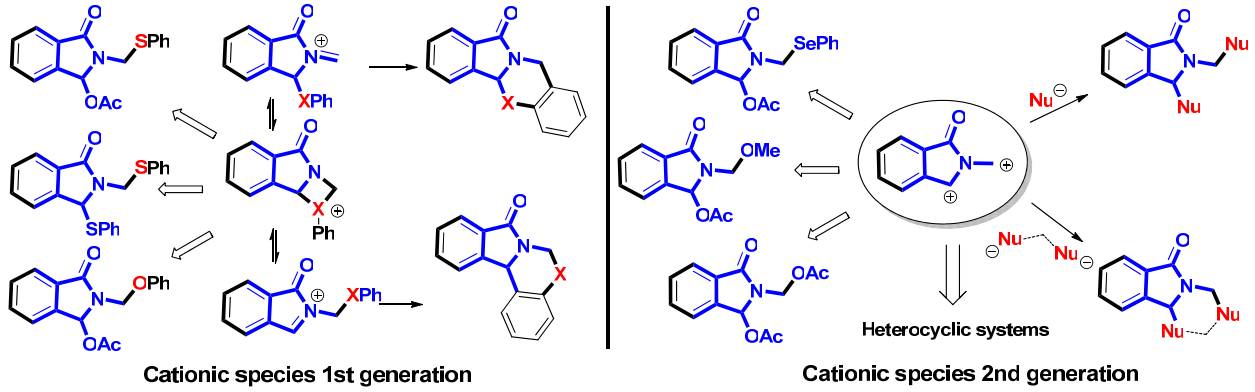
One of our major research areas consists of the development of new synthetic approaches potentially useful in organic and bio-organic chemistry. In this type of activity, the Hazard is omnipresent and the events, unexpected, often bring new perspectives.

The synthetic methodologies we develop in our group since many years now have for heart the formation of *N*-acyliminiums cations, as stable species which generated generally in acid medium.[*] These cationic intermediates, derived from racemic or chiral imides by regioselective reduction, are trapped in an intermolecular or intramolecular manner by diverse types of nucleophiles including heteroatoms such as O, S, Se and N. This provide, after an ultimate functional arrangements, new structures based on new, simple, original and effective processes.[†,‡]



Our general approach consists on aiming the molecular skeletons of pharmaceutical interest sensibly selected for their biological evaluations. In addition, the choice of the target molecules is closely linked to that of the collaborators or mutually depending on the case.

In this presentation, the illustration of these processes comes through few major applications which we shall present. Also the main factors pivotal during these reactions as well as the synthetic and mechanistic aspects will be presented and discussed.

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C3. A Brief History of AMPA Receptors Potentiators

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The amino acid L-glutamate is the major excitatory neurotransmitter in the brain and it plays a major role in learning and memory processes. Two distinct families of L-glutamate receptors have been described: the ionotropic - ligand-gated ion channels – iGluRs, and the metabotropic - G-protein-coupled receptors - GPCRs. Following their sensitivity to selective agonists, iGluRs have been sub-divided into three classes: AMPA, NMDA and kainate receptors.

Reports early ‘90s indicated that molecules reducing the desensitization of AMPA receptors through a positive allosteric modulation may be useful agents in the treatment of CNS disorders characterized by learning and memory impairments such as Alzheimer disease, Parkinson disease, schizophrenia or depressive disorders. Compounds belonging to two distinct chemical classes have been described: the benzamides early represented by aniracetam, and the benzothiadiazines early represented by cyclothiazide and IDRA21. From these starting points lots of successors have been developed by several pharmaceutical companies such as Cortex, Eli-Lilly, Organon, GSK, Pfizer, Servier.

A huge amount of work was done at Servier around benzothiadiazine structures: compound S 18986 entered the clinic late ‘90s but was finally discontinued. The next generations of compounds provided several preclinical candidates. Among them, a large series of original pyrido-, thieno- and benzothiadiazines has been developed in collaboration between the Servier Research Institute in France and Liège University in Belgium. The present communication will be focused on the medicinal chemistry around the benzothiadiazine derivatives – design, synthesis, *in vitro* and *in vivo* evaluation, structure-activity relationships.

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C4. Green access to heterocycles: aqueous media or solventless reactions?

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Today, green chemists and medicinal chemists closely cooperate to develop reactions not only chemo-, regio-, stereo-and enantio-controlled, but also economic and environmentally friendly. The development of novel, simple and cleaner synthetic protocols through the valorization of biomass, the use of catalytic process as well as alternative media ranks among the most important green chemistry principles. Among them, organic reactions in aqueous media and mechanochemistry have attracted much recent attention.

Water is one of the most abundant, cheapest, and environmentally friendly solvents. The discovery of new reagents and catalysts for the production of novel transformations or make a classic reaction more efficient is a very promising area of research. In the last two decades, native and modified cyclodextrins (CD) have been used as nano-reactors in various organic reactions as oxidation, addition, hydrolysis and even more recently in multicomponent cyclisation reactions in water. Furthermore, these supramolecules are inexpensive natural cyclic oligosaccharides. CD can be recovered and reused in subsequent reactions without loss of activity.

One of the main challenges in medicinal chemistry is the design and synthesis of biologically active molecule which calls for clean procedures avoiding the use of harmful organic solvent.

We will discuss herein, a new and efficient catalytic protocol to synthesize various heterocycles using (β-CD) as organocatalyst and also as mass transfer agents in aqueous biphasic conditions. In the second time we will report green alternative for access to heterocyclic compound in solvent less condition by means of mechanochemistry.

Acknowledgements

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C. Rousseau, J. Rousseau, S. Menuel, E. Vaiciunaite, L. Akelis, J. Dodonova, S. Tumkevicius, E. Monflier Green Chem. 2014 (submitted).

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C5. 1,1-Diarylethylenes synthesis: A platform for discovery in chemistry and biology

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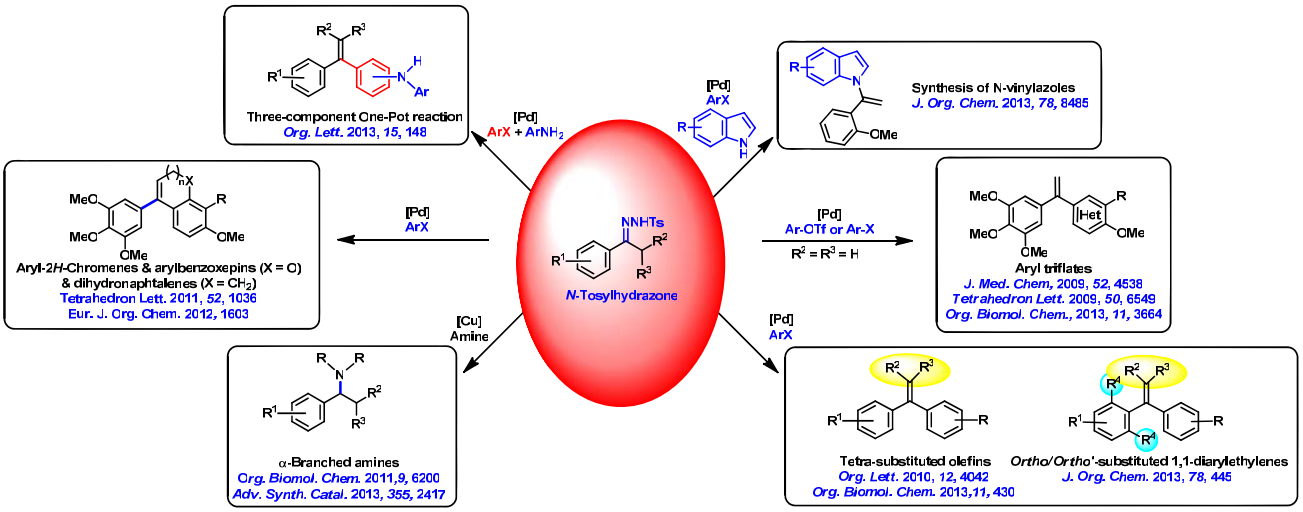
http://www.biocis.u-psud.fr/?-HAMZE-Abdallah-Associate-professor-

Since 2007, we have particularly studied the reactivity of N-tosylhydrazones as intermediates in reactions catalyzed by transition metals (Pd and Cu). These tosylhydrazones, generating in situ metal carbenes are likely large synthetic applications, as we have already shown (see scheme below).[1] The advantage of these methods over conventional couplings lies in the fact that the organometallic compound is no longer used in stoichiometric amount. Under this method, various poly-substituted alkenes are prepared in a convergent way. A chemical library of olefinic compounds has been established and tested for their tubulin polymerization inhibition and cytotoxic activities. These results will be presented here.



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C6. Non-viral vectors for gene therapy

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Gene therapy is one of the most outstanding challenges in modern medicine, and consequently, in the last decade, extensive studies were performed mainly in the field of replacement of defective genes with fully functional copies. In this respect, the nucleic acids chains to be inserted into the cells are generally incorporated into engineered viral or non-viral vectors[i]. Non-viral vectorization of DNA has certain advantages against viral methods, including the ability of large scale production and the simplicity of use, besides the decrease of the occurrence of undesirable immune response. This is why non-viral carriers are of actual interest, and are developed preferentially[ii].

Polyethylene imine (PEI) is one of the most investigated polycation as transfectant entity, due to its abundantly positive charged amine groups. PEI molecule itself, although very effective in DNA packaging and release, shows a high cytotoxicity when tested in cell cultures. Therefore it is aimed to conjugate PEI with various molecules in order to enhance the transfection efficiency in parallel with the cell viability. Biodegradability represents another severe issue, when the biological functionality of the cells must be preserved *in vivo*. The transfection efficiency of PEI is depending on its molecular weight: PEI with molecular weight less than 2 kDa has been proved to be non-toxic, while those in the range 5÷25 kDa are more suitable for gene transfer, although an increased cytotoxicity became inherent. A convenient strategy to increase transfection efficiency and to simultaneously decrease the cytotoxicity was found to be the coupling of low molecular weight PEIs (maximum 2 kDa) together, to form conjugates of 14÷30 kDa.[iii] In the context of the above mentioned theory, the present study demonstrate a pathway to synthesize dendrimer-like compounds containing hyperbranched low molecular weight PEI placed around different cores, such as fullerene C60 or β-cyclodextrin. To reduce the potential cytotoxicity of PEI and simultaneously to increase the biocompatibility of the transfectant carrier, PEG chains were also introduced. EYFP plasmid was used to evidentiate the gene transfer mediated by the synthesized carriers.

Acknowledgements: This work was supported by the PNII-PCCE-ID-2011-2-0028 project.

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C7. Heterocycles of Medicinal Interest from Conjugated Alkynones

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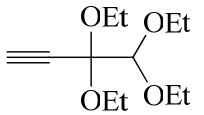
Ring opening of 1,1-dibromo-2-chloro-2-ethoxycyclopropane gives 3,3,4,4-tetraethoxy-1-butyne (TEB) (**1**) as the only product in very good yield [1,2]. This acetylene is very densely functionalized, and by taking advantage of the chemical properties of the various functional groups, a variety of compounds have been synthesized [4-7].

We are currently investigating the reactivity of derivatives of **1**, *e.g.* **2** and **3** [Z = H, Bn, Bz, RC(O), SiR_3], towards a range of mononucleophiles and bisnucleophiles. These studies have resulted in a number of new products, and in the lecture the focus will be on syntheses of a variety of heterocyclic compounds which have been prepared in a regiospecific fashion and in very good yields.



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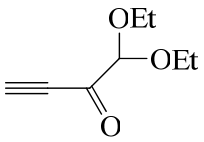

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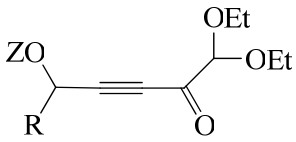

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C8. Macrocycles, porous polymers and self-assembled aggregates with potential applications in Medicinal Chemistry

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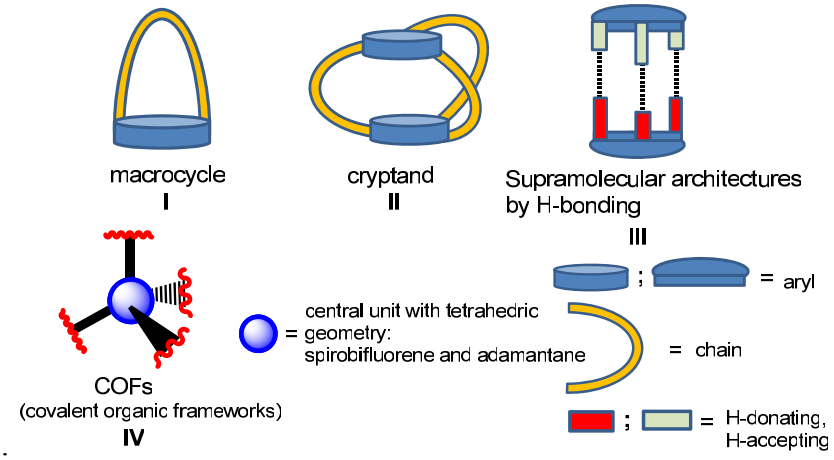
The synthesis of various macrocycles (I) and cryptands (II) exhibiting phenothiazine, thiophene, triazine or tris(1,3-dioxan-2-yl)benzene units was carried out using classic procedures for macrocyclization reactions (etherification, esterification, acetylenic coupling) but also by an original method based on the Suzuki-Miyaura cross-coupling reaction (Scheme 1).

The formation of supramolecular aggregates by hydrogene bonding (III, Scheme 1) starting from di- and tripodands exhibiting triazine, tris(1,3-dioxan-2-yl) or bicyclo[3.3.1]nonane central units and pendant arms decorated with H-donating and H-accepting groups were revealed by single crystal X-ray diffractometry, mass-spectrometry and NMR methods.

Porous polymers (IV, Scheme 1) showing a tridimensional structure based on tetraphenyladamantane or spirobifluorene units were obtained by acetylene coupling or Sonogashira cross-coupling reactions. These polymers revealed large specific surfaces (300-1000 m^2/g) and high absorption properties.



Scheme 1

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C9. White Biotechnology: A tool for Medicinal Chemistry and Pharmaceutical Development

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The Pharmaceutical Development of a Drug Product is a long and extremely costly process. Unfortunately, this process is unlikely to get any easier, as more and more stringent regulations are imposed on the perilous road to obtaining Product Licences.

An answer to overcoming such difficulties may lie in the application of white biotechnology (biotransformations and biocatalysis). Difficult steps, or low-yielding reactions, may be simplified thus leading to major gains in overall selectivities and yields.

We herein present a range of examples whereby different reactions of special interest have been made possible through the application of biotransformations and biocatalysis.

In our group we use the "Microbial Model of Drug Metabolism" to access the synthesis of drug metabolites. Such metabolites are usually formed during the *in vivo* enzymatic transformations of their parents drugs and may often exhibit different toxicities or pharmacological activities. Their isolation and purification however remains time-consuming and therefore highly costly. Microbial biotransformation offers a convenient way of obtaining such metabolites in a clean and cost-effective manner. Such reactions may also allow the metabolite to be isolated in large quantities, thus facilitating their characterisation and use in further studies.

We shall therefore discuss some cases whereby the use of biotransformations has helped to generate new functionalised molecules as NCE or scaffolds for generating NCE allowing easy access to "chemical biodiversity".

As well as being applied, white biotechnology may also be exploited to obtain API's intermediates.

As active pharmaceutical ingredients (APIs) become increasingly more sophisticated, the Pharmaceutical Chemist needs to come up with ever-more effective synthetic strategies to produce these substances. Classical organic synthetic approaches, whether linear or convergent, often limit the availability of material for subsequent steps due to poor yields and/or over-complicated reactions. Here we will present a "case study" from a marketed drug.

