CHARLES UNIVERSITY IN PRAGUE
FACULTY OF PHARMACY
IN HRADEC KRÁLOVÉ

Euro PhD Network
P Ehrlich MedChem

# 4th Meeting of the Paul Ehrlich MedChem Euro-PhD Network

20th – 22nd June 2014, Hradec Králové, Czech Republic

# BOOK OF ABSTRACTS

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OP Education for Competitiveness
INVESTMENTS IN EDUCATION DEVELOPMENT

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INVESTMENTS IN EDUCATION DEVELOPMENT

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# WELCOME

**Dear PhD students of Medicinal Chemistry, Network Members and Colleagues,**

**Welcome to the 4th Paul Ehrlich MedChem EuroPhD Network Symposium organized by the Faculty of Pharmacy, Charles University in Hradec Králové, Czech Republic.**

Faculty of Pharmacy, one of 17 faculties of Charles University in Prague, was established in 1969 and celebrates the 45th anniversary this year. Charles University is one of the oldest universities in Europe and was founded in 1348 by the Czech King and Holy Roman Emperor Charles IV. His statue graces the interior of Magna Aula in Carolinum, which is used for university celebrations and graduation ceremonies. Its main wall is decorated by a famous tapestry with the motive of Charles IV kneeling in front of St. Wenceslas, the national patron of Czechs.

Hradec Králové is a historical town with two dominants: The White Tower and The Cathedral of the Holy Spirit. From the top of the tower there is a nice view not only of the town, but (given good visibility) also of The Giant Mountains with Sněžka (Snow Mountain), the highest peak of the Czech Republic.

We do not have sea like Sicily, Spain or Slovenia, thus we would like to show you something from our historical places. During Saturday afternoon excursion, we will go to see some architecture valuables of this region and the brewery in Dobruška. By the way, did you know that Czech beer is the best in the world?

The Cathedral of the Holy Spirit
and The White Tower in Hradec Králové

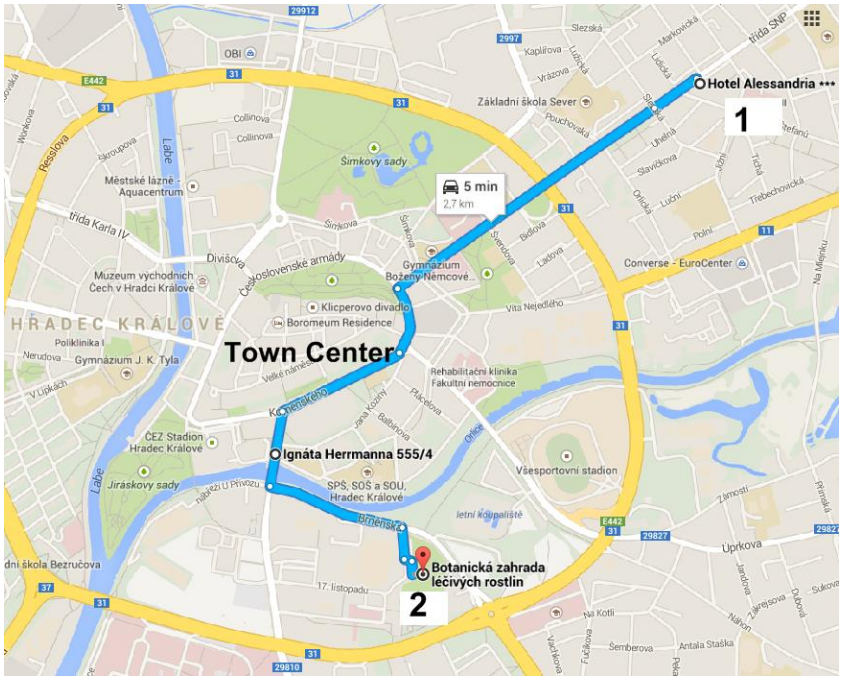
Greenhouse of the Botanic Garden of
Faculty of Pharmacy

# USEFUL INFORMATION

## Organizing Committee

Jarmila Vinšová
Martin Doležal
Martin Krátký
Jan Zitko
Markéta Komlóová
Georgios Paraskevopoulos
Barbora Servusová
Jiří Kratochvíl
Jiří Mikušek
Václav Koula
Martin Štěpán
Lenka Čermáková

## Place of the Meeting




**1 – Hotel Alessandria**
**GPS: 50°13'1.653"N, 15°51'5.342"E**
registation, accomodation and the complete program of Saturday and Sunday

**2 – Botanic Garden of the Faculty of Pharmacy**
**GPS: 50°12'11.497"N, 15°50'20.221"E**
Friday lectures and Welcome Reception

**There will be a bus connection organised on Friday:**

| | |
|---|---|
| 14:30 pm | Hotel Alessandria -> Botanic Garden |
| 20:00 pm | Botanic Garden - > Hotel Alessandria |

# PROGRAM

## Friday 20th June 2014

13:00 Registration, Placement of Posters (Hotel Alessandria)

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15:15 – 16:15 **Opening Lecture**

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16:15 – 16:30 **Paul Ehrlich MedChem Euro-PhD Label Award Ceremony**

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**O-3** A. Gaspar
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**O-23** I. Defrenza
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**O-5** G. Di Vita
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**O-10** D. Knez
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**O-11** G. Pototschnig
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**O-12** L. Wimmer
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# PLENARY LECTURES

**PL-1**

# MAXIMIZING CHANCES OF GETTING PUBLISHED IN THE BEST JOURNALS

F. Švec

The Molecular Foundry, Lawrence Berkeley National Laboratory, Berkeley, USA

Writing a manuscript that has a good chance to be published in a high impact journal is an art. Although not everyone is an artist, there is a certain set of rules that need to be obeyed to maximize the chance that (i) the journal's editors will consider it worth of handling, (ii) the reviewers will like the manuscript and write critical but positive reviews, and (iii) the paper will be published promptly. The success typically results from two major components: (i) excellent results and (ii) skillful writing. In this lecture, major issues will be emphasized and demonstrated that have to be taken into consideration while writing a successful manuscript. My talk will show on numerous examples how a "stop sign" at numerous blatant tumbling blocks can be avoided and the process from writing to publication streamlined.

**PL-2**

# EVOLUTION THROUGH REVOLUTION: CHANGING THE FACE OF DRUG DISCOVERY PARADIGMS TO ACCELERATE THERAPEUTIC RESPONSES FOR MULTIFACTORIAL DISEASES

Fernanda Borges

CIQUP/Department of Chemistry and Biochemistry, Faculty of Sciences, University of Porto

Medicinal chemistry is a dynamic science that changes as the drug discovery paradigms shifts. Before 1990 the lead generation in the drug discovery processes was based on natural compounds and massive synthesis. Usually, the therapeutic purpose was fixed in advance and a large number (several thousands) of molecules were tested on a limited number of experimental models. This method, called as random screening, has been used for the discovery of several drugs, particularly antibiotics. The common criticism of this type of methodology is that it constitutes a sort of fishing and is no longer sustainable. Yet, the steep increase in the knowledge about biological processes, the factors leading to their misregulation and ultimately to disease as well as the development of new technologies have a tremendous impact on the drug discovery approaches. So, one assist to the entrance of a new era the so-called ―rational drug design. Classically, this drug discovery practice (one drug-one target) embraces four stages of: i) target identification, ii) target validation, iii) (hit) lead identification and optimisation, iv) candidate(s) selection.

For some time, drug discovery players have been questioning the success of the reductionist philosophy to ameliorate disease states with multifactorial and polygenic nature. Consequently, it is intuitive that, by targeting different regions or modules of the diseased network, a better regulation of the system can be achieved. The multi-target approach, where a single chemical entity may be able to modulate simultaneously multiple targets seems to be of particular interest in areas that involve multiple pathogenic factors, like neurodegenerative diseases, cancer and infectious diseases. One of the main limitations with this approach is the ability to define the set of targets that is causative of a particular disease state and design compounds that will hit the key targets with a desirable ratio of potencies. This is certainly a daunting challenge but given the current unmet medical needs, and the advantages if successful, such a venture is worthwhile. Case studies of evolution through (re)volution drug discovery processes will be presented.

**PL-3**

# NOVEL APPROACH FOR COMBINATION PHOTODYNAMIC THERAPY

R. Musiol[1,*], A. Mrozek-Wilczkiewicz[2], M. Serda[1], J. Polanski[1], A. Ratuszna[2]

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[2] Institute of Physics, University of Silesia, Bankowa 12, 40-007 Katowice, Poland

Photodynamic therapy (PDT) is the ages old medicinal technique utilizing the light-sensitive agents (photosensitizers) and light in the healing process. Although the most typical use of PDT is in topical skin lesions (dermatological and cosmetic use), the more sophisticated approach allows to successfully treat cancers located in intestines, lungs, even brain. As photosensitizers the porphyrin like structures have been commonly used. They are generally well tolerated and possess unique selectivity allowing to accumulate in cancer cells. On the other hand their poor pharmacokinetics hampered the real efficiency. Real milestone was derived from the observation of biosynthetic pathways leading to photosensitizer protoporphyrine IX (PpIX), a substrate in heme production (**Fig. 1**). Thus supplementation with 5-aminolevulinic acid another biogenic substance and subtle playing with natural machinery of metabolic homeostasis is new approach to PDT. Over the time several prodrugs of aminolevulinic acid were developed into broad armament of cascade prodrugs of PpIX[1].

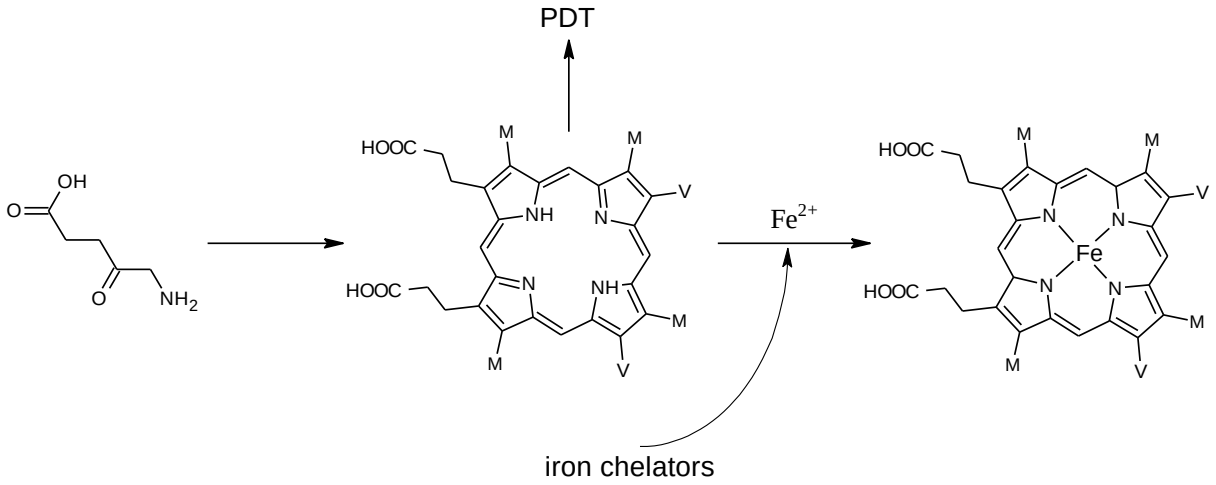


**Fig. 1.** Schematic representation of biosynthetic pathway from 5-aminolevulinic acid to protoporphyrin IX and heme. Combination with iron chelators may deprive iron further increasing level of PpIX.

Another great idea was to use iron chelators to increase the PpIX concentration inhibiting the last step of heme synthesis. On the other hand however, iron chelators may exerts their own anticancer activity. In this regards the combination therapy appeared to be especially promising. Our team has developed several new, highly active thiosemicarbazones that possess ability to alter the iron metabolism in cancer cells[2]. Their use in combination therapy reveals synergistic effects and some interesting aspects of the plausible mechanism of action[3].

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# ORAL COMMUNICATIONS

**O-1**

# IN SILICO INVESTIGATIONS OF DNA G-QUADRUPLEX ANTICANCER STABILIZING AGENTS

Federica Moraca[1*], Anna Artese[1], Giosuè Costa[1], Simona Distinto[2], Francesco Ortuso[1], Lucia Parrotta[1] and Stefano Alcaro[1]

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DNA represents the molecular target for many of the drugs that are used in cancer therapeutics [1]. In the last decade, it has been well demonstrated that, in addition to the familiar duplex, certain DNA sequences can fold into a four-stranded secondary structures called "G-quadruplexes", localized at the telomeric ends of chromosomes [2] and in other important areas of human genome. Recent studies have demonstrated that small molecules, able to interact and stabilize G-quadruplexes, can inhibit the Telomerase enzyme, which is overexpressed in the 80-90% of human cancer [3]. In this study [4] we present a series of both traditional and enhanced computational approaches that we employed to discover new promising DNA G-quadruplex ligands [5] and also to further elucidate the molecular recognition features of the well-known DNA G-quadruplex binding ligands [6].

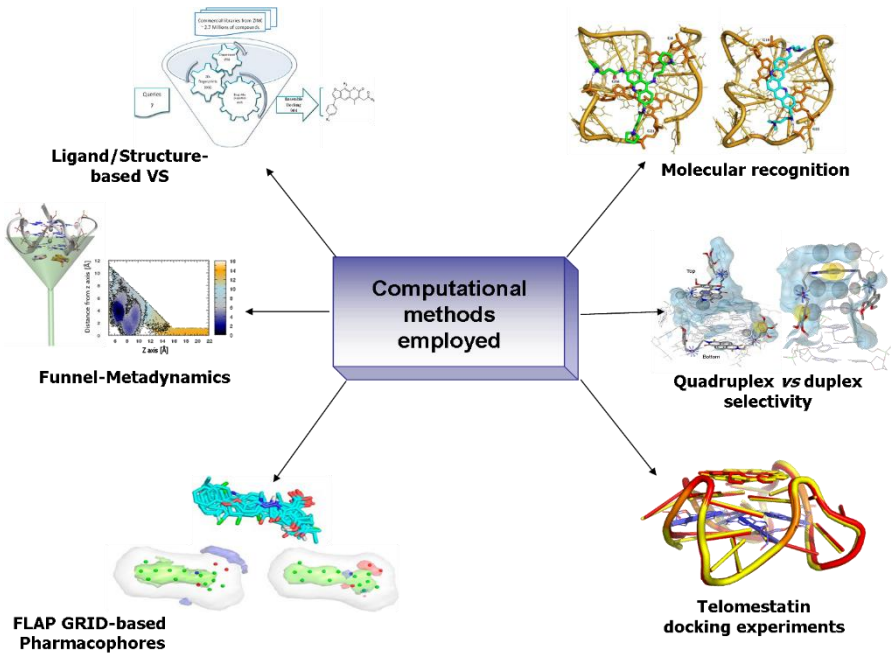


**Fig. 1**: schematic representation of the different computational methods employed to study ligand/DNA G-quadruplex binding.

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**O-2**

# NEW CHALLENGES IN DRUG DISCOVERY: TARGETING PROTEIN-PROTEIN INTERACTIONS

F. Morreale[1,2,*], L. De Luca[1], Z. Debyser[3], A. Ciulli[2], A. Chimirri[1]

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[2] College of Life Sciences, University of Dundee, Dow Street, DD1 5EH, Dundee, United Kingdom
[3] Molecular Virology and Gene Therapy Molecular Medicine, Katholieke Universiteit Leuven and IRC, KULAK Kapucijnenvoer 33, B-3000 Leuven, Flanders, Belgium

Because of the central importance of protein–protein interactions (PPIs) in most cellular process, the ability to interfere with specific PPIs provides a powerful means for the development of alternative therapeutic approaches for the discovery of new drugs.
Controlling PPIs is more challenging than traditional approaches to the identification of small-molecule inhibitors of protein targets, nevertheless researchers are making progress and some of the obstacles are gradually being overcome. Integrating computational and experimental methods is particularly useful when analysing PPIs 'druggability' to identify small-molecule binders. In this context our investigations focused on two distinct protein-protein complexes.

The first PPI considered occurs during the Human immunodeficiency virus (HIV) life cycle and involves HIV-1 integrase (IN) and a host-cell protein called lens epithelium-derived growth factor (LEDGF)/p75. HIV relies on PPIs in almost every step of its life cycle, therefore targeting interactions between virus and host proteins is increasingly viewed as an ideal avenue for the design and development of new therapeutics. The development of small molecules inhibiting IN-LEDGF/p75 interaction successfully led to new antiretroviral compounds with a distinct mechanism of action from FDA-approved drugs.[1] Our research has been focused on the design of new IN-LEDGF/p75 interaction inhibitors using computational tools. The combination of docking studies and molecular dynamics simulations allowed highlighting the most relevant interactions between IN and LEDGF/p75 and comparing them to the interactions achieved by reported PPIs inhibitors.[2] A highly successful virtual screening workflow was set up yielding a hit list of compounds, which exhibited a detectable inhibition of the interaction between the two proteins and provided the basis for a hit-to-lead optimization strategy towards new potent IN-LEDGF/p75 interaction inhibitors.[3]

The second protein-protein complex studied belongs to the E3 Cullin-RING ubiquitin ligases (CRL) and consists of von Hippel-Lindau (VHL) protein, elongins B and C (EloBC), cullin 2, and ring box protein 1.[4] Protein ubiquitination is a post-translational modification that controls protein degradation by the 26S proteasome, and is catalysed by a three-enzyme cascade (E1-E2-E3). The objective of this research is to find ‘druggable’ binding sites on this E3 CRL multiprotein complex using fragment screening and to evaluate and validate the binding of selected fragments to the subunits assembly through biophysical assays.

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**O-3**

# CHROMONE: A VALID SCAFFOLD IN MEDICINAL CHEMISTRY

Alexandra Gaspar[1*], Fernando Cagide[1], Joana Reis[1], Eugenio Uriarte[2], Stefano Alcaro[3], Stefano Moro[4], Karl-Norbert Klotz[5] and Fernanda Borges[1]

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The remarkable progress in diverse research fields, like genetics, immunology, and neurobiology, among others, as well as the advent of more powerful technological tools have made possible to characterize, monitor, and understand more deeply the physiopathology basis of several diseases. Yet, the intensive research performed so far was not yet translated, for several diseases, into therapeutic solutions. Despite the advances in technology, drug discovery is still a lengthy, expensive, difficult, and inefficient process, with a low rate of success. In this context, the innovation challenge by looking for new chemical entities is still a mandatory issue.[1]
The request of new drug discovery approaches/concepts for multifactorial diseases, such as cancer and neurodegenerative diseases, have prompted a switch on the strategy of one-molecule one-target to the multi-target approach, where a single chemical entity may be able to modulate simultaneously multiple targets.[2]
The main challenges of the thesis project were the validation of chromone as a privileged structure for the design of new drug candidates for neurodegenerative diseases, namely Parkinson disease, and the development dual-target lead compounds. Accordingly, the design and synthesis of chromone libraries, along with the development of concise and diversity-oriented synthetic strategies, has been performed. The innovative chromone libraries were screened to ascertain their potential as MAO-B inhibitors as well as $A_{2A}$ adenosine receptor ligands. The output of the biological screening assays gave rise to preliminary structure-activity relationships regarding both of the targets.[3] The overall data showed that chromones are privileged structures for drug discovery and development processes in the field of Parkinson disease and that chromone-3-(3'-hydroxy-4'-methoxyphenyl)carboxamide and chromone-3-(4'-chlorophenyl)carboxamide, exhibiting a $IC_{50}$ for *h*MAO- B in a nanomolar range and affinity towards $A_{2A}$ ARs, can be regarded as putative lead compounds that can undergo a further optimisation process.[3] In addition, during the drug discovery process remarkable $A_3$AR ligands based on chromone scaffold have been found, namely those having the chromone-2-carboxamide framework that present interesting selective indexes.[4] The data was also supported on molecular docking studies performed for the most active chromone derivatives.

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**O-4**

# PROTEIN KINASE C: SYNTHESIS OF A C1-DOMAIN BINDING COMPOUND AS AN IMMOBILIZABLE TOOL FOR AFFINITY CHROMATOGRAPHY.

R. Provenzani[1,*], V. Talman[2], R. Soliymani[3], M. Baumann[3], R. K. Tuominen[2], J. Yli-Kauhaluoma[1], G. Boije af Gennäs[1]

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[3]Meilahti Clinical and Basic Proteomics, Dept. of Biochemistry and Developmental Biology, Institute of Biomedicine, Biomedicum-Helsinki, Faculty of Medicine, University of Helsinki, FI-00014, Helsinki, Finland.

