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ABSTRACTS

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4th French-Romanian Colloquium on Medicinal Chemistry

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C1. Green revolution in chemistry: existing and future challenges

Christophe Waterlot*

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Green chemistry is based on a set of 12 principles in which the main objectives are the reduction of the production and use of hazardous substances, the use of catalysis/biocatalysis to improve efficiency and yields under low temperature, and clean solvent or solvent free conditions, and the use of renewable materials. A new approach that incorporate environment, ecology and chemistry has been recently developed in France. This approach, considered as a new green branch of circular economy, seems to be well accepted by public and private partners, and appeared as a convenient method for rehabilitation of contaminated soils and restoration of ecology.

Due to rapid urbanization and industrialization, soils located in agricultural and urban contexts were highly affected by anthropogenic activities. This probably explains why since the three last decades, soil contamination by inorganic and/or organic pollutants has become a serious environmental concern that has been threatening both sustainability of human health and various agroecosystems.

The problematic related to the contamination of soils is very present in France, especially in the North of France. The past activities of the two lead and zinc smelters, “Metaleurop Nord” and “Nyrstar”, highly contributed to the metallic contamination of soils located in their surrounding area, in particular by cadmium, lead and zinc. In this context, an important challenge is the sustainable management of these contaminated soils in order to avoid dispersion of contaminated dusts, to restore contaminated soils and ecosystems and to maintain an economic activity on these areas.

Phytotechnologies appeared as a promising approach since they include innovative and efficient ways to rehabilitate contaminated areas. In this way, a new concept was designed from phytoextraction experiments and new heterogeneous eco-friendly plant-based catalysts have been recently used as green Lewis acids. Concrete examples of ecocatalysis will be given to illustrate the importance of these biosourced catalysts in organic synthesis and the main results described in the literature will be summarized and discussed. Because hyper-accumulating plants are not always appropriate in the restoration of contaminated area, assisted-phytoremediation could be the main solution to produce bio-sourced catalysts with non-hyper-accumulating plants.

Acknowledgments

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C2. Gene activated matrices for bone repair

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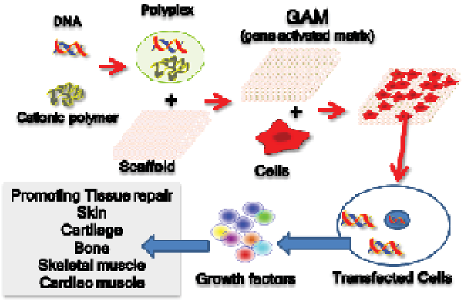
Different techniques have been proposed over the years to cure bone lesions, but they still represent a challenge in the orthopedic field. Bone is the most commonly transplanted tissue. Bone repair treatments focus on transplanting tissue from one site to another in the same patient (an autograft), from one individual to another (a transplant or allograft) or on metal implant strategies (titanium alloys and stainless steel) e.g., in joint prostheses, to provide mechanical and structural support.[1]

An innovative alternative to these strategies is tissue engineering that can offer the restoration, maintenance, or improvement of tissue function by using biomaterial scaffolds acting as template for tissue formation. The scaffolds are typically seeded with growth factors and cells.[2] The newest strategy supposes the combination of gene therapy and tissue engineering to create a novel solution with a high potential for structure and function restoration of damaged or dysfunctional tissues, avoiding growth factors use drawbacks – gene-activated matrix (GAM).[3]

The presentation will discuss the results obtained from *in vitro* testing of a new biodegradable hybrid scaffold loaded with different new polyplexes. Details on the synthesis, physico-chemical and morphological characterization of the used system will be provided.



Gene activated matrix (GAM) promoting tissue repair

Modified from C. Wang, L. Ma, C. Gao, Polym J (2014) 46, 476

Acknowledgements: : This project has received funding from the *European Union's Horizon 2020 research and innovation program* under grant agreement No 667387 WIDESPREAD 2-2014 SupraChem Lab and PNIII-P3-3.6-H2020-2016-0011.

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C3. Diversity in aza-heterocyclic systems based on tandem/domino reactions involving ionic species

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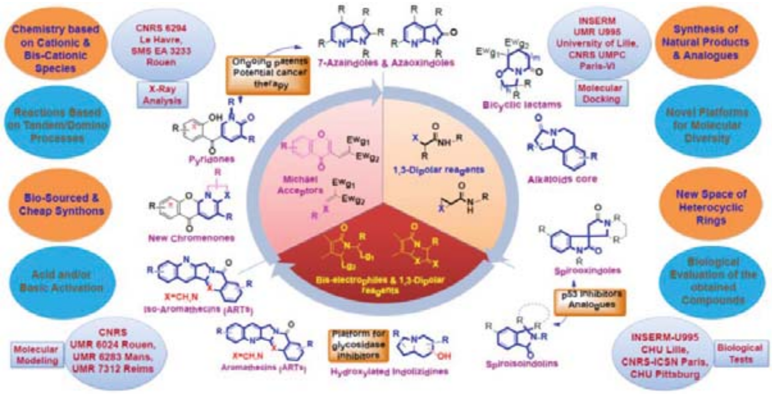
Our group at University of Le Havre is interested since decades now in several research topics based in particular on the exploration of ionic chemistry. The synthetic methodologies we elaborate are generally simple and short and led to the construction of aza-heterocyclic platforms with promising biological activities. Among the targeted structures, below is given a non-exhaustive overview.



Keys Words: Ionic Chemistry; Aza-Heterocycles; Advanced Synthetic Intermediates; Tandem/Domino Process; Alkaloids; SAR Study; Bioactive Compounds; Health.

Besides the molecular hybrids derived of numerous alkaloids mentioned in this scheme (typically protoberberines, camptothecins, aromathecines, rutaecarpines, and luotonines known for their potent antitumor activities), it will be question in this presentation to discuss approaches developed to provide an array of highly functionalized compounds containing an aza-cyclic nuclei such as pyridone, indole, isoindole, oxindole and azaindole.

After determination and optimization of the best possible ways to these systems, certain compounds issued from these investigations showed inhibitive properties of the enzyme topoisomerase-I, tubulin polymerase and farnesyltransferase (FTase) inhibition activities including, more interestingly, tubulin and FTase dual activity explored for the first time.

References

The references relative to these works and in particular those of these five last years can be found via the following link: https://urcom.univ-lehavre.fr/spip.php?article102

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C4. Azopolymeric nanostructured films for biological applications

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The azopolymeric materials are able to present an exotic behavior when interacting with light, generating the so-called surface relief gratings (SRG). The surface nanostructuration is obtained upon exposure to an interference pattern of two coherent laser beams. The origin of the surface deformation mechanism rest unclear, despite plentiful experiments and many theoretical efforts. The interest for azopolymeric systems is continuously increasing, because of their wide range of applications: data storage, holography, display technology, or solar energy. But one of the most interesting application of azopolymeric SRG is in the biological field, as support for cell cultures[1-4]. This is justified by the recent papers showing that the differentiation of stem cells can be exclusively induced by mechanical signals generated by the extracellular matrix.

Several surface relief profiles are presented in the paper, obtained from rigid (polystyrene) or flexible (polysiloxane) polymers, containing different azo-groups connected in the side chain. The capacity to generate a nanostructured surface is investigated in correlation with the polymers chemical structure and laser operational parameters. Cell adhesion and growth were monitored by immunofluorescence microscopy using human hepatoma cells (HepaRG). The polymeric chemical structure and the geometrical characteristics of the surface relief influence in a dramatic way the cell feat. Cells were very sensitive to the chemical and physical properties of the polymeric substrate, which they can integrate and transfer to signaling pathways. The best results concerning the cells division rate were obtained for a relief amplitude value comparable with the collagen diameter fibers from the extracellular matrix (around 60 nm).

Acknowledgements: - This work was supported by UEFISCDI (grant PN III - P4 - no. 31/2017).

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C5. Serendipity: facteur de diversité

Benoît Rigo[1,2]

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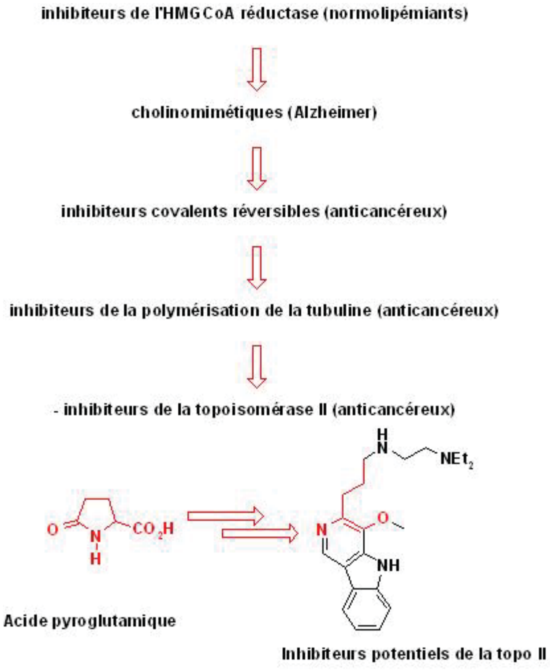
Notre laboratoire s'intéresse entre autre à la chimie de l'acide pyroglutamique, et a appliqué à ce produit de nombreuses réactions «classiques». Dans ce type d'activité, on observe fréquemment la formation de produits secondaires. L'étude systématique des mécanismes réactionnels conduisant à ces sous-produits permet d'aborder les problèmes selon des perspectives nouvelles, et ouvre des portes cachées initialement. Nous avons ainsi travaillé sur les voies d'accès à des composés des types suivants:



C6. Affinity and functionality studies of potent P2X7 receptor antagonists

Christophe Furman

Binding Platform, InsermLIRIC UMR-U995, F-59000, Lille France

P2X7 receptor (P2X7R) is a homotrimeric high concentration sensitive ATP-gated ion channel expressed by a wide variety of cells. Data from gene knock-out studies or experimental results from its activation allowed considering this receptor as an appealing therapeutic target for treating a number of diseases including cancers, neurological disorders, autoimmune diseases and chronic pain.[1] As the activation of the P2X7R is considered as a key regulatory element of the inflammasome complex and linked to the enhanced secretion of the pro-inflammatory cytokine interleukin1β, much research has focused on the discovery of potential antagonists of this receptor.[2] In our lab, we have synthesized more than sixty pyroglutamic acid derivatives and studied their affinity and their functionality using HEK293 cells, stably expressing the human P2X7R. Among these molecules, nine of them exhibited interesting equilibrium inhibition constants (Ki between 44.00 nM and 3.11 μM) in radioligand binding assays using [(3)H]A804598 as the reference ligand. In our test, six compounds even show a better affinity than the GSK1370319A S enantiomer, a compound patented by the GSK company for its antagonistic properties against the P2X7R. Using flow cytometry to simultaneously assess the Ca^{2+} influx, large pore opening and cell viability upon BzATP-mediated P2X7R activation, we have confirmed that these compounds have antagonistic properties (IC50 between 100.00 nM and 3.16 μM), data which correlate perfectly with those described above for affinity. In addition, docking of these inhibitors to the P2X7R reveals that they have a similar mode of binding that the A804598, our compound of reference. We have also observed in preliminary studies that these compounds decrease the secretion of IL1β in P2X7 receptor over expressing cells treated with LPS and BzATP.

In conclusion, we have developed a set of reliable analytical tools to evaluate both affinity constant (Ki) and functionality constants (EC50, IC50) of potent P2X7R ligands with, in our case, antagonistic properties.

Acknowledgments

Authors thank the Digest Science Foundation for its financial support.

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C7. Green chemistry: from principles to applications

Case study of Pinacol Coupling

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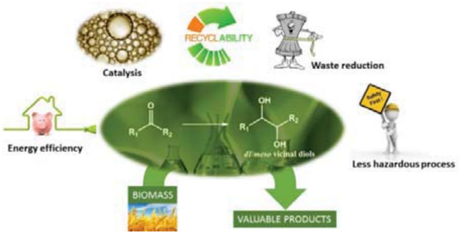
The reductive dimerization of carbonyl compounds, the so-called pinacol coupling, is a useful synthetic method for constructing vicinally functionalized carbon–carbon bonds. These vicinal diols can serve as structural motif in total synthesis, chiral auxiliaries or chiral ligands, crosslinker agents in polymer synthesis, pesticides, and substrates useful in structural biology.

With the notion of green chemistry, organic chemists are strongly encouraged to develop safer protocols. In the frame of an industrial project, we were required to design sustainable pinacol coupling reactions with the restriction induced by the industrial context.

Here will be presented our works over 4 years to meet both the requirements of Green Chemistry Principles and the Industry in the case of pinacol coupling reaction. After identification of the key points of the pinacol coupling reaction and drawbacks of previously reported pinacol coupling methodologies, various "greener" protocols will be discussed in terms of results, applicability and sustainability. Among the 12 Principles of Green Chemistry, some will be particularly commented such as the design for energy efficiency, the use of safer solvents or catalysis, the development of recyclable protocols and the limitation of waste. For each methodology, the chemical efforts for sustainability will be discussed and conclusions will be made on the technical practicability of "green" pinacol coupling reaction.



Acknowledgments
MB thanks the SAS PIVERT and ANR001-01 for financial support.

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C8. Azaheterocycles derivatives with antimycobacterial, antileishmanial and anticancer activity

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Over the past decades, five and six member ring azaheterocycles have received considerable attention due to their important applications from pharmacological, industrial, and synthetic points of view. Azaheterocyclic derivatives, especially azine, diazine and diazols, were reported as valuable scaffolds in medicinal chemistry, showing variously biological activities such as antiviral, anticancer, antituberculosis and other antimicrobials, etc.

As part of our ongoing research in the field of azaheterocycles derivatives, we present herein some core results obtained by our group in the field of nitrogen heterocycles derivatives, focused on chemistry and their pharmacological potential applications as anticancer, antituberculosis and antileishmania.[1]

In this respect, several classes of azaheterocycles (diazols, fused azines and diazines, mono- and bis- indolizines, 1,10- 1,7- and 4,7- phenanthrolines) were designed, synthesized, and tested. Some compounds have proved to have a significant biological activity as anticancer (especially against Melanoma, Renal cancer, Brest cancer and Lung cancer), as antimycobacterial (activity superior to the second-line antitubercular drugs Pyrimethamine and Cycloserine), and against Leishmania donovani intramacrophage amastigote.

For the most active compounds, a complete ADMET studies have been performed (these including Plasma Protein Binding, Caco-2 Permeability, Cytochrome P450 Inhibition, in vitro microsomal Stability, HepG2 Cytotoxicity) with very good and promising results.

Acknowledgements: .

Authors are thankful to COST Action CM1307 and POSCCE-O 2.2.1, No. 257/28.09.2010 Project, CERNESIM.

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1. Relevant literature data could be found to ORCID number 0000-0002-4632-5076.

