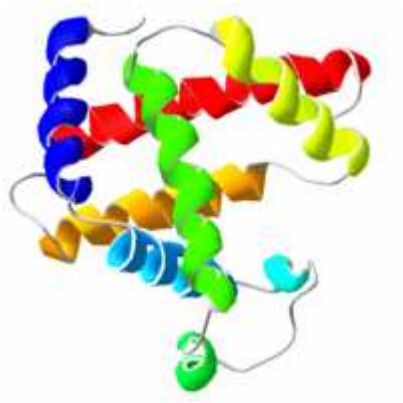
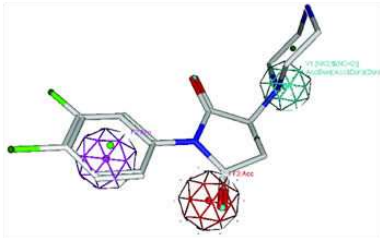
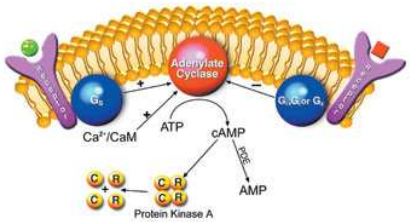


I KONWERSATORIUM CHEMII MEDYCZNEJ

LUBLIN

19-20 września 2008





Polskie Towarzystwo Chemii Medycznej

Uniwersytet Medyczny w Lublinie

Katedra i Zakład Syntezy i Technologii Chemicznej Środków Leczniczych
Wydział Farmaceutyczny
Uniwersytet Medyczny w Lublinie
Autor: dr hab., prof. nadzw. UM Dariusz Matosiuk

Lublin, 2008

Komitet Naukowy:

Prof. dr hab. Katarzyna Kieć-Kononowicz

Prof. dr hab. Janina Karolak-Wojciechowska

Prof. dr hab. Bożenna Gutkowska

Prof. dr hab. Dariusz Matosiuk

Prof. dr hab. Franciszek Sączewski

Prof. dr hab. Zdzisław Chilmończyk

Prof. dr hab. Zdzisław Mahoń

Dr hab. Andrzej Bojarski

Komitet Organizacyjny:

Prof. dr hab. Dariusz Matosiuk - Przewodniczący

Prof. dr hab. Sylwia Fidecka

Prof. dr hab. Jolanta Kotlińska

Dr hab. Grażyna Biała

Dr hab. Krzysztof Jóźwiak

Dr Monika Wujec

oraz

dr Agnieszka Kaczor

mgr Marcin Hus

mgr Joanna Kozak

mgr Urszula Kijkowska-Murak

Plan Konwersatorium

Piątek, 19.09.2008

9.00-9.30 – Otwarcie Konwersatorium

Prof. dr hab. Dariusz Matosiuk,

Prof. dr hab. Ryszard Maciejewski Prorektor ds. Nauki, Uniwersytet Medyczny w Lublinie;

9.30-11.00 – Sesja wykładowa – Projektowaniu leków.

Prowadzący sesję – prof. dr hab. Janina Karolak-Wojciechowska, prof. dr hab. Jerzy Konopa

L-1

Prof. dr hab. Paweł Kafarski, Politechnika Wrocławska,

„ Usefulness and restrictions of the computer aided drug design: leucylaminopeptidase inhibitors."

L-2

Prof. dr hab. Grzegorz Bujacz, Politechnika Łódzka,

„ Protein crystallography in drug discovery."

L-3

Dr Agnieszka Kaczor, Uniwersytet Medyczny, Lublin

„ Homology modelling of ionotropic GluR5/6 receptors and theoretical studies of novel GluR5/6 non-competitive antagonists."

11.00-11.30 – przerwa na kawę

11.30-13.00 – Sesja wykładowa – Nowe cele w poszukiwaniu leków.

Prowadzący sesję – prof. dr hab. Katarzyna Kieć-Kononowicz, prof.dr hab. Paweł Kafarski

L-4

Dr hab. Grażyna Biała, Uniwersytet Medyczny w Lublinie,

„ Protein kinases and phosphatases as cellular substrates of addiction and memory."

L-5

Dr hab. Krzysztof Bielawski, Uniwersytet Medyczny, Białystok

„ Prolidase-convertible prodrugs."