Protein kinase C (PKC), a serine/threonine kinase belonging to the AGC family, plays a critical role in the regulation of various aspects of cell functions, including growth, differentiation, metabolism and apoptosis. PKC isoenzymes are activated by phospholipid-derived second messengers, transmit their signal by phosphorylating specific substrates and represent an interesting molecular target for the treatment of several diseases, such as cancer and Alzheimer's disease.[1] Our team has developed isophthalic acid derivatives able to modify PKC functions by targeting the C1 domain of the enzyme. A structure-based approach was adopted to rationally design and synthesize a set of derivatives using the crystal structure of the PKCδ C1B domain.[2] The bis[3-(trifluoromethyl)benzyl] 5-(hydroxymethyl)isophthalate (**HMI-1a3, Fig. 1**) was selected for further studies due to its high affinity for the C1 domain of PKCα and –δ and its antiproliferative effects in cancer cell lines.[3,4] The aim of the project is to synthesize a derivative that preserves the scaffold structure of **HMI-1a3** with a linker attached to it. The new compound has been designed to function as a probe immobilized on an affinity chromatography column and will be used to identify cellular target proteins from cell lysates, providing new insights into the mechanism of action of **HMI-1a3**.

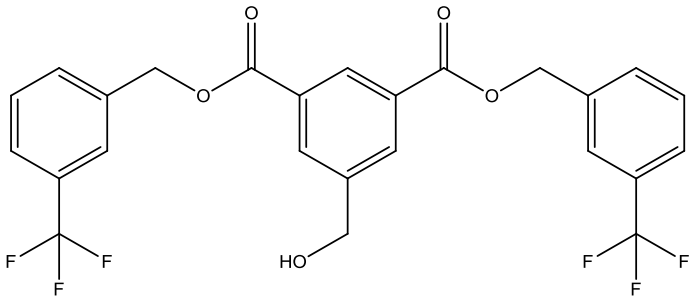


**Fig. 1**: Chemical structure of HMI-1a3.

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**O-5**

# NOVEL NORTOPSENTIN ANALOGUES: PYRROLO[2,3-*b*]PYRIDINE, bis(PYRROLO[2,3-*b*]PYRIDINE AND 7-CHLORO-PYRROLO[2,3-*c*]PYRIDINE ANALOGUES

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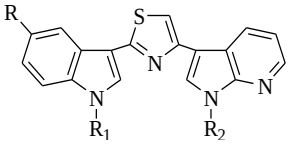
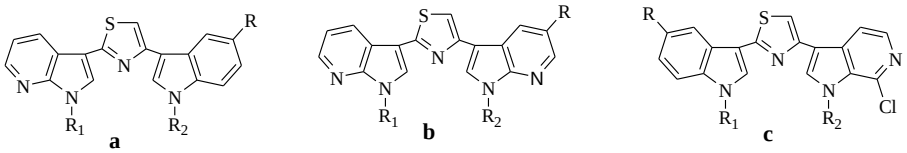
Nortopsentins A-C, having a characteristic 2,4-bis(3'-indolyl)imidazole skeleton, showed *in vitro* cytotoxicity against P388 cells ($IC_{50}$ values: 4.5-20.7 μM).[1] Due to the remarkable biological activities shown, several analogues of nortopsentins, in which the imidazole ring has been replaced by other five-membered heteroclycles such as pyrazole, furan, pyrrole, thiophene, isoxazole and thiazole, and in the thiazole series also an indole ring has been substituted with an azaindole one, have been reported. In particular, some analogues with a 7-azaindole moiety[2] (**Fig.1**) showed antiproliferative activity against a broad spectrum of human tumour cell lines with $IC_{50}$ at micro- to submicromolar range. They reduced the growth of two experimental models of DMPM, inhibited CDK1 activity and consequently induced a marked cell cycle arrest at $G_2$/M compartment, exhibited a synergistic cytotoxic effect with paclitaxel.



R= H, F, Me, OMe, Cl, Br
$R_1$= H, Me, Boc
$R_2$= H, Me

**Fig. 1** Structure of 3[2-(1*H*-indol-3-yl)-1,3-thiazol-4-yl]-1*H*-pyrrolo[*2,3-b*]pyridines.

In our attempts to search for novel antitumor compounds, we synthesized three new series of the 7-azaindole analogues in order to increase the antitumor activity. In particular, 3-[4-(1*H*-indol-3-yl)-1,3-thiazol-2-yl]-1*H*-pyrrolo[*2,3-b*]pyridines **(Fig. 2a)**, in which the indole and 7-azaindole moieties, respectively in position 2 and 5, have been switched; 3,3'-(1,3-thiazole-2,4-diyl)bis(1*H*-pyrrolo[2,3-*b*]pyridines **(Fig. 2b)** in which two 7-azaindole rings are linked to the thiazole central ring; and 7-chloro-3-[2-(1*H*-indol-3-yl)-1,3-thiazol-4-yl]-1*H*-pyrrolo[*2,3-c*]pyridines **(Fig. 2c)**, in which one of the indole unit is replaced by a 6-azaindole moiety.



**a**

R= H, F
$R_1$= H, Me
$R_2$= H, Me, $SO_2$-Ph-Me

**b**

R= H, F, Br
$R_1$= H, Me
$R_2$= H, Me

**c**

R= H, F, Br, OMe
$R_1$= H, Me, Boc
$R_2$= H, Me

**Fig. 2**: a) Structure of substituted 3-[4-(1*H*-indol-3-yl)-1,3-thiazol-2-yl]-1*H*-pyrrolo[*2,3-b*]pyridine; b) 3,3'-(1,3-thiazole-2,4-diyl)bis(1*H*-pyrrolo[2,3-*b*]pyridine); c) 7-chloro-3-[2-(1*H*-indol-3-yl)-1,3-thiazol-4-yl]-1*H*-pyrrolo[*2,3-c*]pyridine.

All thiazoles derivatives **(Fig. 2 a, b, c)** will be proposed to the NCI for evaluation against a panel of about 60 human cancer cell lines derived from nine human cancer cell types. The biological results will be discussed.

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**O-6**

# DESIGN, SYNTHESIS AND LOCAL ANTI-INFLAMMATORY ACTIVITY OF NOVEL 17β-CARBOXAMIDE STEROIDS

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Molecular docking studies[1] were performed on eighteen 17β-carboxamide steroids in order to select compounds with potential local anti-inflammatory activity. These derivatives are potential soft glucocorticoids[2] and represent amides of cortienic acids (obtained from hydrocortisone, prednisolone and methylprednisolone) with methyl or ethyl esters of six amino acids. Interactions with the glucocorticoid receptor, binding energies and ligand efficiency values of these compounds were compared with dexamethasone and cortienic acid obtained from prednisolone (inactive metabolite). On the basis of molecular docking studies, seven compounds were selected and their affinity for the glucocorticoid receptor predicted by use of the three-parameter exponential model created in this study. Subsequently, selected compounds were synthesized in good yields by use of modified N,N'-dicyclohexylcarbodiimide (DCC)/ 1-hydroxybenzotriazole (HOBt) coupling procedure.[3] Finally, croton oil-induced ear edema test[4] was applied in order to examine local anti-inflammatory activity of synthesized compounds and to verify *in silico* results. Derivatives with the best local anti-inflammatory activity (MPEA, MPG and MPA) are presented in **Fig. 1.** Molecular docking studies in combination with the exponential model for the glucocorticoid receptor affinity prediction proved to be a useful *in silico* tool for the rational design of novel 17β-carboxamide steroids with better local anti-inflammatory activity than dexamethasone.

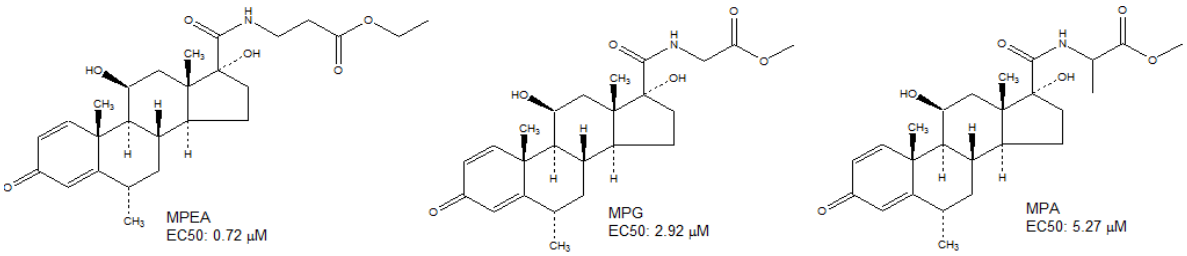


**Fig. 1**: Derivatives with the best local anti-inflammatory activity

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# DIETHYLSTILBESTROL-BASED ANALOGUES AS PREGNANE X RECEPTOR MODULATORS

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Pregnane X receptor (PXR), a member of nuclear receptor subfamily NR1I, is activated by lithocholic acid and protects the tissues against toxic effects of bile acids.[1] PXR is also a major factor involved in drug-drug interactions and a paramount xenobiotic sensor due to its regulation of drug metabolising enzymes and transporters.[2] Our ligand-based design of PXR modulators combined scaffold hopping approach, using our recently reported bazedoxifene scaffold-based PXR antagonists as model compounds and a steroidomimetic approach, with PXR-agonistic marine sulphated steroids solomonsterols A and B as model compounds.[3,4] The strategy involved the substitution of bazedoxifene scaffold of our PXR antagonists with synthetically more favourable scaffold of diethylstilbestrol, an agonist of oestrogen receptors and a weak PXR agonist.[5] To study the structure-activity relationship of diethylstilbestrol-based analogues as PXR modulators, we evaluated the impact of sulphate esters formation, protection of hydroxy groups and the length of the alkyl linker at positions 4 and 4' of the diethylstilbestrol scaffold on the modulation of PXR (**Fig. 1**). The study involving 12 compounds revealed diethylstilbestrol dimethyl ether as a very potent PXR agonist, while some diethylstilbestrol analogues displayed PXR antagonistic activities. In contrast to previous studies, diethylstilbestrol surprisingly functioned as a potent PXR antagonist in the PXR-transfected HepG2 cell line.

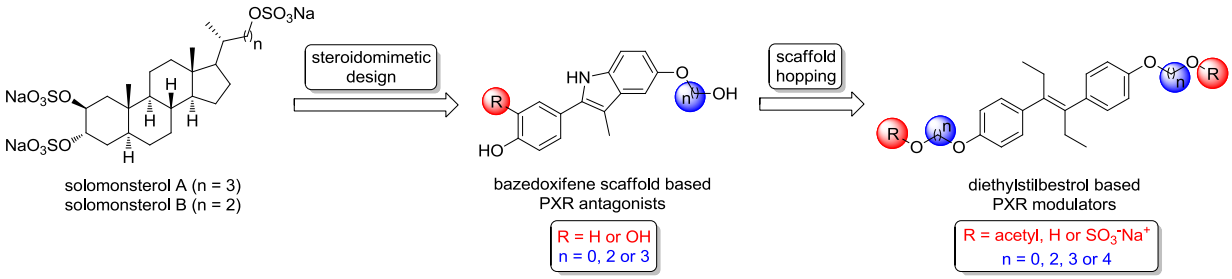


**Fig. 1**: The design of diethylstilbestrol-based PXR modulators.

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**O-8**

# SPUMIGIN ANALOGUES AS A NEW TYPE OF DIRECT THROMBIN INHIBITORS

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Secondary metabolites from cyanobacterium *Nodularia spumigena* such as spumigins and aeruginosins posses potent inhibitory activity to serine proteases, especially thrombin and trypsin.[1,2] Therefore, spumigins can be used as potential lead compounds for the development of new structural type of direct thrombin inhibitors. Spumigins are linear tetrapeptides, structurally similar to the well-known aeruginosins and so far 20 different spumigins were isolated and structurally characterized.[3] In the structures of spumigins and aeruginosins a *D*-Phe-Pro-Arg sequence mimic is present, which is crucial for binding to the pocket of thrombin active site. We designed and synthesized spumigin analogues, where proline as central core was replaced with indoline ring, which can mimic the 2-carboxy-6-hydroxoctahydroindole core of aeruginosins (**Fig. 1**) and evaluated the obtained analogues for inhibition of thrombin.

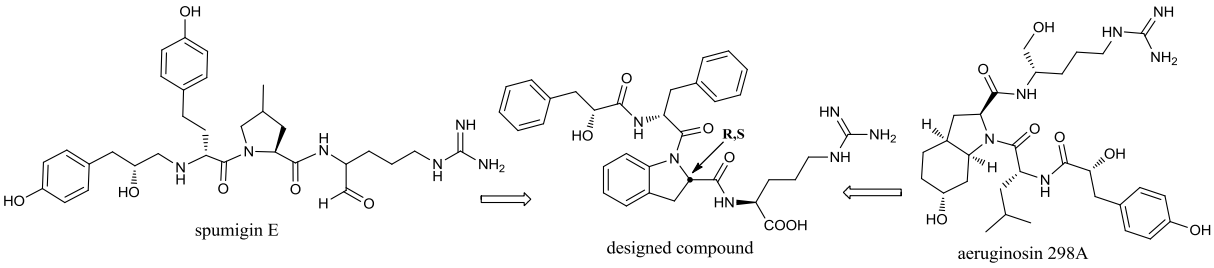


Fig.1: Design of spumigin analogues.

## ACKNOWLEDGMENTS

This work was supported by the European Union FP7 Integrated Project MAREX: Exploring Marine Resources for Bioactive Compounds: From Discovery to Sustainable Production and Industrial Applications (Project No. FP7-KBBE-2009-3-245137).

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**O-9**

# IDENTIFICATION AND APPLICATION OF DOCKING AND MD PROTOCOL FOR LIGAND-MAOB COMPLEXES STUDY

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Given the fundamental role in the metabolism of neurotransmitters, MAO-B has become a very interesting target in medicinal chemistry. MAO-B expression increases with age, causing a decreased availability of dopamine and an increased degree of oxidative damage to neuronal cells. These two factors can lead to neurological and neurodegenerative pathologies; for these reasons selective MAO-B inhibitors have received considerable attention in the treatment of such disorders (1). In this work we validated and applied a molecular docking and MD protocol for the study of a new series of MAO-B inhibitors. Therefore, in order to validate the protocol, seven different ligands-MAO-B complexes have been considered (2). Subsequently, the best settings have been applied to rationalise the putative binding mode of this new class of 3-acetyl-2,5-diaryl-2,3-dihydro-1,3,4-oxadiazoles that inhibits the MAO B isozyme in the nanomolar range. These information could be efficiently employed to optimise this scaffold and to drive the synthetic process towards more potent and selective inhibitors.

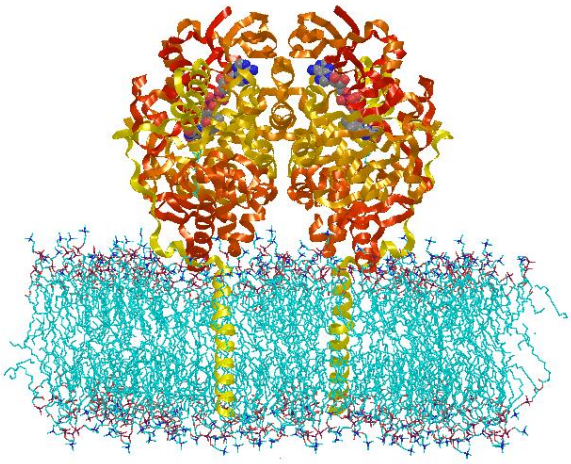

**Fig. 1**: MAO-B isoform in mitochondrial membrane.

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**O-10**

# DEVELOPMENT OF MULTI-TARGET NEUROPROTECTIVE COMPOUNDS AS POTENTIAL ANTI-ALZHEIMER AGENTS

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Alzheimer's disease (AD) is a progressive neurological disorder with impairment in cognition and relentless memory loss as predominant symptoms. AD is characterized by extracellular neuritic senile plaques (SPs), intracellular neurofibrillary tangles and neuronal loss as major neuropathological abnormalities. Amyloid β (Aβ) produced by proteolytic cleavage of amyloid precursor protein (APP) was delineated to be a major constituent of SPs. Aβ increases tau protein phosphorylation and oxidative stress, as well as alters $Ca^{2+}$ homeostasis; these processes lead to neuronal cell death.[1] Among several proteolytic enzymes involved in the turn-over of Aβ, inhibition of cysteine protease cathepsin B shows promising results in reducing Aβ formation and subsequent aggregation.[2] In addition to preventing Aβ formation and aggregation, reducing oxidative stress seems to be an attractive approach to impede the progression of disease.[3]

Based on the first available X-ray crystal structure of cathepsin B with reversible, nonpeptidyl inhibitor and its analogues we developed multi-functional compounds acting on several targets associated with AD development and progression.[4,5] The designed nitroxoline derivatives display cathepsin B and Aβ aggregation inhibition. They also show promising neuroprotective effects through inhibition of butyrylcholinesterase and complexation of metal ions related with amyloide plaques.

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**O-11**

# SCAFFOLD OPTIMIZATION OF THE $GABA_A$ RECEPTOR LIGAND VALERENIC ACID

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Anxiety disorders are amongst the most common mental diseases worldwide. Benzodiazepines represent one of the most prescribed drugs to address anxiety and panic disorders. However, benzodiazepines are known to cause severe side effects like confusion, fatigue and drug addiction.
Valerenic acid, a sesquiterpenoidal compound isolated from roots of *Valeriana officinalis*, acts as subtype selective allosteric ligand on the $GABA_A$ receptor.[1] The highly pronounced selectivity for $\beta_{2/3}$ over $\beta_1$ subunits allows for addressing anxiety rather than sedation in animal models.[2]
Different regions of the complex original structure were modified to gain insight into the so far unknown binding mode and mode of action of this class of $GABA_A$ ligands (**Fig. 1**). Molecules with expanded ring size as well as partially planarized structures were synthesized; steric demand in the receptor was investigated via variation of $R^2$ and $R^3$.

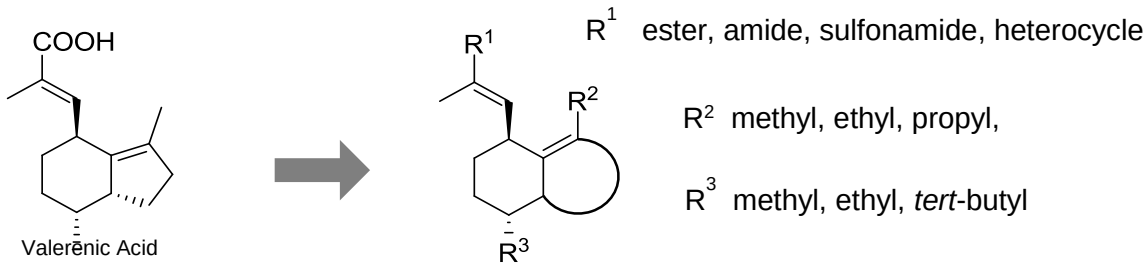


**Fig. 1**: Modifications of the original Valerenic acid structure.

Based on the published total synthesis of Valerenic acid[3], a set of compounds was synthesized and biologically evaluated via electrophysiology.
Results from the above mentioned structural alterations, in regions and functionalities, could give insight in the ligand – receptor interaction and elucidate structural motifs necessary for binding.
We plan to further optimize the structure in terms of synthetic feasibility and biological activity.

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**O-12**

# SYNTHESIS OF PIPERINE ANALOGS AS GABA$_A$ RECEPTOR LIGANDS

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Black pepper is traditionally used in Asian folk medicine as antiepileptic, antianxiety, sedative, and sleep inducing preparation. One of the ingredients of *piper nigrum*, its natural pungent alkaloid piperine, was recently identified as a positive allosteric modulator of the major inhibitory neurotransmitter receptors GABA$_A$ in the brain.[1] Drugs enhancing chloride currents through GABA$_A$ receptors play an important role in the treatment of general anxiety, panic disorders, sleep disturbances, and epilepsy.[2,3] The present study is dedicated to the optimization of the piperine scaffold in terms of ligand potency and receptor subtype selectivity. Compounds were tested for GABA$_A$ receptor activity using a two-electrode voltage clamp assay on *Xenopus laevis* oocytes.

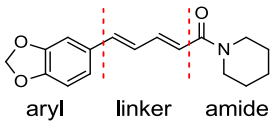


**Fig. 1**: Natural product piperine

The target molecule (**Fig. 1**) was divided into three distinct structural motifs: amide, linker region and the aryl moiety. In an early stage of the project the amide functionality was modified whereasthe di-*n*-propyl, di-*iso*-propyl and di-*n*-butyl amides were identified as the most efficacious residues.
Based on the gained knowledge, modifications of the double bond system, the linker region, was approached. Hence by applying transition metal catalyzed cross coupling reactions, derivatives with 1,2-, 1,3- and 1,4-substituted phenylene, 1,5-naphthalene and 2,5-thiophene as substitute for the double bond system were synthesized. The aromatic benzodioxole ring system was extended to naphtho[2,3-*d*]dioxole, incorporating one of the double bonds.
Further modifications of the aryl-moiety were performed by a palladium-catalyzed Heck cross-coupling reaction of conjugated dienamides. This reaction strategy served as a highly modular platform for library synthesis.
Biological testing revealed several potential hit compounds with up to 5-fold increased efficacy and one particular compound (LAU399) was found to be functionally selective for β2/3-containing receptors, indicating non-sedative anxiolytic properties.