C9. Innovative chemical technologies can improve radical chemistry

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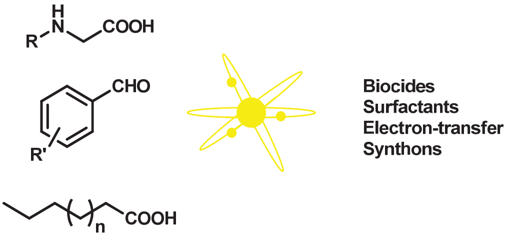
Radical chemistry is of great interest in many chemical areas, such as medicinal chemistry, material chemistry or polymers, or even formulation, in order to understand and prevent radical induced disorders. However, despite the lasting interest in performing radical syntheses, the use of innovative techniques for a more eco-friendly approach remains occasional.

After a short presentation of the Chemistry Group within TIMR laboratory, we will focus on examples showing how natural products can undergo radical transformations under innovative techniques. It will be shown that the combination of uncommon energetic devices with greener solvent can shorten reaction times, or even promote the envisioned reaction.



By using aromatic aldehydes, modified aminoacids or fatty acids, the molecules from such radical processes can be used in a wide range of applications. Biocides, surfactants, electron-transfer materials or even synthons are real options for molecules valorization.

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C10. RAGE-ligand axis, a good target in age-related disorders!

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Glycation is a major mechanism of aging. AGEs (Advanced Glycation End-products) are formed and accumulate during diabetes, renal failure, inflammation and aging (endogenous AGEs). AGEs are also formed during high temperature sterilization and cooking (exogenous AGEs). The human health effects of dietary AGEs are underestimated.

AGEs are irreversibly formed through the Maillard reaction, resulting from the binding of a sugar to a protein. AGEs exert their toxicity through 3 main mechanisms: *in situ* glycation, AGE deposits and interaction with the receptor for AGEs (RAGE).

In our group, we demonstrate that dietary CML (CarboxyMethylLysin), AGE with the highest affinity for RAGE, accelerates vascular and renal aging in a RAGE-dependent manner.

1/ CML-enriched diet is followed by increased arterial stiffness and wall thickness, elastin fiber disruption and decreased expression of SIRT1, a marker of aging.

2/ Dietary CML predominantly accumulates in kidney. CML-enriched diet was followed by a significant accelerated glomerulosclerosis.

3/ RAGEnull animals are protected from

- vascular and renal aging induced by a CML-enriched diet
- physiological vascular and renal aging

The aim of the present work is to present an overview of RAGE-ligand axis during aging. Engagement of RAGE by its multiple ligands is reported as pro-inflammatory and pro-oxidative. Beside ROS signaling, RAGE regulates a number of cell processes of crucial importance such as inflammation, apoptosis, proliferation and autophagy. As a consequence, RAGE is hypothesized as a crucial receptor involved in inflammaging.

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C11. From the search for new antiparasitic agents to chemical biology

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The main concern of our group is to find new antiparasitic agents to fight against protozoan parasites responsible for tropical diseases like malaria, African sleeping sickness, Chagas disease and leishmaniosis. We focused our research on the protein prenylation pathway, a validated antiparasitic target, and, more specifically, on protein farnesyltransferase inhibition.[1] During the last decade, in our group, hundreds of protein farnesyltransferase inhibitors have been designed, synthesized and evaluated on human and trypanosomal recombinant enzymes and against *Plasmodium falciparum*, *Trypanosoma brucei*, *Trypanosoma cruzi* and *Leishmania donovani*. An overview of our results will be presented.

In the course of our hit optimization we were disappointed to obtain molecules displaying more than a 100-fold higher activity on the enzymatic target but exhibiting only little if any improvement in the inhibition of parasite proliferation.[2] Two questions raised: is protein prenylation the real target of these compounds and/or are these compounds in sufficient amounts in parasites? These questions have incited us to develop new tools to quantify prenylation inhibition in cells and to visualize drug entry into parasites. Fluorescence spectroscopy appeared to be the most appropriate method for that purpose. Our concept is based on "click chemistry" that affords a new covalent adduct by cycloaddition. We selected the Strain-Promoted Alkyne-Azide Cycloaddition (SPAAC) because it does not require any catalyst or reagent other than an alkyne and an azide and because it has already been applied in biological media.[3,4] Our first results obtained in that field will be presented and discussed.

Acknowledgements:
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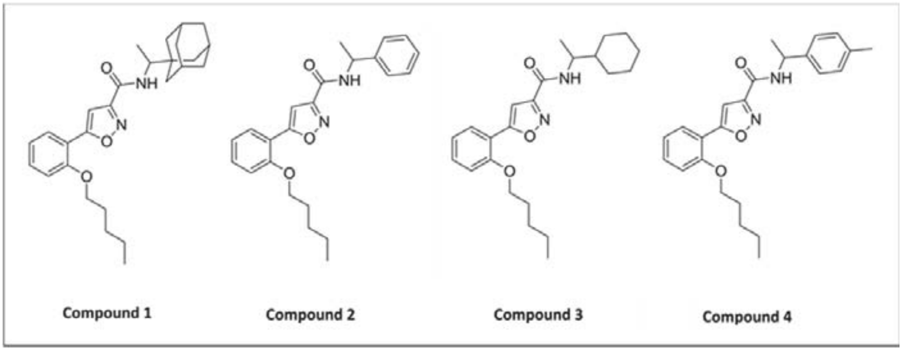
C12. Small scale separation of isoxazole structurally related derivatives by chiral supercritical fluid chromatography

Emmanuelle Lipka

Inserm U995-LIRIC- Laboratoire de Chimie Analytique, Faculté de Pharmacie de Lille- 59000-F- France

The context of this study is the development of new agonists of type 2 cannabinoid receptor (CB2). These molecules belonging to the chemical series 3-carboxamido-5-aryl isoxazole have potential anti-inflammatory action in the case of the Inflammatory Bowel Disease (IBD), a pathology that affects six million people in the world and still has no cure to this day.



These molecules having a chiral center, the separation of enantiomers in order to study their pharmacological activities, is an essential step in the development of any potential drug.

The aim of this work was to separate four pairs of enantiomers by a rapid and an ecological technique: the Supercritical Fluid Chromatography (SFC). This technique uses a mobile phase at a supercritical state, composed mainly of carbon dioxide and under thirty per cent of organic solvent.

First, we have optimized the analytical parameters of the separation of our molecules (chiral stationary phase, mobile phase composition). Then in a second step, we performed a semi-preparative separation of the compounds to obtain a sufficient quantity to implement the pharmacological study.

C13. Extrait de spongiaire anti cancer

Rachid Fadel* et Adil Ed Dahbi

Université Abdelmalek Essaadi
Faculté des Sciences de Tétouan MAROC

Le détroit de Gibraltar est situé au sud de l'Espagne, au nord du Maroc, à l'est de l'océan Atlantique, à l'ouest de la mer Méditerranée. C'est le seul passage maritime entre l'océan Atlantique et la mer Méditerranée, et cela se traduit par une variation de salinité et de température, et ces conditions particulières ont permis à des espèces endémiques d'éponges marines ou spongiaires de se développer dans cette région.

Il s'agit d'animaux formant l'embranchement basal des métazoaires. Elles sont définies comme des métazoaires sessiles.

Avec le concours des biologistes, nous avons recensés une vingtaine d'espèces endémiques.

Au laboratoire nous séparés des extraits non polaires, peu polaires et polaires.

Le laboratoire d'analyse biologique de référence français a procédé leurs études (anti fongique, antibiotique et anti cancer).

Une espèce s'est révélé présenter une activité anti cancéreuse.

Une partie des travaux a été présentée à la *Fondation Lalla Salma de lutte contre le cancer*.

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O1. Toward a new approach in drug design: from polluted soil and non-hyper-accumulating plants to anti-inflammatory agent

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Number of contaminated soils by heavy metals result in a large part of human activities. This pollution may represent, in that case, a threat to health but also an original metal resource. A new approach combining improvement of plant biomass grown on contaminated soil and its enhancement would meet to a dual purpose. The aim of this research is to (i) evaluate the effects of an assisted-phytoremediation technique in order to decrease the phytoavailability of carcinogenic metals and to increase the transfer of macro- and micro- elements from the contaminated soils to non-hyper-accumulating plants and (ii) turn the plant biomass in ecocatalyst, used in synthesis of Meloxicam®, an anti-inflammatory agent.

Kitchen garden soil samples, contaminated by cadmium (Cd: 20 mg kg^{-1}), lead ((Pb: 1400 mg kg^{-1}) and zinc (Zn: 4000 mg kg^{-1}), were sampled in a private garden located in the North of France. After preparation, subsamples of soil (3 kg) were constituted. Plant seeds were then sown in each subsamples, with or without calcium phosphate used as amendment (($Ca(H_2PO_4)_2$ and $CaHPO_4$). The shoots of plants were harvested eight weeks after sowing. In a last step, plant biomass was deployed to produce ecocatalyst (Eco2).

Depending on the amendment, first results showed that the transfer of Cd from the soil to the shoots of plants was similar to that in unamended soil. In contrast, the transfer of Pb decreased while accumulation of Zn in the shoots of plants increased in the presence of phosphates, particularly when $Ca(H_2PO)_2$ was added to the contaminated soils. Moreover, the use of phosphate led to extremely interesting Zn/Cd and Zn/Pb ratios in vegetable ashes, making them suitable for the production of Eco2. This ecocatalyst has proved its efficiency in the synthesis of Meloxicam®, which was obtained in 94% yield instead of 82% using $ZnCl_2$ as commercial Lewis acid.

This original approach highlights the advantages in using non-hyper-accumulating plants grown on contaminated soils, using calcium phosphate as amendment in order to produce plant biomass with high Zn/Cd and Zn/Pb ratios. This plant biomass allowed the design of Eco2, an ecocatalyst which was employed to produce Meloxicam® in higher yield than that using commercial $ZnCl_2$.

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O2. Valorization of montmorillonite K10-supported Lewis acids as new catalysts for the synthesis of new antitumor compounds

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Our current research is focused on the valorization in organic synthesis of different montmorillonite K10 supported catalysts. To test these supported catalysts, several synthetic transformations have been selected, such as aminolyses, esterifications or Friedel-Crafts reactions. These supported catalysts have been further tested on the synthesis of compounds bearing inhibitory potential against human farnesyltransferase. In this study, the aminolyses have been realized with classical $ZrCl_4$, a known catalyst for the amide bond formations,[1] to provide the final products and to have a reference for the conversion. The supported catalysts were then tested on these reactions to evaluate the reproducibility, the repeatability and the recyclability of our catalysts in a second step.

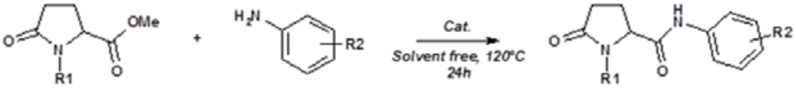

Figure 1. *General procedure for the synthesis of new antitumor compounds.*

Some supported catalysts have been tested on the synthesis of 13 pyroglutamides. The results have shown a similar activity for the supported catalysts and the pure $ZrCl_4$. In a third step, the activity of the supported catalysts used as a reference will be compared with new heterogeneous eco-catalysts obtained from green materials grown on contaminated soils. After evaluation of new compounds on human farnesyltransferase, the eco-catalysts will be tested on the synthesis of the lead compound in order to compare the catalytic activity of these innovative eco-catalysts to that of pure Lewis acids or montmorillonite K10-supported Lewis acids.

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O3. Non-viral vectors based on PEGylated squalene

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One of the most approached field in drug delivery research is represented by lipid based drug carriers due to their capability to increase pharmacokinetics, decrease toxicity, and increase the therapeutic index of the associated drugs, thus encouraging us to look for innovative nano-carriers to safely transport drugs or genes to specific cells.[1-2] In this context, a library of self-assembled vectors based on squalene, benzene-1,3,5-tricarboxaldehyde (TA), branched polyethylenimine (PEI) and linear polyethylene glycol (PEG), connected together via imine, bond was obtained as vectors for gene delivery. We have shown that this type of polymeric vectors possesses a great affinity for binding the nucleic acid and a good transfection efficiency on HeLa cell line.[3,4] The main objective of the presented work was to find the best transfecting vector by tuning the ratios of components in the system, thus maximizing the transfection efficiency keeping a minimum grade of toxicity. In aqueous media this compound adopts a core-shell structure forming micelles confirmed by TEM and CMC. We applied dynamic combinatorial chemistry[5] for the preparation of vectors and it the formation of polyplexes was proved by gel electrophoresis, GelRed Assay and TEM. *In vitro* biological assessments show that the content of PEG in obtained polyplexes, plays a crucial role in transfection efficiency and cytotoxicity on HeLa cell line.

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O4. P2RX7 ligands and their development as anti-inflammatory and anti-cancer agents

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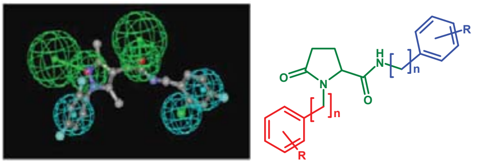
Recent developments related to (neuro-)inflammatory diseases and cancer has shown the ATP receptor, P2RX7, as a promoter of immune anti-inflammatory and anti-tumor responses.[1,2] In the scope of providing usable drugs for inflammatory bowel diseases (IBD) and associated cancers, we have designed, synthesized and evaluated pharmacologically new P2RX7 ligands. Using a sustainable raw material and easy to implement chemistry, we tested more than a hundred compounds among which 6 are currently under pre-clinical trial for the treatment of inflammatory diseases, immune diseases, pain and neurological diseases.

The *panda*-P2RX7 has recently been crystalized[3], confirming the ligand-based *in silico* modelling realized at the beginning of this study. According to the pharmacophore, we designed two lipophilic centers (red and blue on the structure) that had to be linked with an amide type connector (green).



Pharmacophore and designed general structure of the P2RX7 antagonists.

Pyroglutamic acid, issued from the sugar beet industry, is easily converted in methyl pyroglutamate with total conversion.[4] This ester is easy to handle and was the precursor of almost all the products of this study. We developed new methods for the synthesis of amides,[5] and for the functionalization of the lactam ring in different positions.[6,7] Finally, we extended our protocols to similar structures by using the principle of bioisosterism.

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The obtained drug candidates were screened by flow cytometry. We have thus obtained 22 antagonists among which 10 hits were selected for toxicological and other biological assays, revealing their potency to become new treatments for inflammatory diseases. Moreover, some compounds have shown anti-proliferative properties, others were shown to possess an antifungal activity, emphasizing the potency of pyroglutamic acid for the development of new drugs.

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O5. Sensitive dopamine detection using electrodeposited ag-au nanoparticles on carbon nanotubes

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Dopamine is a neurotransmitter that belongs to the catecholamine family and is widely studied in clinical research thanks to of its involvement in motor and cognitive function. In the central nervous system, loss of dopamine can lead to Parkinson's disease, epilepsy, Alzheimer's disease and schizophrenia. The crucial role of this chemical messenger challenged the development of numerous electrochemical sensors based on carbon nanotubes (CNTs) and metal nanoparticles for its electrochemical oxidation.[1]

Abundant applications of metal nanoparticles in electroanalysis have been reported [2,3] in which they perform several important functions, including an increase of the sensing surface area and facilitation of electron transfer. They also facilitate electrical contact between the redox center of a biomolecule and the electrode surface.