L-6

Prof. dr hab. Stefan Chłopicki, CM UJ, Kraków

„ In search for novel endothelium-targeted therapeutics."

13.00-14.00 – Lunch

14.00-15.00 – Prezentacje ustne

Prowadzący sesję – dr hab. Andrzej J. Bojarski,
dr hab. Krzysztof Bielawski

PU-1

Dr Danuta Drozdowska, Uniwersytet Medyczny, Białystok

lub

Dr Beata Kolesińska, Politechnika Łódzka

„ N-triazinylammonium salts as pro-drugs convertible into new analogue of nitrogen mustard with one, two or three 2-chloroethyl-amino fragments.”

PU-2

Mgr Urszula Kijkowska-Murak, Uniwersytet Medyczny, Lublin

„ Theoretical studies on bioactive conformation of long-chain aryl-piperazine ligands of 5-HT_{1A} receptor. “

PU-3

Mgr Anita Płazińska, Uniwersytet Medyczny, Lublin

„ Binding of fenoterol derivatives and stereoisomers of fenoterol to the β_2 adrenergic receptor. A molecular modeling study. “

15.00-15.30 – Przerwa na kawę

15.30-16.15 – Prezentacje ustne

Prowadzący sesję – prof. dr hab. Barbara Malawska,
dr hab. Zofia Mazerska

PU-4

Dr Anita Kornicka, Uniwersytet Medyczny, Gdańsk

„ Synthesis and structure of 1-[(Imidazolidin-2-yl)imino]azoles with cardiovascular activity. “

PU-5

Mgr Kamil Kuder, CMUJ w Krakowie,

„ NBD-labeled 3-methyl-1-(3-phenoxypropyl)piperidine as a novel, active histamine H_3 receptor fluorescent ligand.”

16.30-18.00 – Sesja posterowa

18.00-19.00 – Sprawy Towarzystwa

Sobota, 20.09.2008

9.30-11.00 – Sesja wykładowa – Metody chromatograficzne.

Prowadzący sesję – prof. dr hab. Zdzisław Chilmonczyk,
prof. dr hab. Dariusz Matosiuk

L-7

Dr hab. Krzysztof Jóźwiak, Uniwersytet Medyczny, Lublin

„ Applications of affinity chromatography in drug-binding determination and medicinal chemistry project."

L-8

Dr hab. Michał Markuszewski, Uniwersytet Medyczny, Gdańsk

" Quantitative structure-retention relationships (QSRR) as an objective tool for characterization of HPLC columns."

L-9

Prof. dr hab. Zbigniew Kamiński, Politechnika Łódzka,

„ Supramolecular structures formed by N-lipidated peptides immobilized on cellulose support."

11.00-11.30 – przerwa na kawę

11.30-13.00 – Sesja wykładowa – Rak.

Prowadzący sesję – prof. dr hab. Franciszek Sączewski,
prof. dr hab. Stefan Chłopicki

L-10

Prof. dr hab. Zdzisław Chilmończyk, Narodowy Instytut Leków, Warszawa,

„ Death receptors as molecular target of anticancer drugs."

L-11

Prof. dr hab. Jerzy Konopa, Politechnika Gdańska

" Structure-activity relationship of antitumor 1-aminoacridinones and triazoloacridinones."

L-12

Dr hab. Zofia Mazerska, Politechnika Gdańska

„ Metabolism in vitro *of a new antitumor 9-amino-1-nitroacridine derivative, C-1748, in respect of its diminished general toxicity."*

13.00-14.00 – Lunch

14.00-15.00 – Prezentacje ustne

Prowadzący sesję – prof. dr hab. Elzbieta Brzezińska,
prof. dr hab. Zbigniew Kamiński

PU-6

Dr Monika Wujec/ mgr Łukasz Popiołek, Uniwersytet Medyczny w Lublinie,

„ Synthesis and antibacterial activity of 1-{[(4-phenyl-4H-1,2,4-triazol-3-yl)-sulphanyl]acetyl}thiosemicarbazide derivatives."

PU-7

Dr Anna Stasiewicz-Urban, CMUJ w Krakowie,

„ Physicochemical properties of (thio)carbonyl groups in (thio)barbiturates. "

PU-8

Dr Anna Więckowska, CMUJ w Krakowie,

„ Novel cholinesterases inhibitors with carbamoyloxyphenyl and N-benzylpiperidine moieties."