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**O-13**

# NOVEL DNA GYRASE B INHIBITORS BASED ON A BENZO [*d*] THIAZOLE-2,6-DIAMINE SCAFFOLD

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Bacterial DNA gyrase is one of the most investigated validated target for the development of novel antibacterial compounds due to its absence in mammalian cells as well as its crucial role in bacterial DNA replication. DNA gyrase is a heterodimeric enzyme with an $A_2B_2$ structure. The ATP binding site which is located at B subunit of DNA gyrase enzyme has been studied as potential target for design of DNA gyrase inhibitors.[1]

Oroidin is an alkaloid found in the sponges of the genus *Agelas*, which was found to display a weak gyrase B inhibitory activity. Our aim was to design novel oroidin analogs and evaluate them for gyrase B inhibition. Therefore, we replaced the flexible part in the molecule of oroidin with more rigid benzo[*d*]thiazole-2,6-diamine. A series of compounds were obtained after the acylation of the 2-aminogroup of benzo[*d*]thiazole-2,6-diamine with dibromopyrrol- and dichloropyrrol-2-carboxylic acids as well as acylation of the 6-amino group with substituents of different lengh bearing a carboxylate moiety which is crucial for interaction with gyrase B active site (**Fig. 1**, a). We also synthesized another series of compounds in which we interchanged the positions of the pyrrole and alkyl substituents, namely, by coupling the 6-aminogroup of benzo[*d*]thiazole-2,6-diamine with substituted pyrrole-2-carboxylic acids and acylation on the 2-amino group with the substituents from the previous series (**Fig. 1**, b). *In vitro* assays of the isolated enzyme showed that compounds from both series possess promising inhibitory activities for gyrase B. Some of these compounds inhibited Gyr B with $IC_{50}$ values in the nanomolar range.

In summary, benzo[*d*]thiazole-2,6-diamine based compounds are promising novel DNA gyrase B inhibitors offering many possibilities for improving their inhibitory potency by further structural optimization.

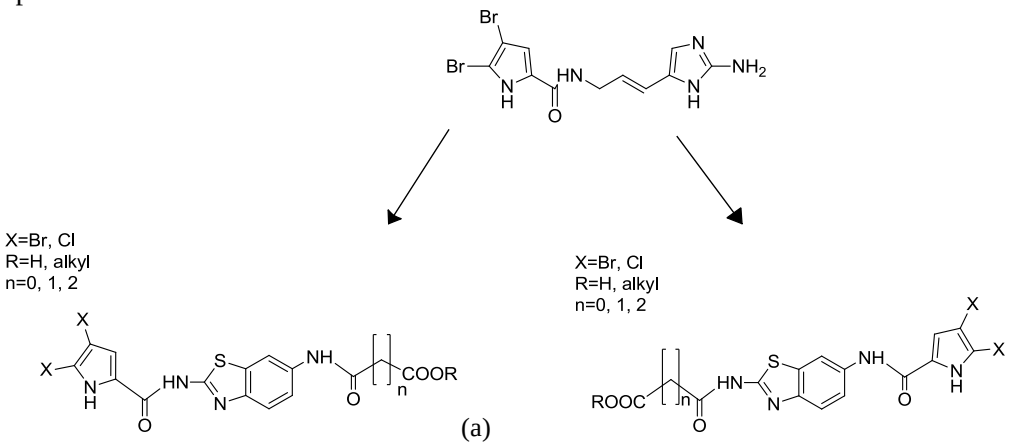


**Fig. 1.** Starting from the molecule of oroidin, we synthesized two series of compounds with the same scaffold of benzo[d]thiazole-2,6-diamine, but different positions of both acyl substituents.

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## ACKNOWLEDGMENT

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# DESIGN AND SYNTHESIS OF AMINOPIPERIDINE DNA GYRASE B INHIBITORS

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The widespread use of antibacterials in modern medical practice is closely followed by increased incidence of bacterial resistance. Arising need for the discovery of new therapeutic targets can be observed, as well as evaluation of new compounds and development of novel mechanistic approaches.[1] One of the established targets is DNA gyrase, a type II topoisomerase, responsible for introduction of negative supercoils in DNA molecule using the energy released from ATP hydrolysis. Enzyme is a heterodimer consisting of two subunits: Gyrase A (GyrA), mainly responsible for operations on DNA molecule and Gyrase B (GyrB), where ATPase active site is located.[2] We have selected alkaloids (namely oroidin, clathrodin) from the sponges of the genus *Agelas* as a lead compounds in the synthesis of a small library of analogues as a potential GyrB inhibitors (**Fig. 1**). Marine natural products present an under-exploited source of natural compounds, generally covering a vast chemical space.[3] Sponges and their sponge-symbiotic microorganisms produce a variety of natural products (cytotoxins, antibiotics, antivirals, anti-inflammatory compounds, antifouling agents, etc.) with selective binding to biological targets.[4] We aimed to identify key pharmacophoric features by structural simplification with the help of *in silico* molecular modelling. We have selected a synthetically approachable molecular scaffold where piperazine central linker replaces the 3-aminoprop-1-enyl moiety in the native compounds and described essential features for DNA gyrase B inhibition (**Fig. 1**). Our small library of compounds combined with scaffold hopping approach using published literature on pyrroloamide DNA gyrase inhibitors, proceeded towards development of 4-aminopiperidine central linker based series of compounds.[5] To study the structure-activity relationship of our aminopiperidine DNA gyrase B inhibitors we evaluated the impact of central linker substitution, length of the molecule, flexibility and structure of acidic terminal moiety on the position 1 of 4-aminopiperidine linker. Biological evaluation with the help of *in silico* consensus molecular modelling of our 40 compound library advanced towards development of low micromolar selective amino-piperidine inhibitors of DNA gyrase B with a great potential for further optimisation.

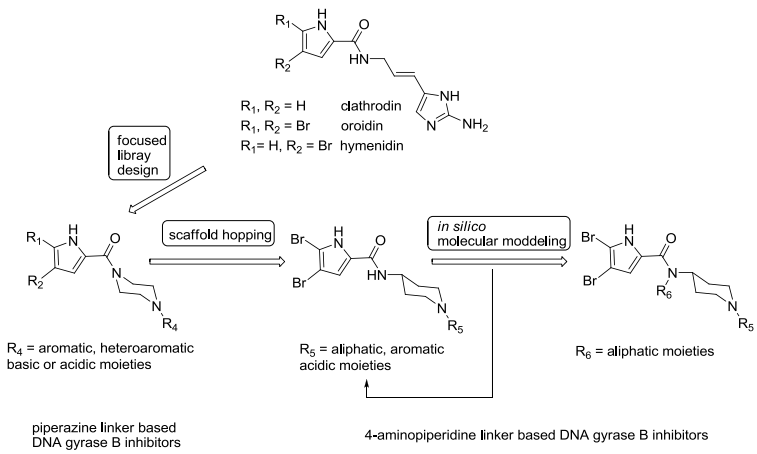


**Fig. 1**: The design of 4-aminopiperidine DNA gyrase B inhibitors.

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**O-15**

# TETRAHYDROBENZOTHIAZOLE-BASED INHIBITORS OF BACTERIAL TYPE IIA TOPOISOMERASES

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Topoisomerase II in eukaryotes is a single-unit enzyme that is active as homodimer ($A_2$), while in prokaryotes DNA gyrase and topoisomerase IV are heterotetrameric proteins $A_2B_2$ and $C_2E_2$, respectively. Both enzymes are type IIA topoisomerases and their function is vital to DNA replication, repair and decatenation, which makes them appealing targets for discovery of novel antibacterial drugs to overcome the bacterial resistance problem.[1] The aim of our study was to design and synthesize naturally derived compounds - analogs of the bromopyrrole alkaloid oroidin from *Agelas* sponges. Computer-aided drug design on *Escherichia coli* GyrB (*PDB entry* 4DUH)[2] was used for the selection of candidates for synthesis. The designed and synthesized oroidin analogs were evaluated *in vitro* for their inhibition of *E. coli* and *Staphylococcus aureus* type IIA topoisomerases.
The results of our efforts are 34 synthesized and optimized novel oroidin analogs bearing (*S*)/(*R*)-4,5,6,7-tetrahydrobenzo[*d*]thiazole-2,6-diamine heterocyclic core, which are coupled on the 6-amino group with different pyrrole-2-carboxylic acid derivatives and analogs (e.g. bromopyrrole, dibromopyrrole, dichloropyrrole and indole moieties). Generally, the best results were obtained on *E. coli* GyrB enzyme, which crystal structure was used for structure-based design of novel compounds, with their activity ranging from low micromolar to low nanomolar range. Our *E. coli* GyrB inhibitors were shown to possess weaker activity against *S. aureus* GyrB and *S. aureus* and *E. coli* ParE, their activity dropping to the micromolar range, possibly due to the small differences present in the hydrophobic pockets of the ATP-binding sites. *In vitro* assays on the isolated *E. coli* GyrB enzyme, using surface plasmon resonance, showed that the structurally optimized dibromopyrrole-based oroidin analogs demonstrated $IC_{50}$ values between 49 and 98 nM, respectively, and are in accordance with values obtained in the screening kit assays.
The primary screening of antibacterial activity was performed on Gram-positive (*S. aureus*, *Enterococcus faecalis*) and Gram-negative (*E. coli*, *Pseudomonas aeruginosa*) bacteria. The concentration used for screening was 50 $\mu$M and the minimum inhibitory concentration (MIC) determination is in progress for selected compounds that showed more than 50% inhibitory activity on Gram-positive bacteria, whereas they were completely inactive on Gram-negative bacteria. Potent *E. coli* GyrB inhibition and observed lack of antibacterial activity against *E.* coli can be partially explained by the results obtained from evaluation of our inhibitors on *E. coli* strains without the efflux pump which are in progress.

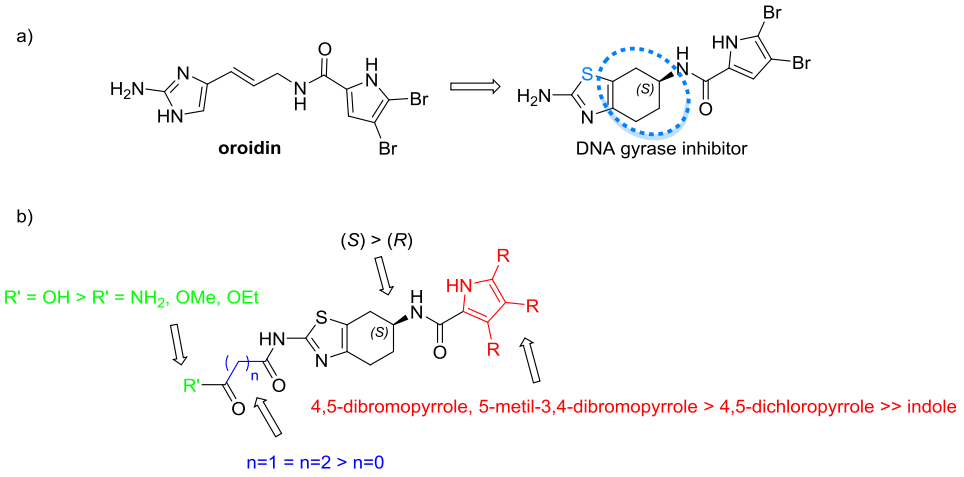


**Fig. 1**: General structural representation of a) the modifications made on the marine alkaloid oroidin leading to our new inhibitors and b) the changes implemented to our series of compounds highlighted by different coloring in the affected regions.

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## ACKNOWLEDGMENTS

This work was supported by the European Union FP7 Integrated Project MAREX: Exploring Marine Resources for Bioactive Compounds: From Discovery to Sustainable Production and Industrial Applications (Project No. FP7-KBBE-2009-3-245137). S. Katsamakas is also thankful to ”CMEPIUS Center of the Republic of Slovenia for Mobility and European Educational and Training Programmes” and “The A. G. Leventis Foundation” for financial support.

**O-16**

# AN EFFICIENT SYNTHESIS OF QUINOLINE-3-HYDRAZONES AS POTENTIAL ANTITUBERCULAR AGENTS

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Tuberculosis is an important global health problem, especially nowadays due to the alarming increase of the multi-drug resistance. Consequently there is a need of new scaffolds to boost the drug discovery process. Recently, a new quinoline derivative[1] (the 2-arylquinoline TMC207) has been disclosed as promising antitubercular agent, confirming the quinoline ring as promising scaffold in the search for new antitubercular compounds. Furthermore, the hydrazone moiety[2] is an important pharmacophore and quinoline-4-hydrazones have been identified as a new and attractive family of compounds with interesting antitubercular activities.[3]

In this context, we present here an efficient synthesis of polysubstituted quinolines bearing a hydrazone moiety as new structural entities to be evaluated for antitubercular treatment. The starting materials for our synthesis were 1,2,3,4-tetrahydroquinolines and 2-acyl-1,2,3,4-tetrahydroquinolines bearing a hydrazone function at the quaternary $C_4$ position and came from the one-pot diastereoselective $InCl_3$-catalyzed Povarov-like imino Diels-Alder reaction between aromatic imines or aromatic α-keto-imines and α,β-unsaturated N,N-dimethylhydrazones.[4] Treatment of the Povarov products with DDQ in toluene affords in one step the target polysubstituted quinolines through an unusual and interesting $C_4$ to $C_3$ functional group rearrangement. Besides their intrinsic interest, these compounds offer opportunities for multi-target drug design thanks to the presence of the reactive dimethylhydrazone moiety, which will allow the generation of single molecular species containing two structural fragments able to interact with different antitubercular targets.


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**O-17**

# *IN VITRO* ACTIVITY EVALUATION OF SUBSTITUTED SALICYLANILIDE ESTERS AND CARBAMATES

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The increase of multidrug-resistant tuberculosis (MDR-TB) is alarming and development of effective new drugs is important. Modifications of antituberculotics are widely used approach. A novel design of new agents is mainly oriented toward the synthesis of prodrug forms; combination of two active molecules in order to achieve their possible interaction with new mechanisms of action.

Salicylanilides (2-hydroxy-*N*-phenylbenzamides) are effective candidates for this purpose due to their *in vitro* antimycobacterial activity[1, 2]. Pyrazine-2-carboxylic acid is the active form of pyrazinamide (PZA) a first-line antituberculotic[3]. Masking the phenolic hydroxyl group in salicylanilides by carbamate formation may protect the molecule against extensive first-pass metabolism, broaden its activity profile and improve its physicochemical and pharmacokinetic properties[4].

Substituted salicylanilides, salicylanilides in combination with 5-chloropyrazine-2-carboxylic acid and salicylanilide carbamates were prepared and chemically characterized. The *in vitro* antitubercular activity of the compounds was determined on *Mycobacterium tuberculosis* (MTB) $H_{37}Rv$ and on MTB A8 MDR cultures. Our study has demonstrated the *in vitro* inhibitory effect of the salicylanilide derivatives on both cultures. The *in vitro* cytotoxicity and cytostatic activity of the compounds on human host cell model (MonoMac-6) were determined and analysed.

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*ACKNOWLEDGEMENT: Hungarian Scientific Research Fund K104275*

**O-18**

# NOVEL PYRAZINAMIDE DERIVATIVES: MICROWAVE ASSISTED SYNTHESIS AND BIOLOGICAL EVALUATION

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Although the total number of new tuberculosis cases has been falling slowly since 2006, new problems have arisen with the appearance of resistant mycobacterial strains. These circumstances issued in effort to find novel, effective and safer antituberculotic agents.
It is known that pyrazinamide (PZA) is the first-line antituberculotic drug and one of its unique properties is sterilizing effect. It is caused by the fact that PZA is active against the dormant forms of *Mycobacterium tuberculosis*. PZA is also very suitable for chemical modifications.

This work is focused on preparation of a series of compounds derived from 5-chloro-6-methylpyrazine-2,3-dicarbonitrile. Starting compound was treated with aliphatic or alicyclic amines. This step was performed in microwave reactor with focused field. Conditions for the aminodehalogenation reaction were set experimentally. All synthesized compounds were characterized by melting point, NMR and IR spectra, elemental analysis and 2 parameters of lipophilicity (calculated and experimentally set).

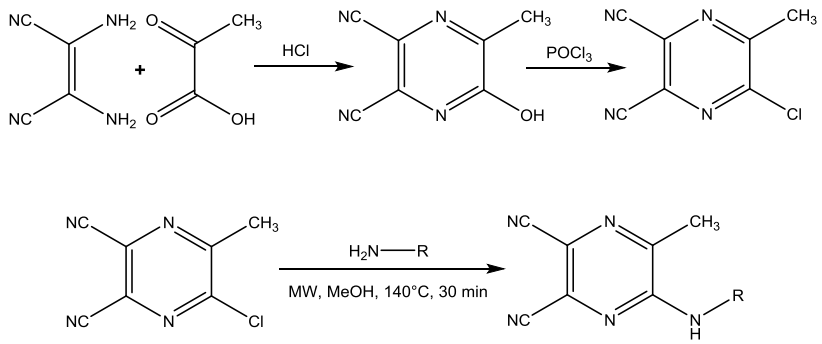


Fig. 1 – Scheme of the preparation of starting compound and final products

There were performed three biological assays. Antimycobacterial screening was accomplished against *M. tuberculosis* and 3 non-tuberculosis mycobacterial strains using isoniazide as standard. The minimal inhibition concentration (MIC) was determined. Herbicidal activity screening was based on the measurement of the inhibition of photosynthetic electron transport in spinach chloroplasts and $IC_{50}$ was pinpointed using DCMU (Diurone) as standard. The antibacterial and antifungal evaluation was performed against 8 bacterial and 8 fungal stems applying 5 antibiotic and 4 antimycotic standards determining MIC.

A lot of compounds showed activity in at least one screening and there was found the relationship between lipophilicity and herbicidal activity in the group with aliphatic substitution.

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**O-19**

# NOVEL POTENTIAL PROTEASOME INHIBITORS BASED ON TRIPEPTIDE SCAFFOLD

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Presented work is aimed to prepare new compounds (*O*-benzyl-5-chlorosalicyl-tripeptide aldehydes, epoxides, boronic acids and Weinreb amides) which should join to a large group of proteasome inhibitors including bortezomib (**I**, Velcade®), ixazomib (**II**, MLN-9708, clinical trials: phase I-II), delanzomib (**III**, CEP-18770, clinical trials: phase I-II), marizomib (**IV**, clinical trials: phase I), carfilzomib (**V**, Kyprolis®). Due to a very similar constitution of mentioned (see **Fig. 1**) they are expected to bear very similar properties and activities as well. Inhibition of proteasome via blocking its protein recycling function is one of promising ways to treat tumor cells or multiple myeloma.[1,2,3,4,5]
During the synthesis a partial racemization occurred and diasteroisomers were formed. To avoid the racemization, to get exact stereospecific synthesis and defined product are the aims, which are achieved by suitable adjustment of used reagents and their ratios. The details are discussed in the following contribution.
Prepared compounds are going to be tested as proteasomal and protein kinase inhibitors, for the type of caused apoptosis and antimicrobial activity.