In our study, cyclic voltammetry and double-pulse amperometry methods have been used for Ag-Au Np deposition onto CNT, and evaluated for the oxidation of dopamine. The electrodeposition was optimized by investigating different parameters and conditions. Along with electrochemical methods we used scanning electron microscopy for morphologic characterization of deposited nanoparticles.

The most effective functionalization of CNT with bimetallic Ag-Au nanoparticles allows a sensitive detection of dopamine around 15 µA/mM with a satisfactory limit of detection. The selectivity for dopamine oxidation was evaluated by investigating oxidation of ascorbic acid and the results demonstrate that there is no interference in the voltammetric measurement of dopamine under optimized conditions.

The combination of bimetallic nanoparticles and carbon materials could afford a novel scheme to prepare promising nanomaterials for the highly sensitive electrochemical sensors.

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O6. MultiDrug Resistance in chemotherapy: new potential modulators of BCRP/*ABCG2*

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Today, cancer disease represents one of the major health public issue in the world. According to the World Health Organisation, cancers cause 1/6 of global death. Moreover, the economic impact was estimated at US$ 1160 billion in 2010. In this way, the research to discover new efficient treatments or to improve the existing ones is a high priority for private as well academic institutions. Chemotherapy is one of the three ways to cure cancer. However, nowadays no anticancer drugs are exclusively selective of cancer cells. Consequently, there is occurrence of side effects which could be uncomfortable and unsafe for patients. In fact, the major cause of failure in chemotherapy is the multidrug resistance (MDR).[1] MDR induction can result in cells becoming resistant against the initial compound as well as other unrelated compounds, which thereby circumvents anti-cancer treatment.[2] The apparition of MDR can be linked to the overexpression of ATP-Binding Cassette (ABC) transporters by cells.[3] The principal role assigned to these transmembrane proteins is to protect and to detoxify cells or tissues against xenobiotic agents. Thus, they are considered as efflux pumps. In terms of clinical impact, the ABC transporter family has a key role in efflux across the blood brain barrier and of anti-cancer drugs from cancer cells.

In our lab, we work on the smallest ABC transporter named the Breast Cancer Resistant Protein (BCRP) as biological target. We had developed one of the best modulator of BCRP/*ABCG2*: MBL-II-141.[4,5] To follow this work, we develop new potent modulators by synthesizing MBL-II-141 analogues containing diverse pharmacomodulations. The principal one is the introduction of a peptide or a pseudo-peptide part on the chromone moiety. Analogues are tested to determine their activity, cytotoxicity and their selectivity.

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O7. Challenges and achievements in analytical chemistry laboratories. Tropane alkaloids as plant-derived pharmaceuticals or ethnobotanical ingredients

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Alkaloids, known as an important chemical family, derived from naturally synthesized secondary metabolites, often have been used as drug precursors or templates for synthetic moieties with potential pharmacological applications.[1] However, in recent years the use of illegal drugs, where the potential of some secondary metabolites to act as bio- or psychoactive components is often refined, has become a serious problem worldwide.[2] Nowadays, appropriate chemical analysis of secondary metabolites from plants seems to be of utmost importance. Over the past few years, great effort has been given to developing testing strategies capable of identifying and quantifying secondary metabolites from various precursors. Gas-chromatography (GC) and its tandem with mass spectrometry (GC-MS, HPLC-MS) are powerful instrumental techniques highly efficient in the analyses of selected new chemical entities. Specific characteristics of such techniques seem entirely to fulfill the requirements of analytical chemical laboratories dealing with compounds at trace levels. Moreover, the World Health Organization accepts chromatographic fingerprints as suitable tools for identification and quality control assessments of herbal medicines.[3-5]

The present work reports about clear evidences on *Datura innoxia* fingerprint profiles complexity where alkaloids bring a significant contribution. Within preparative steps extraction efficiency as high as 97.8% (w/w) could be achieved in methanol. Undertaken investigations on the scopolamine's dynamic throughout the plant's life cycle highlighted potentially very complex biochemical processes. Using appropriate experimental strategy and kinetic approaches possible metabolic processes (***e.g.***, accumulation, loss) at various plant organs levels (flowers, seeds, leaf, roots) could be described. Scopolamine seems to be the mostly abundant alkaloid in secondary root and seeds. However, clear evidences on tropine, 6-methoxy-8-methyl-8-azabicyclo[3.2.1]oct-3-yl acetate, dehydro hyoscyamine, atropine, hyoscyamine and scopolamine alkaloids in *Datura's innoxia* root allow us to propose a potential mechanism responsible on scopolamine biosynthesis in this plant.

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O8. 1,2,4-triazole-3-thione compounds as inhibitors of dizinc metallo-β-lactamases

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Due to human way of life and overuse of antibiotics, the bacterial resistance is growing up every day and is spreading across the world. The main therapeutic class involved against bacterial infections is based on penicillin core: the β-lactams. This class shares a common structural moiety: a four-membered β-lactam ring, essential for the biological activity. The main mode of bacterial resistance is mediated by the expression of enzymes able to hydrolyze this crucial ring: the β-lactamases. The first enzymes described were serine protease enzymes (SBLs) and several inhibitors such as clavulanic acid were developed and are currently used in combination with β-lactams.

Three decades ago, a new class of β-lactamases emerged and was characterized by the presence of one or two zinc atoms into the active site: the Metallo-β-lactamases (MBLs). At the beginning, these enzymes were just considered as biochemical curiosities but right now, they present the most worrying threat to bacterial disease treatments. Due to specific mode of action, covalent SBL inhibitors are inefficient and moreover, the MBLs are able to hydrolyze a broad-spectrum of β-lactams including the carbapanems, already restricted to severe infections in hospital.

The development of specific and potent inhibitors against the MBLs are crucial. We develop an original scaffold based on 1,2,4-triazole-3-thione heterocycle able to inhibit these enzymes. A first series of compound were synthesized and displayed µM range activity towards the main worrying MBLs.[1,2] Based on these results, the preparation of new analogues is currently under investigation. The presentation will include the design, the synthesis and the biological evaluation of this new class of MBL inhibitors.

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O9. Cyclodextrin inclusion complex of indolizinyl-pyridinium salt for fluorescence cell imaging

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Fluorescence microscopy of living cells has become an integral part of modern cell biology.[1] As a consequence, fluorescent dyes have been extensively investigated to improve their abilities of analytical specificity and sensitivity. However, fluorescent dyes do suffer from several fundamental problems including toxicity, low water solubility and poor membrane permeability when they are used for bio-labeling and bio-imaging.

Fluorescent indolizinyl-pyridinium salt (IPS) was designed as potential pH sensitive dye.[2] In order to increase the water solubility of IPS and to decrease its toxic effect, we tested the formation of the host-guest inclusion complex by mixing IPS with β-cyclodextrin in different ratios. The formation of the host-guest inclusion complex was confirmed by ESI mass spectrometry investigations.

Next, the IPS inclusion complex was tested as fluorescent, pH sensitive cell staining agent on two cell lines (human cervical carcinoma cell line (Hela) and normal human dermal fibroblasts (NHDF)) which were used for imaging and cell viability tests. *In vitro* viability study showed the low-to-no toxicity properties of the IPS inclusion complex, the very high cytotoxicity of the initial compound being completely overcome. Next, a cell staining protocol has been established using the IPS inclusion complex, revealing the fact that inclusion complex could easily penetrate cell membrane and stain the investigated cells. Moreover, in time, the investigated compound showed distinct accumulations in specific organelles with a strong increase of the stained color within both types of investigated cell lines.

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O10. Novel Approach on clinical diagnostic of lysosomal storage disease in DBSs by fluorimetry and MRM-MS assays

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The loss of activity of a specific lysosomal enzyme is a characteristic for lysosomal storage diseases (LSDs), a group of genetic metabolic disorders (e.g., muco-polysaccharidosis, Fabry's Disease; Gaucher's Disease etc.).[1] The enzyme substrates resulting from inherited genetic defects or loss of function can no longer be processed and are accumulating in the lysosome causing severe disease symptoms leading to multiple organ failure (e.g., skeletal malformations, pulmonary deficits, short stature, retarded growth etc.) and finally death.[2] State of art now in LSDs diagnostic uses in first stage an enzymatic determinations by fluorimetry or by mass spectrometry (in few cases) based on different substrates-structures with terminal sugar moieties.

Here we describe highly specific and sensitive diagnostics on dry blood spots (DBS) for (i) molecular determinations of LSDs, particularly muco-polysaccaridoses and muco-lipidoses, by simultaneous fluorimetric and mass spectrometric analysis using newly developed, identical substrates and standard derivatives; (ii) clinical diagnostics of LSDs by multiplex- MS-MRM analysis using specific substrate. The quantification of accumulated by-product in DBS by tandem mass spectrometry can be used to monitor more than 40 genetic disorders in newborn-screening programs. We have developed a high-throughput single and multiplexing assay for muco-polysaccaridoses and muco-lipidoses disorders using DBS. In our studies, the enzymatic activity levels in DBSs were determinate by fluorimetry or multiple reactions monitoring mass spectrometry in the presence of an internal standard (4-ethyl umbelliferone) showing a good statistical correlation in singles assays.

The method described here, may be applied to almost any enzyme that retains activity in a rehydrated DBS. We analyzed dried blood spots for single and multiplexing assay from different muco-polysaccaridoses and muco-lipidoses disorders and in all cases the enzyme activities were below the minimum activities measured in healthy controls. The data obtained suggest that the new mass spectrometric assay is fast, reliable and can be successfully used in clinical trials for quantification of metabolites.

Acknowledgements:
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O11. The design and synthesis of biologically active 3d metal coordination compounds of *N*(4)-allylchalcogensemicarbazones and their derivatives

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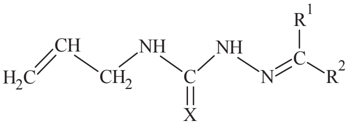
The aim of this work consists in determination of the influence on the biological activity of different substituents in the first position of *N*(4)-allylthiosemicarbazide, alkylation of sulphur atom, and substitution of sulphur atom by selenium atom; determination of the influence of the nature of central atom, nature of ligands, introduction of amines in the inner sphere on composition, structure, physic-chemical and biological properties of the coordination compounds with these ligands; finding of new substances with selective antiproliferative activity against cancer cells and low toxicity. For achievement of these aims, the following objectives were set: synthesis of different 4-allylchalcogensemicarbazones; alkylation of sulphur atom; synthesis of complexes of some 3d metals with these ligands; introduction of amines in the inner sphere of complexes; determination of composition, structure and biological activity of the synthesized substances.



R^1, R^2 = H, alkyl, aryl, heteroaryl; X = S, Se

N(4)-allylthiosemicarbazones coordinate to the 3d metal ions by sulphur atom, azomethinic nitrogen atom and also can coordinate by other donor atom of carbonyl moiety if a five- or six-membered metallacycle is formed. So the *N*(4)-allylthiosemicarbazones can be at least bidentate. Proligands, containing aliphatic carbonyl moiety, possess weaker biological activity. The most active proligands contain α-(*N*)-heteroaromatic carbonyl moiety. Changing of the nitrogen atom's position in the picolidenic fragment leads to a complete loss of anticancer activity of thiosemicarbazones. Replacing of the azomethinic hydrogen atom by a methyl or phenyl group leads to an enhancement of antimicrobial, antifungal and anticancer activities. Coordination with iron usually leads to a decrease of biological activity. Copper(II) coordination compounds with these ligands manifest better antitumor activity than corresponding proligands. The introduction of amines in the inner sphere of copper(II) complexes leads to a significant increase of antimicrobial, antifungal and anticancer activities. *N*(4)-allylthiosemicarbazones, their derivatives and biometal coordination compounds with these ligands in many cases exhibit selective anticancer activity having a much lower inhibition effect on growth and multiplication of normal MDCK cells.

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This work was fulfilled under the direction of the academician of the Academy of Sciences of Moldova Aurelian Gulea.

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O12. Antitumoral chloroacetic esters as dual tubulin/mitochondrial pyruvate dehydrogenase kinase (PDK) inhibitors

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Tubulin is a largely studied biological target for the development of anticancer drugs. By interfering with microtubule dynamics, inhibitors of tubulin arrest the cell into mitosis, leading to cell death by apoptosis or necrosis. In this light, our research team is searching for analogues of phenstatin, a known tubulin polymerization inhibitor, with improved characteristics.[1]

Another biological target that has received attention in oncology is the mitochondrial pyruvate dehydrogenase kinase (PDK). Dichloroacetic acid and dichloroacetate (DCA) are PDK inhibitors and have gained increased attention for the treatment of cancers by targeting altered metabolism that makes cancer cells resistant to death by normal apoptotic pathways. DCA is thus acting by down-regulating the activity of pyruvate dehydrogenase, controlling the switch between oxidative phosphorylation and glycolysis.[2] However, DCA exhibits poor bioavailability and cellular uptake with limited ability to reach its target mitochondria.

In the current work, we propose new molecules with double antitumoral function: DCA or DCA analogues-carriers and antitubulin properties (Figure 1). To the best of our knowledge, this is the first-time association of PDK with tubulin inhibitors in the literature and will allow to gain some insights on the possibility to obtain synergistic antitumoral activity by using such compounds. The biological evaluation on cancer cells has been assessed in order to test the ability of these new molecules to carry DCA into mitochondrial matrix and evaluate their global cytotoxicity potency. The properties of newly synthesized compounds on tubulin polymerization have also been evaluated and highlighted potent inhibitory potential.

The biological evaluation on PDK will be realized in due course.

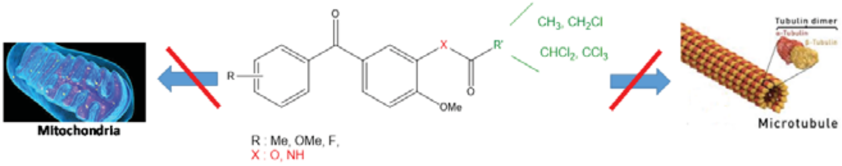

Figure 1. General structure of potential PDK/tubulin dual inhibitors

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O13. Biosourced dual antibacterial and antifungal agents

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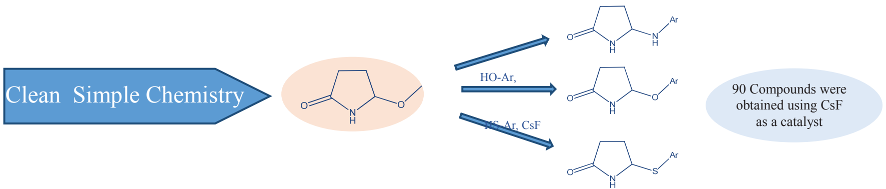
For more than 15 years, neither therapeutic innovation nor new chemical family has been proposed in the field of antibiotics, and this shortage of therapeutic alternatives reaches a critical level, particularly correlated with the appearance of multiresistant bacteria.[1] On February 27, 2017, the WHO published the first catalog of 12 bacterial families with the biggest threat ever raised for humanity and confirmed importance of our project. Within the framework of this project, different biosourced compounds are being modified in order to create new antibiotics. The antibiotics will be not only design for human infection treatment, but will also be formulated in some antimicrobial paints and coatings. In fact, there is a steady rise for non-toxic surfaces and medical equipment to counter infection risk from various microorganisms. As an example, the U.S. antimicrobial paints and coatings market size generates sales of over USD 700 million per year. As a consequence, the French Institute of Agro-Sourced Materials (IFMAS) financially supports this project for the discovery of a series of antimicrobial compounds which could be introduced in coatings and paints.