15.00-15.30 – Przerwa na kawę

15.30-16.15 – Prezentacje ustne

Prowadzący sesję – prof. dr hab. Grzegorz Bujacz,
dr hab. Anna Bielawska

PU-9

Mgr Waldemar Wysocki, Akademia Podlaska w Siedlcach,

„ x-Ray and theoretical studies on the keto-enol tautomerism of the selected dioxo imidazopyrimidine derivatives."

PU-10

Dr Alicja Nowaczyk, CMNCU w Bydgoszczy

„ The 1-[3-(4-arylpiperazin-1-yl)-2-hydroxy-propyl]- pyrrolidin-2-one derivatives as α-adrenocoptor antagonist and antiarrythmic agents: a SAR studies. "

16.30-18.00 – Sesja posterowa

19.00-22.00 – Wieczór pożegnalny „Nad Zalewem"

Lista prezentacji posterowych:

P-1 Bielawska Anna, dr hab.
Synthesis, DNA-binding affinity and cytotoxicity of the dinuclear platinium (II) complexes with berenil and amines ligands.

P-2 Bielawski Krzysztof, dr hab.
Synthesis and biological evaluation of amidine analogs of chlorambucil and melphalan.

P-3 Baran Marzena, mgr
Formation and pro/-antioxidative activity of oxazolo[3,2-b]-benzimidazoles.

P-4 Białas Arkadiusz, dr
Low-molecular-weight inhibitors of gingipains – alternative approach to the treatment of periodontitis.

P-5 Dutkiewicz Zbigniew, dr
Molecular docking studies on thiomethylstilbenes as CYP1A2 inhibitors.

P-6 Gośliński Tomasz, dr
Peripherally modified porphyrazines as spectroscopic chemosensores for aluminium ion.

P-7 Francik Renata, dr
Lipophilicity and antioxidative activity of some β-carboline derivatives.

P-8 Handzlik Jadwiga, dr
Synthesis, SAR-study and drugability prediction for phenylpiperazine derivatives of hydantoin with affinity for α_1-adrenoceptors.

P-9 Janik Agnieszka, mgr
Designing of new potential acetylcholinesterase inhibitors based on computer modeling elements.

P-10 Kędzierska Ewa, dr
Involvement of opioid receptors in the antinociceptive activity of the new derivatives of 1-aryl-2-iminoimidazolidine in the writhing test in mice.

P-11 Kępczyńska Elżbieta, dr
Synthesis and lipophilicity determination of some derivatives of a natural triterpene betuline.

P-12 Koszel Dominik, mgr
Lipophilic derivatives of glucosamine-6-phosphate synthase inhibitors.

P-13 Kozak Joanna, mgr
Molecular modeling of interactions between selected ligands and the Torpedo model of nicotinic acetylcholine receptor.

P-14 Ligęza Agnieszka, mgr
Synthesis of N-alkyl derivatives of dextromethorphan.

P-15 Morak-Młodawska Beata, dr
Recent syntheses and properties of novel azaphenothiazines.

P-16 Obniska Jolanta, dr hab.
Synthesis and physicochemical and anticonvulsant properties of new *N*-[(4-arylpiperazin-1-yl)-methyl]-3,3-dialkyl-pyrrolidine-2,5-diones.

P-17 Płazińska Anita, mgr
Binding of fenoterol derivatives and stereoisomers of fenoterol to the β_2 adrenergic receptor. A molecular modeling study.

P-18 Prokopowicz Monika, mgr
Heterocyclic phosphonates as potential therapeutics in Parkinson's disease therapy.

P-19 Szacoń Elżbieta, dr
Synthesis of new imidazo[1,2-a][1,3,5]triazepines.

P-20 Sączewski Franciszek, prof. dr hab.
Carbonic anhydrase inhibitors.

P-21 Skowerski Krzysztof ,dr
Nitrobenzyl isophosphoramide mustard analogues as prodrugs for GDEPT.

P-22 Stefanowicz Jacek, dr
Synthesis of 1-phenylpiperazine derivatives of 3β-aminotropane with potential antipsychotic activity.

P-23 Stefański Tomasz, dr
Synthesis of methoxy- and methylthiostilbene derivatives.