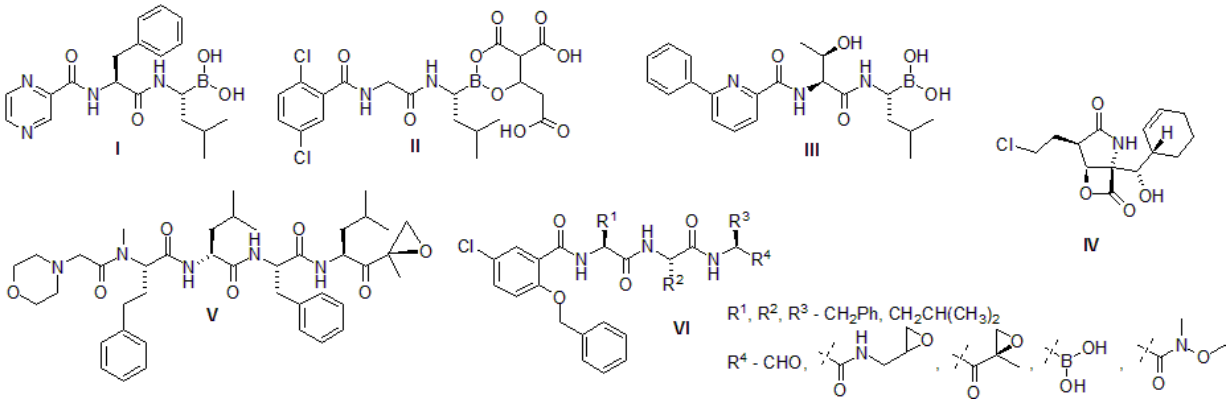


**Fig. 1**: Overview of promising (I-VII) and potential (VIII) proteasome inhibitors.

## Acknowledgement
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**O-20**

# NEW HIGHLY ACTIVE AROYLHYDRAZONE IRON CHELATORS

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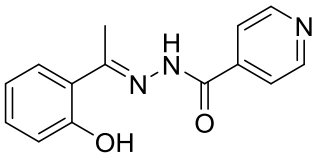
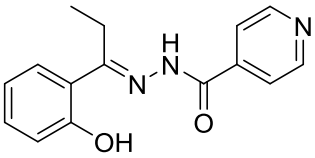
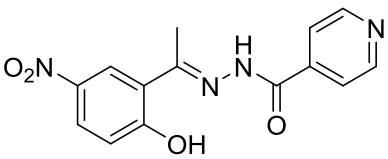
Iron is an essential element for living organisms. However, an excess of free intracellular iron (e.g. due to an iron overload disease) causes tissue damage, for iron catalyses production of reactive oxygen species via Fenton type chemistry[1]. To prevent the harmful potential of iron, iron chelators have been developed. Aroylhydrazones are a group of chelators with high affinity to iron and advantageous pharmacokinetic properties[2]. Apart from protecting tissues from oxidative stress, they are also known to have antiproliferative effect caused most probably by depriving the growing tumor of essential iron[3]. The most active substances from our previous studies were NHAPI, HAPI and HPPI (see picture), which served as model substances for our recent research.
Our research group has recently synthesized and studied more than 40 new aroylhydrazone chelators by modifying either the ketone or the hydrazide part of the molecule. The results of *in vitro* evaluation showed that one of the new substances possesses high protective activity (1,76 μM-ten times higher than HAPI) and eight substances are greatly cytotoxic against cancerous cell lines (the most active substances have selectivity ratio exceeding 100).




HAPI




HPPI




NHAPI

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**O-21**

# EVALUATION OF ALAPTIDE AS POTENTIAL PERMEATION ENHANCER FOR TRANSDERMAL DELIVERY OF MODEL DRUG THEOPHYLLINE

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Transdermal administration of drugs represents an excellent alternative to conventional pharmaceutical dosage forms. However, transdermal drug delivery often faces the problem of insufficient or no permeation of active pharmaceutical substances through the skin. To solve this critical issue various approaches for overcoming the skin barrier were developed. These approaches can be classified as chemical (modification of drugs, using transdermal chemical penetration/permeation enhancers – CPEs) or physical (modification of drug particles size to nanosize, physical enhancement techniques). Another classification can be based on optimization of drug/vehicle or on *stratum corneum* (SC) modification. Optimization of drug/vehicle consists in preparation/application of *i*) lipophilic prodrugs or ion-pairs, *ii*) eutectic systems, *iii*) complexes of drugs with cyclodextrins, *iv*) liposomes and other vesicles (transfersomes, ethosomes, niosomes, etc.), *v*) solid lipid nanoparticles and other nanoparticles and/or nanodelivery systems, *vi*) saturated and supersaturated solutions. Modification, i.e., hydration/lipid fluidization/disrupting, of SC means *i*) application of CPEs, *ii*) overall optimization of formulation using non-hydrophobic excipients or *iii*) application of physical enhancement techniques (electrically assisted methods), such as iontophoresis, electroporation, acoustic methods, microneedles, magnetophoresis or photomechanical waves.[1-3]

The knowledge of the structure and properties of CPEs, the hypotheses of CPE mechanism of action and our previous experience with several other groups of CPEs led us to the thought to evaluate alaptide as a potential CPE.[1,4-6] Alaptide, (*S*)-8-methyl-6,9-diazaspiro[4.5]decane-7,10-dione, is a compound discovered in the 1980s by Kasafírek *et al.*[7,8] Alaptide has unique physicochemical properties and a significant enhancement activity.[9-11] The exact mechanism of action of this type of CPEs is not known. This contribution is focused on investigation of the enhancement effect of various concentrations of alaptide on the permeation of the model drug theophylline through the full-thickness pig ear skin (*Sus scrofa* f. *domestica*) from propyleneglycol/water (1:1) donor vehicles using static Franz diffusion cells. Samples were withdrawn at pre-determined time intervals and the amount of permeated theophylline was determined by the HPLC method.

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**O-22**

# PREPARATION OF RISEDRONATE NANOPARTICLES FOR PERMEABILITY IMPROVEMENT

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Risedronate sodium is a drug from the group of bisphosphonates used for treatment of osteoporosis and other metabolic bones disorders. Risedronate is also used for treatment of Paget´s disease characterized as bone remodelation disorder with increased bone resorption followed by a compensatory increase of structurally imperfect bone tissue. Risedronate has affinity for hydroxyapatite in bone and acts as an antiresorptive agent. At the cellular level risedronate inhibits osteoclasts. Antiresorpting ability is caused by inhibition of farnesyl pyrophosphate synthase, an enzyme of osteoclasts. Risedronate can decrease bone turnover and increase bone mass, especially at the hip and spine in early postmenopausal women. Risedronate can also reduce pain at patients with Paget´s disease and prevent bone loss and fractures at patients treated with corticosteroids for rheumatoid arthritis. Bioavailability of orally taken bisphosphonates is characterized as low (< 1%), and their absorption is inhibited by food. Bisphosphonates must be taken 30 minutes before food intake.[1]

Oral route is the most preferred way of dosing bisphosphonates, despite poor absorption and adverse effects that can occur during oral intake. Bisphosphonates are taken once a week/month about thirty minutes before breakfast and patients must stay in an upright position to avoid oesophagus ulceration. The absolute bioavailability of orally taken bisphosphonates has been evaluated to be about 0.6% and it decreases with food intake.[2]

Research of transdermal transport of risedronate has been done as the possibility of a different route of administration. Risedronate is soluble in water and insoluble in many types of organic solutions. Risedronate is also highly ionized and acidic molecule, this fact can result in low permeation through the skin barrier. Solution can be seen in preparation of ion pairs and getting neutral complex. Ion pairs can increase the penetration of drugs through the skin by decreasing the charge and increasing hydrophobicity.[3]

Risedronate nanoparticles should gain improved properties such as an increase of bioavailability. Precipitation as a method for nanoparticles preparation was chosen for this experiment; to be precise the method was called solvent evaporation. Formation of nanoparticles by this method was proved in the previous experiment.[4] This method is very simple and fast, it is based on a preparation of solutions of risedronate and excipient in different concentrations (1%, 3% and 5%). Excipients were chosen from groups of surfactants (sodium lauryl sulphate, Tween) and polymers (polyethylene glycol, carboxymethyl cellulose sodium salt, carboxymethyl dextran sodium salt). Solutions of risedronate and excipient were stirred for 15 minutes and then put into an ultrasonic bath for 15 minutes. Each of the samples was filtered with a filter with pores of 0.45 μm. Prepared nanoparticles were characterized by the dynamic light scattering and the scanning electron microscopy. Risedronate nanoparticles with different excipients were used for permeability tests that were performed using PAMPA (parallel artificial membrane permeability assay). The permeation of nanoparticles of risedronate sodium was compared with the permeation of the standard substance.

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**O-23 (O-L)**

# 1,3-BENZOTHIAZOLE DERIVATIVES AS NEW PROMISING ANTIMICROBIAL AGENTS

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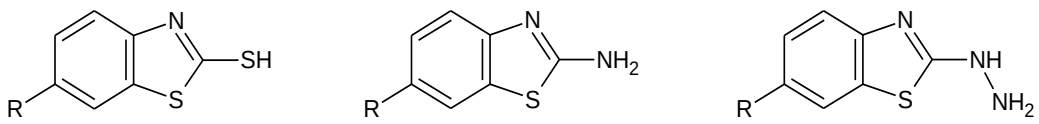
The need for new antimicrobial agents is greater than ever because of the emergence of multidrug resistance in common pathogens and the rapid emergence of new infections. Antibiotic-resistant organisms appear to be biologically fit and are capable of causing serious, life-threatening infections that are difficult to manage because treatment options are limited. We focused our attention on antimicrobials bearing a benzothiazole nucleus. In the past, our research group was interested in the study of a series of 2-mercapto-1,3-benzothiazoles (**1**, Fig. 1) and the corresponding isosters, 2-amino-1,3-benzothiazoles (**2**). All the compounds were tested for their *in vitro* antimicrobial activity against bacteria strains and *Candida* species. Interestingly, the two series showed antibacterial activity against Gram positive and negative and/or antifungal activity, depending on the characteristics of the substituent at the 6-position of the aryl moiety.[1, 2,3] In general, we observed that the isosteric substitution of SH with $NH_2$ brought to the loss of activity against both Gram positive and negative bacteria, while, quite surprisingly, the compounds often exerted interesting antifungal activity. Basing on these positive results, we decided to study a new series of 1,3-benzothiazoles obtained by introducing a hydrazine moiety at position 2 of the aryl moiety (**3**). In order to improve structure-activity relationship studies on 2-amino-1,3-benzothiazoles new coumponds belonging to this class were synthesized. The results obtained were very interesting and will be discussed at the meeting.




series **1** series **2** series **3**

**Fig. 1**

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# POSTERS

**P-1**

# [3,5-DIARYL-(4,5-DIHYDROPYRAZOL-1-YL)-4-OXO-1,3-THIAZOL-5-YLIDENE]-1*H*-INDOL-2-ONES: SEARCHING NEW ANTITUMOR AGENTS THROUGH THE COMBINATION OF INDIVIDUALLY ACTIVE MOIETIES.

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Cancer is a complex, multi-factorial and multistep disease caused by DNA epigenetic mutation that results in an excessive cell proliferation. In spite of decades of researches, neoplastic diseases continue to be a major human health problem worldwide[1]. Traditional therapeutic protocols, as surgery, radiotherapy, chemotherapy and receptor-targeted antibodies exhibit different prospects of success depending on the stage and type of tumor. In particular, the use of chemotherapeutic agents still plays a key role in the antitumor therapy but it is correlated to moderate or severe side effects and, very often, it leads to multi-drug resistance. In order to overcome the issues related to antineoplastic therapies, innovative therapeutic strategies are needed. For example, genetic therapy is one of the new proposed approaches for treatment of cancer[2]. In medicinal chemistry, instead, an increasingly widespread method to obtain drugs having a better therapeutic index is the combination of different bioactive moieties in a single molecule[3]. In this way it is possible to achieve an improvement of the activity of each nucleus, due to a synergetic action, or a larger action spectrum (multi-target compounds).
Our research activity is based on the synthesis of compounds having three different moieties in the same molecule: 4-thiazolidinone-, dihydropyrazole and isatin[3]. Each one of these moieties exhibit antitumor activity, but their combination into a single molecule has the potential to increase such activity[3] (**Fig. 1**). For this reason some series of new derivatives, with different substituents, have been synthesized. In particular, the main goal of the research is to assess the impact of the different substituents on the molecular activity.

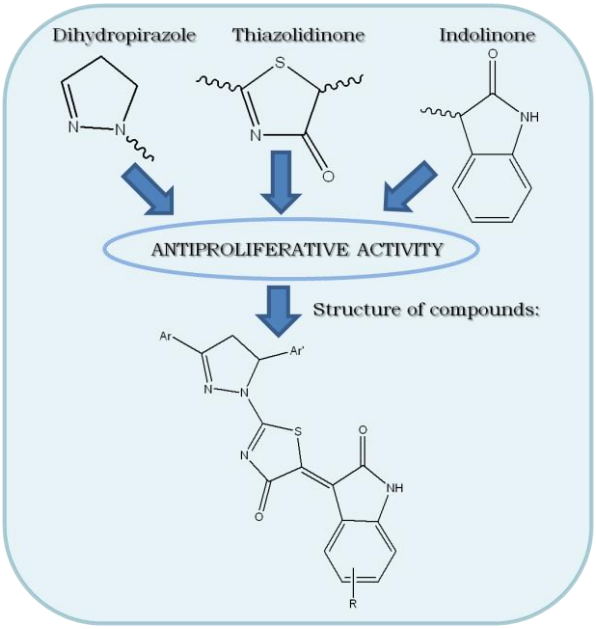


**Fig. 1**: combination of different moieties in one molecule.

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**P-2**

# MOLECULAR DYNAMICS OF NEGATIVE ALLOSTERIC MODULATOR – GPCR COMPLEXES

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Allosteric modulation nowadays gain increasing caution and interest as a mechanism suitable for potential safe and effective drugs. Targeting opioid receptors with such modulators could result in number of benefits e.g. in pain, depression, respiratory and immune disorders treatment, with less side effects due to receptor- and pathway-specific action. There are reports on potential positive and negative opioid receptors' modulators with limited, micromolar efficacy. The data can be a starting point for identification of possible allosteric binding sites and mechanisms of modulation of opioid receptors. In presented work molecular modeling, docking and molecular dynamics studies were used to investigate interactions of known negative allosteric modulators: salvinorin A, THC and cannabidiol on mu opioid receptor[1,2]. An attempt to describe allosteric binding site and identify key residues responsible for modulation was undertaken. The analysis of the molecular dynamics results may give a deeper insight into GPCR allosteric modulation mechanisms, and contribute to development of novel active compounds.

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**P-3**

# DEVELOPMENT OF NOVEL CINNAMOYL-PIPERAZINE DERIVATIVES ENDOWED WITH ANTIOXIDANT-ANTICHOLINESTERASE ACTIVITY

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Neurodegenerative diseases, such as Alzheimer's disease (AD), are pathologies characterized by progressive and irreversible neuronal death associated with central nervous system dysfunction. One mechanism thought to contribute to this type of diseases is the generation of intracellular reactive species (ROS and RNS) by the mitochondrial respiratory chain, which causes oxidative damage, impairs mitochondrial function and leads to cell death.[1] Despite the huge efforts, the pathophysiological events causing the onset and progression of AD remain poorly understood and, consequently, the development of therapeutic agents that attain different pharmacological targets involved in neurodegeneration, besides the cholinergic hypothesis, is attracting progressively more attention.[2] In this context, it is believed that the modulation of mitochondrial functions through antioxidant therapy can be a strategy to prevent or delay the deleterious effects in neurodegenerative diseases.

Antioxidants present in the diet, such as phenolic compounds, may have considerable interest as potential therapeutic agents to combat diseases related to oxidative damage, preventing the formation of ROS and RNS.[3] Hydroxycinnamic acids (HCAs), such as ferulic and caffeic acids are naturally-occurring phenolic antioxidants which have frequently been used as a model for the design and development of new antioxidants.[4] However, despite exhibiting an interesting antioxidant activity *in vitro* their application in therapy was not successful. The clinical failure of antioxidants is often associated with their physicochemical characteristics, particularly their low lipophilicity, which hinders diffusion across biological barriers such as the blood-brain barrier and prevents them from attaining their target-sites.[5]

The aim of this project is design and synthesis of a new set of synthetic piperazine derivatives acetylcholinesterase inhibitors (AChEIs) endowed with antioxidant activity using natural cinnamic acids as templates. Structural characterization of the newly synthesized compounds was carried out by NMR spectroscopy ($^{1}$H, $^{13}$C and DEPT) and electronic impact mass spectroscopy (MS/IE). Biological screening included the assessment the acetylcholinesterase (AChE) inhibition using the Ellman method and antioxidant activity by diverse *in vitro* assays. Furthermore, the determination of redox potentials of the piperazine cinnamic derivatives and their precursors was carried by the techniques of differential pulse and cyclic voltammetry. The results obtained so far will be presented in this communication.

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**P-4**

# $^{1}$H AND $^{13}$C NMR INVESTIGATION OF E/Z ISOMERIZATION OF AN OXIME TYPE ACTIVE PRODRUG, SZV-1287

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We have recently developed a conceptually novel active prodrug, SzV-1287, the oxime derivative of 3-(4,5-diphenyl-1,3-oxazol-2-yl)propanaldehyde, which itself exhibits a potent semicarbazide-sensitive amine oxidase (SSAO) inhibitory activity and, through metabolic transformation, is converted into a known COX-inhibitor, 3-(4,5-diphenyl-1,3-oxazol-2-yl)propanoic acid. In fact, it exerts excellent anti-inflammatory effect in animal models of inflammation.[1,2] Since aliphatic oximes are known to easily undergo E/Z isomerization, NMR study of this compound was carried out in various solvents.
Structure elucidation was based on $^{1}$H-NMR, $^{13}$C-NMR, HSQC, HMBC, and NOESY NMR measurements. Assignments of signal sets of both isomers were made by 1D NOE experiments. Interestingly, we observed solvent- and time-dependent isomerization in $CDCl_3$, methanol-$d_3$ and DMSO-$d_6$. In all solvents, E-isomer was present at higher amounts than the Z-isomer, indicating its higher stability. NMR studies at various temperatures up to 353 K in DMSO and 333 K in $CDCl_3$ and methanol-$d_3$, did not result in coalescence of the signals. Quantum-chemical calculations at different levels of theory (HF 6-31G**, DFT B3LYP 6-31G**, MP2/6-31G**) led to the same conclusion: the energy differences between the E-Z isomers were in range of 2-4 kJ/mol in favor of the E-isomer.

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**P-5**

# MULTICOMPONENT SYNTHESIS OF 2-PIRROLIN-5-ONES AS POTENTIAL HIV INTEGRASE INHIBITORS

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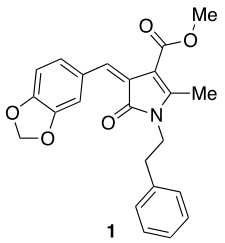
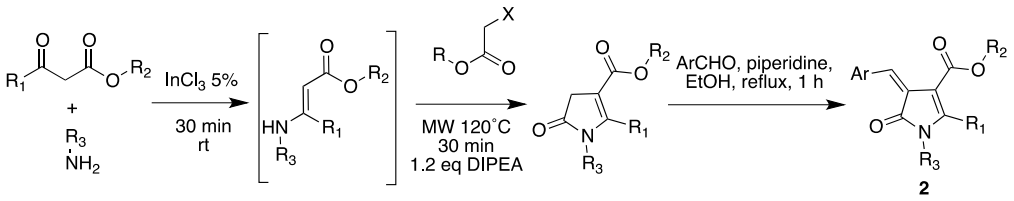
A 2-pyrrolidin-5-one derivative (compound **1**) has been recently identified as a potential HIV integrase inhibitor by computational methods.[1] Furthermore, some pyrazolin-2-one analogues of **1** have been shown experimentally to be potent inhibitors of this key enzyme for HIV infection.[2] However, the detailed study of compound **1** was thwarted by the lack of suitable synthetic methodology. In fact, in spite of its simplicity, the 2-pyrrolidin-5-one framework has received very little attention and has never been previously syntesized using a one-pot protocol.




We describe here a sequential multicomponent reaction[3] leading to an efficient synthesis of 2-pyrrolidin-5-one derivatives from primary amines, beta-dicarbonyl compounds and alfa-haloesters in the presence of indium trichloride as a Lewis acid catalyst and DIPEA as a Brönsted acid trap, under focused microwave irradiation. This reaction can be viewed as a modification of the classical Hantzsch pyrrole synthesis, and has been applied to the preparation of compound **1** and a library of analogues (**2**) that show good binding to the integrase active site in docking studies. This library will be tested for HIV integrase inhibition.

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**P-6**

# DEVELOPMENT OF OXAZOLCARBOXAMIDE VEGFR-2 INHIBITORS

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Cancer treatment represents one of the biggest challenges in current medicine. Angiogenesis plays an important role in tumor growth and metastasis spread[1] and the main regulation is mediated through VEGFR-2[2] therefore its inhibition offers alternative to conventional chemotherapy. Our structures were inspired by AAZ inhibitor form PDB complex 1Y6A with VEGFR-2.[3] We replaced phenyl ring with amide bond in order to reach recently uncovered salt bridge containing pocket (SBCP) and improve synthetic feasibility. (**Fig. 1.**)

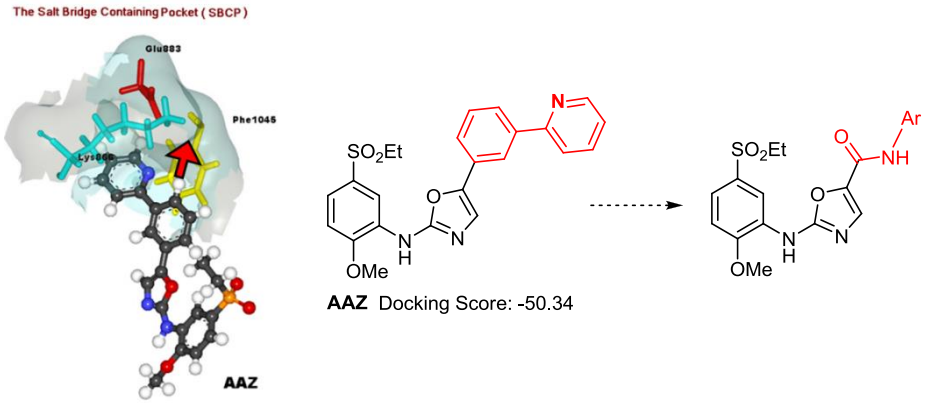


Fig.1. AAZ inhibitor (PDB: 1Y6A) and our aryl - aryl amide replacement.