Many heterocyclic nuclei have been reviewed as antimicrobial agents but our attention was focused on the pyrrolidinone nucleus. Using pyroglutamic acid as platform molecule, a new catalytic chemical methodology was set up and a library of derivatives was synthesized and evaluated on multidrug resistant strains. To our delight, some derivatives were confirmed as hit compounds due to their potent antibacterial activity on *Acinetobacter baumannii,* the most resistant gram negative bacteria combined with an antifungal activity on *Candida albicans.*

From a synthetic point of view, we have been able to demonstrate the potential of CsF as a new catalyst, being able to form new C-N, C-O and C-S chemical bonds, and afforded us a large compound family using a clean, solvent free synthetic pathway with very good yields.



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O14. Vecteurs non viraux basés sur des imines hydrophobes-hydrophiles à travers la chimie covalente dynamique

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L'une des étapes clés de la thérapie génique est l'obtention d'un vecteur approprié pour l'ADN, qui doit répondre à de nombreuses exigences: il doit lier l'ADN par des interactions réversibles, présenter de la biocompatibilité, être biocompatible, biodégradable, protéger l'ADN de la dégradation enzymatique, faciliter l'endocytose, et ainsi de suite[2,3].

On sait que les vecteurs non viraux présentent de nombreux avantages par rapport aux vecteurs viraux, mais aussi un inconvénient principal : une faible efficacité de transfection. C'est pourquoi, au cours des dernières années, l'intérêt des chercheurs pour l'obtention de vecteurs non viraux avec des capacités de transfection élevées augmente de plus en plus.

Cette intervention présente la synthèse et la caractérisation de vecteurs non viraux hydrophobes-hydrophobes pour le transfert de gènes. On a synthétisé des composés amphiphiles sur des liens d'imine irréversibles, qui, du aux processus d'imination et de transimination, se sont avérés capables de s'auto-organiser dans des structures sphériques semblables aux micelles à noyau hydrophobe et enveloppe hydrophile, tel qu'il a été prouvé par la microscopie électronique de transmission (TEM).

La capacité des composés synthétisés de complexer les acides nucléiques formant des polyplexes a été mise en évidence par l'électrophorèse sur gel d'agarose, pour les différentes valeurs du rapport N/P (le rapport molaire entre atomes de N de la structure du vecteur non viral et les atomes de phosphore de la structure des acides nucléiques). Les polyplexes ont été caractérisés du point de vue morphologique par microscopie électronique de transmission, tout comme du point de vue de la stabilité colloïdale, par la détermination du potentiel Zêta. Par la suite, des tests biologiques ont été effectués sur des cultures cellulaires Zêta, et on a déterminé la cytotoxicité des polyplexes et leur efficacité de transfection, tests qui ont validé la méthode de l'exploitation des principes de la chimie covalente dynamique dans l'obtention de vecteurs non viraux pour la thérapie génique.

Remerciements

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O15. Action des complexes de coordination de Cu sur les enzymes antioxydants des microbes pathogènes

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Il est bien connu que les composés contenant du cuivre sont caractérisés par une activité antimicrobienne élevée. Dans le contexte de la résistance accrue des microorganismes pathogènes aux antibiotiques, la recherche de nouveaux agents antibactériens est de plus en plus actuelle.

Des recherche antérieures sur les composés de coordination du 4-allyl-s-alkylthiosemicarbazone salicylaldéhyde et leurs dérivés ont montré une activité antimicrobienne très élevée contre *Escherichia coli, Salmonella abony, Staphylococcus aureus, Enterococcus faecalis* et *Candida albicans*. Ces recherches nous ont permis d'établir, que l'introduction d'un groupe méthoxy dans la troisième position du fragment salicylidène augmente de 2 à 33 fois l'action des complexes sur toute la gamme des microorganismes. La substitution de la fraction salicylidène par le groupement 2-hydroxy-1-naphtylidène entraîne une activité deux fois plus élevée contre les bactéries gram-négatives, et 1500 fois plus élevée contre les bactéries gram-positives et *Candida albicans*.

Afin d'élucider certains des mécanismes de l'action antimicrobienne, l'action des doses sublétales sur l'activité des enzymes antioxydantes pour les composés étudiés a été déterminée dans les cellules des pathogènes. Les enzymes antioxydantes primaires - superoxyde dismutase (SOD), catalase (CT) et peroxydases (POx) sont des substances protéiques qui s'engagent directement dans le processus d'élimination des radicaux libres formés dans des cellules de microorganismes en réponse à l'action des agents chimiques. Une diminution statistiquement significative de l'activité des enzymes mentionnées a été enregistrée pour toutes les souches des pathogènes et les complexes testés. La diminution la plus prononcée de l'activité enzymatique antioxydante a été enregistrée lors de l'utilisation des composés de haute activité bactéricide et fongicide.

On sait que les enzymes catalase et superoxyde dismutase sont activement impliquées dans la protection des cellules des microorganismes pathogènes contre les facteurs biochimiques produits par les macrophages *in vivo* pour arrêter l'infection. Ainsi, par l'augmentation de la production de catalase et de superoxyde dismutase, les microorganismes pathogènes neutralisent les radicaux de peroxyde d'hydrogène et superoxyde formés par les cellules immunitaires, en évitant ainsi le scénario létal. La diminution significative du niveau d'activité de ces deux facteurs de protection importants conduit à une augmentation du niveau de vulnérabilité des cultures *in vivo*, ce qui serait un argument pour la recherche biomédicale afin de promouvoir davantage ces composés précieux.

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O16. Dynamic hydrogels for bio-applications

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Hydrogels based on chitosan and monoaldehides were synthesized based on dynamic covalent chemistry which enabled the self-organization of the imine units in ordered clusters which acted as crosslinkers. This new concept of chitosan hydrogelation allowed the preparation of a large variety of hydrogels using monoaldehydes with intrinsic biologic properties.[1-6] Thus, were obtained hydrogels with antifungal activity against planktonic yeasts and biofilms (Fig. 1a), hydrogels with antitumor activity (Fig. 1b), superporous hydrogels with high absorption ability (Fig. 1c) or luminescent hydrogles (Fig. 1d). The hydrogels properties were close related to the nature of the monoaldehyde.

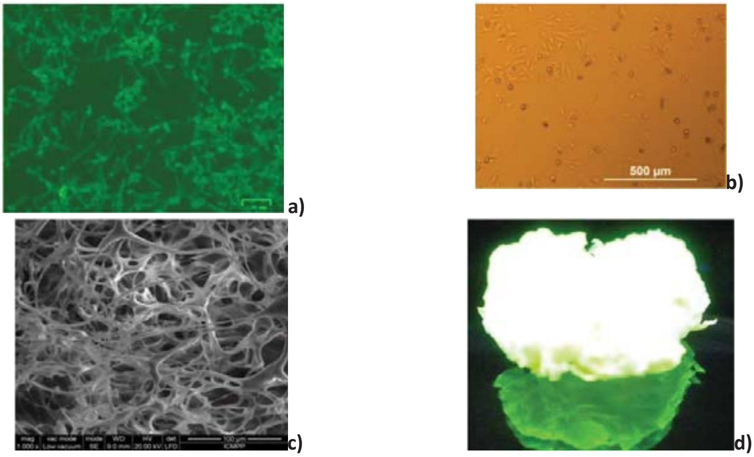

Figure 1. a) *C. albicans* biofilm after the treatment with a hydrogel based on chitosan and 2-formyl-phenyl-boronic acid; b) Bright-field microscopy images of HeLa cells incubated with a hydrogel based on chitosan and nitrosalicylaldehyde for 24 , at 37 °C; c) SEM microstructure of superporous hydrogel based on chitosan and salicylaldehyde; d) luminescent hydrogel based on chitosan and phenothiazine-bearing aldehyde.

This project has received funding from the *European Union’s Horizon 2020 research and innovation programme* under grant agreement No 667387 WIDESPREAD 2-2014 SupraChem Lab and supported by a grant of the Romanian National Authority for Scientific Research and Innovation, CNCS/CCCDI – UEFISCDI, project number PN-III-P3-3.6-H2020- 2016-0011, within PNCDI III.

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O17. Anticancer, antioxidant and toxicity activities of new compounds along with their ability to induce hemolysis and methemoglobin formation in human RBCs

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This work represents a series of comparative biological studies of the new synthesized compounds CMJ-23 and CMJ-33 exhibiting selective cytotoxicity.

The antiproliferative effect of these compounds was tested on five cell lines of different origin. It was established that CMJ-23 exhibited cytotoxic activity against cell lines BxPC-3, RD, HeLa, MeW-164 with IC_{50} values of 2.5±2.7; 0.30±0.04; 18.7±1.0; 0.36±0.20 μM, respectively. CMJ-33 showed the highest anticancer activity against cell lines BxPC-3, RD, HeLa, MeW-164 with IC_{50} values of 0.10±0.04; 0.20±0.03; 0.4±0.2 μM, respectively. Comparative study between test compounds and doxorubicin (DOX) in regard to cancer cell lines was showed that CMJ-33 exhibits stronger inhibitory activity on cancer cells proliferation than DOX, and the antiproliferative activity of CMJ-23 are comparable to that of the DOX. An additional experiment aiming on the evaluation of the nephrocytotoxic effect on normal cell line MDCK revealed that CMJ-23 and CMJ-33 are significantly less toxic than DOX.

In order to exclude the eventual presence of concomitant adverse effects associated with oxidative stress, compounds were tested by several antioxidant-capacity (AC) assays. Thus, analyzing the ORAC results was observed that CMJ-23, CMJ-33 showed the highest AC compared with trolox and DOX. Selective ABTS, DPPH - radical scavenging ability of the tested compounds and the standards can be ranked in the order CMJ-23 > CMJ-33 > DOX > trolox > rutin, and CMJ-23 > trolox > rutin > CMJ-33 > DOX, respectively. CMJ-23 and CMJ-33 were more effective in quenching $ABTS^{\bullet+}$ in the system with IC_{50} values of 6.20±0.01 and 11.4±1.4, respectively. The enhanced inhibition displayed on the ABTS radicals shows that the compounds are capable of donating electrons to neutralize free radicals, what indicate their potentials as chemotherapeutic agents for radicals chains terminator.

Drug-induced hemolysis and methemoglobin formation is a relatively rare but serious toxicity liability, so test compounds were performed to screen for toxic hemolysis and methemoglobin formation in human RBCs. This study showed results, which did not exceed the permissible values in the therapeutic concentration range.

Direct toxic evaluation of compounds was performed by Paramecium colorimetric bioassay. It was founded, that the LC_{50} for compound CMJ-23 is 45 times less and for compound CMJ-33 is 24 times less than DOX.

In summary, these results suggest that the tested compounds CMJ-23 and CMJ-33 are of great interest due to their possible use as less toxic and more effective anticancer drugs.

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P1. New leads in the development of PLK1 inhibitors via the expected cyclization of aromatic cycloimmonium salts and ethyl cyanoformate. Discovery of a potent growth inhibitor of *C. albicans*

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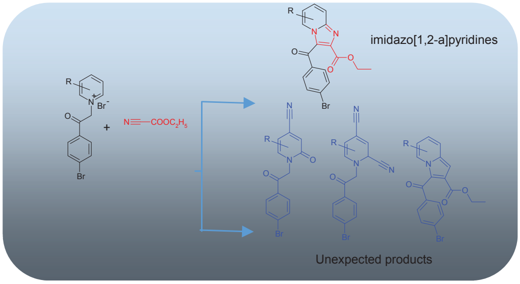
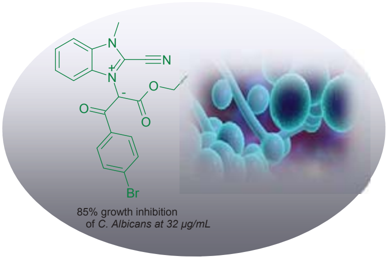
Human polo-like kinase 1 (PLK1) was discovered to play key roles in regulating a broad spectrum of critical cell cycle events and in the maintenance of genomic stability. The PLK1 enzyme is expressed only in dividing cells and is a major regulator of the cell cycle. It controls entry into mitosis and regulates the spindle checkpoint. The expression of Plk1 in normal cells is not nearly as strong as that in cancer cells, which makes Plk1 a discriminating target for the development of cancer-specific small molecule drugs, and as a result, pharmaceutical companies are interested in developing a drug which targets this kinase.[1] 3-Aroylindolizine systems have attracted considerable interest from our research group in recent years for their antitumoral potential.[2] Based on our previous results, a new family of imidazo[1,2-a]pyridines was designed, synthesized and evaluated for their ability to inhibit Plk1. The NCI cell growth proliferation assays have shown that imidazo[1,2-a]pyridines are not as efficient as indolizines, information which enriches our knowledge on structure-activity relationships and new series will be designed in the future. On the other hand, one of the cycloaddition's side products, was found to inhibit the growth of *C. albicans* with 85% and deserves further chemical and biological efforts to obtain analogues with improved characteristics.





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P2. Synthesis and antimycobacterial activity of some new monoindolizine mono-salt based on 4,4`-bipyridine skeleton

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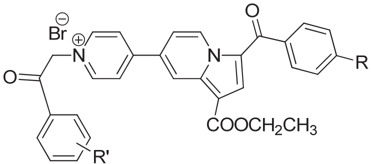
Tuberculosis is one of the major causes of disability and death worldwide[1], remaining one of the top 10 causes of deaths in 2015. Major efforts are done for the discovery and development of new TB drug targets and candidate drugs, and evaluate novel TB drugs and optimal drug combinations in preclinical and clinical studies[2,3]. One of the important strategies involves the synthesis of analogous of the existing drugs, and second one refers to the search for novel structures rational or not designed. Between the various classes of organic compounds, fused N-heterocyles, especially pyridine fused systems, showed promising anti-TB activity against replicating Mycobacterium tuberculosis (Mtb) H_{37}Rv, similar to isoniazid[4,5].

Five compounds having a monoindolizine mono-salt skeleton were designed and synthesized in order to evaluate their antimycobacterial activity. The synthesis involves three steps: two alkylations and one 3+2 dipolar cycloaddition. The assay demonstrating that our compounds are potent against both replicating and non-replicating Mtb, have a bactericidal mechanism of action, are active against drug-resistant Mtb strains, present a moderate to good activity against nontuberculous mycobacteria, a good intracellular activity, and a moderate to high cytotoxicity. For one compound showing a promising anti-TB profile, a complete absorption, distribution, metabolism, excretion and toxicity (ADMET) study has been performed (including Plasma Protein Binding, Caco-2 Permeability, Cytochrome P450 Inhibition and in vitro Microsomal Stability studies).