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C10.1. Conformationally Constrained Analogs of 4-Oxo-1,4-dihydroquinoline-3-carboxamide: Medicinal Chemistry Approach Leading to the Discovery of the First CB_2 Cannabinoid Receptor Agonist Orally Active Against Experimental Colitis.

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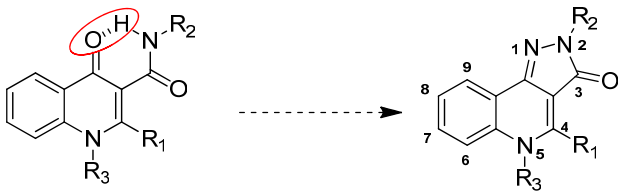
Inflammatory bowel disease (IBD) represents a group of chronic inflammatory lesions of unknown etiology that affect the digestive tract. The CB2 cannabinoid receptor emerged as a promising therapeutic target in the treatment of these pathologies. Indeed, this GPCR has been identified within the gastrointestinal tract and plays a key role in the regulation of intestinal inflammation. Additionally, the CB2 receptor agonists have been shown to exert an anti-inflammatory effect both in intestinal epithelial cells and in experimental models of colitis in mice. In vitro experiments highlighted that CB2 receptor activation results in suppression of the release of pro-inflammatory cytokines. Data from in vivo studies emphasized the importance of this receptor in mediating protection against experimental colitis.

Our groups previously described a series of 4-oxo-1,4-dihydroquinoline-3-carboxamide as selective ligands of the CB2 receptor. One of the commonly used strategies in drug design to increase affinity and selectivity of a given "flexible" lead for its pharmacological target is to conformationally constrain it to mimic the so-called bioactive conformation. Therefore, we designed constrained analogues of the 4-oxo-1,4-dihydroquinoline-3-carboxamide series based on a 2*H*-pyrazolo[4,3-*c*]quinolin-3(5*H*)-one scaffold.



The present study shows that 2*H*-pyrazolo[4,3-*c*]quinolin-3(5*H*)-ones are potent and selective CB2 agonists. The rigidification approach applied resulted in increased affinity for the CB2 receptor but also improved the selectivity over the CB1 receptor, while not altering the functional activity. ALICB459, the lead of this series, exerts a very strong protective effect in the experimental model of TNBS-induced colitis. This effect was achieved after oral administration and was shown to be dose-dependent.

C10.2. 3-Carboxamido-5-aryl-isoxazoles: new CB_2 agonists and FAAH inhibitors for the treatment of colitis

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The endocannabinoid system (ECS) includes two G-protein-coupled receptors (CB_1 and CB_2), endogenous ligands, named endocannabinoids, and several biosynthesis and degradation enzymes as the fatty acid amide hydrolase (FAAH) or the monoacylglycerol lipase (MAGL)).[1-3] The modulation of the ECS through the activation of cannabinoid receptors and the inhibition of degradation enzymes consists in a promising therapeutic strategy. Indeed, this system has shown beneficial effects in several diseases like osteoporosis,[4] pain[5] or chronic inflammation disorders.[6]

More specifically, the ECS is implicated in gut homeostasis, gastrointestinal motility and Inflammatory Bowel Diseases (IBD).[7-8] These diseases, which two main forms are Crohn's disease and ulcerative colitis, affect more than 2.2 million people in Europe and are characterized by an inflammation of the gastrointestinal tract due to a hyperactivity of the immune system. Recently, it has been demonstrated that cannabinoid receptors are overexpressed *in vivo* and in patients suffering from IBD.[7-9] The beneficial role of CB_2 in intestinal inflammation has been highlighted in several *in vivo* and *in vitro* studies.[10-13] Moreover, the genetic invalidation of FAAH in animals with 2,4-dinitrobenzene sulfonic acid (DNBS)-induced colitis significantly reduced tissue inflammation.[14] It has also been showed that URB597, a FAAH inhibitor, increased survival and decreased inflammation in mice suffering from trinitrobenzene sulfonic acid (TNBS)-induced colitis.[15-16]

According to the implication of the endocannabinoid system in IBD, we decided in our laboratory to develop selective CB_2 agonists and FAAH inhibitors to treat these diseases. 3-carboxamido-5-aryl-isoxazoles designed as CB_2 agonists were evaluated for their FAAH inhibition activity.[17] The pharmacological results led to identify structure–activity relationships enabling to switch cannabinoid response from CB_2 agonists to FAAH inhibitors. Two compounds were selected for their FAAH and/or CB_2 activity, and evaluated in a colitis model for their anti-inflammatory activity. Results showed that these compounds inhibit the development of DSS-induced acute colitis in mice and then, are interesting leads to explore new drug candidates for IBD.

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C11. Séparation chirale par chromatographie en phase supercritique

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Un grand nombre de molécules pharmaceutiques comportent un ou plusieurs centres d'asymétrie donnant naissance à des énantiomères aux propriétés pharmacologiques différentes. Depuis le drame socio-sanitaire de la Thalidomide®, une attention particulière a été portée sur la chiralité. Aujourd'hui chaque isomère doit faire l'objet d'une étude pharmaco-toxicologique complète au cours de son cycle de développement. La synthèse asymétrique est le premier moyen d'obtention de ces énantiomères. Cependant elle présente plusieurs inconvénients : elle ne génère qu'un seul isomère à la fois, le risque de racémisation est important et cette voie est longue, fastidieuse et couteuse. Les techniques chromatographiques préparatives se sont alors développées comme alternative à la synthèse. La plus connue est la Chromatographie Liquide Haute Performance (CLHP), mais depuis quelques années elle tend à être détrônée par la Chromatographie en Phase Supercritique (CPS) qui met en œuvre, comme phase mobile, un fluide porté au-delà du point critique par un contrôle adéquat de la température et de la pression, le plus souvent du dioxyde de carbone (CO_2). La CPS possède des caractéristiques propres, liées aux propriétés des fluides supercritiques, à savoir une masse volumique comparable à celle d'un liquide, associée à une plus faible viscosité et une grande compatibilité avec les détecteurs de la Chromatographie en Phase Gazeuse (CPG) et de la CLHP, qui en font une technique très performante :

- des sélectivités importantes sont observées en raison des interactions entre les solutés, la phase stationnaire et la phase mobile que l'on peut faire varier par l'ajout de faibles quantités (< 30%) de modificateurs organiques, polaires (méthanol, acétonitrile) ou apolaire (heptane) à la phase supercritique ;
- la CPS, du fait qu'elle utilise majoritairement du CO_2, atoxique, comme phase mobile à la place des solvants organiques généralement utilisés en CLHP, est une technique «verte». En effet, le CO_2 peut être recyclé et purifié pour les applications à l'échelle préparative, grosses consommatrices de solvants ;
- la CPS préparative présente, par ailleurs, l'avantage de permettre une récupération des solutés par simple détente de la phase mobile, les seules traces de solvants résiduels provenant des additifs polaires éventuellement ajoutés.

Une approche préparative [1] puis une approche analytique de cette nouvelle technologie, plus écologique et plus rapide, à l'interface entre la CPG et la CLHP feront l'objet de cette présentation. Elle concernera l'étude de deux candidats médicaments ayant respectivement pour cible : un récepteur purinergique nouvellement identifié d'intérêt pharmacologique dans le traitement des Maladies Inflammatoires Chroniques de l'Intestin, et un récepteur couplé à une protéine G potentiellement impliqué dans le traitement du diabète.

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C12. Biological Activity of Some New Azaheterocycles

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Azaheterocycles are invaluable compounds demonstrating fascinating potential applications for medicine, opto-electronics, agriculture, etc.

As part of our ongoing research in the field of biologically active compounds with azahetrocycle skeleton, we report here the design, synthesis, structure and biological activity of some new fused and non -fused five and six member ring azaheterocycles. The syntheses were straight and efficient and were performed under microwave (MW) and ultrasound (US) irradiation as well as under conventional thermal heating (TH). A rational drug design was performed and show us that some certain fused and non -fused five and six member ring azaheterocycles are potential antimicrobials (antibacterial, antifungal and antimycobacterial), anticancer and grow up plant regulators.

Concerning the antibacterial and antifungal of our azaheterocycles, the obtained results show us that some compounds have a remarkable activity against Gram positive germs, very good activity against some Gram negative germs and fungus, comparative with standard drugs; in some cases the results were spectacular. The primary cycle high throughput screening reveals that several compounds are potent inhibitors against Mycobacterium tuberculosis, their antitubercular activity being superior to the second-line antitubercular drug Pyrimethamine and equal to Cycloserine. The MIC, MBC, LORA, intracellular (macrophage) drug screening, and MTT cell proliferation, indicate the intracellular drug effectiveness against Mtb of these compounds, the lack of toxicity, a significant activity against both replicating and non-replicating Mtb and, a bactericidal mechanism of action.

The anticancer activity against of some fused and non -fused five and six member ring azaheterocycles was tested against HeLa cell lines and against an NCI 60 human tumour cell line panel. Comparative with standard drugs, some of the tested compounds proved to have an excellent antitumor activity against HeLa cell lines and against Non-Small Cell Lung Cancer NCI-H460, Leukemia MOLT-4, Leukemia CCRF-CEM and Breast Cancer MCF7. Feasible explanations for anticancer efficiency of our azaheterocycles derivatives have been furnished, being correlated with the mechanisms of action. SAR correlations have been done.

The effect of some fused and non -fused five and six member ring azaheterocycles on germination and seedling growth was investigated. The tested compounds exhibited a general stimulating activity on the hypocotyls growth, especially at lower concentrations. A possible relationship between structure and biological activity are mentioned.

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O1. Tricyclic flavonoids with 1,3-dithiolium substructure: Synthesis and antibacterial activity

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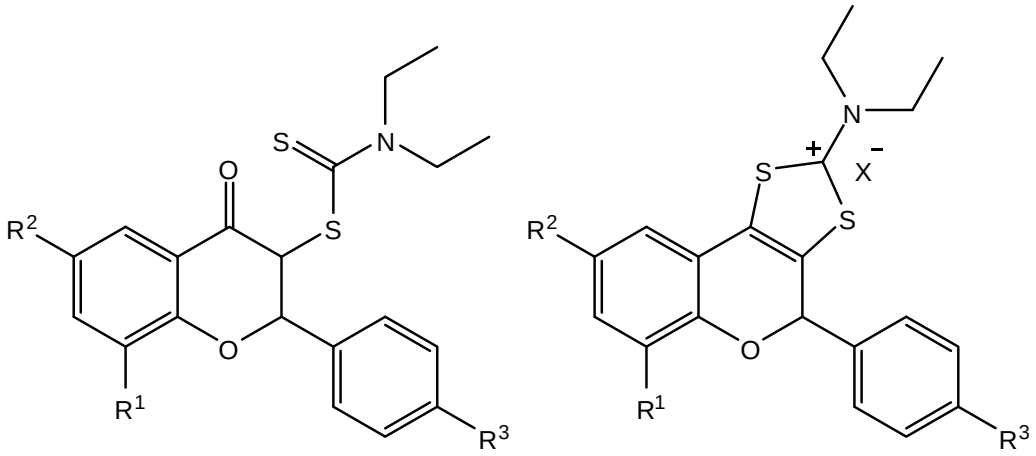
The synthesis of new 3-dithiocarbamic flavonoids has been accomplished by the reaction of the corresponding 2-hydroxyaryl dithiocarbamates with aminals. These flavonoids were obtained as a mixture of diastereoisomers, the *anti* isomer being the major one. The heterocyclization of these compounds provided a little known class of tricyclic flavonoids bearing a 1,3-dithiolium-2-yl ring fused at the 3,4-carbon positions of the benzopyran moiety.

Sulfur containing flavanones and tricyclic flavonoids were tested for antibacterial activity against *Staphylococcus aureus* ATCC 25923 (Gram-positive) and *Escherichia coli* ATCC 25922 (Gram-negative), using disc diffusion assay with gentamicin as reference and minimum inhibitory concentrations were determined where activity was found present.



While the tested flavanones did not yield the desired results, good antibacterial activities were recorded for the tricyclic flavonoids. The introduction of the 1,3-dithiolium cation produced results comparable to those of gentamicin and in some cases, MIC values were less than 1μg/ml.

The ion-dissociation *vs.* formation of a tight ionpair appears to be of significant importance on how cationic tricyclic flavonoids interact with bacteria. The major component of bacterial cell wall is represented by negatively charged phosphatidylethanolamine (70%). Thus, the positively charged 1,3-dithiolium flavonoids target the oppositely charged biological structures such as cell walls of microorganisms which leads to the leakage of intracellular substances.

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O2. A selective synthesis of quinolines *versus* enamines

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Cytotoxicity of 1,3,5-triazine derivatives is well known as, for example, hexamethylmelamine (HMM) (**1**) that was discovered as an effective agent against breast, lung and ovarian cancer,[1] but caused severe nausea and vomiting, and some structural analogues of **1** were prepared and tested.[2] Over time, numerous structural modulations of the HMM consisting in the substitution of dimethylamino groups with another moieties such as dialkylamino, aryloxy, alkyloxy-, alkylaryl- or cyclic amines, have been reported.[3] From these studies it was shown that nonsymmetrical substitution of s-triazine cycle and the replacement of the dimethylamino groups with methoxy units, maintained the antitumor potential. This was observed for compounds **2-5**.[2]

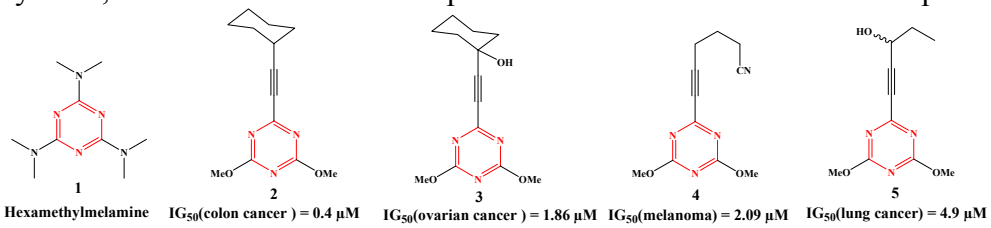
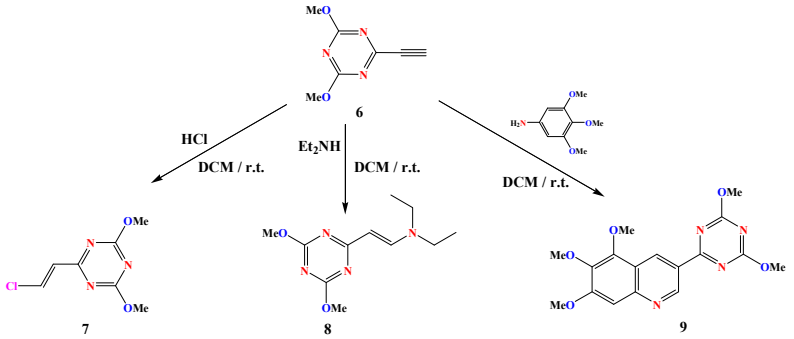


Figure 1. *Antitumoral s-triazine derivatives*

During the synthesis of 2-ethynyl-4,6-dimethoxy-1,3,5-triazine **6**, 2-((*E*)-2-chlorovinyl)-4,6-dimethoxy-1,3,5-triazine **7** was also isolated, as by-product issued from the addition of hydrochloric acid on the triple bond. This encouraged us to study the reactivity of compound **6** in the presence of primary and secondary amines. The reaction of **6** with a secondary amine has led us to the expected enamine **8**, but after the reaction with primary aromatic amine, bearing three methoxy groups, unexpected quinoline **9** has been isolated.