We performed docking studies to predict binding energies and poses which helped us to choose substitution on newly added aromatic moiety. Chosen compounds will be prepared from 2-(5-(ethylsulfonyl)-2-methoxyphenylamino)oxazole-5-carboxylic acid and corresponding aromatic amine derivatives through coupling with EDC and HOBt. (**Fig. 2.**)

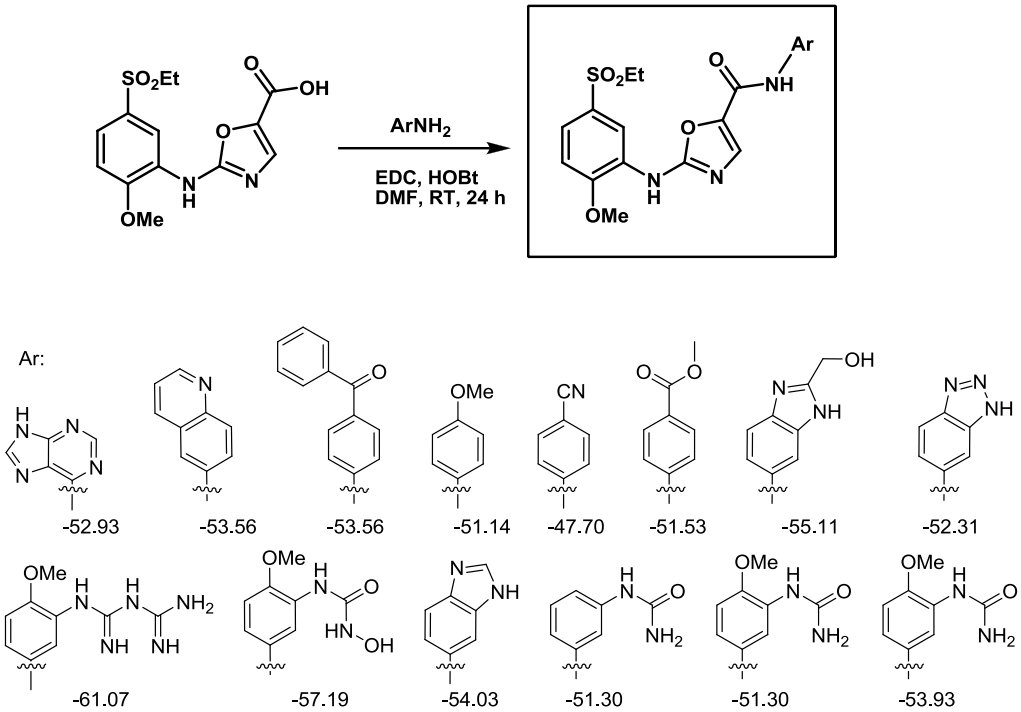


**Fig. 2.** Proposed synthetic route to obtain amides with predicted binding energies.

Obtained $IC_{50}$ values will be compared to predicted energies to validate computational model therein existence of SBCP and its SAR.

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**P-7**

# SYNTHESIS OF POTENTIAL ANTI-INFLAMMATORY AGENTS INSPIRED BY NATURE

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PPAR$_\gamma$ belongs to the superfamily of nuclear receptor proteins and upon activation by ligands acts as a transcription factor and regulates genes that are involved in glucose metabolism, lipid metabolism and cellular differentiation. Furthermore, activation of PPAR$_\gamma$ shows antiinflammatory effects.[1] Clinically used agonists (thiazolidinediones) are potent full agonists but have serious side effects. Recently, three different neolignans (dieugenol, tetrahydrodieugenol and magnolol) were found to be PPAR$_\gamma$ partial agonists.[2] In the frame of this project it was sought to optimize magnolol as a PPAR$_\gamma$ ligand. Preliminary molecular dockings studies[2] and the crystal structure of PPAR$_\gamma$ and magnolol[3] revealed that two copies of magnolol bind to the active binding site of the receptor simultaneously. The hypothesis was established that a molecule combining two magnolols would have increased affinity to the receptor and furthermore, it was hoped to have less side effects due to its expected partial agonism. In consequence, a magnolol dimer was designed by computational studies linking two magnolol molecules covalently *via* a spacer. Here, we report the synthesis of a model compound featuring one and a half magnolol motifs (sesqui magnolol, **Fig. 1**).

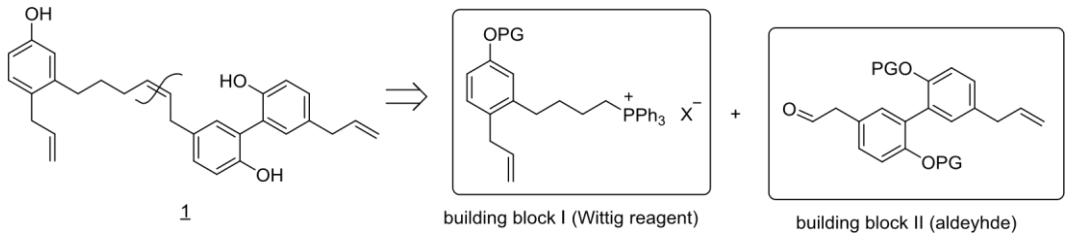


**Fig. 1**: Sesqui magnolol 1 as a pharmaceutical probe and its synthesis

For the synthesis of target compound 1 a classical Wittig reaction was envisioned as the crucial step to introduce the olefin in the required Z-configuration. Both building blocks were successfully synthesized starting from commercially available anisoles. Subsequent Wittig olefination gave the desired Z-isomer exclusively. Pharmacological probe 1 was obtained in good yields over 7 steps and was submitted for evaluation of the biological activity on PPAR$_\gamma$.

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**P-8**

# DISCOVERY OF NEW LEADS FOR OLD TARGETS: INSIGHTS ON THE LEAD OPTIMIZATION PROCESS OF A NEW MAO-B INHIBITOR BASED ON CHROMONE SCAFFOLD

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Monoamine oxidases (MAOs) are intracellular flavine-containing enzymes that play a major role in the *in vivo* inactivation of biogenic amines, both in peripheral and central neuronal tissues. MAO-A and MAO-B are two isoforms of MAOs, which are expressed in mammals, that can be distinguished based on their substrate preference and their interaction with specific inhibitors. In human brain the primary substrates of MAO are neurotransmitters and albeit dopamine (DA) can be metabolised by both isoforms it has a higher affinity for MAO-B isoform. Expression levels of MAO-B in neuronal tissue enhance 4-fold with aging resulting in an increased level of dopamine metabolism and in the production of higher levels of hydrogen peroxide, which are thought to play a major role in the etiology of neurodegenerative diseases. Accordingly, selective MAO-B inhibitors, alone or combined with DA, are important drugs in the treatment of neurodegenerative disorders, such as Parkinson and Alzheimer diseases.[1]
Although the development of MAO inhibitors have been the focus of extensive investigations considerable efforts are being performed to discover new chemical entities (NCEs) endowed with potent, selective and reversible MAO-B inhibitory activity. In this context, our research group have shown that chromone is a valid scaffold for the development of MAO-B inhibitors and that chromone-3-carboxamide is a lead compound.[2-4] Accordingly, the work herein described regards the data acquired in the lead optimization process, namely the design and synthesis of a small library based on the chromone structure shown in **Fig. 1** and the structure-activity-relationships (SARs) data obtained so far.

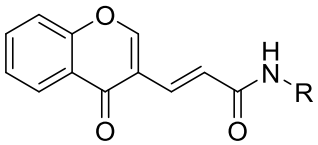


**Fig. 1**: General structure of 3-(4-oxo-4*H*-chromen-3-yl)acrylamide derivatives

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## ACKNOWLEDGMENTS

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**P-9**

# TOWARD THE DISCOVERY OF NOVEL COUMARIN-BASED ACETYLCHOLINESTERASE/BUTYRYLCHOLINESTERASE INHIBITORS

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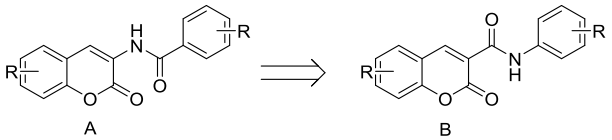
A wide range of different substituted coumarins and their biological properties are well known due to their synthetic accessibility, along with their abundant presence in plants and others natural products. These heterocyclic compounds play an important role in a variety of areas, but stand out in the field of Medicinal Chemistry as several coumarins have been previously described as anticancer, antiviral, anti-inflammatory, antimicrobial, enzymatic inhibitory and antioxidant agents.[1]
Within the field of neurodegenerative diseases and dementia, Alzheimer's disease (AD) is the most predominant and like the other events still remains without cure. Classic features found in the brains of AD patients include neuronal loss in regions associated with memory and cognition, particularly of cholinergic neurons, neurotransmitter depletion (mainly acetylcholine, ACh) and synaptic dysfunction. Current therapies with acetylcholinesterase inhibitors (AChEIs) and *N*-methyl-D-aspartate (NMDA) receptor antagonists are based on the cholinergic and glutamatergic hypothesis, respectively. Though active at ameliorating AD symptoms, none of the current drugs are able to modify disease progression, a fact that has provided the driving force behind the ongoing research for new and potent anti-Alzheimer compounds.[2] Furthermore it is known that butyrylcholinesterase (BuChE) plays a part in the progression of AD and that its inhibition can recover some cholinergic activity in the brain.[3] With this in mind, the development of AChE/BuChE dual-target inhibitors, which can stabilize or even enhance the ACh levels in the brain, is a stimulating drug discovery approach.
In this context, our group has developed coumarin-based compounds that exhibit remarkable activity towards AChE (Scheme 1 - A).[4] In this communication we will describe the structure-activity studies performed so far, namely with the obtention of a library of 3-carboxamidocoumarins (Scheme 1 – B), to optimize the scaffold and to attain potent AChE/BuChE inhibitors suitable for the treatment of AD (Scheme 1 – B). Following this study, docking studies are currently in progress for the most promising compounds.




Scheme 1

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**P-10**

# SYNTHESIS, DRUG-LIKE PROPERTIES AND BIOLOGICAL ACTIVITY OF 1,3,5-TRIAZINE DERIVATIVES

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The youngest member of histamine receptors family is $H_4$ receptor ($H_4R$) which was discovered at the turn of 2000 and 2001 year independently by several research groups[1]. Because of $H_4R$ expression mainly in cells and tissues of immune system its role in inflammatory and (auto)immunological processes and disorders was suggested. Positive effects were observed in treatment of animal models of some diseases in the presence of $H_4R$ antagonists/inverse agonists[2,3].

Extending our SAR investigations in the group of 1,3,5-triazine derivatives - basing on previous research results, patent and literature data[4,5] we looked for a potent, active and selective $H_4R$ ligands in the group of (4-methylpiperazin-1-yl)-1,3,5-triazin-2-amines. Two newly obtained series of compounds possesed in triazine 6-position (un)substituted aromatic ring which was directly connected (series I) or outlying through an ethenyl group (**Fig. 1**).

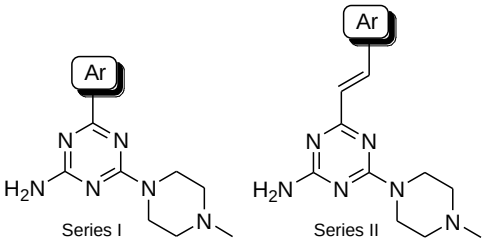


**Fig. 1**: General chemical structures of obtained compounds.

As the results of our studies radioligand binding assays to the $H_4R$ as well as theoretical predictions and *in vitro* studies of toxicity and druglikeness were carried out. All compounds showed the $H_4R$ affinity in (sub)micromolar range.

This work was kindly supported by Polish Ministry of Science and Higher Education Grant No. 594-N/COST-2009/0, National Science Center DEC-2011/02/A/NZ4/00031, FP7 EU COST Actions BM0806 and BM1007 and GPCR – GLISTEN Action CM1207.

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**P-11**

# NOVEL THIAZOLIMINO–5–ARYLIDEN–4- THIAZOLIDINONES AS POTENT ANTIMICROBIAL AGENTS. ESTIMATION OF STRUCTURE–ACTIVITY RELATIONSHIP

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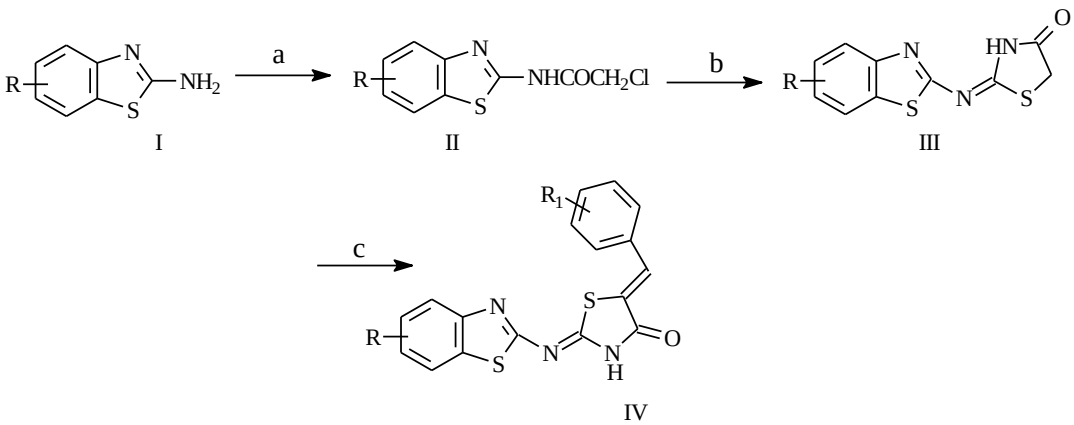
Despite the rapid progress of science, the treatment of infectious diseases the need for the design of novel antimicrobial agents is even greater for the treatment of infections of hospitalized patients, undergoing organ transplants, anticancer chemotherapy and for patients with and also due to the increased number of pathogenic microorganisms with multiple resistance to drugs.

Heterocycles are capable of binding to receptors with high affinity. During our project on the synthesis of compounds with potent biological action, was testified that many thiazole derivatives act as antimicrobial agents. The synthesis and structures of the compounds are shown in Scheme 1.

The antibacterial activity *in vitro* of synthesized compounds, was determined against human pathogenic bacteria by using the microdilution method. The following Gram-negative bacteria were used: *Escherichia coli, Pseudomonas aeruginosa, Salmonella typhimurium, Enterobacter cloacae (human isolate) and the following Gram-positive bacteria: Listeria monocytogenes, Bacillus cereus (clinical isolate), Micrococcus flavus, and Staphylococcus aureus.As reference drugs were used ampicillin and streptomycin.*

For the evaluation of the antifungal activity, the following fungi were used: *Aspergillus ochraceus, Aspergillus fumigatus, Aspergillus niger, Aspergillus versicolor, Aspergillus flavus, Penicillium funiculosum, Penicillium ochrochloron, Trichoderma viride, Candida albicans and Fusarium sporotrichloides.* As reference drugs were used ketoconazole and bifonazole.




**Scheme 1.** Synthesis of title compounds.

**P-12**

# SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EFFECTS OF 16-SPIRO-IZOXAZOLINES IN THE ANDROSTANE SERIES

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Spiro steroids, an important class of compounds that are found in nature, are generally exhibit highly noticeable biological activities, such as neurological or cardiovascular effects. Moreover, among them several compounds are known as efficient antitumor agents.

Our aim was to synthesize new 16-spiro-isoxazolines (**6a–e**) in the androstane series *via* 1,3-dipolar cycloaddition (**Fig. 1**). The precursors of *p*-substituted aryl nitrile oxides (**5a–e**) were prepared in two steps. Firstly, the corresponding aryl aldehydes (**2a–e**) were converted into aryl aldoximes (**3a–e**) with hydroxyl amine *via* condensation reaction, then subsequent oxidative halogenation with *N*-chlorosuccinimide afforded imidoyl chlorides (**4a–e**). Aryl nitrile oxides (**5a–e**) were generated *in situ* from the appropriate imidoyl chlorides (**4a–e**) by dehydrohalogenation in the presence of a strong base (DIPEA). Intermolecular 1,3-dipolar cycloadditions of 3β-acetoxy-16-methylidene-androst-5-en-17-one (**1**) with different aryl nitrile oxides (**5a–e**) in toluene were carried out to furnish 16-spiro-isoxazolines (**6a–e**) in excellent yields.

It is envisaged that the addition of nitrile oxides (**5a–e**) to the α,β-unsaturated ketone (**1**) leads to stereo- and/or regioisomers Structure determination of the products (**6a–e**) by NMR techniques revealed that the reactions are regiospecific and stereoselective. In all cases, the major isomers (**6a–e**) were converted to the 3β-hydroxy analogs (**7a–e**) by deacetylation, and to **8a–e** by reduction. Compounds **6–8** were screened for *in vitro* antiproliferative activity against a panel of three human cancer cell lines.

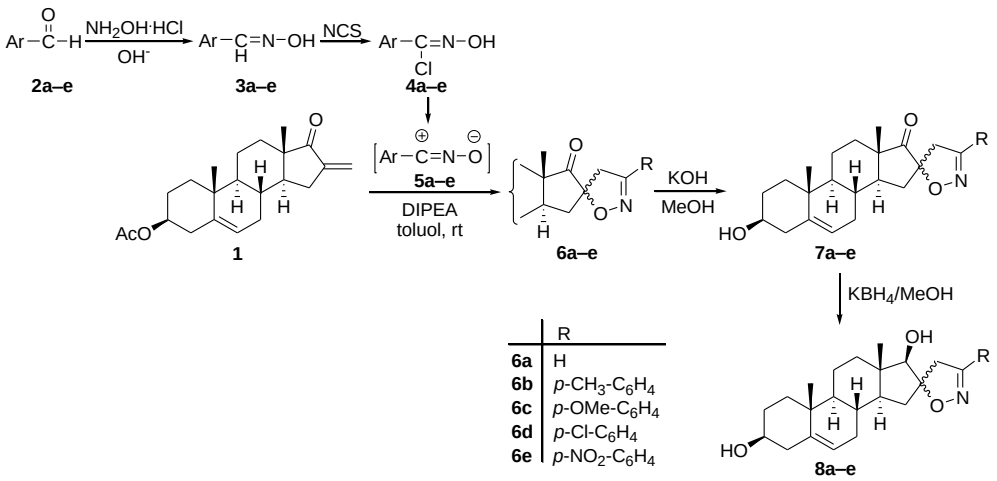


**Fig. 1**: Efficient approach to novel 16-spiro-isoxazolines in the androstane series

The financial support by TÁMOP (TÁMOP-4.2.2/B-10/1-2010-0012) is gratefully acknowledged. This research was realized in the frames of TÁMOP 4.2.4. A/2-11-1-2012-0001 „National Excellence Program-Elaborating and operating an inland student researcher personal support system". The project was subsidized by the European Union and co-financed by the European Social Fund.

**P-13**

# EFFICIENT APPROACH TO NOVEL ANDROSTENE-FUSED ARYLPYRAZOLINES AS PONTENT ANTIPROLIFERANT AGENTS

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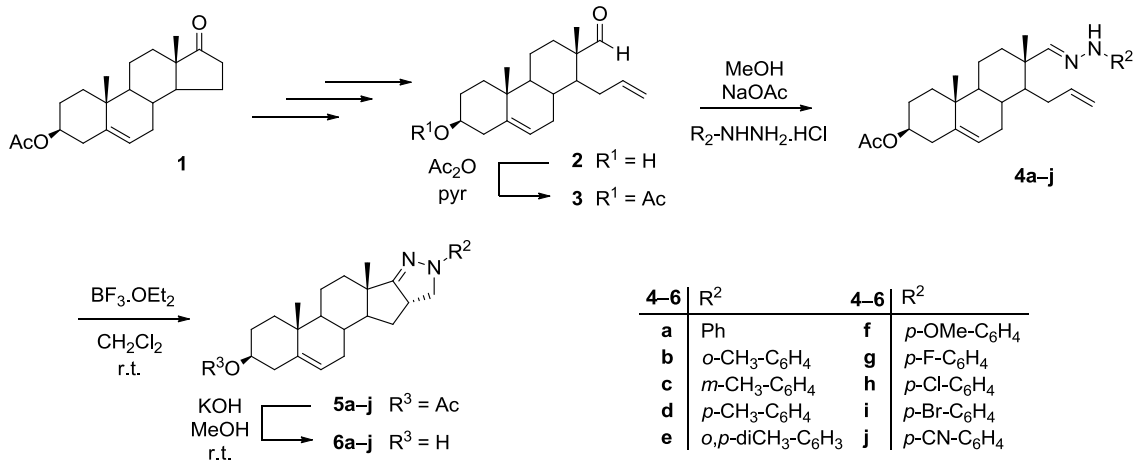
One of the main driving force towards the preparation of steroidal compounds nowadays is the development of novel analogs with a biological target other than a hormone receptor, and therefore the reduction or elimination of unwanted hormonal effects. Experimental results during the past few years have revealed, that a number of synthetic steroidal heterocycles affect the proliferation of human cancer cells without influencing the division of intact cell.