1a-e

1a. R= H; R'= Me(*p*)
1b. R= Cl; R'= OMe(*p)*
1c. R= Cl; R'= OMe(*m*)
1d. R= Br; R'= OMe(*m)*
1e. R=Cl; R'=Me*(p*)

Acknowledgement
We thank the POSCCE-O 2.2.1, SMIS-CSNR 13984-901, Project no. 257/28.09.2010, CERNESIM, for the NMR experiments

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P3. On the discovery of new anti-inflammatory compounds targeting the P2X7 receptor: emerging pyrrolidines

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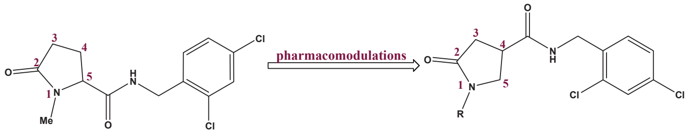
The P2X7 receptor (P2X7R) is an ATP-gated ion channel, a purinergic receptor that is mostly expressed in immune system cells. Consequently, the P2X7 receptor is involved in many neurodegenerative pathologies, inflammatory bowel diseases (IBD) and their associated forms of cancer.[1] The purinergic receptors have only begun to be extensively studied in recent years and there are currently no marketed products that target the causal treatment of inflammatory bowel diseases.

Since 2009, more P2X7R antagonists have been developed by companies such as Evotec or GlaxoSmithKline. Among those compounds, the GSK1370319A has shown good results in inhibiting the human P2X7R,[2] confirming the relevance of the pyrrolidin-2-one as an important scaffold for this biological target.

Taking this molecule as reference, we have synthesized compounds which contain the amidic group in the 4th position rather than in the 5th, and assessed their biological activities.



GSK1370319A

Itaconic acid, a natural, resource-efficient compound produced by the fermentation of glucose or molasses using fungi, was used as starting material. The acid can be easily converted into dimethyl itaconate, which was further used in the syntheses. The biological evaluation of obtained products is currently under way.

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P4. Synthesis and anticancer evaluation of new azaindolizines

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Considerable efforts have been focused in the past decades, on the design and development of new anticancer drugs with improved efficiency, limited toxicity and less prone to develop multidrug (MDR) resistance.[1]

Among the huge variety of structures synthesized and tested as anticancer agents in the last years, Phenstatin[2] stand as ones of the most potent tubulin polymerization inhibitors binding to the colchicine site of the tubulin and thus, interfering with the equilibrium dynamics associated with the cell division process.

Because of the structural simplicity of this compound, it continues to be a target for the design in anticancer therapy, the recent literature being rich in pharmacomodulators of Phenstatin. Inspired by reports in which by the replacement of 3-hydroxy-4-methoxyphenyl ring of Phenstatin with indolizine derivatives,[3] the authors obtained compounds showing an interesting cytotoxic activity, we decided to synthesize new analogs containing azaindolizines in substitution of the 3-hydroxy-4-methoxyphenyl ring of Phenstatin in order to evaluate their anticancer properties.

Pyrrolo[1,2-b]pyridazines and pyrrolo[2,1-a]phthalazines are compounds well known for their strong blue luminescence, but in the same time, they are promising for the drug design, some derivatives being reported to have antimicrobial or anticancer effect, or to act as acyl CoA:diacylglycerol acyl transferase (DGAT1) inhibitors. The development of biologically active organic compounds showing luminescent properties should as well help in a better understanding of their mechanism of action.

Considering all these above data we describe here the synthesis and cytotoxicity evaluation of new analogues of Phenstatin, bearing an pyrrolo[1,2-b]pyridazin-7-yl ring (unsubstituted or 2-substituted) or a pyrrolo[2,1-a]phthalazin-3-yl group (in substitution of 3-hydroxy-4-methoxyphenyl ring) combined with either a 3,4,5-trimethoxyphenyl ring or a 3,5-dihydroxyphenyl ring.

Acknowledgements:
We thank the POSCCE-O 2.2.1, SMIS-CSNR 13984-901, Project no. 257/28.09.2010, CERNESIM, for the NMR experiments
The authors gratefully acknowledge National Cancer Institute (NCI) for biological evaluation of compounds on their 60- cell panel: the testing was performed by the Developmental Therapeutics Program, Division of Cancer Treatment and Diagnosis (the URL to the Program's website: http://dtp.cancer.gov/).

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P5. MS-based footprinting methods for characterization of specific protein aggregates

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The aggregation of proteins is of critical importance in a wide variety of biomedical situations, ranging from abnormal disease states (such as Alzheimer's disease) to the production, stability and delivery of protein drugs (e.g. Insulin). A significant proportion of elderly population is affected by progressive neurodegenerative disorders. Formation and accumulation of fibrillar plaques and aggregates of ß-amyloid peptide (Aß) in brain have been recognized as characteristics of Alzheimer's disease (AD).[1] Although a wide range of techniques such as circular dichroism, atomic force microscopy, electron microscopy, light scattering, were used in several studies, a detailed understanding of protein aggregation mechanism remains to be achieved. Understanding aggregation is also important for the successful production of protein drugs and for maintaining their stability and insuring effective delivery.[2]

In this application, we have investigated one aggregating protein, Aß peptide as model systems using an appropriate protein footprinting approach. A specific approach for footprinting is to map proteins with reactions of OH radicals. FPOP (fast photochemical oxidation of proteins) may be useful for determining protein-protein interfaces, aggregating species, affinities for tiny amounts of proteins in biophysics and drug discovery.

Our results shows that: (i) HDX-MS in combination with pepsin digestion may give structural information of aggregated species at the amino acid level; (ii) Using recombinant Abeta (1-40) peptide will bypass the challenges associated with impurities in synthetically produced Aβ peptide; (iii) FPOP strategy seems to be a good method for studying the molecular mechanism for formation of protein aggregates.

Acknowledgements:
This work was supported by the Romanian National Authority for Scientific Research, CNCS–UEFISCDI, project number PN-II-RU-TE-2014-4-0920.

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P6. Synthesis and biological evaluation of new 1,2,3-triazole derivatives

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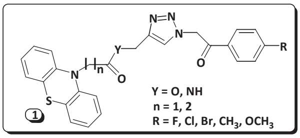
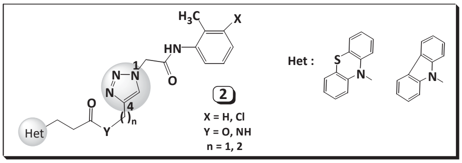
Carbazole and phenothiazine derivatives are an important type of nitrogen-containing aromatic heterocyclic compounds. This type of compounds have special pharmaceutical interest because of their versatile biological activity, such as antiinflammatory, antibacterial, antifungal, antiviral and anticancerigen activity.[1,2]

Phenothiazin-triazole derivatives with general structure 1 are inhibitors of farnesyltransferase, *in vitro*, some compounds showed IC_{50} values in the micromolar range.[3]



In order to enhance inhibitory activity we achieved structural modifications of the compounds with general structure **1**. The obtained compounds have general structure **2**.



Structures of new compounds obtained were characterized by IR and NMR spectroscopy (^{1}H, ^{13}C).

The compound with Het = 10*H*-phenothiazine, Y= NH, n= 1, X= Cl, was evaluated for their antiproliferative activity on a NCI-60 cancer cell line panel (SUA). This compound exhibited selectiv cell growth inhibitory activity, *in vitro*, with 80% inhibition of OVCAR-4 cell lines, of ovarian cancer, and 62% inhibition of SNB-75 cell lines, CNS cancer.

Keywords: 1,2,3-triazole, phenothiazine, carbazole.

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P7. Synthesis benzofuran derivatives with anticipated anticancer activity

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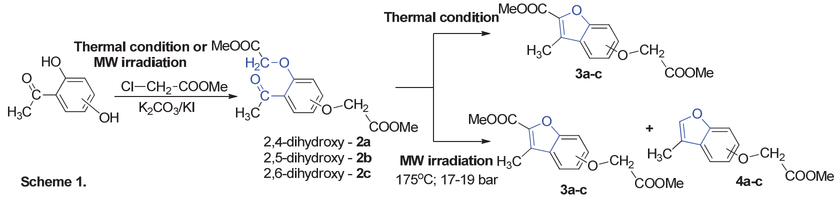
The synthesis of benzofuran derivatives has attracted a special attention thanks to their appearance in large number of natural products[1] and synthetic pharmaceuticals.[2] Various other classes of benzofurans are attractive to chemists for their biological activities such as antimicrobial,[3] antioxidant, anti-inflammatory,[4] antifungal, PPARd agonists, antifeedant, anti-HIV, anti-tumor and antiplatelet activities, and in other field of chemistry and agriculture.

In the first part of the study were obtained a series of dihydroxyacetophenone derivatives with antimicrobial and anticancer activity. In the case of the first stage (O-alkylation) was observed if that the reaction is carried out at a higher temperature (160-165ºC) instead of obtaining dihydroxyacetophenone derivatives, benzofuran derivatives was obtained with quantitative and good yields. Under microwave (MW) irradiation, the reaction was carried out at a higher temperature (165 ºC) and higher pressure (17-19 bars). Reactions have occurred very slowly (5-8 h), but instead of obtaining only compounds (**3a-c**), we obtained a mixture of benzofuran derivatives (**3a-c** and **4a-c**). Scheme 1.



Scheme 1. Reaction pathway for preparation of benzofurane derivatives.

The structures of all compounds were proved unambiguously by spectral analysis (IR, ^{1}H-NMR, ^{13}C NMR, two-dimensional experiments 2D-COSY, 2D-HETCOR (HMQC), long range 2D-HETCOR (HMBC).

Also was tested the cytotoxicity for the six new compounds. Cytotoxicity was measured on HeLa S3 and Hep G2 cells using an AlamarBlue assay. Alamarblue was purchased from BioSource Europe.

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P8. Biosynthesized dextran coated magnetic nanoparticles with antifungal activity

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Biofilm formation is a challenging problem of the modern world, the most serious implications being associated with severe microbial infections in humans. The solution can be the use of nanostructures which can interact directly with the microorganism's cell wall. We engineered dextran coated iron oxide nanoparticles, loaded with propiconazole, in order to test the hypothesis of a combined effect of the polymer and drug, both known for their antifungal activities. Magnetic nanoparticles were coated with biosynthesized dextran (obtained from an exopolysaccharides producing strain) of 1% and 2% concentrations, followed by the embedding of propiconazole onto the dextran shell. FT-IR, EDX, DLS and TEM measurements showed a successful polymer coating, while the 2% formulation nanoparticles revealed an activity on Candida albicans strain, breaking 77% of biofilm. The improved version of the system (loaded with propiconazole) showed a maximum antifungal activity on Candida albicans, in both planktonic and biofilm phase.

Acknowledgement: This work was financed by Horizon 2020 ERA Chairs Project, no: 667387: SupraChemLab Laboratory of Supramolecular Chemistry for Adaptive Delivery Systems ERA Chair initiative and Partnership program in priority areas – PN II, project nr. 2011-3.1-0252 (NANO-ABLATION).

P9. New imidazole/benzimidazole derivatives and their biological interest

Dorina Amăriucăi-Mantu*, Dumitrela Cucu, Bogdan Ionel Bratanovici, Costel Moldoveanu, Gheorghiță Zbancioc, Ionel I. Mangalagiu

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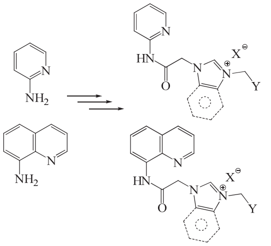
Nitrogen heterocyclic compounds have received considerable attention over the years due to their important applications in various domains, such as: medicine and pharmacy, optoelectronic, agriculture.[1]

It is well known that imidazole and benzimidazole, as well as pyridine and quinoline, are important constituents of many drugs with interesting biological properties: antimicrobial, anti-inflammatory, antihypertensive, anticancer.[2,3]

The aim of the present work was to synthesize new hybrid derivatives containing both imidazole/benzimidazole and pyridine/quinoline scaffolds and to evaluate their biological properties.

The desired compounds were obtained starting from 2-aminopyridine and 8-aminoquinoline and the strategy for synthesis involved three steps: *N*-acylation, *N*-alkylation and quaternization of *N*-heterocycle.



The structure of the newly compounds was proven by elemental (C, H, N) and spectral analysis (IR, 1H NMR, 13C NMR, 2D-COSY, HMQC, HMBC).

Some of the newly obtained compounds have been selected for evaluation of their anticancer and antimycobacterial activity.

Acknowledgements: The authors are thankful to the National Cancer Institute for the *in vitro* evaluation of anticancer activity and National Institutes of Health and the National Institute of Allergy and Infectious Diseases for the *in vitro* evaluation of anti-TB activity and the POSCCE-O 2.2.1, SMIS-CSNR 13984-901, No. 257/28.09.2010 Project, CERNESIM, for the NMR spectra.

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P10. Searching for a *N*-heterocyclic lead compound - Docking on biomolecules

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Molecular docking is one of the most used tools in structure-based rational drug design. Usually, it is used to investigate the interactions of small ligands with large compounds in order to find the suitable geometrical arrangements.[1] Lately, various studies were carried out to evaluate the complex formation of *N*-heterocyclic compounds with large biomolecules, such as acetylcholinesterase (AChE).[2] Several kinetic models for AChE proposed that the binding pocket of AChE consists of two substrate-binding sites, the catalytic anionic site (CAS), near the bottom of the active site gorge, and the peripheral anionic site (PAS), near its entrance. The binding of ligands at the PAS affects catalytic activity.[3]

The aim of the present study was to investigate the interactions between acetylcholinesterase and five *N*-heterocyclic compounds from pyridinium and indolizine families, previously synthesized by us. In this purpose docking simulations were developed through Glide docking tools, using two methods: SP (standard precision) and XP (extra precision). The most suitable method was found to be the XP docking. In this case, the values of Glide Score and RMSD have been improved. In addition, it was observed that when water molecules from protein structure were removed, the ligands were docked better inside of the AChE. This fact was also confirmed by the improvement of Glide Score values.

From the five ligands, a pyridinium ligand showed the best docking inside of the AChE molecule. However, this ligand has docked quite far from the active CAS site, being more close to the peripheral site (PAS). Promising results were also obtained using indolizine ligands, but their larger structure did not allow them to dock in the sites of interest.

Acknowledgements:
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P11. Towards new elicitors of wheat plant defense responses against *Zymoseptoria tritici*

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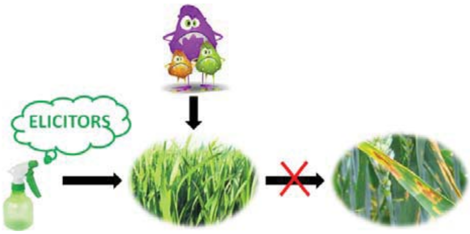
Innovation toward plant protection products compatible with sustainable agriculture and healthy food is today strongly encouraged. *Zymoseptoria tritici*, is a species of filamentous fungus, an ascomycete in the family *Mycosphaerellaceae*. It is a wheat plant pathogen causing septoria leaf blotch that is difficult to control due to resistance to multiple fungicides. The pathogen today causes one of the most important diseases of wheat, characterized by necrotic blotches on the foliage.

Elicitors are highly specific structures that, at very low molecular concentrations, induce plant defense responses. When elicitors are in contact with the plant, signals are perceived and this information is transduced to the plant, so that defenses mechanisms can be turned on. The application of elicitors, which is currently the focus of research, should allow avoiding or at least reducing the use of pesticides.