Scheme 1. *Reactivity of 2-ethynyl-4,6-dimethoxy-1,3,5-triazine*

Acknowledgment: This work was supported by the strategic grant POSDRU/159/1.5/S/137750, Project "Doctoral and Postdoctoral programs support for increased competitiveness in Exact Sciences research" cofinanced by the European Social Found within the Sectorial Operational Program Human Resources Development 2007 – 2013.

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O3. Sels de N-acyliminium et induction de chiralité

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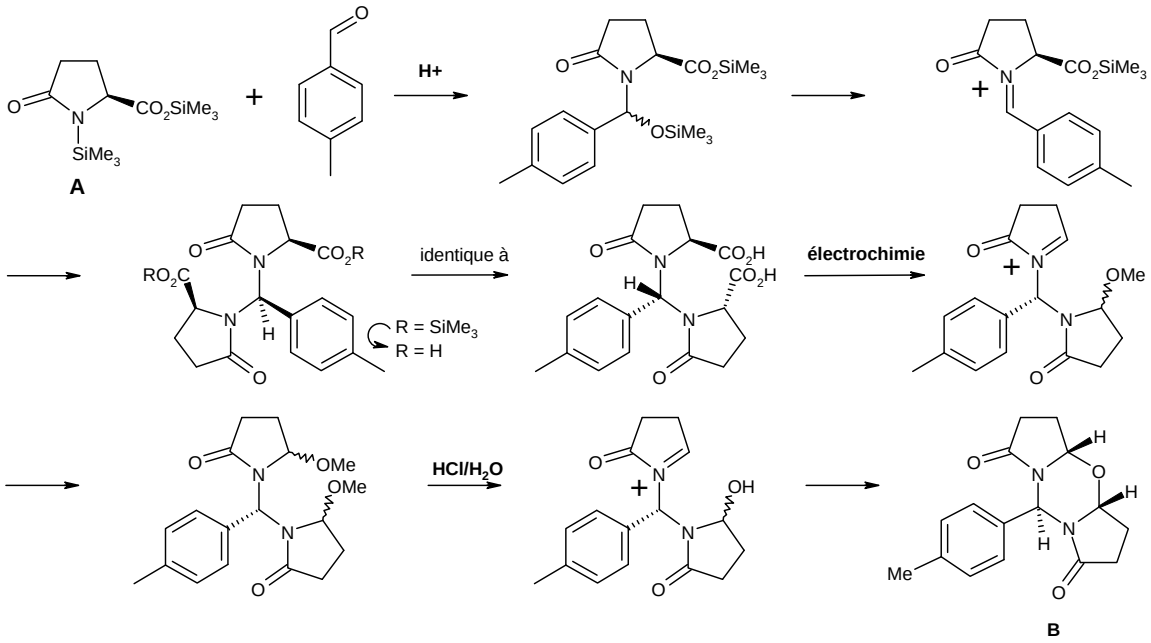
Les sels de N-acyliminium sont des cations plans. L'addition de nucléophiles sur ceux-ci conduit à des produits racémiques. Cependant, ils sont très sensibles aux contraintes stériques, et lorsqu'un centre d'asymétrie est présent, l'induction d'un nouveau centre chiral est possible.



La synthèse stéréosélective du composé B à partir de l'acide pyroglutamique disilylé A illustre cet aspect de la chimie des sels de N-acyliminium.

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O4. Persistent organic pollutants and their metabolites in human serum from obese children living in Eastern Romania

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Organohalogenated contaminants (OHCs), such as polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs), as well as brominated flame retardants (BFRs) were shown to be ubiquitous in the environment and humans. Contrarily to Western Europe where well-developed programs exist for the OHCs monitoring in humans, only limited information concerning the human exposure to such contaminants is available from Eastern European countries, such as Romania.[1] In the present study, we have evaluated the levels and profiles of several PCB congeners and their hydroxylated metabolites, polybrominated diphenyl ethers, and selected OCPs in obese versus normal weight children living in Galați, Eastern Romania.

Serum samples were collected from obese children visiting the Children Emergency Clinical Hospital "Sf. Ioan" Galati, Romania. These patients participate in a hospital monitoring program due to the diabetes mellitus pathology associated with obesity. Serum was sampled when children entered the monitoring program (N=47) while a control group (N=43) was randomly selected in a similar time interval (homogenously distributed for age and gender). Consistent with previous literature[2], due to body dilution, higher levels were measured for the control group when compared to obese children although the results were adjusted for the serum total lipids. Among the measured contaminants, from the PCBs, the most important in term of levels were CB 180, 153, 138, 187 and 170 congeners with a contribution up to 75% to the total PCB levels. DDTs were the most abundant contaminants from the OCPs, with DDE being measured at the highest levels. Our results corroborate the hypothesis that some endocrine disrupting chemicals might play a role in the occurrence of obesity. In case of weight loss programs will follow later for the obese children, given the lipophilic nature of such contaminants, the increasing internal exposure dose might interfere with the children development.

The results included in this study show the high exposure of Romanian population to these OHCs and therefore an extensive program for monitoring the contamination with OCPs, PCBs and BFRs in different Romanian environmental compartments becomes necessary in the light of adverse health effects reported for these contaminants.

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O5. Mass spectrometric based approaches for studying aggregation of ß-amyloid peptide

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Aging is a major risk factor for the neurodegenerative disorders such as Alzheimer's disease (AD) and the number of AD patients is increasing worldwide. The accumulation of fibrillar plaques of ß-amyloid peptide (Aß) in the brain have been recognized as characteristics of AD [1]. Although circular dichroism, atomic force microscopy, electron microscopy, light scattering were directed at understanding these molecules, the biological mechanism of protein aggregation remains to be achieved. Understanding how this peptide assembles will provide new targets for developing aggregation modifiers that could potentially limit their toxicity. In our work, we are investigating the aggregating Aß (1-40) peptide as model systems by using mass spectrometric based approaches.

Various protein footprinting strategies were employed to study oligomerization of different neurodegenerative peptides/proteins: high resolution MS in combination with affinity-biosensor system, H/D amide exchange, and FPOP (fast photochemical oxidation of proteins). FPOP [2] is a chemical footprinting method whereby exposed amino-acid residues are covalently labeled by oxidation with hydroxyl radicals produced by the photolysis of hydrogen peroxide. Modified residues can be detected by standard trypsin proteolysis followed by LC/MS/MS, providing information about solvent accessibility of various residues of the protein.

Here, we present the FPOP data of ß-amyloid (1-40) peptide during different aggregation times. Experimentally, to obtain the oligomeric conformation, Aβ(1-40) peptide was used right after dissolution in HFIP followed by dilution with PBS at a concentration of 20μM. From time to time the aggregating solution was exposed to hydroxyl radicals produced in FPOP experiment, followed by quenching, trypsin digestion and mass spectrometric measurements. Using Mathcad, a mathematic algorithm program, FPOP data gave us indications of every single amino acid modification within different times of Aβ aggregation process. We observed that several C-terminal amino acids were not exposed to the oxidation after 4 to 7 days of ß-amyloid (1-40) peptide incubation. Also we observed several ß-amyloid (1-40) amino acids having a high dynamic during the aggregation process.

Acknowledgements The financial support by the Romanian National Authority for Scientific Research, CNCS – UEFISCDI, project number PN-II-RU-TE-2011-3-0038 is gratefully acknowledged.

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O6. Synthesis and antimycobacterial properties of new derivatives of 1,7-phenanthroline

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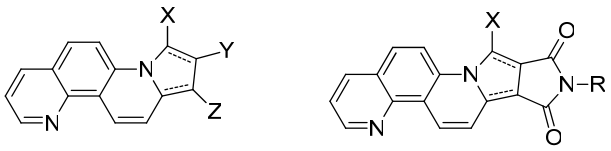
Human tuberculosis (TB), a contagious disease caused by *Mycobacterium tuberculosis* (Mtb), remains the leading infectious disease among humans, claiming approximately 1.8 million life's every year worldwide[1]. The association with HIV infection, and the emergence of multi-drug-resistant (MDR) and extensively drug-resistant (XDR) to Mtb, is a deadly synergistic factor for TB[2-4].

Phenanthrolines polycyclic skeletons are present in sterols, sex hormones, cardiac glycosides, bile acids and morphine alkaloids. While 1,10-phenathroline derivatives have been widely studied both for synthesis and applications, much less interest has been shown for the other phenanthrolines because of difficulties in their synthesis.

As part of our ongoing research aiming the synthesis of novel anti-TB compounds with azaheterocycles skeleton[5-6], we report here the design, synthesis, structure and *in vitro* antimycobacterial activity of new 1,7-phenanthroline derivatives.

Therefore, we synthesized new pyrrolo[1,2-*i*][1,7] phenanthroline derivatives *via* 3+2 cycloaddition reactions of the symmetrical and unsymmetrical dipolarophiles to the *in situ* generated cycloimmonium ylides from monoquaternary 1,7-phenanthrolinium salts. These salts were obtained by the reaction of 1,7-phenanthroline with halogenated ω-bromoacetophenone, α-bromoacetate or α-bromoamides. As dipolarophiles we used activated alkyne or alkene, achieving indolizines, tetrahydroindolizine or dihydroindolizine derivatives with polycyclic skeleton.



A selection of the new compounds was tested in order to determine their antimycobacterial activity against *Mycobacterium tuberculosis* (Mtb), and a study of antitumoral properties of part of the new compounds is underway.

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This work was supported by the strategic grant POSDRU/159/1.5/S/137750, Project "Doctoral and Postdoctoral programs support for increased competitiveness in Exact Sciences research" cofinanced by the European Social Found within the Sectorial Operational Program Human Resources Development 2007 – 2013.

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O7. Unexpected synthesis of new aza-indolizino-indolizines

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Due to the extent of cancer nowadays, the necessity to find a cure is constantly increasing. Two of the promising agents that inhibit cell growth are combretastatin A-4 and its analog, phenstatin, two molecules that target tubulin polymerization.[1,2] In order to increase the anticancer potency of these compounds, various chemical modulations have been made. Some of the structural modifications that have been shown to maintain good activity against cell proliferation involve the usage of phenothiazine derivatives.[3] Encouraged by these facts we have decided to synthesize new phenstatin and combretastatin analogs bearing the phenothiazine heterocycle. We also chose to use the indolizine moiety based on its various biological properties.[4] Therefore, the general structure of the desired compounds is presented in **Figure 1**.

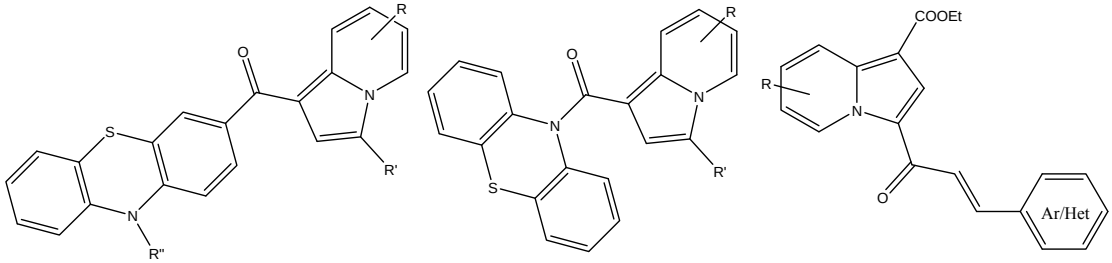

Figure 1.General structures of the target compounds

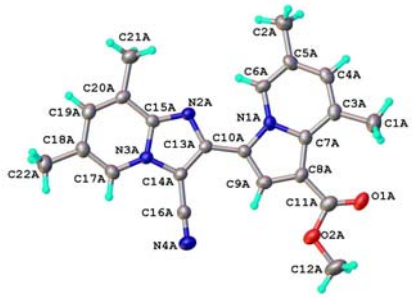

Figure 2. Structure of unexpected compound

The synthesis pathway for some indolizine derivatives provided an unexpected product. After investigating the molecule, we discovered a structure that possessed both an indolizine and a 1-aza-indolizine ring (**Figure 2**).
All synthesized compounds have been characterized (IR, ^{1}H and ^{13}C NMR). They were submitted for biological screening at NCI and they will be tested for their ability to inhibit tubulin polymerization.

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O8. The synthesis and characterization of new imino-chitosan biopolymeric films with antimicrobial properties

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[2] *"Ion Ionescu de la Brad" University, Laboratory of Antimicrobial Chemotherapy, 8, Aleea Sadoveanu, Iasi, Romania*

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The pathogen colonization on medical implants, medical indwelling devices or simply medical devices which come into contact with patients represents one of the most important problems from both the financial and medical point of view, the infections caused by microorganisms being the main postsurgical complication. To overcome this problem, the development of new and really efficient materials with antimicrobial properties received considerable attention over the last years. The use of chitosan, a natural biopolymer, for the development of such materials, brings many other advantages, among all, very important being its lack of toxicity and its biocompatibility.

The objective of this study was to obtain imino-chitosan biopolymer films with antimicrobial properties in order to apply them as thin layer protective systems for medical devices. The imino-chitosan films have been obtained by condensation of the chitosan amino groups with different aldehydes, in aqueous medium, followed by slowly water evaporation. FTIR spectra of the obtained films showed significant changes compared to the chitosan, indicating the obtaining of the imine bond but also modifications regarding the supramolecular structure.

Wide angle X-ray diffraction measurements confirmed the self-assembling of the imino-chitosan biopolymer chains based on hydrophobic-hydrophilic layering. Contact angle and surface free energy determination indicated a higher biocompatibility of the new biopolymers as compared to chitosan, while the microbiological screening demonstrated their self-defense properties against three common and virulent pathogen agents encountered in care-associated diseases.

It was concluded that the reversibility of imine bond promotes the self-assembling of the imino-chitosan biopolymer films into a lamellar morphology and, on the other hand, the slow release of the antimicrobial aldehyde in the microbiological culture.

Acknowledgements

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O9. Conception, synthèse et évaluation de l'efficacité de nouveaux stimulateurs de défense des plantes (SDPs)

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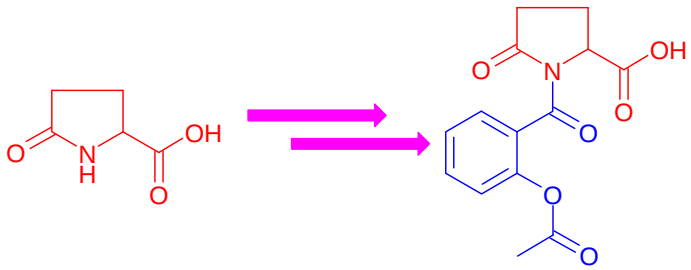
Les stimulateurs de défense des plantes (SDPs) sont des biomolécules agissant comme un « vaccin » sur la plante contre les bio-agresseurs, sans effet biocide direct. Les plantes possèdent en effet des mécanismes de défense naturels et intrinsèques qui sont activés en cas d'attaque par un bio-agresseur. Les SDPs sont des substances qui vont simuler ces signaux d'attaque, permettant ainsi à la plante de déclencher ses mécanismes de défense et donc de mieux résister en cas d'attaque réelle.[1,2]

La septoriose (*Septoria tritici*) est l'un des principaux bio-agresseurs du blé, pouvant détruire jusqu'à 40 % de celui-ci. La septoriose se reconnaît grâce aux taches présentes sur le feuillage. Elles peuvent être blanches et allongées ou brunes, de formes ovales ou rectangulaires. Au sein de ces taches, des pycnides noires (petits points noirs très visibles) sont présentes et caractéristiques de la maladie. Différentes méthodes de lutte peuvent être mises en œuvre pour limiter les contaminations par *Septoria tritici*.[3] Une alternative pour lutter contre cette maladie est basée sur l'utilisation de fongicides conventionnels, mais leur utilisation est de plus en plus controversée. Ainsi, il existe un besoin grandissant de méthodes de lutte alternative. Les stimulateurs de défense des plantes (SDPs) peuvent être une solution respectueuse de l'environnement et de la santé humaine.