According to our previous results, the introduction of five-membered N-containing heterocyclic moieties either connected with or condensed to the sterane core may cause a significant change in the original biological activities and several newly-synthesized derivatives were found to exert pronounced antiproliferative action on human malignant cell lines.[1] Thus we set out to prepare novel sex hormone-derived ring-condensed heterocyclic steroidal derivatives containing a pyrazoline ring in 16,17 position.




| 4–6 | $R^2$ | 4–6 | $R^2$ |
|---|---|---|---|
| a | Ph | f | *p*-OMe-$C_6H_4$ |
| b | *o*-$CH_3$-$C_6H_4$ | g | *p*-F-$C_6H_4$ |
| c | *m*-$CH_3$-$C_6H_4$ | h | *p*-Cl-$C_6H_4$ |
| d | *p*-$CH_3$-$C_6H_4$ | i | *p*-Br-$C_6H_4$ |
| e | *o*,*p*-di$CH_3$-$C_6H_3$ | j | *p*-CN-$C_6H_4$ |

**Fig. 1**: The syntheses of five-membered N,N-heterorings condensed to ring D of the sterane skeleton.

The presence of the formyl group and the unsaturated side chain in **3** makes an excellent starting material for condensation and subsequent 1,3-dipolar cycloaddition to give fused heteroatom-containing frameworks *via* intramolecular sequences (**Fig. 1**).

The $BF_3 \cdot OEt_2$-catalyzed ring-closures were carried out under mild conditions to get a diverse set of novel derivatives **5a–j**. The reaction rates depended strongly on the electronic character of the substituents of the phenylhydrazines. The cyclizations of **4a–j** exhibited high regio- and stereoselectivity. The synthetized androst-5-ene arylpyrazoline derivatives exerted *in vitro* cytotoxic activity.

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**P-14**

# SYNTHESIS AND IN-VITRO ANTITUMOR ACTIVITY OF NEW *b*-FUSED CARBAZOLE DERIVATIVES

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Polycyclic heteroaromatic compounds featuring a *b*-fused carbazole skeleton have been known for some time as anticancer agents. As prototypical lead structures can be regarded the pyrido[4,3-*b*]carbazole alkaloids, *ellipticine* and *olivacine*.[1] Many structural modifications have been carried out, leading to more potent drugs like *retelliptine*[2] and *pazelliptine*,[3] which are bearing basic side chains at ring D. As previously shown by our group, the pyridine ring (ring D) of such tetracyclic compounds can be replaced with a pyridazine unit[4] or a pyrrolinedione structure,[5] with tumor cytotoxicity retained. In continuation of these studies, we now extended our compound library by modifying also ring A of the system. For this purpose, the diester **1** was regioselectively brominated at C-6 with NBS (chlorination with NCS was found to lack selectivity) or nitrated with urea nitrate. The intermediates **2a** and **2d** were transformed into fused *b*-carbazoles of type **3** and **4**. These target compounds show significant *in-vitro* cytotoxicity towards several human tumor cell lines. Viability assays were performed at fixed concentrations of 10 µM and 1 µM, using an XTT assay (EZ4U®) on a representative panel of cancer cell lines consisting of SW480 (colon carcinoma), A549 (lung carcinoma), Hep3B (liver carcinoma), U373 (glioblastoma) and HTB65 (melanoma) cells.

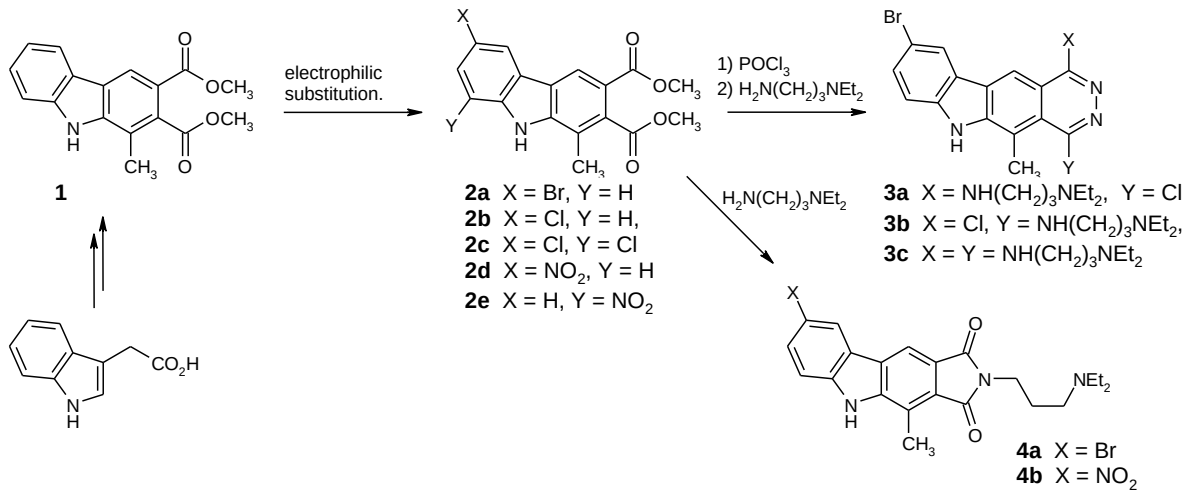


**Fig. 1**: Synthesis of cytotoxic *b*-fused carbazoles of type 3 and 4.

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**P-15**

# STRUCTURAL ANALYSIS OF ALKALOIDS ISOLATED FROM *Berberis vulgaris* L. (*Berberidaceae*)

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Numbers of alkaloids were isolated from the root bark of *Berberis vulgaris* L. (Berberidaceae). The botanical family Berberidaceae is known for the production of isoquinoline alkaloids, including, in particular, protoberberines (8-oxoberberine[1]) and bisbenzylisoquinolines (berbamine[2], etc.). Among the isolated compounds, there were some new, undescribed, structures such as berbanin[3] and others.

Typically, these alkaloids consists free and protected phenols. The position of the ether bridge can be usually confirmed by gHMBC or NOESY cross peaks. Because of rapid exchange of phenolic protons, there are no couplings in gHMBC, and NOESY. Isotopic inductive effect of deuterium can be used to determine position of phenol. 5 µL $D_2O$ was added to the sample and the chemical shift change was observed as $\Delta\delta = \delta_D - \delta_H$ (refer to berbamine **Fig. 1**).

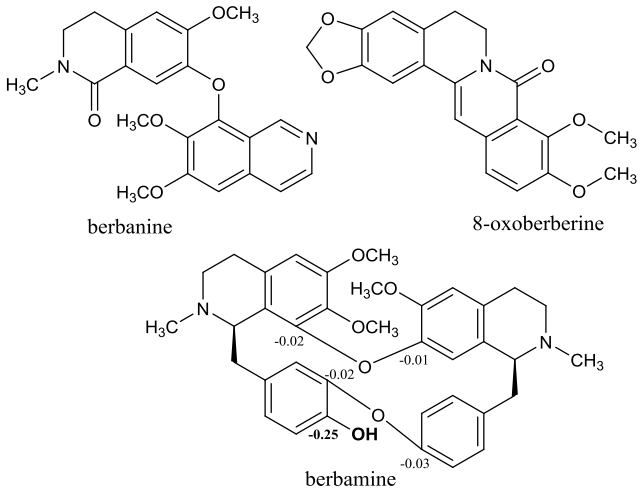


**Fig. 1**: Isolated alkaloids from *Berberis vulgaris* L.

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**P-16**

# FUNCTIONAL CHARACTERISATION AND EVALUATION OF ADENOSINE RECEPTORS ROLE IN PC-3 CANCER CELLS PROLIFERATION

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Adenosine is a signaling molecule, which was found in cancer tissue microenvironement at a concentration that is able to modulate tumor growth by interacting with G protein-coupled adenosine receptor (AR) subtypes. Moreover, AR subtypes ($A_1$, $A_{2A}$, $A_{2B}$, $A_3$) were also detected up-regulated in various tumor cells.[1,2]
Therefore, adenosine receptors role in growth, proliferation and metastasis of cancer cells has been already studied in many research centers.[1,2,3,4]

In our studies we investigated well-established adenosine receptor ligands for their anticancer potential. First, we tested functional adenosine receptors expression in PC-3 prostate cancer cells by performing cAMP accumulation assay. Both selective and non-selective agonists and antagonists of respective adenosine receptor subtypes were used in functional assays at PC-3 cells. In our study presence of the functional $A_{2A}$ and $A_{2B}$ receptors in PC-3 cells was shown. On other hand we were not able to detect the effect of $A_1$AR and $A_3$AR stimulation.

Various adenosine receptor ligands were further tested for their potential to inhibit PC-3 prostate cancer cell line growth, measured in MTS assay. We tested selective $A_{2A}$ agonist (CGS-21680) and non-selective AR agonists (CADO, NECA, R-PIA) as well as $A_{2A}$ AR (MSX-2) and $A_{2B}$ AR (PSB-603, PSB-1115, DPCPX) antagonists. Doxorubicin was used as a positive control in our experiments.

Surprisingly, among tested ARs ligands only CADO significantly influenced growth rate of cultured prostate cancer cells. However, adenosine receptors antagonists used in the experiment were not able to reverse this effect. To conclude -
although antiproliferative effect of CADO against PC-3 cells was revealed we were not able to fully verify the hypothesis that observed effect is related to G protein-coupled receptors signaling. For that purpose more detailed experiments should be performed to examine the mechanism of the cellular cytotoxicity of CADO.

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**P-17**

# DEVELOPMENT OF NOVEL MULTI-FUNCTIONAL NITRONES AS NEUROPROTECTIVE AGENTS

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Alzheimer's disease (AD) is currently associated to cell-altered oxidative stress status, a fact that is related with a failure in the antioxidant protective system and/or an increment in reactive species production/accumulation, which can cause the destabilization of cellular membranes, damage of blood-brain-barrier, disintegration of DNA and ultimately, neuronal death. In this context, neuroprotective antioxidant agents with an extended therapeutic window are therefore urgently needed. In fact, free radical scavengers, such as nitrones and several dietary antioxidants have been already tested and their efficacy validated in experimental studies. However, the majority of antioxidants studied so far have limited success in clinical trials, a fact that could be related with their poor distribution throughout body and with the inherent difficulties to cross the brain-blood-barrier and attain the target sites.

As the neuroprotective activity depends in great part on the connectivity and the nature of substituents, the aim of this project is the design and synthesis of innovative lipophilic hybrid arylnitrones and nitrates antioxidants using natural phenolic antioxidants as a scaffold. The hybridization strategy encloses the introduction of fragments able to show neuroprotection properties, such as nitrone or nitrate moieties, to antioxidant phenolic acids, which are known to be able to stabilize the generated free radicals, and lipophilic linkers. After synthesis, purification and structural identification of the novel compounds, their antioxidant profile was evaluated either using ABTS, DPPH and galvinoxyl assays or by electrochemical techniques (cyclic, differential pulse and square wave voltammetry). The compounds were also screened toward acetylcholinesterase as it is a key AD target. The results of this preliminary work will be presented.

Finally, new therapeutic agents are thus expected to be obtained by this innovative medicinal chemistry artwork and there is the hope that, in a near future, this new therapeutic approach can improve the lifestyle of people who suffer from diseases related to oxidative stress, namely of neurodegenerative nature.

The authors thank the Foundation for Science and Technology (FCT) of Portugal (PEst-C/QUI/UI0081/2013 and QREN FCUP-CIQ-UP-NORTE-07-0124-FEDER-000065 projects) and doctoral grants of C. Oliveira (SFRH/BD/88773/2012) and T. Silva (SFRH/BD/79671/2011).

**P-18**

# ARYLIDENEIMIDAZOLONES AS NEW TOOLS TO RESTORE EFFICACY OF ANTIBIOTICS

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The bacterial multidrug resistance (MDR) is a factor seriously limiting treatment of various infectious diseases. One of the most prominent mechanisms involved in developing antibiotic resistance in MDR bacteria is the active drug efflux by protein pumps that extrude all usual classes of antibiotics out of the bacteria cell[1]. Blocking the bacterial efflux system by the efflux pump inhibitors (EPIs) is an attractive strategy to overcome MDR and consequently to restore efficacy of antibiotics. Based on the results[2,3] obtained previously, a new series of piperazine arylideneimidazolone compounds was evaluated on their EPI properties in two strains of *Enterobacter aerogenes* with different expressions of AcrAB-TolC pump. The following tests were carried out: (1) determination of the compounds minimal inhibitory concentrations (MIC), (2) compounds influence on the MIC values of antibiotics: chloramphenicol, doxycycline nalidixic acid and erythromycin, (3) compounds cooperation with antibiotics utilizing isobolograms, (4) the real-time efflux test identifying the compounds that act on an efflux by blocking the expelling of the fluorescent dye. The chemical modifications performed influenced the EPI activity of the arylidenehydantoin derivatives comparing to the derivatives described previously[2,3]. The compounds possessing a naphthylmethylidene or chlorobenzylidene substituent at position 5, decreased significantly the MIC of antibiotics whereas no activity was observed for the derivatives possessing (di)methoxybenzylidene substituent. We found that for the tested derivatives of hydantoin the amphiphilic nature of a molecule seems to be crucial for their EPI activity. This amphiphilic nature could be obtained by the presence of hydrophobic moiety at position 5 together with hydrophilic N3- terminal basic fragment.

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**P-19**

# DESIGN AND SYNTHESIS OF POTENTIAL INHIBITORS OF CHOLINESTERASES

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Over 100 years ago Dr. Alois Alzheimer described the most common form of dementia which today bears his name [1]. The oldest hypothesis, which tried to explain the pathogenesis of Alzheimer's disease (AD) is cholinergic hypothesis, which proposes that symptoms of disease are caused by decreased level of a significant neuromediator - acetylocholine. This pathomechanism has become the most important biological target for searching anti-AD drugs [2]. Three of the four currently used drugs act by inhibiting acetyl- and butyrylcholinesterases - key enzymes that break down acetylcholine: rivastigimine, donepezil and galantamine [3].

The aim of our study was to design new inhibitors of cholinesterases using molecular modelling technique, synthesis of selected compounds and test the inhibition of cholinesterases.

New potential inhibitors of cholinesterases were sought within the ZINC database. ZINC is a huge source of available compounds to look for new biological active substances. The current ZINC12 database contains compounds in an accessible format to dock. The process of virtual screening was preceded by a selection of only these compounds with a good absorption and distribution into the central nervous system. Pharmacophore models were built, based on the crystal structures of complexes cholinesterases with well-known inhibitors (for acetylocholinesterase donepezil, bis-tacrine, decamethonium and tacrine, for butyrylcholinesterase bis-nor-meptazinol). The screening procedure yielded 5202 compounds of which were selected for further study only 88 from the donepezil model with potential high selectivity against AChE. After a detailed docking study 9 hits were chosen. Some of the selected structures were synthesized and tested for inhibition acetylocholinesterase and butyrylocholinesterase in the Ellman test. The structures of designed inhibitors, results of chemical synthesis and biological assays will be presented.

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**P-20**

# TOWARDS SYNTHESIS OF NOTOINCISOL A AND NOTOICISOL B, NATURAL PRODUCTS WITH POTENTIAL ANTI-INFLAMMATORY EFFECT

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Regulation of the inflammation is desirable as inflammation is directly linked with many serious diseases, as for instance diabetes, cardiovascular diseases or cancer.[1,2] Since the involvement of PPARγ receptor in the inflammatory process was revealed, this transcriptional factor has become a potential target for treatment of the inflammation.[3] Besides regulation of inflammation, activation of PPARγ receptor leads to the increased sensitivity towards insulin and cell proliferation.[4] Therefore, PPARγ is nowadays used in clinic to treat type II diabetes by its full agonists represented by thiazolidinediones (TZD). TZD however possess many serious side effects. Some studies suggest that using partial agonist could lead to retaining of desired effects and elimination of the side effects due to the inducing alternative receptor configuration.[5] Notoincisol A and Notoincisol B are natural polyacetylenes recently isolated by our partners from *Notopterygium incisum*. They showed to be partial agonists of PPARγ receptor. In this contribution, we will focus on the development of synthesis of both natural products, confirming their stereochemistry and in latter stage synthesis of derivatives for SAR study.

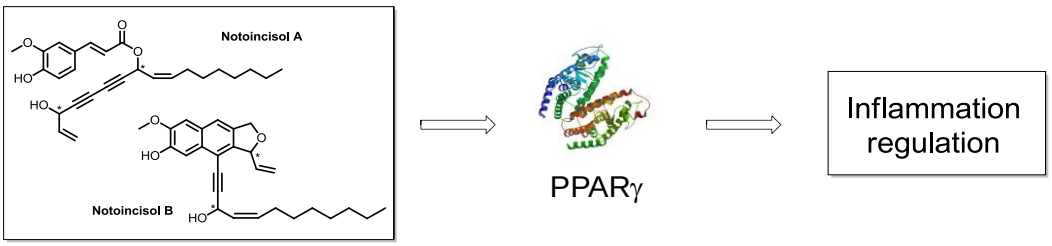


**Fig. 1**: Notoincisol A and B as potential anti-inflammatory agents acting via PPARγ.

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**P-21**

# SYNTHESIS OF *N*-ALKYL-(3-ALKYLAMINO)PYRAZINE-2-CARBOXAMIDES AS POTENTIAL ANTITUBERCULOTIC DRUGS

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Tuberculosis (TB) is a serious infectious disease, which has been one of the most common causes of death around the world for a long time. Despite WHO effort to find effective procedures for the treatment and continuous development of new potential drugs, TB is still a major global problem. The development and progress of the resistant forms of this disease and co-infection with HIV is the main cause.

Pyrazinamide (PZA) is the first-line drug used in TB-therapy. One of the mechanisms of action is competitive inhibition of NADPH binding to Mycobacterium tuberculosis Fatty Acid Synthase I (FAS I), which is an important enzyme in mycolic acid synthesis.1 Synthesis of novel PZA derivatives is one of the perspective ways for the new drugs development.

A series of new pyrazinamide derivatives, i.e. N-alkyl-3-chloropyrazine-2-carboxamides and N-alkyl-(3-alkylamino)pyrazine-2-carboxamides, were prepared.

These structures were designed based on the results of antimycobacterial evaluation of 5-(alkylamino)pyrazine-2-carboxamides and 6-(alkylamino)pyrazine-2-carboxamides reported previously.2 Compounds with long alkyl chains can facilitate penetration through mycobacteria outer shell and cell wall, reaching the intracellular compartments.2

The title compounds were characterized with analytical data and tested in vitro for their antimycobacterial, antibacterial and antifungal activity.

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**P-22**

# DEVELOPMENT AND SYNTHESIS OF AAZ-REGIOISOMERIC VEGFR2 TK MODULATORS

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Tumor diseases are considered the most widespread and the most dangerous diseases at all. New formation of the supportive vascular system that is essential for the birth, growth and survival of tumor cells is primarily done by means of the biological process called angiogenesis. Vascular endothelial growth factors (VEGFs) and their corresponding tyrosine kinase receptors (VEGFR TKs) function as central regulators of angiogenesis. VEGF signalization through VEGFR2 TK receptor is a key angiogenic pathway whose therapeutic inhibition using specific small-molecule compounds represents an interesting and promising strategy of the fight against cancer.

Our project is focused on a development of novel **AAZ**-regioisomeric compounds for VEGFR2 TK inhibition. Particularly, we want to prepare the selected basic regioisomeric pair compounds (ArNHoxazolPh-3-Heteroaryl: pyrol-2-yl, pyrid-2-yl, triazol-2-yl and triazinyl) and determine their TK inhibition activity by *in vitro* enzymatic assay ($IC_{50}$ VEGFR2). Subsequently, we plan to screen the most interesting inhibitors in other *in vitro* (endothelial cells) and *in vivo* (CAM, Zebrafish) assays to determine their biological mechanism and efficiency.