As a consequence, one area of research in the lab team is to evaluate the potential of series of compounds to elicit plant defense responses against the wheat pathogen *Zymoseptoria tritici*. As an elicitor has no direct activity on the pathogen, a first step is to evaluate the biofungal activity of all compounds on *Zymoseptoria tritici*. The compounds which exhibit no direct activity are then selected for *in planta* testing for elicitation.

In this presentation, the activities (direct inhibition of the pathogen or elicitation) of series of compounds will be discussed. A whole part is biosourced and obtained by simple chemical pathways in large quantity.



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P12. 1,3-Dithiolium flavonoids with antibacterial activity

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A series of halogenated 1,3-dithiolium flavonoids has been synthesized and their antibacterial activity has been assesed against both Gram-positive and Gram-negative bacteria.

It was found that the derivatives containing heavier halogen atoms (bromine and iodine) displayed potent antibacterial properties. The mechanism of action is likely to involve the bacterial cell wall as a target, while no evidence has been found that the tested compounds act against the bacterial DNA. SEM studies of the exposed microorganisms show that the tested flavonoids lead to the agglutination of the affected cells.

Further studies are underway, aimed at better understanding the involved mechanism of action, as well as determining the cytotoxicity of the tested 1,3-dithiolium flavonoids.

P13. New enzymatically activated glyco-doxorubicin prodrugs synthesized by a catalysis free diels-alder reaction

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Prodrugs are drug molecules that have been chemically modified in order to change properties including solubility, bioavailability and toxicity as well as to introduce functions such as targeting.[1] The active drug is released *in vivo* either by enzymatic or chemical modification. Recent advances in chemoenzymatic synthesis of carbohydrates and in bioconjugation techniques are now facilitating the use of oligosaccharides in the design of prodrugs, hereafter referred to as glyco-prodrugs. Well known properties of carbohydrates include high aqueous solubility and targeting of specific cells through carbohydrate-protein interactions. Most of the existing examples of glyco-prodrugs consist of monosaccharides, including the glucuronic acid derivatives of anti-cancer drugs.[2]

In the present work, we have synthesized glyco-prodrugs of oligosaccharides conjugated to doxorubicin, an anti-cancer compound (figure 1). The carbohydrate moieties were chosen to facilitate different modes of administration. Depending on the intended use, glyco-prodrugs with linkers cleavable either by esterases or by specific proteases have been synthesized. The carbohydrate part was conjugated with the drug-linker part using a catalysis free Diels-Alder type reaction which can be performed in aqueous media.[3] The strategy allowed for late stage conjugation, eliminating the need for extensive carbohydrate protecting group strategies. The design, synthesis and biological evaluation of the drug release will be presented.

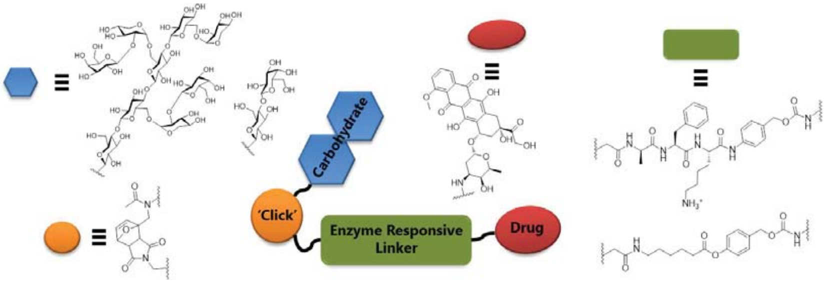

Figure 1. General design principle for glyco-prodrugs.

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P14. Composition and biological activities of *Morinda lucida* extracts used in Benin traditional medicine

Dah Nouvlessounon Marius Durand[1, 2], Mihaela Cudălbeanu[2], Ioana Otilia Ghinea[2*], Daniela Borda[3], Rodica Mihaela Dinica[2*], Baba-Moussa Lamine[1]

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Herbal products derived from roots, leave or barks are the most important components of traditional medicine in West Africa, where traditional healers provide the primary health care for treatment of many diseases. This is the case of *Morinda lucida* used in Benin for the treatment of certain diseases. In order to scientifically explain some of the anecdotal, folkloric ethno medical uses of *M. lucida*, this study aimed at performing a phytochemical screening and evaluating some biological properties of plant leaves extracts. Organic and water extracts were obtained using ultrasonication. Thin Layer Chromatography (TLC) with five solvents systems was used for qualitative screening. Gas Chromatography-Mass Spectrometry (GC-MS) was used to identify the volatile compound. 96-well microplate method was used to quantify total polyphenols and flavonoids which were also analyzed with HPLC method. For the bioassays, the disc diffusion method was used to evaluate antibacterial activity with 10 pathogen reference strains. Antioxidant activity was determined by two methods (DPPH assay and β-carotene bleaching). Microplate method based on the starch test was used for α-amylase enzyme inhibition (acarbose as reference molecule) while *p*-nitrophenyl-β-D-glucopyranoside was used as substrate for β-glucosidase enzyme inhibition. Polyphenols and flavonoids content, vary according ($p < 0.05$) to the extracts. HPLC chromatograms show a good separation of different compounds and show that *M. lucida* methanolic extracts have more bioactive compounds. The results show the interesting biological activity of the all extracts. These activities vary according to the extracts type. These results confirm some uses of *M. lucida* in traditional medicine and pave the way for further studies.

Keywords: Enzyme inhibition, Antioxidant, GC-MS, HPLC, antimicrobial activity

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P15. Composition chimique des métabolites secondaires de *Trichoderma gansii* et activité antimicrobienne contre deux phytopathogènes

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Trichoderma spp sont des champignons saprophytes filamenteux ubiquitaires, qui ont la capacité de sécréter une large gamme de métabolites secondaires possédant plusieurs activités biologiques. Le présent travail a pour objectif de caractériser les métabolites secondaires issus de *Trichoderma gansii* et d'évaluer leur potentiel antimicrobien contre *Pythium myriotilum* et *Phythium ultium* agents responsables de la pourriture racinaire du macabo et du haricot commun, respectivement. Après fermentation de *Trichoderma gansii* sur milieu liquide pendant 14 jours, l'extrait brut a été obtenu par lavage du filtrat à l'acétate d'éthyle. La teneur en composés phénoliques et en flavonoïdes a été déterminée par spectrophotométrie. L'analyse des métabolites volatiles s'est faite par chromatographie en phase gazeuse couplée à la spectrométrie de masse (GPG/SM) alors que les métabolites non volatiles ont été analysés par chromatographie liquide haute performance (CLHP) à 320 nm. L'activité antimicrobienne montrent que l'extrait brut a une concentration de 60,13 mg/ml avec 2,4mEq/ml de composés phénoliques et 0,952 mg/ml de flavonoïdes. L'analyse par CPG/SM révèle la présence de 32 composés avec le benzothiophene-2-carboxylic acid, 4,5,6,7-tetrahydro-7-hydroximino-3-(2-(4-morpholyl)-1-oxoethylamino)-ethyl ether (20,23 %) ; le 3,5-bis(ter-butyl)-hydroxy-propiophenon (9,88 %) et le 10,12,14-nonacosatriynoic acid (8,31 %) comme composés majoritaires. L'analyse par CLHP a révélé la présence de deux composés distincts dont l'identisation est en cours. L'activité antimicrobienne montre qu'à 400 µg et à 100 µg, l'extrait brut inhibe totalement (100 %) la croissance mycélienne de *P. myriotilum* et de *P. ultimum*, respectivement. Ces résultats montrent que *T. gansii* peut être utilisé comme agent de lutte biologique. Cependant, l'isolement et la caractérisation des métabolites est nécessaire.

Mots clés : *Trichoderma gamsii* ; métabolites secondaires ; activité antimicrobienne ; *Pythium myriotilum* et *Pythium ultium*

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P16. Evaluation of methacrylic microparticles for the treatment of peri’ase

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Good oral hygiene is very important for the human health. A poor oral hygiene can lead to some dental diseases, such as gum diseases, infection, bone loss, heart disease and strokes. The first stage of gum disease is called gingivitis which is a mild and reversible form of this disease, but if not treated it can lead to periodontitis.

The periodontitis represent a chronic inflammatory disease characterized by damage of soft tissue and destruction of the supporting structure of the teeth. Various drug delivery systems have been developed for the treatment and prevention of the periodontal diseases, some of them being commercially available such as Periochip, Actisite, Atridox and Arestin. The periodontal pocket has been investigated as a site for local drug delivery, many research topics being directed towards the development of various devices including fibers, gels, films, nano and microparticles.

Micro and nanoparticles can be synthesized from monomers (by polymerization and polycondensation reactions) as well as from performed polymers (by crosslinking reactions, coacervation method, solvent evaporation method and spray drying technique). The development of the polymer science has led to the preparation of the micro and nanoparticles starting from both natural and synthetic polymers, each class of polymers presenting a number of specific advantages.

The aim of this study was to develop a new drug delivery system for sustained release of metronidazole by grafting the chitosan on the surface of porous microparticles based on glycidyl methacrylate (GMA), hydroxyethyl methacrylate (HEMA) and dimethacrylic monomers (mono-, di- and triethylene glycol dimethacrylate). The methacrylic microparticules were obtained by a simple method namely, suspension polymerization technique. The synthesized microparticles were characterized by various techniques such as, FTIR spectroscopy, TG analysis, SEM, AFM and DVS methods. The results obtained indicate that the presence of polysaccharides in structure of polymeric materials lead to microparticles characterized by the high values of the specific surface areas and better sorption capacities compared to the microparticles based on GMA, HEMA and dimethacrylic monomers. At the same time the possibility to use the microparticles as local delivery of metronidazole for the treatment of periodontal disease has been investigated.

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P17. Volatile constituents of *Hexalobus monopetalus* (A. Rich.) Engl. & Diels and *Securidaca longepedunculata Fresen* plants used in the treatment of gout in Chad

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Traditional medicine is a cultural and economic heritage for Africa in general and Chad in particular. It is still alive in Chad where almost 75-80% of the population is rural. The distance to a health center is one of the many factors that discourage patients from using modern treatments. In addition, there is a shortage of human resources: in 2012, for a population estimated at more than 11 million, there are 7534 health workers.[1]

Hexalobus monopetalus (A. Rich.) Engl. & Diels is used to treat many diseases.[2,3] It contains terpenes, flavonoids and tannins. Several indole alkaloids have been isolated in various organs of the plant. *Securidaca longepedunculata* is widely used in traditional medicine. From the point of view of chemistry, this plant contains alkaloids, saponins, and terpenes/sterols, reducing sugars, glucosides, flavonoids, organic acids, resins, silicates and their derivatives.[4,5]

In the present work, the thin-layer chromatography of the cyclohexane extracts made it possible to demonstrate the presence of volatile compounds in the analyzed plants. GC-MS analysis of the cyclohexane extracts confirmed the presence of various terpenes, mostly diterpenes. For the species of plant *S. longepedunculata* a very intense peak (RT = 36.26) corresponds to methyl salicylate. These results could explain the use of these plants in the treatment of gout.

Acknowledgements:
This work was supported by an Eugene Ionesco grant, accorded by A.U.F.

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P19. Some new Cu(II), Co(III) Fe(III) and Cr(III) complexes containing an ONN donor isothiosemicarbazone: Synthesis, crystal structures and biological activity

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The metal complexes with organic ligand derived from isothiosemicarbazide fragment has received considerable attention due to their bioinorganic applications. In recent years, research has proved the ability of isothiosemicarbazones and their complexes to be antimicrobial, antiviral, anti-inflammatory and chemotherapeutic agents, potentially useful for inhibiting the activities of cancer cells.[1-3]

The aim of this work was the synthesis of some metal complexes with 2-hydroxybenzaldehyde *N*(4)-allyl-*S*-methylisothiosemicarbazone (**HL**) and their characterization, and investigation of antimicrobial and antiproliferative activity through *in-vitro* experiments. The ligand was obtained by refluxing in ethanol an equimolar amount of *N*(4)-allyl-3-thiosemicarbazide with 2-hydroxybenzaldehyde in the presence of iodomethane. Metal complexes were synthesized using ligand **HL** and different metal salts. All complexes were characterized by ^{1}H, ^{13}C NMR, IR, UV-Vis, elemental and thermal analysis, molar conductibility, and magnetic susceptibility. In addition, the structures of the ligand and of six complexes has been determined by X-ray diffraction method. The complexes were tested for their *in-vitro* antimicrobial activity against: *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Salmonella abony* and *Candida albicans* strains. Also, the antiproliferative activity was tested on human leukemia HL-60, cervical cancer HeLa and normal MDCK cells.

The physical-chemical analyses confirmed the newly obtained structures. The isothiosemicarbazone acts as a mononegative tridentate ligand coordinating to the metal center through the O–N–N chelating system. From the tested complexes, the Cu(II) and Fe (III) complexes have shown significant biological properties.

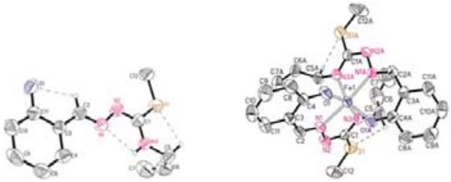

Figure 1.
Crystal structure of **HL** and iron complex.

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P20. Cytotoxic activity of some dihydroxyacetophenone derivatives

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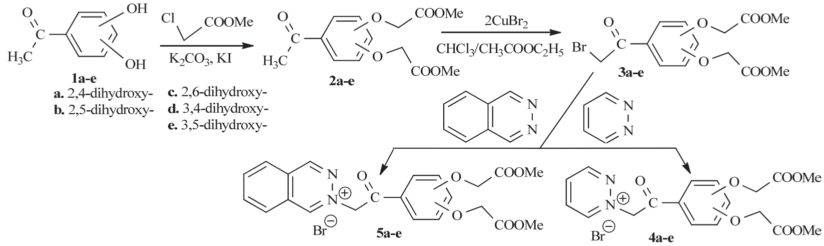
Cancer chemotherapy is complex and complicated, mostly because of the significant levels of toxicity and the emergence of drug resistance and multidrug resistance. It is obvious that development of new chemotherapeutics is of major interest in academic and industrial research, in order to discover newer and more potent molecules, with higher specificity and reduced toxicity than the existing ones.[1-2] One of the most promising approach in cancer therapy remains targeting DNA, DNA alkylators agents being one of the most class used in chemotherapy.[1,2]

The strategies adopted for the synthesis of our dihydroxyacetophenone derivatives **2-5** is facile and efficient. The preparation involves three steps: *O*-alkylation and α-bromination of dihydroxyacetophenone followed by an *N*-alkylation of 1,2-diazine derivatives,[2] Scheme 1.



Scheme 1. Reaction pathway for preparation of dihydroxyacetophenone derivatives

The *in vitro* cytotoxicity of the synthesized compounds was evaluated on HeLa cells by the MTT assay according to Mosmann's method. All compounds were tested at 400 µg/mL concentration. Each experiment was performed five times; the results were expressed as means ± SD.

Acknowledgements:
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P21. NPK analysis of the thermal degradation of two brominated flame retardants

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Due to the low volatility of brominated flame retardants, high elution temperatures are needed when GC-MC techniques are used during their analysis, leading to thermal degradation that generates errors and under-estimation.