Dans le cadre d'une nouvelle thématique de recherche dans le laboratoire à l'interface chimie-biologie, nous nous sommes investis dans la synthèse des composés qui présentent une activité SDP sur le pathosystème blé-septoriose. La recherche de nouveaux bioproduits efficaces vis-à-vis de la septoriose du blé en s'appuyant sur la chimie de l'acide pyroglutamique, matière première renouvelable, a été appliquée dans le cadre de ce projet.



Acide pyroglutamique — stimulateur potentiel de défense des plantes

Cinq composés ont été obtenus à partir d'acides carboxyliques via la chimie des dérivés silylés. Ces composés sont actuellement en évaluation biologique *in planta* (en serre).

Remerciements : Ce projet de recherche est soutenu par le Groupe HEI-ISA-ISEN, Lille.

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O10. Silylated assisted synthesis of aminals with potential microtubule-interacting properties

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[2]*Univ Lille Nord de France, F-59000 Lille, France*
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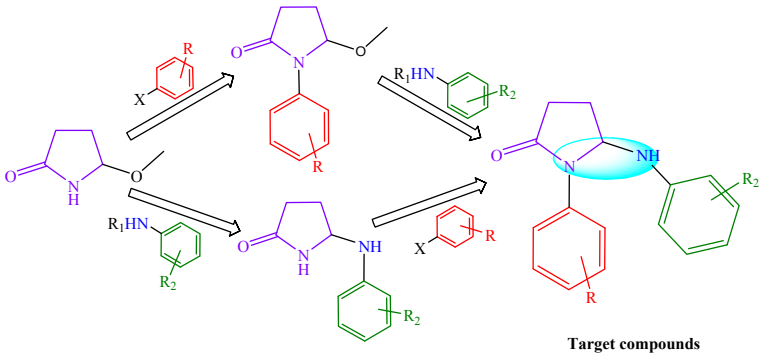
Alkylation of amines via oxidative Csp^3–H bond activations has been reported by many groups. However, most of the reagents were limited to amides, sulfonamides, azoles, or anilines with strong electron withdrawing-groups.[1–5] To the best of our knowledge, alkylation of anilines with Csp^3–H bonds adjacent to a nitrogen atom via oxidative C–H bond activation is rarely realized, although it has been achieved in tandem cyclization reactions.[6,7]

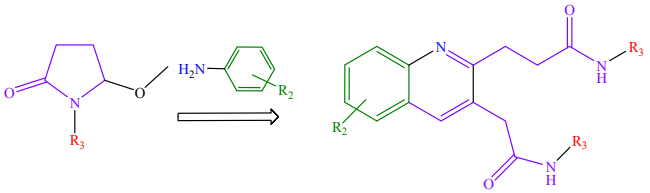
Recently, a new method for synthesizing acyclic aminals by the iron-catalyzed or copper-catalyzed Csp^3–H amination of lactams with arylamines under mild conditions was reported. However, in this papers the reactions with the anilines or the corresponding amines with electron-donating groups were not stable in this oxidizing reaction system.[8,9]

In the present paper, we describe the results for optimization of silylated assisted synthesis of *N,N*-aminals. General synthesis of the target compounds is represented in Scheme 1.



Scheme 1. General synthesis of the target compounds

Unpredictably, some of these reactions conducted us to the synthesis of quinoline derivatives (Scheme 2).



Scheme 2. Synthesis of new quinoline derivatives

Acknowledgment: This work was supported by the strategic grant POSDRU/159/1.5/S/137750, Project "Doctoral and Postdoctoral programs support for increased competitiveness in Exact Sciences research" cofinanced by the European Social Found within the Sectorial Operational Program Human Resources Development 2007 – 2013 (PhD scholarship G.-M. D.).

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P1. Pathophysiological oxidative protein modifications: nitration versus hydroxylation of tyrosine

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Nitration of tyrosine residues represents an oxidative post-translation modification in proteins. This occurs in physiological conditions and increases in several pathophysiological processes such as diabetes, chronic hepatitis, atherosclerosis, neurodegenerative disease, asthma and lung disease. Different *in vivo* pathways for tyrosine nitration are known in the literature, but peroxynitrite and heme peroxidase mediated modification are the most studied mechanisms.

In a previous proteomics study of sputum sample from patients with Cystic Fibrosis, the presumed nitrated proteins sites were investigated. While western blot analysis showed very low extend of protein nitration based on using anti-3-nitrotyrosine antibodies, the mass spectrometric data reveals novel oxidative protein modification, hydroxy-tyrosine containing peptide as endogenous modification [1].

In this study we have investigated the cross-reactivity of anti 3-nitro-tyrosine (NT) antibodies to nitrated/ hydoxylated tyrosine containing peptides. The peptides were synthesized by solid-phase peptide synthesis (SPPS), purified by reversed phase- high performance liquid chromatography (RP-HPLC), and characterized by electrospray (ESI) and matrix-assisted laser desorption-ionization (MALDI) mass spectrometry [2]. Binding affinities and specificities of synthetic peptides with different Tyr-modified sites were determined by using anti-nitrotyrosine antibodies in two immuno-analytical methods [3]. Dot blot analysis and surface acoustic wave biosensor (SAW biosensor) has been successfully applied for studying binding affinities and specificities of nitrated model peptides to a monoclonal anti-3NT-antibody. SAW technology in comparison with other immuno-analytical techniques was found to be a high performing tool for direct and rapid determinations of association/dissociation constants using only small amount of samples.

Acknowledgements

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P2. Design, synthesis, and biological evaluation of novel pyrrolidinone-bridged analogues of Combretastatin-A4

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

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Microtubule polymerization dynamics can greatly affect the ability of cells to change and maintain their shape and undergo critical processes such as cell signaling and mitosis.[1] Combretastatin-A4 (CA-4, I, Fig. 1) is one of the representative molecule of vascular disrupting agents that have been designed, synthesized, and tested in various biological models as potential therapeutic candidates for cancer treatment.[2,3] Research on combretastatin A-4 in order to improve its in vivo activity led to the discovery of phenstatin (II, Fig. 1).[4]

Modifications of the ethylenic bridge from CA-4 or carbonyl group from phenstatin have also led to diverse structural variations that maintain cytotoxic properties. Five-membered heterocycles have been shown to be appropriate isosters for the ethylenic bridge. Consequently, examples that include furanone (III),[5] isoxazole (IV),[6] imidazole (V),[7] triazole (VI),[8] thiazolone (VII), (Fig. 1)[9] have been reported in the literature.

Modifications made on the two phenyl rings led to hundreds of active compounds that possess desirable cytotoxicity while retaining varying degrees of antitubulin activities.[10] Recently, our research team reported phenstatin analogs with phenothiazine as an A-ring and different B-rings (VII, Fig. 1) in order to explore some structure–activity relationships in this new family of compounds.[11]

In order to develop this new family of compounds we have synthesized novel pyrrolidinone-bridged analogues of CA-4, with a phenothiazine A-ring (target compounds, Fig. 1).

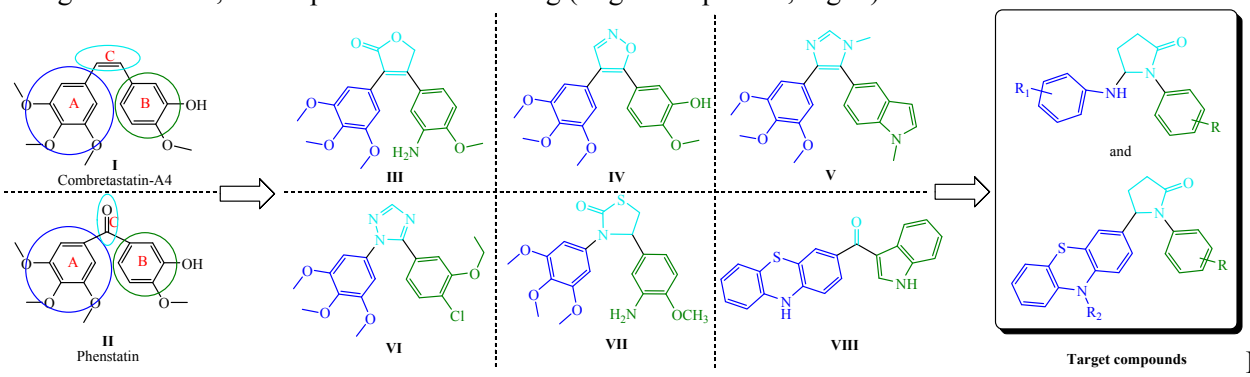

Figure 1. Analogues of Combretastatin-A4 and phenstatin

Acknowledgment: This work was supported by the strategic grant POSDRU/159/1.5/S/137750, Project "Doctoral and Postdoctoral programs support for increased competitiveness in Exact Sciences research" cofinanced by the European Social Found within the Sectorial Operational Program Human Resources Development 2007 – 2013 (PhD scholarship G.-M. D.).

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P3. Synthesis and Anti-inflammatory Activity of Some $P2X_7$ Antagonists

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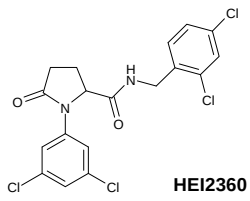
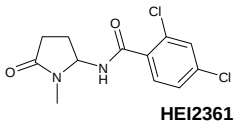
Inflammatory bowel diseases (IBD) are crippling diseases and an estimated 200 000 people suffer from them in France. Currently, there are no effective treatments. In fact, existing therapies only focus on suppressing symptoms to give patients better quality of life. However, the development of potential new treatments is on-going, in particular with the development of new antagonists of the $P2X_7$ receptor ($P2X_7R$).

The $P2X_7$ receptor is part of the purinergic signaling system. It belongs to the super-family of ion-channels. Recent *in vivo* and *in vitro* studies are showing the implication of $P2X_7$ in many biological pathways, including inflammation and cancer mechanisms.[1,2] The $P2X_7$ receptor is responsible for the liberation of interleukins and so, takes part in the inflammatory process of IBD patients. Finally, even though its role in cancer is not well understood many arguments exist in favor of using $P2X_7$ antagonists and exploiting them for their implication in cell death.

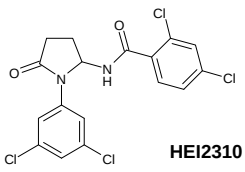
Based on a previous study in our research team and data from the literature,[3] we designed, synthesized and evaluated new $P2X_7R$ ligands with potential antagonist activity, based on a pyrrolidin-2-one central connector.



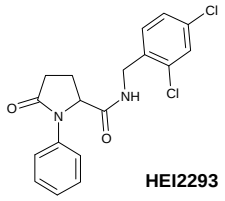
HEI2360
CI_{50} (*h*-$P2X_7R$) > 10 µM



HEI2361
CI_{50} (*h*-$P2X_7R$) = 0.47 µM



HEI2310
CI_{50} (*h*-$P2X_7R$) = 6.74 µM



HEI2293
CI_{50} (*h*-$P2X_7R$) = 10 µM

Some antagonists have been identified *in vitro* with IC_{50} values in the micromolar range and have allowed us to establish new SAR for further development of new compounds. The most active products will be tested *in vivo* on TNBS-induced colitis mice models.

Our on-going studies, on the one hand, will focus on designing and synthesizing new ligands of $P2X_7$ based on new SAR; on the other hand, we will handle the problematic of distribution and metabolism of active antagonists that we have already identified.

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P4. Synthesis and biological evaluation of some new triazinyl-isoxazole derivatives

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Isoxazoles are an important class of heterocycles, which are largely employed in the area of pharmaceuticals and therapeutics such as insecticidal, antibacterial, antibiotic, antitumour, antifungal, antituberculosis, anticancer and ulcerogenic. Isoxazole derivatives are used in the market as anti-inflammatory drugs. Isoxazole derivatives such as sulfamethoxazole, sulfisoxazole, oxacillin, cycloserine and acivicin have been in commercial use for many years.[1]

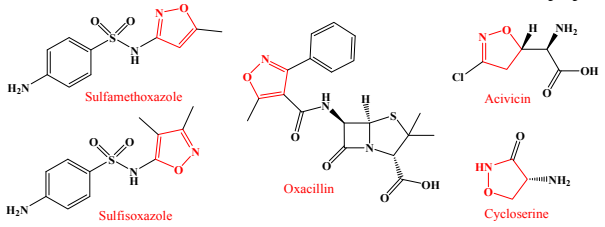

Figure 1. *Isoxazole-containing drugs*

Recently, by replacing the ethylene bridge in combretastatin A-4 structure with an isoxazole unit, new antiproliferative compounds against leukemia HL60 cells (IC_{50}=3 μM) were obtained.[2] Taking this into account and the antitumor properties of compounds bearing a *s*-triazine cycle,[3] we propose the synthesis of new analogues of combretastatin A-4: the ethylene bridge to be replaced by an isoxazole unit and with dimethoxy-*s*-triazine ring as the B cycle.

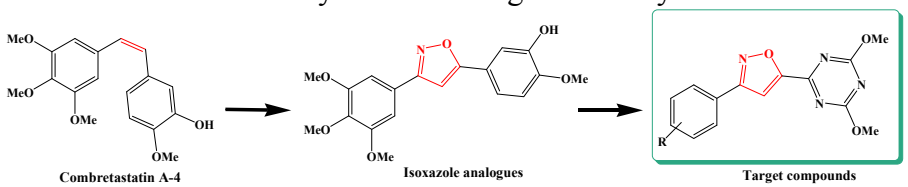

Figure 2. *Design of target compounds*

All new synthesized compounds were IR, NMR characterized and some of them were biological evaluated against tubulin polymerization and against the NCI 60-tumor cell lines.

Acknowledgment: This work was supported by the strategic grant POSDRU/159/1.5/S/137750, Project "Doctoral and Postdoctoral programs support for increased competitiveness in Exact Sciences research" cofinanced by the European Social Found within the Sectorial Operational Program Human Resources Development 2007 – 2013.

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P5. Synthesis of cyclic PHEMA brushes via post-polymerization loop closure

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The aim of this work was to develop efficient grafting-from strategies for the preparation of loop polymer brushes. Loop-like polymer brushes represent an exciting new macromolecular topology. We present here the synthesis and characterization of linear and loop PHEMA brushes, biocompatible and hydrophilic. Two principal strategies have been explored for the preparation of loop brushes: direct surface-initiated atom transfer radical polymerization and post-polymerization loop-closure. The 'grafting from' approach was used to synthesize linear PHEMA brushes. Reaction conditions were adjusted to successfully polymerize the functional, polar methacrylate monomer with reactive bromide end groups (90%-95%), in order for the halogen end group to be converted into other functionalities using standard organic procedures. A protocol has been developed for the post-polymerization modification of the bromide end group of the PHEMA brush to obtain loop-like structures. Using the ability of halogen end groups to be converted into other functional groups, bimolecular nucleophilic substitution (S_N2) reactions were used to incorporate allyl end groups. The PHEMA brushes were functionalized with allylamine with a 70% success rate. Subsequently, the allylamine functionalized PHEMA brushes were linked together by a ring-closing metathesis reaction, in order to form loop PHEMA brushes.

The properties of these brushes were determined mainly by Attenuated Reflectance-Fourier Transformed-Infrared Spectroscopy (ATR-FTIR), X-Ray Photoelectron Spectroscopy (XPS), Ellipsometry, Atomic Force Microscopy (AFM), Water Contact Angle (WCA) and Sum Frequency Generation (SFG) Spectroscopy.

We here-by emphasize the hypothesis that conformational restricted polymer thin film architectures, as loop PHEMA brushes, possess superior surface and interfacial properties as compared to linear polymer brushes. For these loop PHEMA brushes we foresee various applications, such as ultrasensitive biosensors or non-biofouling surfaces.