ArNHoxazolic compound AAZ was developed by GlaxoSmithKline as VEGFR2 TK ATP-competitive Type 1 inhibitor.[1] Because AAZ possesses good pharmacokinetic properties and strong enzymatic inhibitory activity against VEGFR2 TK ($IC_{50}$: 22 nM), this compound was selected as a promising drug candidate.[2] AAZ belongs to 5-aryl N-aryloxazole-2-amine compounds containing 2,5-disubstitued oxazole ring. 4-Aryl N-aryloxazole-2-amine (AAZ-regio) represents regioisomeric compound to AAZ. We proposed that this compound can take the same binding position in VEGFR2 kinase and similar inhibition properties as known for AAZ (PDB: 1Y6A). (**Fig. 1**)

Oxazolic AAZ-regio represents new compound. Oxygen present in 1,3-oxazolic core is an isosteric atom to oxazolic nitrogen. Therefore appropriate conformer of AAZ-regio is possible bioisostere of **AAZ** for VEGFR2 tyrosine kinase. We named this effect as Regioisomeric Bioisostery (RegBio). The principle of RegBio arises from the preservation of position of substituents on pseudosymetric heterocyclic core while this core turns round (180 °) and still remains able to keep similar intermolecular interactions known of the other regioisomer. This research can be important for development of new TK inhibitors even in the IP crowded space.

**P-22**

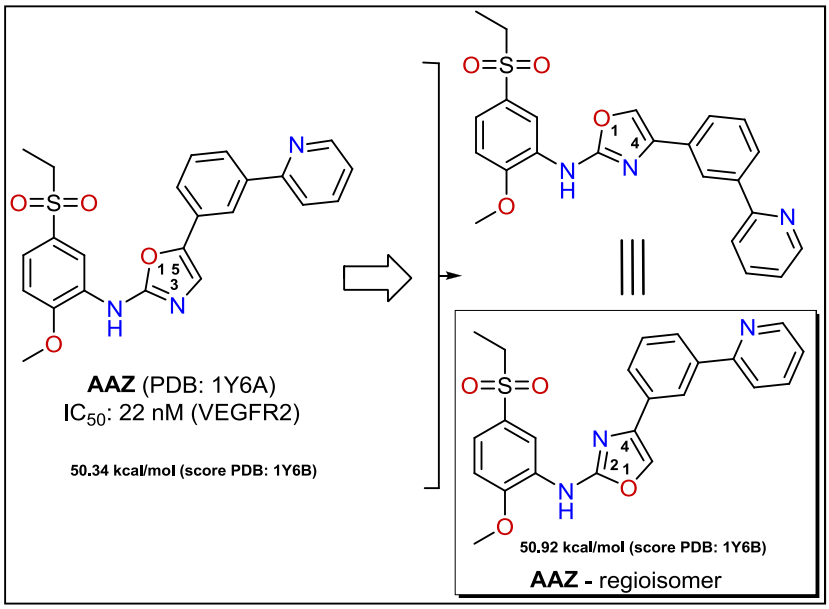


Fig. 1. Structures of AAZ inhibitor and two conformers of its regioisomer (on the right). After docking AAZ – regioisomer can adopt similar conformation as one that is known for AAZ ligand in complex with VEGFR2 TK (PDB: 1Y6A).

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**P-23**

# SYNTHESIS OF SALICYLANILIDE DERIVATIVES AND THEIR ANTIMYCOBACTERIAL EFFECT

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Tuberculosis (TB) and particularly the development of latent TB, drug-resistant forms (multi-drug-resistant tuberculosis, extensively drug-resistant TB and recently totally drug-resistant TB) represents currently a serious global problem. According to the WHO report, about 1/3 of the world population is infected by the latent TB. These alarming facts are reflected in an intensive search for new antimycobacterial drugs. Current development is focused, e.g., on the unique steps in the biosynthesis of cell walls, the mapping of metabolic pathways or identification of specific genes affecting virulence and latent state of *Mycobacterium tuberculosis*.[1,2]

Salicylanilide derivatives belong to the potentially promising groups of compounds. It has been reported that esterification of phenolic drugs to form its prodrugs produces compounds with improved properties – enhanced bioavailability or absorption, which are often the limiting factor for their activity, improved physicochemical properties (lipophilicity etc.) or reduced toxicity.[3] Some salicylanilide esters have shown a high *in vitro* activity against both drug-sensitive and resistant TB strains with minimum inhibitory concentrations $\geq$ 0.125 μmol/L. Salicylanilides derived from 5-bromo/chlorosalicylic acid and variously substituted anilines were esterified by isonicotinic and pyrazine-2-carboxylic acids to obtain new salicylanilide mutual prodrugs. Based on previous results, the design has been focused on the compound with introduced electron-withdrawing substituents (especially $CF_3$ group) into the aniline ring. This substitution pattern contributes to the increased efficacy against both *M. tuberculosis* and nontuberculous mycobacteria (*Mycobacterium avium* and *Mycobacterium kansasii*).[4]

The synthesis of these esters involves two steps. The first step is the preparation of salicylanilides, which are obtained routinely by the reaction of appropriate salicylic acids with various anilines in the presence of $PCl_3$ in a microwave reactor.[5] Yields of salicylanilides were general 78%. Following esterification of salicylanilides is based on the direct esterification by corresponding carboxylic acid chlorides in the presence of triethylamine with yields of esters about 50%.

Synthesized derivatives undergo currently *in vitro* evaluation against drug-sensitive *M. tuberculosis* $H_{37}Rv$ and atypical strains of *M. avium* and *M. kansasii*. The most active derivatives will be assayed against one extensively drug-resistant TB and five multidrug-resistant tuberculosis TB strains with different resistance patterns and for their cytotoxicity.

The work was financially supported by the Research project IGA NT 13346 (2012).

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**P-24**

# NOVEL NITROPHENYL UREA GSK-3 INHIBITORS WITH ANTIPROLIFERATIVE PROPERTIES

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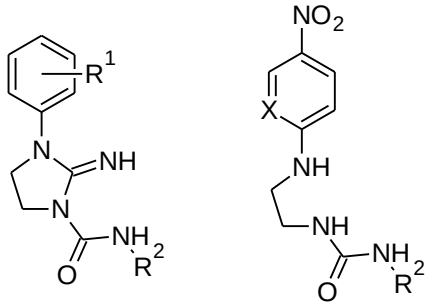
GSK-3 has become recently an attractive drug target in medicinal chemistry. Initially discovered in 1980 to be responsible for regulation of glycogen synthase[1] now it remains fully established target implicated in cancer and a variety of neurological disorders like Alzheimer's, bipolar disorder or Huntington disease[2].
In this work we present a synthesis of novel compounds together with biological data. Some of the obtained compounds showed activity in GSK-3 assays and closely related CDK. Together with data from apoptosis and viability studies on two cancer cell lines these newly designed compounds are promising structures that might lead to incorporation of new scaffolds into kinase inhibitors research.

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**P-25**

# INFLUENCE OF PERIPHERAL SUBSTITUENTS ON INTRAMOLECULAR CHARGE TRANSFER IN AZAPHTHALOCYANINES

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Azaphthalocyanines (AzaPcs) are planar macrocyclic compounds structurally close to porphyrins with unique photochemical and photophysical properties. This project is a follow-up to our recent discovery, that so called "intramolecular charge transfer" (ICT), which can occur at AzaPc[1]. Peripheral amine serves as a donor and AzaPc macrocyclus as an acceptor of the electron. This phenomenon can be used for sensoric applications[2,3]. The aim of this study is to investigate influence of electronic effects of peripheral substituents bounded to the acceptor moiety of AzaPc (electron-withdrawing or electron-donating groups) on ICT efficiency.

Synthesis of pyrazine-2,3-dicarbonitriles disubstituted in positions 5 and 6 by various functional group (butoxycabronyl-, tert-butylsulfanyl-, neo-pentyl-, butoxy-), precursors "A", was the first step of this work. These precursors were prepared by nucleophilic substitution of 5,6-dichloropyrazine-2,3-dicarbonitrile by appropriate nucleophilic agent (butoxide, terc-butylthiolate). 5,6-dineopentyl- and 5,6-dibytoxycarbonyl substituted pyrazine-2,3-dicarbonitriles arose from condensation of diaminomaleonitrile and corresponding diketone. Donor moiety of AzaPc is represented by precursors "B" bearing 4-(2-hydroxyethyl)piperidin-1-yl group (AzaPc 2-4) or diethylamino group (AzaPc 1). Cyclotetramerization of precursors A and B was performed using magnesium butoxide as an initiator of the reaction. Magnesium complexes were converted to metal-free AzaPcs using p-TSA. Metal-free AzaPcs reacted with zinc acetate to form zinc complexes AzaPc (AzaPc 2-4). Due to unsuccessful attempts with butoxide method, synthesis of AzaPc with butoxycarbonyl substitution (AzaPc 1) was performed by metal ion template effect using anhydrous zinc acetate in DMF. Fluorescence and singlet oxygen quantum yields were determined and their sum (indicator of ICT efficiency) was correlated with Hammett substituent constant $\sigma_p$.(see Fig. below). Increasing of ICT efficiency along with growing value of σp of peripheral substituents was observed.

*The financial support from the GA UK 1182313/2013 is gratefully acknowledged.*

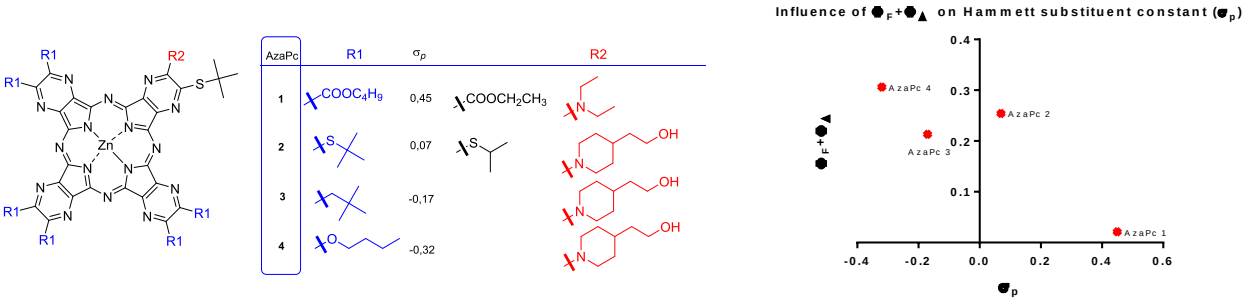


**Fig. 1**: Structures of AzaPc 1-4 and Influence of $\phi_\delta + \phi_F$ on Hammett substituent constant

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**P-26**

# NEW POTENTIAL ANTITUBERCULOTICS WITH TETRAZOLE MOIETY

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The search for new antituberculotics due to increasing occurrence of multidrug-resistant (MDR) tuberculosis strains is an important task for medicinal chemistry nowadays. We focused our effort to synthesis of 1-substituted-5-benzylsulfanyl-1*H*-tetrazoles **1** and 2-substituted-5-benzylsulfanyl-2*H*-tetrazoles **2** (**Fig. 1**). These compounds exhibit high antimycobacterial activity.

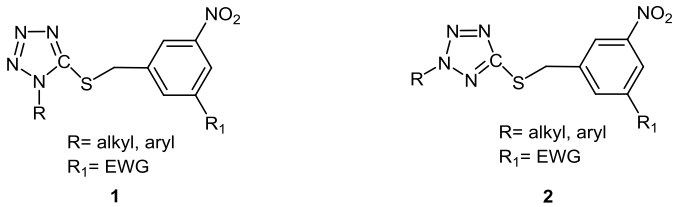


Fig 1. Antimycobacterially active compounds

In this work, derivatives with various side chains on tetrazole ring, which are probably responsible for the pharmacokinetics, were prepared and their antimycobacetrial activity were evaluated.

*The work was supported by* the European Social Fund and the state budget of the Czech Republic. Project no. ***CZ.1.07/2.3.00/30.0061***

**P-27**

# NOVEL SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF ENANTIOPURE 3,5-DISUBSTITUTED PYRROL-2-ONES

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Five membered nitrogen heterocycles are pervasively found in the nature. Pyrrolone is a class of such heterocycles, mostly present as an integral part of a number of alkaloids and toxins. Additionally, they serve as intermediates in the synthesis of various biologically active compounds, for instance, epolactaene (neuritogenic compound), lepadiformine (antitumor agent), and preussin (antifungal agent).[1] In our previous paper, we have reported that 3,5-disubstituted furan-2-ones exhibit excellent antifungal activity.[2] Prompted by these investigations and in continuation of our research on the heterocyclic compounds of pharmaceutical interest, it was conspicuous to synthesise lactam analogues of the reported furanones, and evaluate their antimicrobial activity (Fig.1).


3,5-disubstituted-2,5-dihydrofuran-2-one

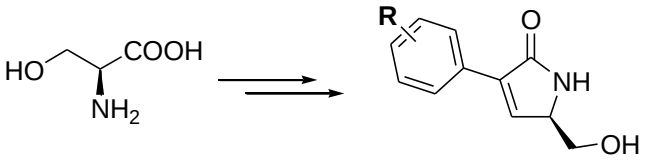
**$R_1$**: -$OCH_3$, Cl, Br
**$R_2$**: -$COCH_3$

3,5-disubstituted-2,5-dihydropyrrol-2-one

**R**: H, $CH_3$, $OCH_3$, Cl, Br

**Fig. 1**: Anti-fungal 2,5-dihydrofuran-2-ones and synthesized 2,5-dihydropyrrol-2-ones.

In the presented work, we describe a facile synthetic route to enantiopure 2,5-dihydropyrrol-2-ones (scheme 1). This synthetic approach is availed with the metal catalysed, high yielding reactions and is in accordance with the requirements of green chemistry.[3] The antimicrobial activity for these pyrrol-2-ones will also be presented.




**R**: H, $CH_3$, $OCH_3$, Cl, Br

**Scheme 1:** Synthesis of 2,5-dihydropyrrol-2-ones.

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**P-28**

# NOVEL ABAD AND Aβ-ABAD INTERACTION MODULATORS FOR TREATMENT OF ALZHEIMER'S DISEASE

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Alzheimer's disease (AD) is one of the most frequent neurodegenerative disorders in elderly. Even though the extracellular accumulation of amyloid β-peptide (Aβ) is one of the hallmarks in AD pathogenesis, it is also well known that intracellular Aβ interacts with various proteins and thus interferes with their proper function. One of the affected proteins is amyloid-binding alcohol dehydrogenase (ABAD), enzyme known for its direct interaction with Aβ. Either altered or diminished function of ABAD by Aβ may lead to disruption of energy metabolism and cell homeostasis, consequently resulting in cell death. For these reason, ABAD-Aβ interaction and ABAD itself might represent a potential target for AD treatment.[1,2]

The aim of the project was to prepare a series of disubstituted benzothiazolyl ureas. Original structure template was established on already described inhibitor of ABAD-Aβ interaction, frentizole. Further structural modifications were designed to improve the potency of formerly prepared compounds.[3]

Synthesis of the compound series was performed in three steps (**Fig. 1**). The final products were purified by either recrystallization or column chromatography. Identity and purity of prepared compounds were confirmed by $^{1}H$ and $^{13}C$ NMR and HRMS.

The ability of prepared compounds to modulate ABAD activity was evaluated. Two compounds showed stronger inhibition of ABAD compared to the standard compound. Moreover one compound exhibited ~20% increase in ABAD activity. Further *in vitro* experiments, such as $IC_{50}$ determination, kinetic profile and ability to inhibit ABAD-Aβ interaction, are currently in progress.

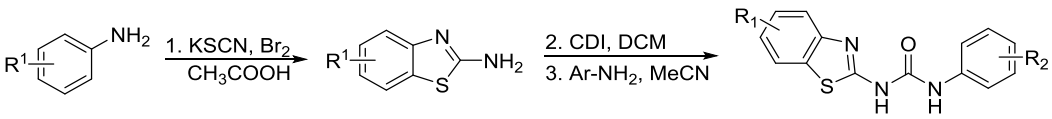


**Fig. 1**: Preparation of substituted benzothiazolyl ureas.

The work was supported by the European Social Fund and the state budget of the Czech Republic (Project no. CZ.1.07/2.3.00/20.0235, the title of the project: TEAB).

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**P-29**

# SALICYLANILIDE CARBAMATES: SYNTHESIS AND BIOLOGICAL PROPERTIES

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Tuberculosis still represents a global health and social problem and the increasing emergence especially of drug-resistant forms is alarming.[1] Novel anti-tuberculosis agents with innovative mechanisms of action without any cross-resistance are demanded. The modification of known molecules represents one promising approach.
Salicylanilide *N*-alkyl carbamates exhibited high *in vitro* activity against both drug-susceptible and resistant strains of *Mycobacterium tuberculosis* (MTB) as well as nontuberculous mycobacteria. Additionally, they share alleviated cytotoxicity when compared to parent salicylanilides.[2] That is why we synthesized new salicylanilide carbamates as potential antimycobacterial and antimicrobial agents.
Firstly, parent salicylanilides were prepared by the reaction of salicylic acids and anilines with $PCl_3$ in a microwave reactor. Secondly, *N*,*N*-disubstituted carbamates were obtained *via* direct acylation of salicylanilide triethylammonium salt by carbamoyl chlorides.[3] *N*-Aryl, *N*-cycloalkyl or *N*-arylalkyl carbamates were synthesized in a similar way as reported previously by Férriz et al.[2]
Novel derivatives were evaluated *in vitro* against *M. tuberculosis* $H_{37}Rv$, drug-resistant MTB strains, nontuberculous mycobacteria (*M. avium*, *M. kansasii*) as well as some bacterial and fungal strains. The *in vitro* cytotoxicity and cytostatic activity on human cell models (MonoMac-6, HepG2) were determined by MTT assay.
The antimicrobial activity of *N*,*N*-disubstituted carbamates were mostly in micromolar range,[3] whilst *N*-monosubstituted carbamates showed higher activity but also cytotoxicity.

This publication is a result of the project implementation: “Support of establishment, development, and mobility of quality research teams at the Charles University”, project number CZ.1.07/2.3.00/30.0022, supported by The Education for Competitiveness Operational Programme (ECOP) and co-financed by the European Social Fund and the state budget of the Czech Republic.
The work was financially supported also by the Research project IGA NT 13346 (2012).

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**P-30**

# CHEAPER PALLADIUM CROSS-COUPLINGS – EN ROUTE TOWARDS HIGHLY SUBSTITUTED HETEROCYCLES

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Originally, our primary effort was to develop a synthetic protocol towards $C_4$-substituted six-membered heterocycles containing an exocyclic double bond structurally related to gelastatin A and B as they might possess interesting biological properties.[1,2,3] The route established employs new type of catalyst as well as mild reaction conditions. Good functional group tolerance and reliable control of stereoselectivity were achieved, too.
With this protocol in hand we have synthesized over 20 new pyranones (see **Fig. 1**). The chemical and biological properties of these molecules will be investigated.

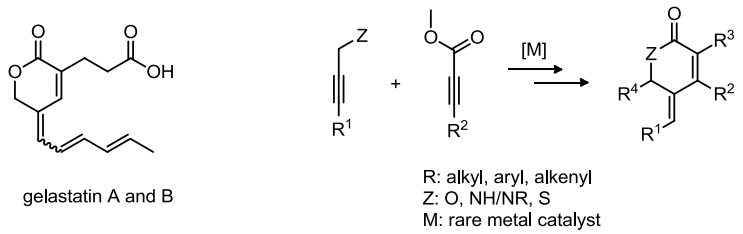


**Fig. 1**: Synthesis of highly substituted heterocycles

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**P-31**

# CYCLOALKYLIDENHYDRAZO-4-ARYLTHIAZOLES: A NEW CLASS OF LANOSTEROL 14 ALPHA-DEMETHYLASE?

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Over the past 20 years the incidence of invasive fungal infections and associated mortality have increased significantly as a consequence of the rising number of immune-compromised patients, the wide development of organ transplantation, tracheal intubation and endoscopic techniques, and the extensive application of broad-spectrum antibiotics, immunosuppressant drugs and corticosteroids. [1,2] In this contest is the aim of our study. Indeed, *Candida* spp. and especially *Candida albicans*, account for a large number of invasive fungal infections, placing itself at the first place as the major fungal pathogen in humans. [3] This organism, together with related *Candida* species, has become one of the commonest agents of hospital-acquired and AIDS patients infection. [2-4]
So far there are four classes of antifungal agents, (polyenes, 5-fluorocytosine, azoles and echinocandins) that can be used for the treatment of systemic infections. Azoles, and in particular Fluconazole (FLC), have been extensively used in clinical practice due to their great efficacy and low toxicity. However, due to the excessive exposure to this drug, Fluconazole-resistant *Candida albicans* species have emerged.
In order to contrast this tendency, different efforts have been made to overcome the emergence of resistant fungi by using multi-drugs therapy. Unfortunately high costs and serious side effects have put limitation on the combinations of antifungal agents. In addition, contradictory results on synergistic or antagonistic actions of various antifungal combination have been reported.
Our research group has already synthesised similar compounds that exhibited potent activity towards several species of *Candida*. [5]
In this context, as a continuation of our previous reports on the discovery of new anti-*Candida* agents, we decide to focus our attention on the synthesis and biological evaluation of cycloalkylidenhydrazo-4-arylthiazoles in order to evaluate their activity towards Fluconazole resistant *Candida albicans* and to add more information on the SARs and the mechanism of action of these compounds. Thus, in this report we wish to present the synthesis and the preliminary biological results of a series of cycloalkylidenhydrazothiazoles, that exhibit an interesting activity towards Fluconazole resistant *C. albicans* species.