We have investigated thermal degradation behavior of decabrominated diphenyl and decabrominated diphenyl ether by simultaneous thermal analysis (TG/DTA), on a STA 449 F1 Jupiter (Netzsch). A comparative analysis was conducted based on thermoanalytical data. Kinetic analysis was performed by the non-parametric (NPK) method, allowing for some insight into the degradation pathways.

Degradation onset was found to occur at rather low temperatures, around 300 °C. Non-parametric kinetic analysis (NPK) method was applied to experimental data. Investigation of the obtained isoconversional and isothermal vectors allowed for two parallel major degradation pathways to be identified, corresponding to two different bond breakage patterns. The relative importance of the two reaction pathways in the global degradation mechanism were found to be temperature-dependent, correlated to the obtained variation of the global activation energy with temperature. These findings are supported by molecular modeling results, providing additional insight for interpreting GC experimental results, and serving as a basis for designing proper GC analytical methods for BFRs.

Acknowledgement: This work was supported by a grant of the Romanian National Authority for Scientific Research and Innovation, CNCS-UEFISCDI, project number PN-II-RU-TE-2014-4-1010. TG experiments were employed with an instrument (STA 449 F1 Jupiter, Netzsch) acquired by a grant supported by the ANCS, Ministry of Economy, Trade and Business Environment, through the National Program Capacities, Project No. 257/28.09.2010 (CERNESIM).

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P22. Occurrence and assessment of some chemical contaminants in drinking water from Eastern Romania

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In this study we report on the chemical quality evaluation of drinking water samples collected from Eastern Romania, with the main aim on determining the compliance with the official regulation and its influence on the human health for the population living in this area. Therefore, we have collected paired water samples from multiple locations, in total being analyzed a number of 45 drinking water samples. By using national standard analytical methodologies, the chemical parameters targeted for analyses included: polycyclic aromatic hydrocarbons (PAHs), trihalometanes (THMs) and organochlorine pesticides (POC). After chemical analysis and data processing, 86% among samples were found to be compliant with the Romanian regulation. However, in one of the analyzed samples the level of benzo(a)pyrene exceeded the maximum admissible concentration. Also, 12% of the samples presented levels above the regulation limits for THMs, chloroform being the most abundant trihalomethane, with concentration levels ranging from 31 µg/L to 120 µg/L. Additionally, organochlorine pesticides were measured at levels above the method limits of detection in all analyzed samples while occasionally the pesticide levels were significantly above the regulatory limits. Given the potential health risks on humans health acknowledged for the contaminants measured at high levels in analyzed samples, this study evidenced the needs for continuous monitoring of drinking water quality, in order to increase bather hygienic practices and awareness of the risks.

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P23. Mathematical modelling of dissolution profiles for a BCS class II candidate drug immediate release tablet and prediction of the in-vivo release profile using convolution method

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Convolution technique, less commonly reported in the literature, uses *in-vitro* dissolution data to derive blood drug levels, combined with pharmacokinetic parameters of a test product.[1] This method provides a simple and practical approach to develop IVIVC and product evaluation. Thus, the dissolution testing is employed for the assessment of the impact of formulation and manufacturing attributes on drug (active pharmaceutical ingredient, API) release characteristics from solid oral dosage products, for both product development and quality control purposes.[2]

The purpose of the study was to develop an IVIVC, based on dissolution results, using convolution technique, for *Candesartan Atb® 16 mg, immediate release tablets*, as a BCS class II drug. The predicted concentrations obtained from the dissolution profiles were compared with the *in vivo* studies performed on these products.

Convolution method was a useful tool in initial product development stages, by establishing the most appropriate method of dissolution and also by reducing risk associated with the failure of *in vivo* bioequivalence studies.

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P24. Stability of atorvastatin polymorphic form VI in simulated condition of manufacturing processes

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Atorvastatin Calcium is a member of the class of drugs called statins. Statin drugs are currently the most therapeutically effective drugs available for reducing low density lipoprotein (LDL) particle concentration in the blood stream of patients at risk for cardiovascular disease.

Atorvastatin Calcium exhibits polymorphism. It has been reported in literature that this drug crystallizes in different polymorphic forms, hydrates and solvates, depending on the crystallization solvents used.

The existence of various polymorphic forms is an opportunity for the generic companies to develop a product with another polymorphic form than be innovator product.

The present research deals with the stability of polymorphic form VI of Atorvastatin Calcium, with different grades of PSD: form VI milled, form VI micronized once and form VI triple micronized.

The objective of the study is to verify the stability of the polymorphic form in different simulated conditions of a manufacturing process, in order to develop an immediate release solid oral dosage form.

The active substance, atorvastatin form VI, was submitted to direct compression and wet granulation processes. For wet granulation methods three of the most used solvents were studied: water, ethanol and isopropyl alcohol.

The stability of the polymorphic form in the samples was tested by XRD technique.

The results indicate that polymorph form VI of atorvastatin calcium is stable under all tested conditions. The micronisation process has no impact in stability of the polymorphic form VI and it could be used in the formulation of atorvastatin tablets.

Keywords: atorvastatin, polimorph, stability, micronisation.

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P25. Synthesis, structure and antimicrobial activity of some 3d-metal coordination compounds with 2-hydroxy-3-methoxybenzaldehyde 4-(dimethylphenyl)thiosemicarbazones

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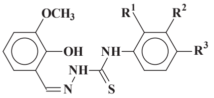
The aim of this work is the synthesis, determination of the composition, structure, physicochemical, antimicrobial and antifungal properties of 2-hydroxy-3-methoxybenzaldehyde 4-(2,4-dimethylphenyl)thiosemicarbazone (H_2L^1) and 4-(3,4-dimethylphenyl)thiosemicarbazone (H_2L^2) as well as iron(III), cobalt(III), nickel(II), and copper(II) coordination compounds with these ligands.

The thiosemicarbazones H_2L^{1-2} react with chlorides, bromides, nitrates and perchlorates of stated above metals forming colored solutions. Upon cooling the precipitates of coordination compounds are formed: $Cu(HL^{1-2})X \cdot nH_2O$ ($X = Cl^-, Br^-, ClO_4^-, NO_3^-$, $n = 0, 4$), $Co(HL^{1-2})_2X$ ($X = Cl^-, NO_3^-$), $Cu(L^{1-2})H_2O$, $Fe(HL^1)_2X \cdot nH_2O$ ($X = Cl^-, NO_3^-$; $n = 0, 2$), $Ni(L^{1-2})H_2O$. The composition and structure of these compounds were determined using elemental analysis, magnetochemical research and IR-spectroscopy. It was determined that all coordination compounds have monomeric structure. The thiosemicarbazones H_2L^{1-2} act as tridentate ligands with O, N, S set of donor atoms.



H_2L^{1-2}

H_2L^1: $R^1 = R^3 = CH_3$, $R^2 = H$;
H_2L^2: $R^2 = R^3 = CH_3$, $R^1 = H$.

Synthesized coordination compounds show selective antimicrobial activity towards a series of standard strains of *Staphylococcus aureus, Escherihia coli*, and *Candida albicans* in the range of concentration 0.0039-0.5 mg/mL. It was shown that the nature of the central atom has a main influence on the antimicrobial activity of these complexes. For the homotypic complexes the activity diminishes in the following way: Cu > Ni > Co ≥ Fe. The nature of thiosemicarbazone and acid residue also has an influence on antimicrobial activity. The antimicrobial activity reduces in the following way: $H_2L^1 > H_2L^2$ and $NO_3^- > ClO_4^- > Cl^- \geq Br^-$. Synthesized compounds manifest the best activity towards the standard strains of *Staphylococcus aureus* and *Candida albicans*.

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P26. Synthesis, structure and antimicrobial activity of copper salicylidene-4-allylthiosemicarbazidates with some heteroaromatic amines

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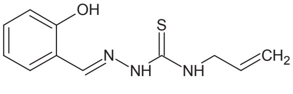
The aim of this work is the synthesis of copper(II) coordination compounds of salicylaldehyde 4-allylthiosemicarbazone (H_2L) with different heteroaromatic amines (imidazole (Im), 4-methylpyridine (4-MePy), 3,5-dibromopyridine (3,5-Br_2Py), 2,2'-bipyridine (2,2'-Bpy), 1,10-phenanthroline (1,10-Phen)), determination of their composition, structure, and antimicrobial activity.



H_2L

The composition of these compounds was determined using elemental analysis for copper and nitrogen: Cu(A)(HL)X (X=Cl^-, NO_3^-; A=Im, 4-MePy, 3,5-Br_2Py) and Cu(A)(L) (A = 2,2'-Bpy, 1,10-Phen). The magnetochemical research showed that coordination compounds that contain imidazole, 4-methylpyridine and 3,5-dibromopyridine have polynuclear structure, but coordination compounds that contain 2,2'-bipyridine and 1,10-phenanthroline have monomeric structure. Thiosemicarbazone H_2L behaves like a mono- or double-deprotonated tridentate ligand with O, N, S set of donor atoms.

Synthesized coordination compounds show selective antimicrobial activity towards a series of standard strains of *Staphylococcus aureus, Escherihia coli*, *Klebsiella pneumonae* and *Candida albicans* in the range of concentration 1.5-1000 µg/mL. It was determined that insertion of these amines into inner sphere results in enhancement of antimicrobial activity in comparison with the corresponding coordination compounds without amines in the inner sphere.

The substitution of nitrate ion by chlorine ion leads to a decrease of antimicrobial activity. The nature of amine has an influence on the antimicrobial activity of these complexes. Coordination compounds with imidazole and 4-methylpyridine are the most active ones from this series. Synthesized compounds manifest the best activity towards the standard strains of *Staphylococcus aureus* and *Candida albicans*.

Acknowledgments.
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P27. Synthesis and antitumor activity of copper(II), nickel(II) and cobalt(III) coordination compounds with 2-[(pyridin-2-ylmethylidene)amino]butan-1-ol and its derivatives

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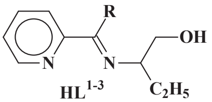
The aim of this work is the determination of synthesis conditions, composition, structure, antitumor properties of copper(II), nickel(II) and cobalt(III) coordination compounds with 2-[(pyridin-2-ylmethylidene)amino]butan-1-ol (HL^1), 2-{[1-(pyridin-2-yl)ethylidene]amino}butan-1-ol (HL^2) and 2-{[phenyl(pyridin-2-yl)methylidene]amino}butan-1-ol (HL^3).

The synthesis of coordination compounds was performed in ethanolic solutions using template method. 2-Aminobutanole reacts with 2-formylpyridine (HL^1), 2-acetylpyridine (HL^2) and 2-benzoylpyridine (HL^3) in presence of copper(II), nickel(II) and cobalt(II) chlorides, bromides, nitrates, perchlorates and acetates taken in molar ratio 2:2:1 or 1:1:1. The composition of these compounds was determined using elemental analysis: $Cu(HL^{1-3})X_2$, $Cu(L^{1-3})X$, $Ni(L^{1-3})_2$ and $Co(L^{1-3})_2X$ ($X = Cl^-, Br^-, NO_3^-, ClO_4^-$). The magnetochemical research showed that the synthesized coordination compounds of copper are polynuclear, coordination compounds of nickel and cobalt have octahedral structure. Azomethines HL^{1-3} behave as neutral or mono-deprotonated tridentate ligands with N,N,O set of donor atoms.

The antiproliferative activity of the synthesized coordination compounds was studied on cancer cells Hep G-2 and BxPC-3. It was determined that these compounds inhibit the proliferation of these tumor cells in the range of concentration 100-0.1 μmol/L. The inhibitory concentrations IC_{50} towards the Hep G-2 cells are in the range of 26.7-99.6 μmol/L. Towards the BxPC-3 cells IC_{50} values are in the range of 11.7-40.7 μmol/L. It was shown that the nature of the central atom and substituent R in the corresponding azomethine and also the acid residue have an influence on the antitumor activity of these complexes. For the homotypic complexes the activity diminishes in the following way: Cu > Co ≈ Ni; $HL^1 > HL^2 \approx HL^3$; $Cl^- \approx Br > NO_3^- \approx ClO_4^-$. Synthesized compounds manifest better activity towards BxPC-3 cells.



HL^{1-3}

$R = H(HL^1), CH_3(HL^2), C_6H_5(HL^3)$

The determinated properties of the synthesized substances are of interest for medical practice for enhancement of the arsenal of antitumor preparations.

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P28. Synthesis of bioactive diterpenoids from the ent-kaur-16-en-19-oic acid

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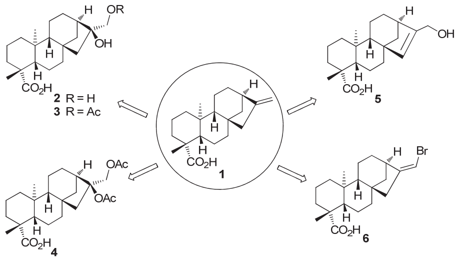
The *ent*-kaur-16-en-19-oic acid (**1**) was isolated from different vegetal sources, especially from sunflower (*Helianthus* sp).[1] We have described isolation of acid (**1**) from the integral sunflower (*Helianthus annuus* L.) dry wastes.[2-3] The scientific interest for tetracyclic diterpenic *ent*-kaur-16-en-19-oic acid (**1**) and its derivatives can be explained by their broad spectrum of biological activities.[4-6] We report in the current communication a series of chemical transformations leading to additional functionalization at exo-methylenic double bond of (**1**).



The synthesized diterpenic compounds (**2**) – (**5**) have been identified on comparison of their spectroscopic data (IR, ^{1}H- and ^{13}C-NMR) with those given in the literature. The structure and stereochemistry of the new compound (**6**) was established on the basis of the spectral data.

Preliminary investigation of the biological activity profile of diterpenic acids (**3**), (**4**) and (**6**) showed a selective inhibition of **HELA B_xP_c-3, RD** tumor cells.

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P29. Synthesis, structure and antitumor activity of some 3d-metal coordination compounds with methyl *N*-prop-2-en-1-yl-*N'*-(pyridin-2-ylmethylidene)carbamohydrazonothioate

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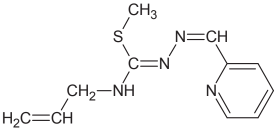
The relevance of this study is determined by the increasing practical importance of thiosemicarbazones, which are used as medicaments. However, at the same time there is no systematic information about the features of their structure and the effect of the structure on biological activity.

The aim of this work is the synthesis, determination of the composition, structure, physicochemical and antitumor properties of methyl *N*-prop-2-en-1-yl-*N'*-(pyridin-2-ylmethylidene)carbamohydrazonothioate (HL) as well as iron(III), cobalt(III), nickel(II), and copper(II) coordination compounds with this ligand.



HL

For achieving these objectives 4-allylthiosemicarbazide was alkylated with iodomethane. After that, the 2-formylpyridine was added to the reaction medium. The resulting hydroiodide of 4-allyl-*S*-methylisothiosemicarbazone was neutralized with sodium carbonate. The purity of HL was proved by NMR (^1H, ^{13}C) and IR spectroscopies.