Acknowledgements: This work was partially supported by a grant of the Romanian National Authority for Scientific Research, CNCS – UEFISCDI, project number PN-II-ID-PCCE-2011-2-0028 and a SCIEX - Scientific Exchange Programme NMS-CH grant (The Swiss contribution to EU enlargement, for the SCIEX Fellowship 12.089).

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P6. Synthesis and biological evaluation of new indolizine derivatives as antitumoral agents

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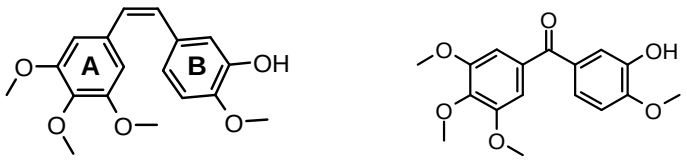
The microtubule system, formed of α- and β- tubulin heterodimers, is involved in many essential cell functions[1] and is recognized as an attractive pharmacological target for anticancer drugs.[2] Tubulin is a heterodimer of closely related and tightly linked globular α- and β-tubulin proteins, capable to polymerize in hollow tubes called microtubules. These cytoskeletal structures are involved in many cellular functions. 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. The phosphate prodrug of CA-4 (Zybrestat,® Fosbretabulin) is currently undergoing phase III clinical trials for the treatment of anaplastic thyroid cancer. Research on combretastatin A-4 in order to improve its *in vivo* activity led to the discovery of phenstatin (**2**, Fig. 1).[3]



Combretastatin, **A-4** **Phenstatin**

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

A new family of microtubule-targeting agents with an indolizine B-ring (Fig. 2) was synthesized and tested for interactions on tubulin polymerization and evaluated for cytotoxicity on the NCI-60 human cancer cell lines panel. Some new indolizines showed potent cell growth inhibition with IC_{50} values on the nanomolar range.

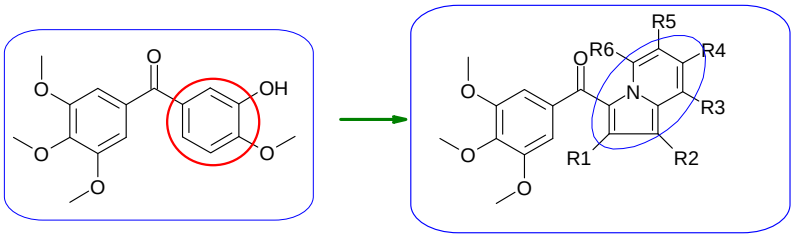


Figure 2. Design of some new phenstatin analogues

Keywords: tubulin, anticancer drugs, indolizine derivatives

Acknowledgements: This work was supported by a grant of the Romanian Ministry of Education, CNCS-UEFISCDI, project number PN-II-RU-PD-2012-3-0426. The authors gratefully acknowledge the National Cancer Institute (NCI) for biological evaluation of compounds on their 60-cell panel.

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P7. Conception, synthèse et évaluations pharmacologiques de ligands naphtofuraniques des récepteurs de la mélatonine.

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La dépression est l'un des troubles mentaux les plus fréquents de nos jours. C'est une maladie psychiatrique qui résulte de problèmes génétiques, physiologiques, psychologiques et environnementaux. Les antidépresseurs actuels agissent sur le cerveau à un niveau monoaminergique, présentent de nombreux effets secondaires et peuvent conduire à une accoutumance psychologique. Malgré l'augmentation d'antidépresseurs sur le marché, les dépressifs sont traités de manière inadaptés ou résistent au traitement disponible. Aussi le besoin en antidépresseurs plus efficaces, dénués d'effets indésirables, mieux tolérés et d'action plus rapide est important. Récemment, il a été démontré que des perturbations des rythmes circadiens étaient impliquées dans cette pathologie. Dans ces conditions le développement de nouveaux antidépresseurs possédant des propriétés chronobiotique est à envisager. C'est dans cette optique que l'agomélatine (Valdoxan®) issu de la recherche du laboratoire de chimie thérapeutique (EA - GRIIOT) et des laboratoires Servier est apparu. C'est un agoniste non sélectif des récepteurs mélatoninergiques MT1 et MT2 avec des Ki respectifs de 0.13 nM et 0.47 nM et un antagoniste sélectif des récepteurs 5-HT2c avec un Ki de 630nM utilisé dans le traitement de la dépression majeure chez l'adulte. Son intérêt thérapeutique est cependant limité, dû à sa faible biodisponibilité d'une part qui n'est que de 11% et à son faible profil sérotoninergique. Les recherches entreprises dans ce domaine par notre laboratoire ont considéré l'agomélatine comme nouveau chef de file ainsi, plusieurs pharmacomodulations ont été réalisées afin d'obtenir un successeur potentiel présentant un profil pharmacocinétique amélioré et une biodisponibilité supérieure à 30%. Les techniques de « Drug Design » et le concept de bioisostérie ont été appliqué, nous permettant ainsi la synthèse de nouvelles familles de composés présentant des profils pharmacologiques intéressants.

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P8. Spectral Study of New Ln - Heterocyclic Combinations

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The lanthanide metal ions complexes have been paid much attention for many years. They are one of the important new challenges, not only as important compounds for industry and in high-tech products, but as well for the medical applications (markers in detection of cancer cells, treatment of diseases, cancer therapy). Synthesis and characterization of new lanthanide complexes with N-heterocyclic ligands is of current interest[1-2]. Lanthanide compounds present magnetic, optical and catalytic particular properties[3]. To create a new generation of metal complexes one of the key questions is to understand the behavior of physico-chemical and optical properties of the ligand when its structures are changed.

Synthesis of new complexes based on lanthanide metal salt (La^{3+}, Nd^{3+}) and two N-heterocyclic ligands in the presence of ethylenetetramine was performed. The N-heterocyclic ligand was noted as rigid ligand (L_r) and respectively mobile ligand (L_m). Absorption spectra of Ln- N-heterocyclic combinations have been recorded by UV-Vis and fluorescence spectroscopy. Absorption spectra of the new synthesized compounds were studied in methanol showed a maximum of absorbance in ultraviolet range. The complexes with Nd (III) - L_m (ε=30644 $mol^{-1}\cdot cm^{-1}$) shown the higher absorbance at 220 nm, compared with Nd (III) – L_r (ε=20076 $mol^{-1}\cdot cm^{-1}$) at 212 nm. La (III) – L_m (ε=14984 $mol^{-1}\cdot cm^{-1}$) complexes shown a maximum at 208 nm while La (III) - L_r (ε=10164 $mol^{-1}\cdot cm^{-1}$) shown a maxim at 206 nm. These bathochromic shifts of the spectral bands can be assigned physical interaction with the solvent and they showed the preferential arrangements of the ligands in Ln electronic structure. The obtained fluorescence data showed the maximum excitation peak at 324-326 nm and smaller maxim at 456-460 nm. The spectral evaluation of the new Ln combinations was performed. The reaction product was dissolved in methanol and repeated three times by adding each time 10 mL methanol. Analysis of the spectral behavior revealed small changes of the absorption, hypsochromic shifts and hyperchromic effects dependent on structure of the ligand (L_r; L_m) in the lanthanide combinations as which yields information on the transition state.

Acknowledgements: This paper was co-financed from the European Social Fund, through the Sectorial Operational Programme Human Resources Development 2007-2013, project number POSDRU/159/1.5/S/138907 "Excellence in scientific interdisciplinary research, doctoral and postdoctoral, in the economic, social and medical fields - EXCELIS", coordinator The Bucharest University of Economic Studies.

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P9. Antioxidant Potential of a New Family of Pyridinium Compounds

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Oxidative stress is produced either by an overproduction of reactive oxygen species or by a reduction of the effectiveness of antioxidant in the cell or entire organism, or both. Reactive oxygen species appear in redox reactions, in which the major structural changes occur, the compound changing its biological function, becoming more soluble or interfering with other metabolic chain etc. During oxidative stress, pro-oxidants inactivate cellular antioxidant defense system, and cellular constituents undergo morphofunctional alteration processes leading to quick apoptosis[1]. Because of oxidative stress, antioxidant activity of many compounds is often determined in the assessment of their potential biological effects.

Determination of antioxidant activity was done, in this work, through two methods, which fit into two general classes of methods for determining the antioxidant activity: DPPH method, and method using β-carotene. The antioxidant capacity was tested on twelve quaternary ammonium salts[2], of which five are derived from pyridine, three are derived from 4, 4'-bipyridine and four are derived from, 4-[2-(pyridin-4-yl)ethyl]pyridine. The test was meant to highlight the antioxidant potential of compounds through the two methods. All tested compounds had good antioxidant activity, the molecules with methoxy moieties presented an antioxidant activity generally better than those possessing a p-nitro functional group. We have identified three compounds with the lowest IC 50 value, inhibiting 50% of the free radicals in solution at a concentration below 20 μg / mL.

Acknowledgement This work was supported by a grant of the Romanian National Authority for Scientific Research, CNCS – UEFISCDI, project number PN-II-ID-PCE-2011-3-0226

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P10. Organochlorine pesticides and polychlorinated biphenyls in human serum from Iasi, Romania, and their relation to non-Hodgkin lymphoma prevalence

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Persistent Organic Pollutants (POPs) are highly lipophilic chemicals that persist in the environment, bioaccumulate through the food chain and pose a risk of causing adverse human health effects. Relatively recent reports on POPs from human serum samples collected from Eastern Romania suggested a higher exposure of the Romanian population than previously reported for other European countries.[1,2] Therefore, in the present study, we analyzed human serum samples from persons living in Iasi, Romania for *p,p′*-DDT and its metabolites, hexachlorobenzene, hexachlorocyclohexane (HCH) isomers, chlordane and metabolites and 14 polychlorinated biphenyl (PCB) congeners. Serum samples included in the present study were collected from individuals with non-Hodgkin lymphoma (N=30, further in text as NHL-samples) and compared with serum POPs levels previously reported for general healthy population living in the same area.[1] In all samples, *p,p′*-DDE (principal metabolite of *p,p′*-DDT) and *β*-HCH were the most abundant organochlorine pesticides with median concentrations of 2230 and 1930 ng/g lipid weight (*lw*) for NHL and of 1975 and 923 ng/g *lw* for control samples, respectively. Hexachlorobenzene and *p,p′*-DDT were also detected in all samples, but at a lower median concentration of 40 and 115 ng/g *lw* for NHL and 30 and 340 ng/g *lw* for control samples, respectively. Chlordane and its metabolites were in most cases close to the limit of quantification suggesting a very low use of chlordane formulations in Eastern Romania. In case of the PCBs, they were present in all samples at median levels of 480 ng/g *lw* for sum of 14 PCB congeners in NHL and 380 ng/g *lw* for the control population. The PCB profile consisted of persistent congeners such as 138, 153, 170 and 180 which contributed for approximately 70-75% to the sum PCBs.

The results included in this study show the high exposure of general Romanian population to these OHCs and in particular of humans with leukemia pathology.

Acknowledgements: This work was supported by the strategic grant POSDRU/159/1.5/S/133652, co-financed by the European Social Fund within the Sectorial Operational Program Human Resources Development 2007 – 2013.

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P11. Reversed phase high performance liquid chromatographic assay method of active pharmaceutical ingredients in anti-tuberculosis 2-fixed dose combination tablets

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Tuberculosis (TB), assigned as a major infectious disease, even nowadays remains a serious and considerable threat to global health.[1] Isoniazid, pyrazinamide, rifampicin and ethambutol are among the most important anti-tuberculosis first-line drugs used recently also in fixed-dose combination.[2] Prescription for two months of a combination of these four drugs, usually followed by isoniazid and rifampicin alone for four additional months, represents the standard treatment for TB.[3] In former work performed in our laboratory an HPLC method was developed for the analysis of individual anti-tuberculosis first line drugs.[4] The present work reports a simple, rapid and sensitive reversed phase-high performance liquid chromatographic (RP-HPLC) assay method for the simultaneous determination of isoniazid and rifampicin in 2-FDC tablets. Separation of the interest active pharmaceutical ingredients (APIs) has been achieved under gradient elution mode on a Zorbax SB-C18 (150 × 4 mm, 5 μm) stainless steel column with a guard column containing the same stationary phase. The gradient elution has been carried out with a mobile phase of 10% CH_3CN in water for channel A and 50% CH_3CN in phosphate buffer, 20 mM, pH = 6.8 (plus 1.5 mL triethylamine, TEA) for channel B. An optimal wavelength for the analysis, i.e. λ = 269 nm, has been selected after scanning in the 190 to 600 nm range the absorption spectra of the individual first line drugs of interest. The proposed method is assumed to save time (10 minutes chromatographic run for the analysis of both isoniazid and rifampicin) as well as organic solvents consumption. Acceptable percentage contents were obtained in batches of various origins when compared to the judged limits for the interest APIs drug products.

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The POSCCE-O 2.2.1, SMIS-CSNR 13984-901, No. 257/28.09.2010 Project, CERNESIM, is gratefully acknowledged for the infrastructure used in this work.

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P12. Physico-chemical behaviour of newly synthesized organic compounds. A reality between expectations and experimental evidences

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Nowadays researchers' interest to develop new sensitive, selective and rapid methods for the determination and removal of toxic metals from the environment has enhanced.[1] Development and application of chemical sensors for the detection of heavy metal ions, even at trace levels, is a modern research topic. Supramolecular chemistry offers wide possibilities for azobenzocrown functionalization, lipophilic crowns being successfully applied as ionophores in order to obtain miniaturized ion-selective membrane electrodes.[2] Newly synthesised macrocyclic amidic compounds, GZ-I (A), GZ-II (B), GZ-III (C) (**Figure 1**), have been tested for their potential to act as chelators for various metals.

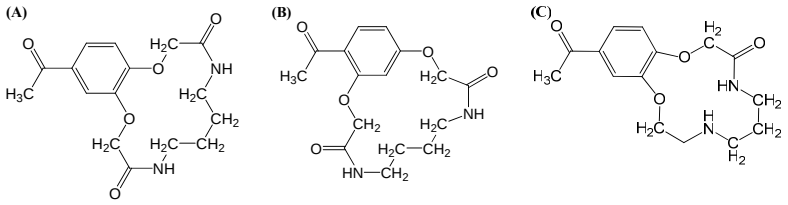

Figure 1. Chemical structure of the newly synthesized macrocyclic compounds.

Spectroscopic (FTIR, fluorescence, UV-VIS absorption) and electrometric (conductimetry) techniques have been used to characterize the chelating potential of the newly synthesized macrocyclic compounds towards metals such as Ag, Al, Ca, Cd(II), Co(II), Cr(III), Cu(II), Fe(III), Mg, Mn(II), Ni(II), Pb(II) and Zn. Experimental investigations have been undertaken at M:L or L:M ratios of 1:1, 1:2, 1:3 and 1:4. From the interest potential chelators only for GZ-I some experimental evidences have been obtained for its possible implication in silver ions chelating in both methanol (MeOH) and methanol-dimethyl sulphoxide (MeOH-DMSO) binary system.

Drying to sec the organic-aqueous mixture between GZ-I and Ag^+ resulted in the formation of very fine acicular crystals (**Figure 2**). Further work should be undertaken to confirm the present experimental observations and to investigate whether or not the macrocyclic structure GZ-I can be used to develop a specific sensor for Ag^+.

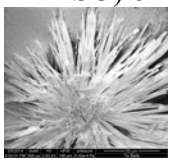

Figure 2. SEM details for the crystals formed between GZ-I and Ag^+.

Acknowledgements
CERNESIM Center is gratefully acknowledged for the infrastructure used in this work. PN-II-PCE-2011-3-0471 Project, No. 200/05.10.2011 is also acknowledged.