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**P-32**

# DEVELOPMENT OF NOVEL QUATERNARY AMMONIUM TENSIDES AS PART OF DECONTAMINATION AND DISINFECTION MEANS

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The work deals with the preparation and testing of compounds of type cationic surfactants such as disinfection and decontamination agents. Since the quaternary cationic surfactants are substances widely used in many of applications (pharmaceuticals, chemical industry, food industry etc.) are still of great interest. It was designed and prepared more than 40 surfactants based on quaternary nitrogen. Substances derived from structures commonly used (benzalkonium, cetylpyridinium or cetyltrimethylammonium). We have prepared several sets of surfactants (with different hydrophilic part). Each set contain seven homologues differing in two methylene units (C8-C20). Prepared structures were confirmed with analyzes of NMR, MS and EA. Furthermore HPLC method was developed to distinguish the individual homologues in the mixture.

For most compounds was measured the critical micelle concentration as a fundamental characteristic of surfactants. It was confirmed the structure relationship between the value of CMC and lipophilic chain length in the molecule. A few coumpounds were tested as a micellar catalysts for a model organophosphorus compounds or pesticides.

Several compounds were then evaluated for antimicrobial activity expected. Some compounds significantly influenced the growth of several strains of bacteria or fungi.

*The work is co-financed by the European Social Fund and the state budget of the Czech Republic. Project no. CZ.1.07/2.3.00/30.0061*

**P-33**

# SYNTHESIS OF SUBSTITUTED PYRIDINES USING TRIS(2-FURYL)PHOSPHINE GOLD(I) CATALYST

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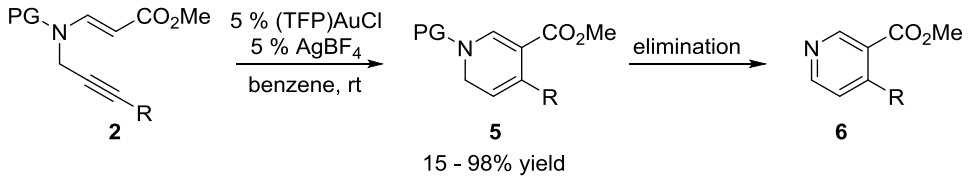
Synthesis of various types of heterocycles is possible from enyne precursors using cationic gold(I) species as a catalyst. In order to expand our research[1] on cyclisation of propargyl vinyl ethers to dihydropyrans using tris(2-furyl)phosphine gold(I) chloride and silver tetrafluoroborate we employed the same catalytic system on protected propargyl vinyl amines. The synthetic protocol was optimized and a series of substituted pyridines was synthesized.




R = phenyl, 4-bromophenyl, 4-methoxyphenyl, 4-methylphenyl, 4-aminophenyl, thiophene-2-yl, chloromethyl
PG = mesyl, tosyl, 4-fluorbenzenesulfonyl, 4-methoxybenzenesulfonyl, BOC

**Fig. 1**: Cyclisation of enynes to substituted pyridines.

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**P-34**

# QUINOLINES AS LIPOPHILIC DYES FOR SUBCELLULAR IMAGING

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Quinoline derivatives has been investigated for their potential use as fluorescent dyes. Series of compounds based on styrylquinoline skeleton and analogues as well as benzylamide derivatives were synthesized and tested.[1-3] Microwave assisted synthesis and Sonogashira coupling was exploited (**Fig. 1**). The biological activity was assessed by means of in vitro cytotoxicity tests.

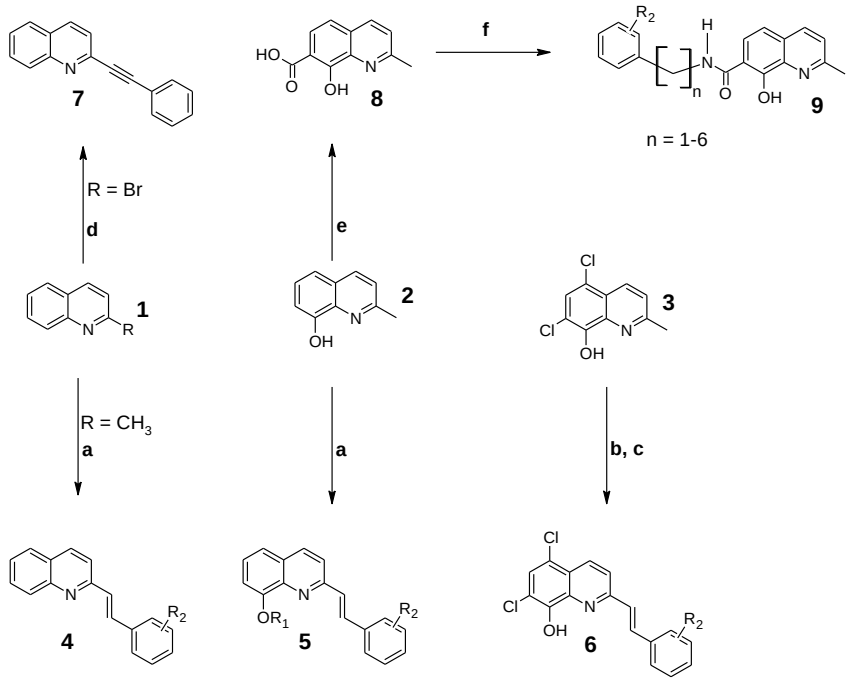


**Fig. 1**: Schematic representation of synthetic routes a) aldehyde, MW 10 min, b) Ac2O, reflux 12h, c) pyridine/water 3h, d) terminal alkyne Pd, 2h, e) KOH, DMF then $CO_2$, f) amine, EDCI.

Photophysical properties of the studied compounds seems to be preferable for application as dyes for biological imaging. Relatively high quantum yield of fluorescence and Stockes shift are their advantage. On the other hand low toxicity along with lipophilic structure is desirable for survival dying. The tested compounds penetrate the cells fast and accumulate in lipophilic structures. Especially some styrylquinoline analogues appeared to selectively accumulate in mitochondria. Further investigations are warranted for more practical application of these compounds.

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**P-35**

# THE ANTIMYCOBACTERIAL ACTIVITY OF NITRO-SUBSTITUTED SALICYLANILIDES

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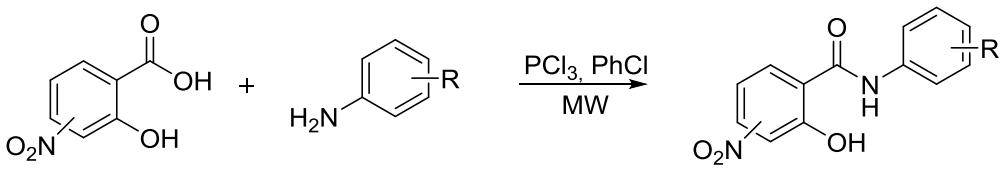
Salicylanilides (N-substituted 2-hydroxybenzamides) possess antiviral potency and a plethora of different biological activities.[1] Additionally, several derivatives of substituted salicylanilides proved to have antibacterial and antifungal activity.[2] Recent progress in antituberculotics revealed that nitro-group is present in numerous compounds with enhanced activity.[4,5,6]

Herein we present the synthesis of novel nitro-salicylanilides, resulted from the conjugation of four nitro-substituted salicylic acids and eleven substituted anilines. All compounds were evaluated in-silico for their toxicity risk and found to possess minimum to acceptable risk of toxicity. Furthermore, the biological activity of the synthesized compounds was evaluated against *Mycobacterium tuberculosis*, *M. avium* and *M. kansasii*. The results indicate that nitro-group is favored in positions 4 and 5 of the salicylic part, while 3,4-dichloro and 4-trifluoromethyl groups are favored for the aniline part.




**Scheme 1:** Schematic representation of the synthesis of nitro-substituted salicylanilides.

The study was supported by the European Social Fund and the state budget of the Czech Republic. Project no. ***CZ.1.07/2.3.00/30.0061***

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**P-36**

# EFFECT OF SHORT ACYL CERAMIDES ON PERMEABILITY AND MICROSTRUCTURE OF THE MODEL SKIN LIPID MEMBRANES

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Ceramides (Cer), cholesterol (Chol), free fatty acids (FFA) and cholesteryl sulfate (CholS) are the main barrier lipids of the stratum corneum (SC). They form an organized lamellar structure in the SC extracellular spaces, which prevents excessive water loss and permeation of exogenous substances. An increased level of Cer with a shorter chain length (C16 compared to C24) in SC of patients with atopic eczema has been recently published[1]. The presence of short Cer has been concerned as responsible for aberrant lipid organization and a decreased skin barrier function. However, it is difficult to link this particular change in Cer chain length to the higher skin permeability because of the multifactorial nature of atopic dermatitis. More mechanistic insight in the problem can be brought by the study of model lipid membranes with well-defined lipid composition. We investigated permeability and microstructure of membranes containing NS-type Cer either with long acyl chain (CerNS24) or with shorter acyl chain (CerNS16). Further variation was achieved using either lignoceric acid (LIG) or mixture of various SC fatty acids (mFFA; C16, - C24 acyl chains).

The permeability of model membranes was assessed in Franz-type diffusion cells using following permeability markers: flux of theophylline (TH), flux of indomethacin (IND), water loss through the membrane and electrical impedance. The microstructure was revealed by X-ray powder diffraction in the both small and wide-angle region. The membranes containing CerNS16/Chol/mFFA/CholS showed 1.6-time higher flux of TH, 1.8-time higher flux of IND and 1.6-time higher water loss than CerNS24/Chol/mFFA/CholS. The electrical impedance of CerNS16/Chol/mFFA/CholS was 2.3-time higher than CerNS24/Chol/mFFA/CholS indicating lower ability of CerNS16/Chol/mFFA/CholS to conduct alternating current. Similar results were obtained with CerNS16/Chol/LIG/CholS in comparison with CerNS24/Chol/LIG/CholS. We can conclude that the membranes with CerNS16 were slightly more permeable for the used permeability markers (except the electrical impedance) than membranes containing CerNS24. Furthermore we have found significantly worse barrier properties of membranes containing mFFA in comparison with membranes containing LIG for all studied markers. The CerNS24/Chol/mFFA/CholS membranes formed regularly arranged lamellar phase with repeat distance d = 5.3 nm. It was much longer than the lamellar phase of corresponding CerNS16/Chol/mFFA/CholS membranes with d = 4.1 nm. Membranes with shorter Cer expressed also several separated phases, which may explain their higher permeability.

ACKNOWLEDGEMENTS

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**P-37**

# PYRAZINAMIDE: ANTIMYCOBACTERIAL ACTIVITY OF SELECTED ALKYLAMINO DERIVATIVES

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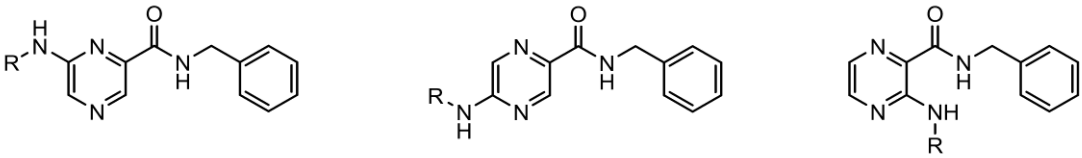
Tuberculosis (TB) belongs to the most dangerous and frequent infection diseases worldwide. Although incidence of TB have been decreasing since the beginning of the millennium, there were about 8.6 million new cases of TB and 1.3 million deaths associated with TB in 2012.[1]
Resistant TB-forms, namely multi-drug resistant (MDR) and extensively drug-resistant (XDR) TB, as well as increasing number of patient co-infected with HIV (1.1 million of all TB cases)[1,2] constitute a serious problem and emphasize the need for novel antitubercular drugs. Pyrazinamide (PZA), an essential component of short-course anti-TB chemotherapy, is used as a model compound for substances referred in this research project.
Based on the results of previously published active alkylamino derivatives[3], series of position isomers of alkylamino derivatives of *N*-benzylpyrazine-2-carboxamide was synthesized, characterized by analytical data and screened for *in vitro* antimycobacterial activity (against *Mycobacterium tuberculosis* H37Rv, *M. kansasii* and two different strains of *M. avium*) and also for their antibacterial and antifungal activity. 6-Alkylamino (**I**) and 5-alkylamino (**II**) isomers exhibited similar antimycobacterial activity against *M. tuberculosis* H37Rv expressed as minimal inhibition concentration (MIC, activity in the range 3.13 – 25 µg/mL). On the other hand, 3-alkylamino (**III**) derivatives were completely inactive against all tested strains.



**I** **II** **III**

$R = C_3H_7 - C_8H_{17}$

**Fig. 1**: Final structures I – III.

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**P-38**

# SYNTHESIS OF 2-ARYLOYLHYDRAZINECARBOXAMIDES, 1,2-DIACYLHYDRAZINES AND 1,3,4-OXADIAZOLES AS NEW POTENTIAL ANTIMYCOBACTERIAL AGENTS

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Tuberculosis (TB) is a bacterial infection caused by pathogen *Mycobacterium tuberculosis*. Nowadays, TB is once again considered to be a major global problem. According to WHO report, 1.3 million people died from the disease in 2012.[1] A serious phenomenon related to the therapy of TB is the growing occurrence of the multidrug-resistant and extensively drug-resistant forms. Considering the growing numbers of newly described totally resistant form in the population, the therapy calls for the search of new antimycobacterial agents.

In previous studies with 2-isonicotinoylhydrazinecarboxamides[2] and 2-(pyridine-4-yl)-1,3,4-oxadiazoles,[3] some of the prepared compounds showed satisfactory inhibitory activities for both tuberculous and atypical mycobacteria. We have introduced other recently prepared derivatives of INH analogues. These compounds were assayed against *M. tuberculosis* and nontuberculous mycobacteria.

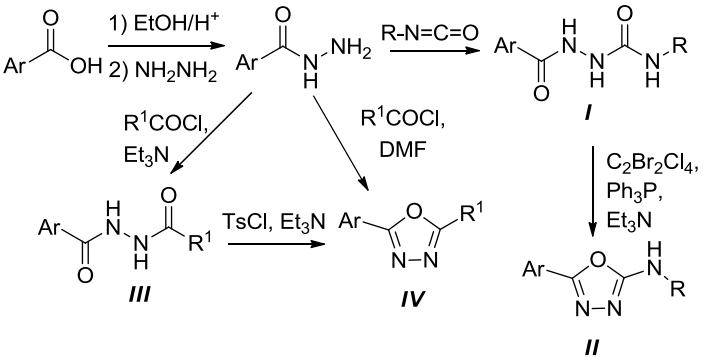


**Fig. 1**: Preparation of 2-aryloylhydrazinecarboxamides *I*, 1,2-diacylhydrazines *III* and 1,3,4-oxadiazoles *II* and *IV* (Ar = pyridine-4-yl, substituted phenyl; R and $R^1$ = alkyl, aryl).

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# STRUCTURAL MODIFICATIONS OF ANTITUBERCULAR 5-ALKYLAMINO-*N*-PHENYLPYRAZINE-2-CARBOXAMIDES

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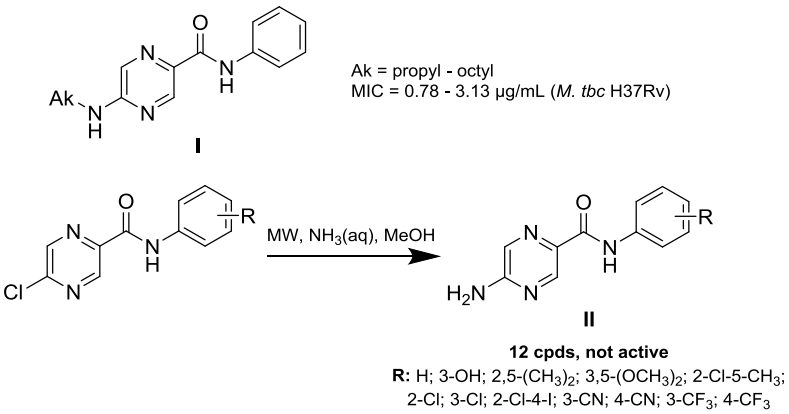
Recently, we have described *in vitro* antitubercular activity of 5-alkylamino-*N*-phenylpyrazine-2-carboxamides **(I)**, which inhibited the growth of *Mycobacterium tuberculosis* H37Rv with MIC = 0.78–3.13 µg/mL. Interestingly, all homologues from propylamino to octylamino derivative were approximately of the same activity. Oxidative *N*-dealkylation is a frequent metabolic pathway of xenobiotic compounds. Therefore we speculated that the long alkyl chains could serve as a transport form of the drug (facilitate the penetration of the compound through highly lipophilic mycobacterial outer envelope) and that the active form itself could be the 5-amino-*N*-phenylpyrazine-2-carboxamide. To test whether the dealkylated possible metabolites of **I**, *i.e.* the 5-amino-*N*-phenylpyrazine-2-carboxamides **(II),** retain any antimycobacterial activity, a series of 12 compounds with different substituents R in the phenyl part were prepared. The synthesis was carried out from 5-chloro-*N*-phenylpyrazine-2-carboxamides[1] *via* nucleophilic substitution of chlorine, accomplished in over-pressurized vessels using microwave heating (CEM Discover; CEM Corporation, Matthews, NC, USA) – see **Scheme 1.** Prepared compounds were tested for activity against *M. tuberculosis* H37Rv, *M. kansasii* and *M. avium.*




**Scheme 1.** Conditions: 160 ºC, 60 min, MeOH - $NH_3$ (aq) 1:1

Independently on the R substituent, none of the prepared 5-amino-*N*-phenylpyrazine-2-carboxamides **(II)** expressed any antimycobacterial activity up to concentrations of 100 µg/mL. At this stage, we can interpret the results in two ways. Either the 5-amino-*N*-phenylpyrazine-2-carboxamides lack the activity and the 5-alkylaminoderivatives **(I)** are the active form; or the free 5-amino group leads to compounds with insufficient lipophilicity, which cannot enter the mycobacterial cell efficiently.

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EVOLUTION THROUGH REVOLUTION: CHANGING THE FACE OF DRUG DISCOVERY PARADIGMS TO ACCELERATE THERAPEUTIC RESPONSES FOR MULTIFACTORIAL DISEASES

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**O-3** A. Gaspar, CIQUP/Departamento de Química e Bioquímica Faculdade de Ciências, Universidade do Porto, 4169-007 Porto, Portugal
CHROMONE: A VALID SCAFFOLD IN MEDICINAL CHEMISTRY

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PROTEIN KINASE C: SYNTHESIS OF A C1-DOMAIN BINDING COMPOUND AS AN IMMOBILIZABLE TOOL FOR AFFINITY CHROMATOGRAPHY.

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**O-16** G. Bianchini, Departmento de Química Orgánica y Farmacéutica, Universidad Complutense, Facultad de Farmacia, 28040 Madrid, Spain
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**O-21** A. Černíková, Department of Chemical Drugs, Faculty of Pharmacy, Faculty of Veterinary and Pharmaceutical Sciences Brno, Palackého 1-3, 612 42, Brno, Czech Republic
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## POSTERS

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**P-11** K. Kositzi, School of Pharmacy, Department of Pharmaceutical Chemistry, Aristotle University of Thessaloniki, 54124, Greece
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**P-20** L. Rycek, Vienna University of Technology, Getreidemarkt 9/163-OC, 1060 Vienna, Austria
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**P-23** R. Vosátka, Department of Inorganic and Organic Chemistry, Faculty of Pharmacy, Charles University, Heyrovského 1203, 500 05 Hradec Králové, Czech Republic
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**P-27** M. Ghavre, Charles University in Prague, School of Pharmacy in Hradec Králové, Heyrovského 1203, Hradec Králové, CZ-500 03, Czech Republic
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**P-28** L. Hroch, Charles University in Prague, Faculty of Pharmacy in Hradec Kralove, Department of Pharmaceutical Chemistry and Drug Control, Heyrovskeho 1203, 500 05 Hradec Kralove, Czech Republic
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**P-29** M. Krátký, Department of Inorganic and Organic Chemistry, Faculty of Pharmacy, Charles University in Prague, Heyrovského 1203, 500 05, Hradec Králové, the Czech Republic
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**P-32** J. Marek, Department of Pharmaceutical Chemistry and Drug Control, Faculty of Pharmacy, Charles University, Heyrovskeho 1203, 500 05 Hradec Králové, Czech Republic
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**P-34** R. Musiol, Institute of Chemistry, University of Silesia, Szkolna 9, 40-007, Katowice, Poland
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