The experiments showed that ethanolic solutions of copper, nickel, cobalt and iron salts react with synthesized methyl *N*-prop-2-en-1-yl-*N'*-(pyridin-2-ylmethylidene)carbamohydrazonothioate in 1:1 molar ratio in case of copper and nickel salts, or 1:2 molar ratio in case of other metals forming fine-crystalline colored coordination compounds. The composition, structure of the coordination compounds and the way of ligand coordination were determined on the basis of data from elemental analysis, magnetochemical research, IR spectroscopy, and X-ray diffraction analysis. The elemental analyses on iron, cobalt, nickel, copper and gravimetric analysis of water content indicate the general formulae $Me(HL)X \cdot nH_2O$ (Me= Cu^{2+}, Ni^{2+}; X=Cl^-, Br^-, I^-, NO_3^-, ClO_4^-; n=0-2) and $Me(L)_2X$ (Me= Co^{3+}, Fe^{3+}; X=Cl^-, NO_3^-).

The study of antitumor activity showed that synthesized substances inhibit proliferation of the human leukemia HL-60 and cervical cancer HeLa cells at 10 μM and 1μM. It was established that free ligand manifests biological activity only in case of HeLa cells.

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P30. Antioxidant activity of iron(III), cobalt(III), nickel(II), and copper(II) coordination compounds with 2-hydroxybenzalehyde and 2-hydroxy-1-naphtaldehyde (*o*-, *m*-, and *p*-methoxyphenyl)thiosemicarbazones

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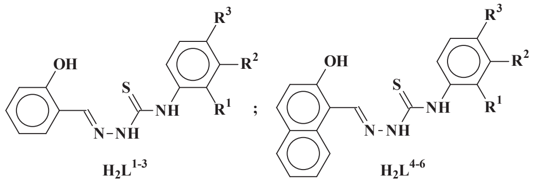
Thiosemicarbazones are of considerable interest because of their potentially beneficial biological activities. It is found that in many cases, their useful properties correspond well to their ability to form chelates with metal ions. Iron, cobalt, nickel and copper salts react with 2-hydroxybenzaldehyde (H_2L^{1-3}) and 2-hydroxy-1-naphthaldehyde (H_2L^{4-6}) (*o*-, *m*-, and *p*-methoxyphenyl)-thiosemicarbazones in ethanolic solutions forming coordination compounds: $M(HL^{1-6})X$ ($M = Fe^{3+}$, Co^{3+}; $X = Cl^-$, NO_3^-), $M(HL^{1-6})X \cdot nH_2O$ ($M = Ni^{2+}$, Cu^{2+}; $X = Cl^-$, NO_3^-; $n = 0\text{-}3$), $M(L^{1-6})H_2O$ ($M = Ni^{2+}$, Cu^{2+}). The composition and structure of the coordination compounds were determined using elemental analysis, magnetochemical research, IR spectroscopy and also X-ray analysis for some of them.



H_2L^{1-3} **H_2L^{4-6}**

H_2L^1: $R^1 = OCH_3$, $R^2 = R^3 = H$; H_2L^2 : $R^1 = R^3 = H$, $R^2 = OCH_3$; H_2L^3 : $R^1 = R^2 = H$, $R^3 = OCH_3$; H_2L^1: $R^4 = OCH_3$, $R^2 = R^3 = H$; H_2L^5 : $R^1 = R^3 = H$, $R^2 = OCH_3$; H_2L^6 : $R^1 = R^2 = H$, $R^3 = OCH_3$.

Antioxidants are substances capable to transform free radicals into inactive forms. The study of antioxidant activity of the synthesized coordination compounds was performed using spectrophotometric method. The antioxidant activity was studied on the radical cation $ABTS^{\bullet +}$ (2,2'-azino-bis-(3-ethylbenzothiazoline-6-sulfonate)). It was determined that all synthesize coordination compounds manifest selective antioxidant activity in the concentration range 100-0.1 μM. The IC_{50} values of the coordination compounds depend on the nature of the central atom, thiosemicarbazone and acid residue. For the homotypic complexes the IC_{50} changes in the following way: $Cu \geq Ni > Co > Fe$; $H_2L^{1-3} > H_2L^{4-6}$(o-> m- ≥ p-); $Cl^- > NO_3^-$.

The determinated properties of the synthesized substances are of interest for medical practice for enhancement of the arsenal of synthetic antioxidant agents.

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P31. Chemical modification of the amine group of the sulfasin by introducing *N'*-[1-(pyridin-2-yl)ethylidene]methanthiohydrazide fragment

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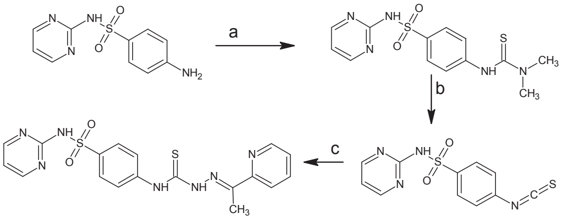
The sulfasin drug is widely used in the treatment of inflammation in digestive tract.[1] Considering the fact that this above-named medicament possesses an amine group, it is chemically possible to modify by at least three known reactions the aromatic amine group into the thiosemicarbazone fragment.

The purpose of this work is to study the influence of *N*-{4-(pyrimidin-2-yl)benzenesulfonamide on antioxidant and antimicrobial activity. Synthesis of 4-[(dimethylcarbamothioyl)amino]-*N*-(pyrimidin-2-yl)benzene-1-sulfonamide proceeds relatively mildly under gentle conditions, according to the following Scheme:



a) The mixture of the initial amine and tetramethylthiuram disulfide dissolved in DMF (1:1.1) for 10 hours. Amine consumption is checked chromatographically. The reaction product is recrystallized.

b) The reaction of 4-[(dimethylcarbamothioyl)amino]-N-(pyrimidin-2-yl)benzene-1-sulfonamide with acetic anhydride in the aprotic solvent at a molar 1:1, for 1 hour in the water bath. Consumption of benzene-1-sulfonamide is checked by chromatography. The reaction product is recrystallized

c) The mixture of 4-isothiocyanato-N-(pyrimidin-2-yl)benzene-1-sulfonamide and 2-[1-hydrazinylideneethyl]pyridine in ethanol at a molar ratio of 1:1, and is refluxed for 5 hours after which 2-[1-(pyridin-2-yl)ethylidene]-N-{4-[(pyrimidin-2-yl)sulfamoyl]phenyl}hydrazine-1-carbothioamide cristallized. The consumption of 4-isothiocyanate is checked by chromatography. Both intermediate and final products were characterized by IR spectroscopy, ^{1}H NMR and ^{13}C NMR.

Acknowledgment:
This work was fulfilled with the financial support of the Institutional Project 15.817.02.24F

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P32. Antioxidant properties of coordination compounds of copper(II) and nickel(II) with 2-acetylpyridine 4-(4-(acetylamino)phenyl)thiosemicarbazone

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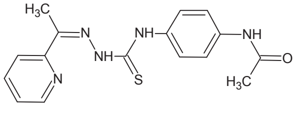
Three coordinating combinations of copper(II) and nickel(II) were obtained based on *N*-{4-[({2-[1-(pyridine-2-yl)ethylidene]hydrazinecarbothioyl}amino)-phenyl]acetamide (HL).



HL

The ligand was synthesized according to known methodologies.[1] This thiosemicarbazone contains the *N*-phenylacetamide fragment which is found in medicaments with analgesic, anti-inflammatory and antipyretic properties such as Acetofen, Phenacetin, and Thioacetazone.[2] It is known that coordination of the organic molecules to metal ions leads to an increase of the biological activity comparing to the uncoordinated organic molecules.[3]

The coordination compounds were synthesized by the reaction between ethanolic solutions of copper(II) and nickel(II) salts and thiosemicarbazone HL. The reaction mixture was stirred at 50-60 °C for 30 minutes. Upon cooling the coordination compounds are formed: $Cu(L)Cl\cdot 3H_2O$, $Cu(L)NO_3\cdot 2H_2O$, Ni(L)Cl. These precipitates were filtered off, washed with cold ethanol and dried at room temperature. The yield of these complexes was in the range of 54-88%. Composition and structure of the coordination compounds were determined using elemental analysis, IR spectroscopy, and X-ray analysis for some of them. Thiosemicarbazone HL behaves as a mono-deprotonated tridentate ligand with N, N, S set of donor atoms.

Antioxidant activity of copper and nickel coordination compounds is significant and have the values in the range 23.3 – 24.3 µM: IC_{50} ($CuLCl\cdot 3H_2O$) = 24.3µM; IC_{50} ($CuLNO_3\cdot 2H_2O$) = 23.3µM; IC_{50} (NiLCl) = 24.0 µM and are higher that antioxidant activity of trolox.

Acknowledgment:

This work was fulfilled with the financial support of the Institutional Project 15.817.02.24F.

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P33. Synthesis, structure and antioxidant activity of some carbonyl compounds of *N*(4)-(2,4-dimethylphenyl)thiosemicarbazones

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The aim of this work was to synthesize of *N*(4)-(2,4-dimethylphenyl)thiosemicarbazones, determine of their composition, structure and antioxidant activity.

Firstly, the thiocarbamides were obtained by the reaction of 2,4-dimethylaniline with TDMT. Then thiosemicarbazides were obtained by two step process. Finally, thiosemicarbazones were synthesized by the condensation of corresponding thiosemicarbazide with carbonyl compounds: *pyridine-2-carboxaldehyde,* 1-(pyridin-2-yl)ethanone, 2-hydroxybenzaldehyde and 2-hydroxy-3-methoxybenzaldehyde.

The purity of all the organic substances was proved by NMR (^{1}H and ^{13}C) spectroscopy. The single crystals of some substances were obtained and their structures were determined by single-crystal X-ray diffraction analysis. These molecules represent almost planar structures, and the thiosemicarbazone is found to be in the thione form in solid state.

The substances were screened for their antioxidant activity by free radical scavenging ability using the stable radical 1,1-diphenyl-2-picrylhydrazyl (DPPH) and the long-life radical cation 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) (ABTS), and compared with that of 6-hydroxy-2,5,7,8-tetramethychroman-2-carboxylic acid (Trolox) standards. All of synthesized compounds exhibited a very good scavenging activity against DPPH free radical. On the other hand, they exhibited the higher antioxidant activity against radical cation ABTS. This demonstrates, that the introduction of big radicals at the *N*(1) and *N*(4), leads to a higher antioxidant activity.

Identified properties of thiosemicarbazones are of interest in terms of expanding the arsenal of the reserve of antioxidants to prevent or reduce the impact of oxidative stress on cell.

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P34. Bioactive coordinative compounds action on the antioxidant system intensity in animals under physiological conditions

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Background: Particularly valuable have proved to be the research on the directed synthesis of the non-platinum metals coordinative compounds with macrocyclic and chelates ligands based on halogen semicarbazides. These complexes exhibit non trivial pronounced cytostatic and cytotoxic effects on cancer cells [Gulea A., 2008], but their biochemical mechanisms of action are not known in detail.

The **aim** of research was to study the peculiarities of the influence of the new non-platinum metal coordinative compounds (CC) with chelation and macrocyclic ligands – CMA-18, CMA-34, CMG-41, MG-22, TIA-123 and TIA-160 on the antioxidant system activity in the blood serum of the experimental animals under physiological conditions.

Methods: Biological activity of the CC was evaluated in experiments on a group of 50 male rats Wistar line, randomly divided into 7 groups. The first group – control (sham), were injected i/m saline solution daily for 30 days. The experimental animals from groups 2 - 7 were administered i/m 10 µmol/kg the studied bioactive compounds (BAC) - CMA-18, CMA-34, CMG-41, MG-22, TIA-123 and TIA-160 three times a week for 30 days. The antioxidant system indices – the activity of superoxide dismutase (SOD), glutathione-S-transferase (G-S-T), ceruloplasmin (CP) and total antioxidant activity levels (TAA) were determined.

Results: The study revealed that the most of the studied CC practically maintained at the normal levels activity of SOD, except the compounds CMA-18 and MG-22 that increased statistically conclusive by 13%-25% activity of enzyme compared with the control group, which denotes antioxidant activity of the tested compounds. At the same time the level of TAA decreased significantly by 28%-54% after administration of the compounds CMA-18, CMG-41, MG-22, TIA-160, which probably indicates exhaustion of the antioxidant system. The amount of CP increased statistically conclusive by 17% - 20% by all the investigated compounds, especially by CMA-34, CMG-41, MG-22 and TIA-160. The tested CC practically maintained at the normal levels the activity of G-S-T, except the compound CMA-34 that produced a 14% veritable statistical decrease of the G-S-T activity compared with the control.

Conclusions: This study demonstrates that the CC tested had a significant influence on the intensity of the antioxidant system. Therefore, further investigation is needed to improve our understanding of the mechanisms of their powerful antiproliferative and cytotoxic selective action on tumor cells, but not only on healthy ones.

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P35. Influence of new bioactive compounds on the intensity of the oxidative stress in animals in the blood serum under physiological conditions

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Olga Garbuz[2], Valentin Gudumac[1]

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Background: The biologically active compounds - new Schiff bases and their coordinative compounds (CC) with [3d] metals exhibit pronounced antiproliferative and cytotoxic properties, exceeding tens and hundreds of times antitumor activity of doxorubicin [Gulea A., et al., 2007, 2009], but their action on normal tissues is insufficient studied.

The **aim** of research was to study the peculiarities of the influence of the new non-platinum metal CC – CMA-18, CMA-34, CMG-41, MG-22, TIA-123 and TIA-160 on the intensity of the oxidative stress in the blood serum of the experimental animals under physiological conditions.

Methods: Biological activity of the CC, was evaluated in experiments on a group of 50 male rats Wistar line, randomly divided into 7 groups. The first group – control (sham), were injected i/m saline solution daily for 30 days. The experimental animals from groups 2 - 7 were administered i/m 10 μmol/kg the studied BAC - CMA-18, CMA-34, CMG-41, MG-22, TIA-123 and TIA-160 three times a week for 30 days. The amount of the serum oxidative stress markers – malonic dialdehyde (MDA), nitric oxides metabolites NO_2+NO_3, the ischemia-modified albumin (IMA), advanced glycated end products (AGE), and advanced oxidative protein products (AOPP) was determined.

Results: The study revealed that the level of the MDA is basically maintained at the normal levels by CMG-41, MG-22 and TIA-123, and the most of the studied CC induced just a discrete increase tendency, which denotes the pro-oxidative effect of the tested compounds at the final stages of lipid peroxidation. AOPP changes due to the influence of the tested compounds have been shown to be of no statistical relevance. The content of nitric oxides metabolites NO_2+NO_3 practically remained at the level of intact animals. The study revealed that the AGE content decreased statistically conclusive by 18%-22% after the administration of TIA-160, CMG-41 and MG-22. The tested CC did not influence conclusive the levels of IMA, except MG-22, that produced a veritable statistical increase of the IMA and CMA-18 decreased its content compared with the control.

Conclusions: The influence of the tested CC on the studied indices of the oxidative stress is selective. This selectivity can be the foundation of their particular strong antiproliferative and cytotoxic selective action upon the tumor cells, but not only on healthy ones. Further studies are needed to investigate the structural features in relation to their biological activity.

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