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P13. Synthesis and self-assembling of phenothiazine and pyridine-*N*-oxide based AIE-active triazoles

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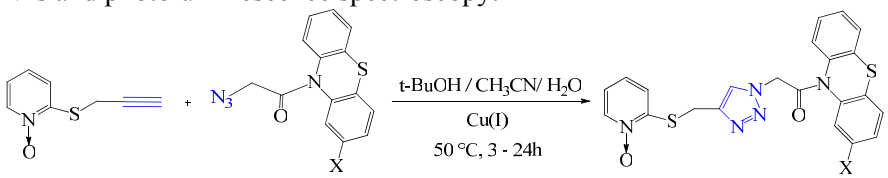
Aggregation induced emission (AIE) is an intriguing optical phenomenon which consists in light emission appearance once the compounds aggregate, while it actually misses or is very weak in solution[1].

The aim of this paper was to explore the AIE properties of new synthesized AIE-active triazoles containing flexible spacers between rigid units, in order to better understand the molecular design – AIE properties relationships. To do this, three new AIE triazoles were synthesized through „click" chemistry of pyridine-*N*-oxide carrying out triple bond functionality with azide-containing phenothiazine (Scheme 1) and their morphology and photophysical properties were studied, by dynamic light scattering, scanning electron microscopy, UV-Vis and photoluminescence spectroscopy.



1

2a[2] **X**= H (78%)
2b[3] **X** = Cl (76%)
2c[4] **X** = CF_3 (70%)

3a X= H (78%)
3b X = Cl (76%)
3c X = CF_3 (70%)

Scheme 1. Synthetic pathway to phenothiazine and pyridine-*N*-oxide based triazoles

The compounds proved ability to self assembly into microcrystalline structures (Figure 1) and to emit blue light in solid state or as suspensions in water (Figure 2). A close correlation between the aggregation way and intensity of the emitted light has been evidenced.

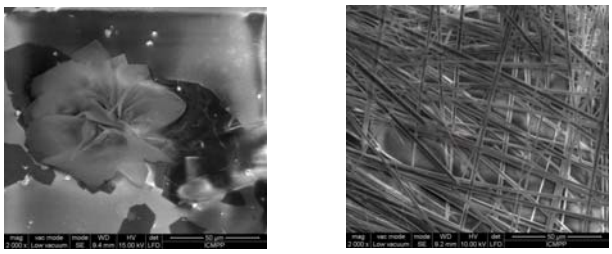


Figure 1. Scanning Electron Microscopy

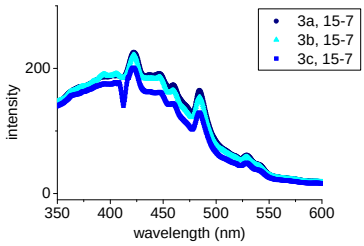


Figure 2. PL spectra of the crystalline films

These properties suggest that these compounds may be useful for optical applications, the biological ones being envisaged.

Acknowledgements:

This work was supported by the strategic grant POSDRU/159/1.5/S/137750, *"Project Doctoral and Postdoctoral programs support for increased competitiveness in Exact Sciences research"*.

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P14. New triazole-indolizine derivatives with potential anticancer activity

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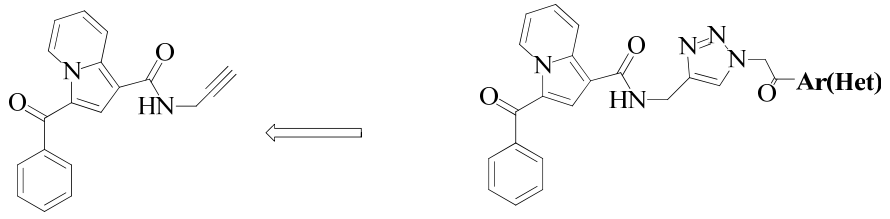
1,4-Disubstituted 1,2,3-triazole and indolizine derivatives present many biological activities in the field of medicinal chemistry, being studied in terms of anticancer, anti-inflammatory, anti-tuberculosis and other activities.[1, 2] To the best of our knowledge, triazolo-indolizine derivatives have not been encountered in the anticancer field. In order to study the anticancer activity of the triazole-indolizine compounds, we have synthesized molecules **2a-f** starting from indolizine derivative **1**.[3]



1

2a Ar=*p*ClC_6H_5 **2d** Het=phenothiazine-10-yl
2b Ar=*p*BrC_6H_5 **2e** Het=2-chlorophenothiazine-10-yl
2c Ar=3,4,5$(OCH_3)_3C_6H_2$ **2f** Het=2-trifluoromethylphenothiazine-10-yl

The new triazole-indolizine compounds **2a-f** were synthesized through Huisgen 1,3-dipolar cycloaddition[4] between 3-benzoyl-*N*-(prop-2-yn-1-yl)indolizine-1-carboxamide (dipolarophile) and corresponding organic azides (1,3-dipoles). In order to obtain only the 1,4-disubstituted 1,2,3-triazole regioisomer, the reactions were catalytically conducted in the presence of Cu(I) generated in the reaction medium.

The four triazole-indolizine derivatives (**2a** and **2c-e**) and the indolizine **1** were selected by NCI for screening against 60 human tumor cell lines. The results showed that the triazolo-indolizine compounds exhibit superior selective inhibitory activity on cancer cells compared to the propargylamide **1**.

Acknowledgements:

This work was supported by the strategic grant POSDRU/159/1.5/S/137750, *"Project Doctoral and Postdoctoral programs support for increased competitiveness in Exact Sciences research"*.

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P15. 1,3-Dipolar cycloaddition reaction of 1-carboxymethyl-pyridinium bromide with ethyl propiolate

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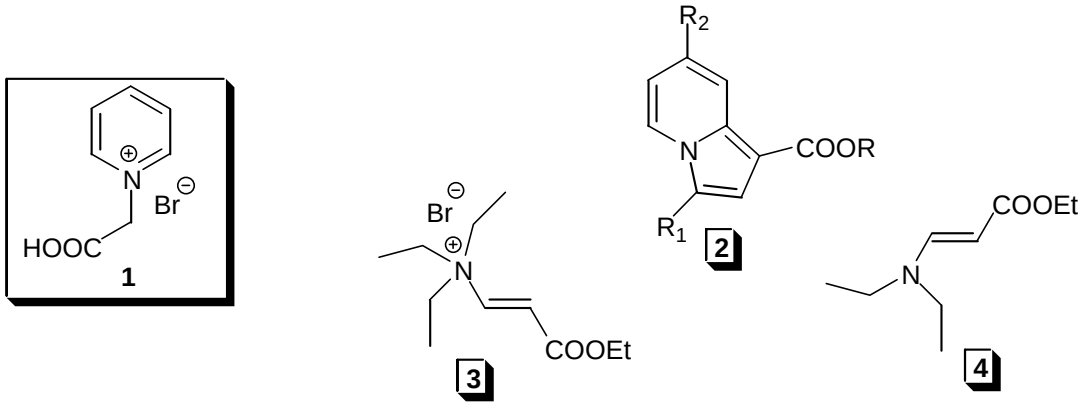
Indolizines[1] constitute a class of heteroaromatic compounds containing two condensed rings (5- and 6-membered) and a bridging nitrogen atom. The indolizine and hydrogenated indolizine structures are found in many alkaloids. These natural and synthetic derivatives have been found to have a variety of biological activity.[2-4]

Our recent research[5,6] has been oriented towards the synthesis of new indolizine derivatives. Thus, in order to obtain 1,3,7-trisubstituted indolizine (**2**), we carried out the reaction of cycloimonium salt **1** with ethyl propiolate, in the presence of potassium carbonate or tertiary amines with base role.

Small amounts of indolizine derivatives were identified when the reaction was conducted in dimethylformamide. The main isolated products (**3**, **4**) were the result of the Michael addition of tertiary amine on ethyl propiolate.



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P16. A facile synthesis of 2*H*-1,4-benzoxazin-2-ones

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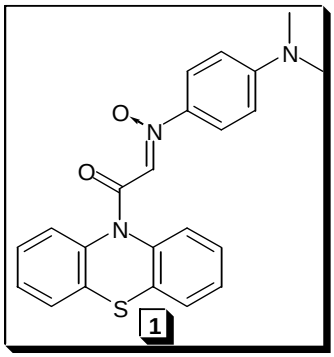
The 2*H*-1,4-benzoxazin-2-ones, also called azacoumarins have been described in 1897 by Wislianus[1-4].

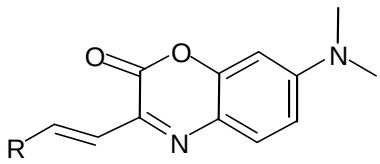
These heterocyclic compounds show a strong fluorescence which, due to the bathochromic effect of the heterocyclic nitrogen, is shifted towards red when compared to the analogous 7-aminocumarines.

We report here an unexpected method for the synthesis of 2*H*-1,4-benzoxazin-2-one derivatives **2**, starting from nitrone **1**.

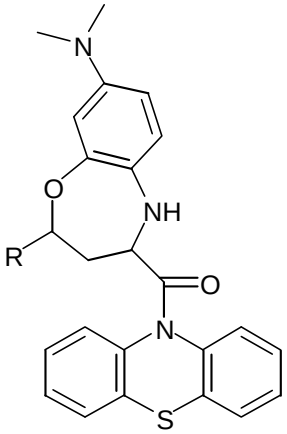
Two unexpected compounds (**3**, **4**) were detected in the synthesis of 2*H*-1,4-benzoxazin-2-one derivatives. They were isolated and characterized, their yields being dependent upon the reaction condition used.



1



2



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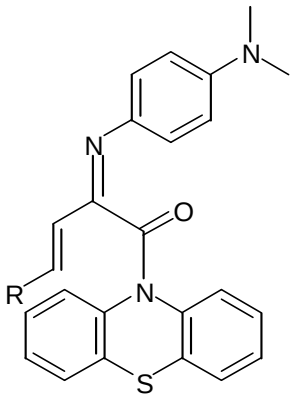

4

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P17. Synthesis and anticancer activity of new indolizine derivatives

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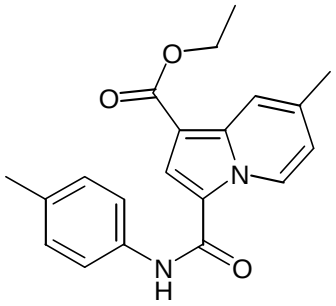
The indolizine scaffold constitutes the basic skeleton in many compounds with diverse pharmacological activities[1-3]. Our interest in the field of indolizines was focused on the design and synthesis of 1,3,7-trisubstituted indolizine derivatives, with potential anticancer activity.

Thus, by 1,3-dipolar cycloaddition,[4,5] we obtained compounds **I** and **II**, which were evaluated for their antiproliferative activity on a NCI-60 cancer cell lines panel.



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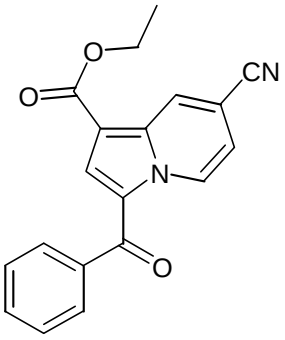

II

The results show that both compounds exhibit anticancer properties, the *in vitro* percentage growth inhibition depending on the nature of the tumor cell lines tested (Table 1).

Table 1. Results of the *in vitro* human cancer cell growth inhibition

Cell type	Cell line	Inhibition ratio (%) at 10 µM	
		I	II
Leukemia	K-562	8	43
	SR	38	24
Colon cancer	HCT-116	57	25
Non-Small Cell Lung Cancer	HOP-92	23	100
Ovarian cancer	OVCAR-4	42	15
Renal cancer	A498	38	55
	UO-31	10	42
Prostate cancer	PC-3	31	33

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P18. Selenium halide induced bridge formation in [2.2]paracyclophanes

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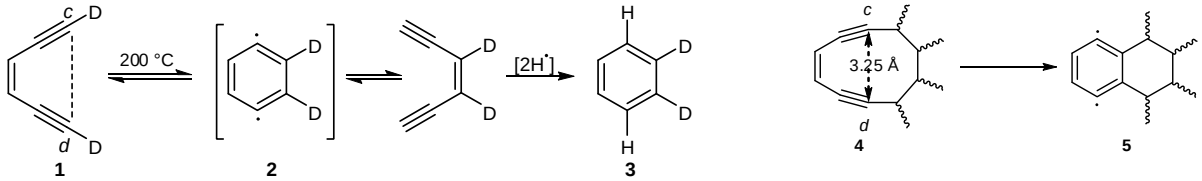
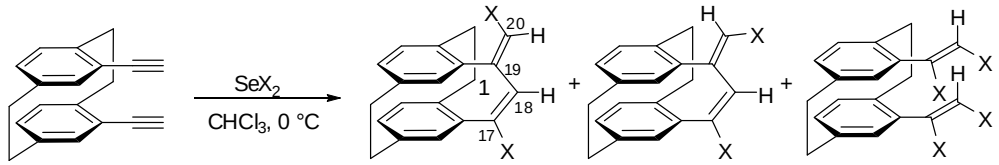
The thermal cyclization of (*Z*)-acyclic enediyne **1** to 1,4-dehydrobenzene **2** and via hydrogen abstraction to benzene **3** was studied in 1970s by Bergman.[1] A number of natural products, such as calicheamicin, esperamicin and dyneamicin, which contain the cyclic enediyne **4**, can generate a bicyclic 1,4-dehydrobenzene fragment **5**, which is capable of abstracting hydrogen atoms from DNA.[2] Studies on simple monocyclic enediynes revealed that the distance between the terminal carbon atoms of the triple bonds strongly affects the activation energy for ring closure. It was found that monocyclic enediynes in which the distance *cd* is less than 3.2 Å cyclize spontaneous at 25 °C (Scheme 1).[3]



Scheme 1. Cycloaromatization of enediynes

Functional groups in *pseudo-geminally* substituted [2.2]paracyclophanes often undergo highly specific reactions, due to the rigid framework and the short distance (3.09 Å) between the two aromatic rings within the [2.2]paracyclophane unit. Following the idea to use [2.2]paracyclophane as a spacer for model enediynes, we decided to investigate the synthesis of new enediynes analogs. Thus, an addition/elimination sequence of selenium halides to *pseudo-geminally* bisacetylene substituted [2.2]paracyclophanes leads to new bridges with an *endo-exo*-diene substructure. The reactions have been found to be sensitive to the substitution of the ethynyl group. The formation of dienes with a *zig-zag* configuration is related to that observed for nonconjugated cyclic diynes of medium ring size.[4]



Scheme 2. Reactions of selenium dichloride and selenium dibromide with *pseudo-geminal* bisacetylene **6**

Acknowledgements

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P19. Synthesis, Characterization, Crystal Structure of Copper(II) Complexes Containing an ON Donor Schiff Base. Antimicrobial Activity

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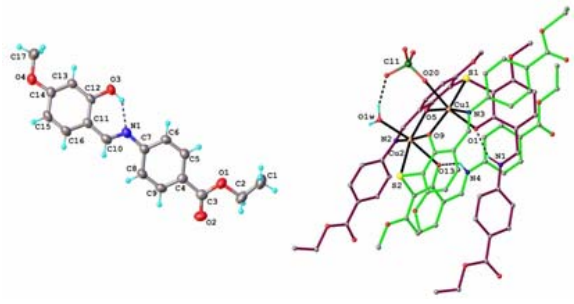
Schiff base ligands synthesized by using salicylaldehyde or salicylaldehyde derivatives presents a lot of applications and microbial activities. Their O and N donor atoms plays an important role in coordination chemistry related to catalysis and enzymatic reaction, magnetism and molecular architecture. Transition metal complexes with Schiff base ligands are important class of compounds in medicinal and pharmaceutical field, and show a variety of biological applications.

We have synthesized and characterized new Cu(II) complexes: $[Cu(L)(NO_3)(H_2O)_2]$ (1), $[Cu(L)_2]$ (2), [Cu(L)(OAc)] (3), $[Cu_2(L)_2Cl_2(H_2O)_4]$ (4), $[Cu(L)(ClO_4)(H_2O)]$ (5) and $[Cu_2(L_2S)(ClO_4)(H_2O)]ClO4{\cdot}H_2O$ (6) were HL= ethyl 4-[(E)-(2-hydroxy-4-methoxy-phenyl)methyleneamino]benzoate. These new complexes of copper (II) were synthesized using HL and different metal salts. All complexes have been characterized by molar conductivity, magnetic susceptibility measurements, electronic, infrared, mass and EPR spectral studies. The crystal structure of Schiff base has been determined by X-ray diffraction studies, as well as the crystal structure of one of its copper(II) complexes, $[Cu_2(L_2S)(ClO_4)(H_2O)]\ ClO_4{\cdot}H_2O$ (6).



Perspective view of HL and complex 6.

The in vitro antimicrobial activity against gram-positive bacteria (Staphylococcus aureus and Enterococcus), gram-negative bacteria (Escherichia coli and Salmonella enteritidis), and Candida albicans was studied and compared to the activity of the free ligand. The antimicrobial data given for the compounds presented in this paper allowed us to state that the metal complexes generally have a better activity than the free ligand and the antimicrobial activity depends on the tested compound structure.

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P20. Vibrational spectroscopic studies on 3-(N,N-diethyldithiocarbamate)-2-(4-methoxyphenyl)chroman-4-one

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In this paper, a derivative of 3-substituted dithiocarbamic flavanone was investigated from vibrational point of view at DFT/B3LYP/6-311G(d,p) level of theory. The flavanone was obtained as an inseparable mixture of diastereoisomers, with the *anti* isomer (Figure 1) as the major one [1]. The vibrational frequencies were evaluated for the computed equilibrium geometries by the analytic evaluation of energy second derivatives based on the harmonic approximation. Because of the large numbers of fundamental frequencies, the assignments of absorption bands were made on the basis of potential energy distribution (PED) calculations by transforming the normal coordinate displacements from the cartesian to an internal coordinate basis using the VEDA 4 program. For title compound the total number of vibration normal modes is of 144. The nature of each vibration normal mode was identified using the animation option of GaussView 3.09. program.

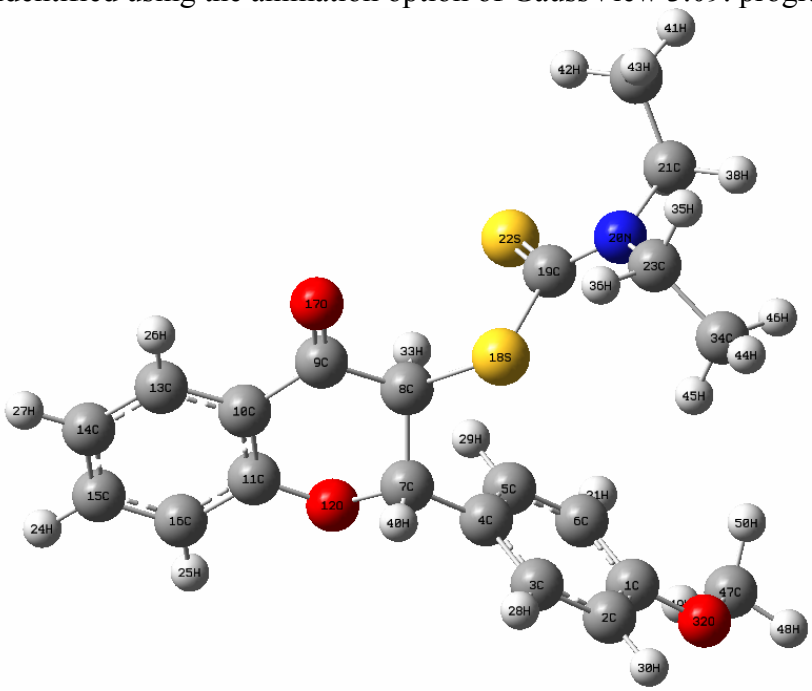

Figure 1

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P21. Molecular docking study of anticancer flavonoids

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Cancer chemoprevention, which can be defined as the use of substances to prevent the process of carcinogenesis, is one of the major strategies currently being developed for cancer control. Natural flavonoids, which may have the ability to halt or retard carcinogenesis, are important phytonutrients found in a large variety of fruits, vegetables and beverages [1]. In this paper we performed an exploratory analysis of the interactions between flavonoidic compounds as ligands, and PI3Kα isoform used as receptor in the molecular docking simulations. All ligands were optimized at DFT/B3LYP/6-31G(d) level of theory. The X-ray crystal structure of PI3K kinase was retrieved from the Protein Data Bank (PDB code: 2RD0). The molecular docking process was performed using AUTODOCK 3.05 software. The docking simulation results are presented.

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P22. Design of new drug delivery systems based on ion exchangers

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The ion exchangers XE "ion exchangers" represent an important tool to develop controlled /sustained release systems or to improve old pharmaceutical forms, because of their excellent properties such as, physico-chemical stability, inert nature, uniform size, spherical shape, presence of functional groups, high capacity of drug loading and prevention of dose dumping. The goal of this study was to prepare a new drug delivery system based on a complex of gellan gum and an acrylic ion exchanger. The drug used is a bactericidal cephalosporin antibiotic, namely cefuroxime sodium salt (CFR) which is active against *Gram-negative* and *Gram-positive* organisms. CFR is indicated for the treatment of infections of the ear, sinus, throat, lower respiratory tract, skin and soft tissue, urinary bladder and for treatment of the early stage of Lyme disease. The acrylic microparticles were obtained by the aminolysis-hydrolysis reaction of ternary copolymer (ethylene glycol dimethyl acrylate - acrylonitrile- ethyl acrylate) with hydrazine hydrate. To increase the biocompatibility of the microparticles, gellan gum was selected to cover the surface of these acrylic beads.

The microparticles based on interpolymeric complex have been characterized by FT-IR spectroscopy, SEM microscopy, AFM and thermogravimetric analysis. In order to evaluate the adsorption process of CFR, it requires under consideration of two important physico-chemical aspects as follows: the equilibrium and the kinetics of adsorption. The Langmuir, Freundlich and Temkin adsorption isotherms were used to model this behavior. The kinetic parameters were fitted with the pseudo-first order, pseudo-second order, Elovich and intraparticle diffusion models. The thermodynamic parameters were also calculated and the values indicate that the adsorption process was endothermic and spontaneous. A higher capacity of drug loading on the complex microparticles was observed in comparison to the capacity of drug loading on the microparticles based on ion exchanger. To analyze the *in vitro* release data various mathematical model were used, such as, first order, Higuchi model, Korsmeyer-Peppas model and Baker-Lonsdale-model.

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Paper dedicated to the 65th anniversary of "Petru Poni" Institute of Macromolecular Chemistry of Romanian Academy, Iasi, Romania.

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P23. Synthesis and Anti-proliferative Activity of Coordinative Combination of Copper, Cobalt, Nickel and Zinc with 2-acetylpyridine Semi- and Thiosemicarbazone and their 4-Phenyl Substituents

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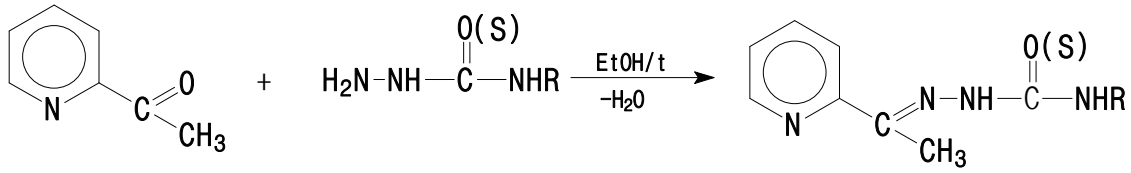
It is well known that many semi- and thiosemicarbazide derivatives display biologic activity and are widely used in medicine in treating infections caused by different microorganisms. Many of these substances form with the salts of transition metals coordination compounds that display physiological activity, and can be examined as preparations with biochemical and pharmacologic application. Thus, the synthesis and study of new coordination compounds of bio-metals with semi- and thiosemicarbazide derivatives are of scientific and practical interest.

The aim of the given paper is to establish optimum conditions of synthesis, structure, physicochemical and biological properties of cobalt, nickel, copper and zinc coordination compounds with semicarbazone (L^1), 4-phenylsemicarbazone (L^2), thiosemicarbazone (L^3), and 4-phenylthiosemicarbazone (L^4) 2-acetylpyridine.

First were synthesized the L^1-L^4 compounds, whose synthesis scheme can be presented in the following way:



where R=H, C_6H_5

Then, the interaction of ethanol solutions of chloride, bromide, copper (II) nitrate and sulphate with the L^1 – L^4, taken in 1:1 molar ratio led to microcrystalline substances for which the compositions $CuL^{1-4}X_2$ (X = Cl, Br, NO_3, $1/2SO_4$) were determined on the basis of elemental analyses data. However, when copper salts are replaced with chloride, bromide, nitrate, acetate of cobalt, nickel and zinc, the reaction results in substances with the composition $M(L^{1-4}\text{-}H)_2X$. Comparing the IR spectra of the initial semi- and thiosemicarbazones with those of the synthesized complexes showed that the L^{1-4} act as monodeprotonated tridentate N,N,O (for $L^{1,2}$) and N,N,S (for $L^{3,4}$) ligands and coordinate to central atoms through the atoms of pyridinic and azomethinic nitrogen and oxygen (for $L^{1,2}$) or sulphur (for $L^{3,4}$).

Furthermore, indentifying the anti-proliferative activity of the synthesized complexes was of high interest.

It was found that the copper complexes of these ligands inhibit the growth of myeloid leukemia cells, and that a 4-phenyl substituent increase the activity. For 4-phenyl semicarbazone 2-acetylpyridine high activity is also manifested for cobalt and nickel complexes (in comparison with the medicine - doxorubicine - used currently in the medical science for treating and preventing leucoses).

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P24. Di(μ-S)-bis{chlorin-[phenyl(pyridine-2-il)methanone-tiosemicarbazone (1-)]copper} as an Inhibitor of Breast Cancer T-47D Cells Proliferation

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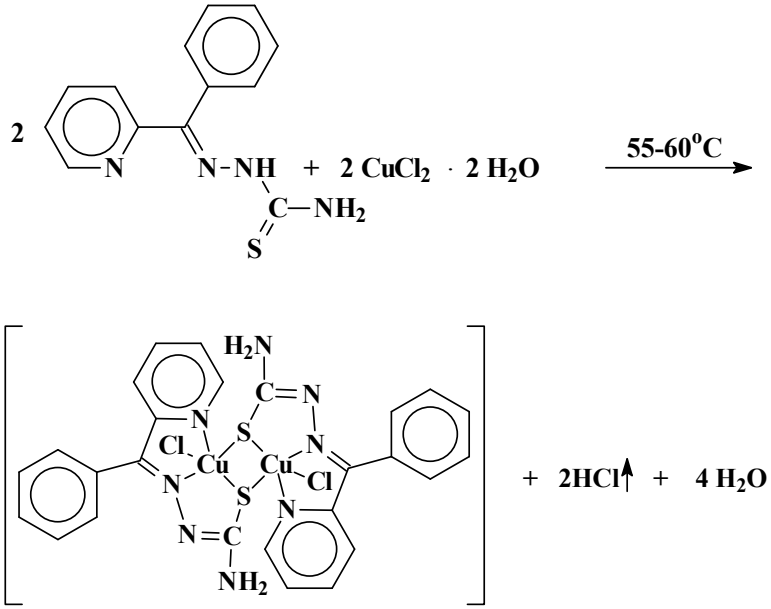
The objective of this paper consists in the determination of the optimum conditions for synthesis; determination of the composition structure; physicochemical, biological and antiproliferative properties of the copper (II) complex compound with 2-benzoylpyridine thiosemicarbazone.

During the interaction of the boiling ethanol solutions of $CuCL_2\ 2H_2O$ (55-60°C) with 2-benzoylpyridine thiosemicarbazone, taken in 1:1 molar ration, Di(μ-S)-bis{chlorin-[phenyl(pyridine-2-yl)methanone-thiosemicarbazone(1-)]copper} complex compound is obtained according to the following scheme:



The visual observation of the synthesized coordinative compound through a microscope has displayed that it has a phase homogeneity. Due to the small dimensions and absence of monocrystals of this complex, elemental analysis, IR spectroscopy, magnetochemistry and thermogravimetric analysis were used to determine its individual features and structure.

The obtained compound was tested on antiproliferative activity. The experimental data indicate that at 10^{-5} mol/L this compound inhibits 100% of growth and multiplication of breast cancer T-47D cell, but at 10^{-6} mol/L 38±3,5% of cell growth was inhibited.

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P25. Bioactive coordination compounds action on the intensity of the oxidative stress and antioxidant system activity in animals under physiological

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Background: Non-platinum metal coordination compounds (CC) with halogensemi-carbazides based chelation and macrolydic ligands exhibit strong antiproliferative and cytotoxic properties, exceeding tens and hundreds of times antitumor activity of e.g. doxorubicin [Gulea A., et al., 2007, 2009], but their action on normal tissues is insufficient studied. Based on these considerations, the **aim** of research was to study the peculiarities of the influence of the new non-platinum metal CC with chelation and macrolydic ligands – CMD-4, CMD-8, CMJ-23, CMJ-33 şi CMT-67, on the intensity of the oxidative stress and antioxidant system activity in the liver of the experimental animals under physiological conditions.

Methods: Biological activity of the CC, was evaluated in experiments on a group of 46 male rats Wistar line, randomly divided into 8 groups. The first group – control (sham), were inject i/m saline solution daily for 30 days. The experimental animals from groups 2-12 were administered subcutaneously the studied CC twice weekly for 30 days: group 2 – CMD-4 (100 nM/kg), group 3 – CMD-4 (1000 nM/kg), group 4 – CMD-8 (100 nM/kg), group 5 – CMJ-23 (100 nM/kg), group 6 – CMJ-33 (100 nM/kg), group 7 – CMJ-33 (1000 nM/kg), group 8 – CMT-67 (100 nM/kg). The amount of the oxidative stress markers – malonic dialdehyde (MDA), nitric oxide (NO), advanced glycation end products (AGE), the ischemia-modified protein (IMP), advanced oxidation protein products (AOPP) and the content of S-nitrosothiols, was determined. Changes the antioxidant protection were assessed by evaluating the activity of superoxide dismutase (SOD), catalase, histidine dipeptide's content and total antioxidant activity levels (AAT).

Results: The study revealed that the level of the MDA, decreases statistically significant by 14%-40% in the liver under the influence of most of the studied CC, except CMD-8 (100 nM/kg) and CMJ -33 (100 nM/kg) that induced just a discrete decrease tendency. The tested CC did not influenced conclusive the levels of NO, except CMD-8 (100 nM/kg), that produced a 40% increase of the NO content compared with the control. The results of our studies show the ability of the tested CC to induce a tendency to decrease the intensity of AGE products formation in the liver. CMD-4 and CMJ-33 (1,000 nM/kg) diminished the amount of the S-nitrosothiols by 16%-20% ($p<0.05$) compared with the control group. The study reveals that SOD activity decreased statistically conclusive by 24% ($p<0.05$) after the administration of CMD-4 (1000 nM/kg), while CMD-4 (100 nm/kg) and CMT-67 (100 nM/kg) diminished by 23% ($p<0.05$) the activity of catalase.

Conclusions: The influence of the tested CC on the studied markers of the oxidative stress and AOS is selective. This selectivity can be the foundation of their particular strong antiproliferative and cytotoxic selective action upon the tumor cells, but not on the healthy one.

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P26. Influence on new bioactive compounds on carbohydrate metabolism markers in experimental liver disease

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Background: Currently considerable interest in the study of the various biologically active compounds, which could exert a significant influence on metabolic processes, arouses.
The research **aim** was to study the mechanisms of action of the non-platinum metal coordination compounds with halogensemicarbazides based chelation and macrolydic ligands – CMD-4, CMD-8 and CMJ-23, on metabolic processes in experimental hepatopathy (HP) and justification of their application efficiency in hepatology for the treatment efficiency monitoring.

Methods: Toxic HP was induced by the administration of ethylene glycol (EG). In the liver tissue were measured glucose metabolism markers: isoforms of lactate dehydrogenase - LDH-L (catalyzes the conversion of lactate into pyruvate) and the LDH-P (catalyses the conversion of pyruvate to lactate), as well as the activities of glucose-6-phosphate dehydrogenase (G-6-P DH) and NADP-dependent malate dehydrogenase (MDH-NADPd). The medication was carried out using new complex compounds – CMD-4, CMD-8 and CMJ-23.

Results: In ethylene glycol induced HP the activity of LDH-P, LDH-L and MDH-NADPd increased, while the functional level of G-6-PDH decreased compared with controls. CMD-4 administration to the animals with HP significantly reduced LDH-L activity by 35% ($p<0.05$) compared to animals with untreated HP and induced a tendency to restore the LDH-P and G-6-P DH levels. CMD-4 and CMJ-23 inconclusive increased the activity of MDH-NADPd by 23% -32% compared to the controls. The activation of the investigated NADP-dependent dehydrogenases - G-6-PDH and MDH-NADPd, by CMD-4 and CMJ-23, registered in our research in animals with liver disease is the expression of their anabolic effect.

CMD-8 returned the activity of NADPd MDH to the control group values, while CMJ-23 contributed to the recovery of G-6-PDH.

Conclusions: The tested non-platinum metal coordination compounds return to normal values the activity of most studied glucose metabolism enzymes in the liver tissue. Relevant changes can be appreciated as manifestations of adaptation processes in the purpose of maintaining optimal cellular homeostasis. The studied compounds exhibit selective action on the tissue enzymes, which probably depends on the degree of their engagement at different stages of the pathological process. Thus, the compounds included in the research can be used as remedies for the pathogenic correction of metabolic disorders that accompany toxic liver injury.

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P27. Activité Antibactérienne de Composés de Coordination de Cuivre et Nickel avec l'Isatine β-(N-pyridin-2-yl)thiosemicarbazone

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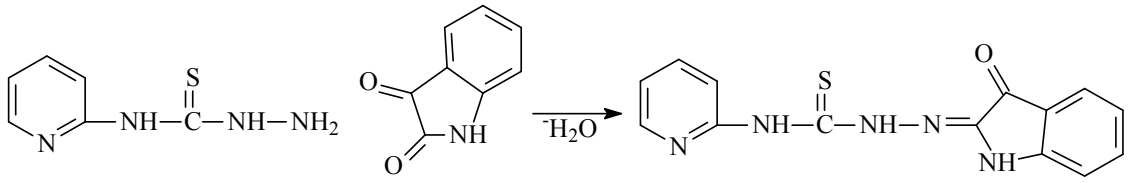
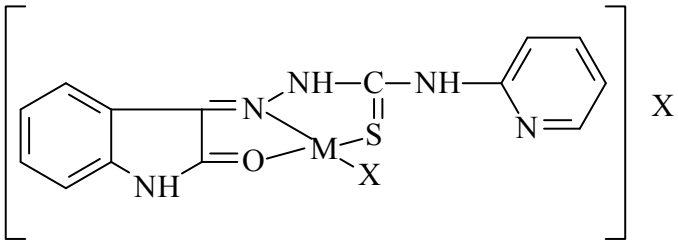
Le but de cette présentation est la synthèse de composés de coordination du cuivre (II) et nickel (II) avec l'isatine β-(N-pyridin-2-yl)thiosemicarbazone, la détermination de la composition et de la structure de nouveaux composés, la recherche de l'activité antimicrobienne sur bactéries gram-positif et gram-négatif.

Le ligand suivant a été synthétisé :



L'interaction de solutions éthanoliques de sels de cuivre(II) et de nickel(II) avec le ligand, pris dans un rapport de 1:1 fournit les composés de coordination suivants :



où M= Cu(II), Ni(II) ; X=Cl^-.

La détermination de l'activité antimicrobienne des complexes synthétisés a été effectuée dans un milieu nutritif liquide (bouillon de viande de 2%, pH 7) par la méthode des dilutions successives. Comme culture de référence pour les expériences in vitro » ont été utilisés les souches standards de *Staphylococcus aureus (ATCC 25923), Bacillus cereus (ГИСК 8035) Escherihia coli (ATCC 25922)* et *Salmonella sonnei Shigela Abony (3.3 ГИСК).* La dissolution des composés de coordination du cuivre (II) et du nickel (II) dans le diméthylformamide, la culture des micro-organismes, l'obtenir des suspensions, la détermination de la concentration minimale inhibitrice (CMI), et la concentration minimale bactéricide (CMB) ont été effectuées par les méthodes standards décrites dans la littérature. Les données expérimentales obtenues montrent que les complexes synthétisés présentent des concentrations bactériostatiques et bactéricides dans la limite de 0,12 à 0,25 mg / ml.

Ce travail a été soutenu par le projet institutionnel 11.817.08.48A.

P28. Synthesis, structure and *in vitro* antiproliferative activity of some hydrazones

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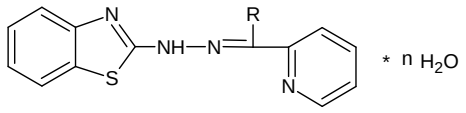
Heterocyclic compounds containing nitrogen and sulphur possess potential pharmacological activities. Benzothiazoles are bicyclic ring systems which have been the subject of great interest because of important biological activities. Benzothiazole moiety possesses diverse type of biological activities: antifungal [4], antibacterial [6], antihelminthic [5], antimalarial [3], analgesic [1], anti-inflammatory [7], anticancer [2] and various central nervous system (CNS) activities.

The present paper describes the synthesis, characterization and tested as inhibitors of human leukaemia (HL-60) cell growth of some benzothiazoles, Schiff bases. For this purpose, 2-[2- (pyridin-2-ylmethyliden)hydrazino]-1,3-benzothiazole (HL^1) and 2-[2-(1-pyridin-2-ylethyliden)hydrazino]-1,3-benzothiazole dihydrate (HL^2) have been synthesized. The composition and the structure of the synthesized substances have been determined by ^1H and ^{13}C NMR spectroscopy. The substances were tested on antiproliferation activity (Table 1).



HL^1: R=H, n=0
HL^2: R=CH_3, n=2

Table 1. Antiproliferative activity of some compounds against human myeloid leukaemia (HL-60),

Inhibitor	Concentration, μM/L		
	10	**1.0**	**0.1**
HL^1	93	88.9	
HL^2	99	95	92
Doxorubicin	95	92	16

Therefore, it can be inferred that the antiproliferative activity of the compounds HL^1-HL^2 is influenced by the nature of R^1, and its grows in the following order: H< CH_3.

The organic compounds extend the range of highly active inhibitors of human myeloid leukemia they are more active than Doxorubicin.

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P29. Antimicrobial Effect of 3d-Metal Coordination Compounds with 2,4-Pentanedione bis(4-Allylthiosemicarbazone)

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The aim of this work is the synthesis of chromium, manganese, cobalt, nickel, and copper coordination compounds with the product of condensation of 4-allylthiosemicarbazide and acetylacetone, determination of their composition, structure, physicochemical and antimicrobial properties.

The experiment showed that ethanolic solution of 4-allylthiosemicarbazide reacts with 2,4-pentanedione in 2:1 molar ratio forming a new white compound with composition $C_{13}H_{22}N_6S_2$ (HL). Monocrystals of this compound were obtained as a result of recrystallization from ethanol, and its crystal structure was determined by X- ray analysis. It was determined that the obtained product of condensation is 3,5- dimethyl-N-(prop-2-en-1-yl)-5-[2-(prop-2-en-1-ylcarbamothioyl)hydrazinyl]-4,5-di hydro-1H-pyrazole-1-carbothioamide. Its formation apparently can be explained in the following way. At first, the process of condensation of one molecule of 4-allylthiosemicarbazide to one carbonyl group of acetylacetone takes place. After that the second carbonyl group condensates simultaneously to a new molecule of 4-allylthiosemicarbazide and thiocarbamidic nitrogen atom forming the resultant compound HL. The NMR study of the powder of this compound also confirmed its structure.

The experiments showed that chlorides, nitrates, acetates, and perchlorates of these metals react with the HL forming colored solutions. After cooling of these solutions synthesized coordination compounds MLX (M = Cu^{2+}, Ni^{2+}, Mn^{2+}; X = Cl^-, NO_3^-, ClO_4^-), M(L-2H) $\cdot$ $2H_2O$ (M = Cu^{2+}, Ni^{2+}, Mn^{2+}), MLX_2 (M = Cr^{3+}, Co^{3+}, X= Cl^-, NO_3^-) precipitate. The structure of two coordination compounds of nickel Ni(L)X (X = NO_3^-, ClO_4^-) were determined using the X-ray analysis. It was determined that in the process of forming these coordination compounds the pyrazolic cycle is breaking up and the compound HL transforms into 2,4-pentanedione bis(4-allylthiosemicarbazone). It acts in the composition of complexes as a tetradentate monodeprotonated ligand.

Biological research showed that synthesized coordination compounds show bacteriostatic and bactericidal activity for tested gram-positive and gram-negative microorganisms in the range of concentration 0.03-10.0 mg/mL. It was shown that the nature of the central atom has a main influence on the antimicrobial activity of these complexes. Depending on the nature of the central atom of homotypic complexes the biological activity changes in the following way Cu > Ni > Co ≥ Mn ≥ Cr. Synthesized compounds manifest the best activity towards the standard strains of gram-pozitive microorganisms (*Staphylococcus aureus, Enterococcus faecalis*).

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P30. Influence of bioactive coordination compounds on erythrocyte glutathione system in asthma

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Background: Identification, study and testing of new remedies for the correction of the glutathione system disorders in respiratory diseases, including asthma, are of particular interest due to the increased incidence of this disease and its severity leading to disability in people of working age. An increased interest is manifested for the nonplatinum metal coordination compounds with halogensemicarbazides based chelation and macrolydic ligands which exhibit important bioactive properties [Gulea A et al., 2007, 2009]. But their influence on erythrocyte glutathione system in asthma (BA) has been not studied.

The study **aimed** to elucidate the influence of the new nonplatinum metal coordination compounds on erythrocyte glutathione system *in vitro* in asthma with different severity.

Methods: The research was performed on peripheral blood samples collected from 23 patients diagnosed with persistent BA. The control group consisted of 13 practically healthy persons. Patients were divided into 3 groups according to the severity: I - mild; II - moderate; III - severe form. Nonplatinum metal coordination compounds CMD-4, CMD-8, CMJ-33 and CMJ-23 were tested. Peripheral blood samples was diluted in Dulbecco's modified Eagle's nutrient medium (DMEM) and incubated at 37° C for 24 h with the compounds mentioned above. The erythrocyte reduced glutathione content (GSH), glutathion reductase (GR), glutathion peroxidase (GPO) and glucose-6-phosphate dehydrogenase (G-6-PDH) activity were evaluated.

Results: The research revealed that the tested coordination compounds statistically conclusive increased the GSH content in erythrocytes of BA patients. The highest values were registered after incubation with CMJ-33 (+46% in mild BA, +61% in medium severity BA; +19% in severe BA), and CMJ-23 (+26% in mild BA, +36% in medium severity BA; + 13% in severe BA).

Functional level of GR was increased statistical significantly by CMD-4 (+112%), CMJ-33 (+93%) and CMJ-23 (+118%) compared with controls only in the mild form of BA.

All studied compounds decreased the activity of erythrocyte G-6-PDH in healthy persons compared to baseline, whereas in the patients with BA the enzyme activity increased 6.5 times in the mild form, 4.6 times in the moderate and 2 times in the severe one compared to control values ($p<0.001$).

In mild and moderate forms of BA all tested substances maintained the GPO functionality higher than the control level (34%-70%). In the severe form of the disease the coordination compounds did not induce significant changes in the level GPO of the RBC relative to control.

Conclusions: The results demonstrate the potent modulatory effects of the studied coordination compounds on the glutathione metabolism in BA of varying severity, as confirmed by the increase of the GSH content and GR, G-6-PDH and GPO activity in erythrocytes in the mild form of the disease compared with the levels specific for the healthy individuals. In the moderate and severe forms of BA the tested coordination compounds influence the GPO and G-6-PDH activity, maintaining their values increased compared to the control.

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P31. In Vitro Antioxidants and Antilipoxygenase Activity Of Some Thiosemicarbazones and Their Non-Platinum Coordination Compounds

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Various studies have shown that an important role in the initiation, promotion, and progression of several types of human cancers plays the oxygen free radicals (ROS), since they are involved in mutagenesis, apoptosis, ageing, and carcinogenesis. Many anticancer agents cause severe side-effects, which is due to its cytotoxic effect on normal cells. Therefore, the development of novel antioxidant chemotherapeutics is very important. In this sense, the non-platinum metal coordination compounds with macrocyclic ligands based on halogensemicarbazides are of great interest. They exhibiting nontrivial anticancer properties (potent inhibitors of the proliferation of breast cancer cells, prostate, liver, and other leukemias), exceeding tens and hundreds of times antitumor activity of doxorubicin - preparation currently used extensively in oncology.

The aim of present investigations was to investigate the antioxidant activity and antilipoxygenase activity of some non-platinum metal coordination compounds in vitro experiments. The total antioxidant activity of 18 coordination compounds of various concentrations was determined according to the method described by Re et al.(1999) with modifications. The lipoxygenase (LOX) activity was tested by the ferrithiocyanate (FTC) assay method of Weiqiang Luet al.(2013) with some modifications.

Analyzing the research results of ABTS test, we state that tested coordination compounds - CMT-104, CMC-38, CMT-122, CMT-67, CMG-17, CMD-8, CMA-4, CMC-4, CMG-69 - show the best antioxidant activity (IC_{50} was found to be in the range 1,0 - 9,1 μM) compared with trolox (33,3 μM), ascorbic acid (28,0 μM) and doxorubicin (9,3 μM). The compounds CMJ-33, CMSA-4, CMSA-21 and CMG-33 have a good antioxidant activity [IC_{50} – 16,0 - 16,7 μM]. The antioxidant activity of other coordination compounds is lower, comparable with the ascorbic acid and trolox. The research results of the lipoxygenase activity show that the complexes (CMC-4, CMC- 34, CMC-38, CMT-67, CMT-104, CMT-122, CMD-4, CMD-8, CMD-23, CMJ-33, CMC-4, CMC- 34, CMC-38) have a better result [IC_{50} – in the range 0.025 – 0.400 μM] in comparison with quercetin [IC_{50} - 15,6 μM].

Thus, the studied complexes because of their potential antioxidant properties can show chemopreventive effects through interference with ROS, which act as secondary messengers in signaling pathways crucial for cancer cell proliferation and invasion, and also by inhibiting inflammation and tumor promotion via deactivation of pro-oxidative enzymes, including inhibition of LOX-mediated arachidonic acid metabolism.

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