P-24 Kuran Bożena, dr
Synthesis of new N-substituted derivatives of 2-hydroxy-4,9-diphenyl-4,9-epoxy-3a,4,9,9a-tetrahydro-1*H*-benzo[f]isoindole-1,3(2*H*)-dione and 2-hydroxy-5,8-dimethyl-3b,9-epoxy-3a,4,5,6,7,8,9,9a-octahydro-1*H*benzo[e]isoindole-1,3(2*H*)-dione with an expected anxiolytic activity.

P-25 Struga Marta, dr
Synthesis of new thiourea derivatives of tricyclic imides with an expected antimicrobial activity.

P-26 Pakosińska-Parys Magdalena, mgr
Synthesis of some N-substituted derivatives of1,8-dietoxy-17-azapentacyclo-[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadec-2,4,6,9,11,13-hexaen-16,18-dione with a potential pharmacological activity.

P-27 Pakosińska-Parys Magdalena, mgr
Synthesis of new N-substituted aminoalkanol and aminoalkyl derivatives of 1,7,8,9-tetrachloro-10,10-dimethoxy-4-azatricyclo-[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione as potential β-adrenolytic and/or psychotropic drugs.

P-28 Struga Marta, dr
Synthesis of new 2-aminobezimidazole derivatives with an expected antimicrobial activity.

P-29 Krawiecka Mariola, dr
Synthesis of new derivatives of 5-methoxy-2-methyl-benzo[b]-furan-3-carboxylic acid with an expected biological activity.

P-30 Krawiecka Mariola, dr
Synthesis of halogen derivatives of selected furobenzopiran-4-one and benzo[b]furan-2-carboxylic acid with an expected biological activity.

P-31 Płazińska Anita, mgr
A phytochemical studies of *Heracleum dissectum* Ledeb. aboveground parts.

P-32 Tarsa Monika, dr
Investigation of N-methyl-2,4-dithiophenobarbital stability as a function of pH and temperature.

P-33 Tarsa Monika, dr
Implementation of thin layer chromatography for investigation of N-methyl-2,4-dithiophenobarbital hydrolyses.

P-34 Wujec Monika, dr
Synthesis and antitumor activity of N-substituted amides of 3-(3-ethylothio-1,2,4-triazol-5-yl)propenoic acid.

P-35 Wujec Monika, dr
Synthesis and antibacterial activity of 4-substituted-3-nitromethyl-1,2,4-triazoline-5-thione derivatives.

P-36 Wierzchowski Marcin, dr
Synthesis and molecular modeling study on cationic phthalocyanines derived from 3,6-bis[2-(dimethylamino)ethoxy]-benzene-1,2-dicarbonitrile.

P-37 Żylewski Marek, dr
The attempt to use NMR spectroscopy in observation of ligand – micelle interactions.

P-38 Aletańska-Kozak Monika, dr
Synthesis of new fused aminoguanidine derivatives.

P-39 Szymańska Ewa, dr
Antitumor activity among 5-benzylidenehydantoin derivatives.

P-40 Szymańska Ewa, dr
Synthesis and structure-activity relationship studies on phenylalanine-based AMPA/KA receptor antagonists.

P-41 Pękala Elżbieta, dr
Anticonvulsant activity of some *trans*- and *cis*-2-amino-1-cyclohexanol derivatives.

P-42 Cytarska Joanna, dr
New tsophosphoramide mustard analogues as prodrugs for gene therapy.

P-43 Kieć-Kononowicz Katarzyna, prof. dr hab.
Synthesis and biological evaluation of novel dialkylpyrimido-purinediones.

P-44 Marona Henryk, dr hab.
Antibacterial activity of the xanthone derivatives against multidrug-resistant strains.

P-45 Kościółek Tomasz, stud.
Homology modelling as an aid in rational synthesis of nonclassical cannabinoids .

P-46 Kurczab Rafał, mgr
Comparison of FlexX and Surflex docking algorithms based on Astex diverse set.

P-47 Mordalski Stefan, stud.
Experimental and theoretical studies on conformations of arylpiperazines with pyrimido[5,4-c]quinolin-4(3H)-one terminal.

P-48 Szafrański Przemysław, stud.
Therapeutic potential, design and synthesis of cannabinoid drugs.

P-49 Karolak-Wojciechowska Janina, prof. dr hab.
C=O...H-N Interactions - main motives in the crystals of xanthine derivatives.

P-50 Mrozek Agnieszka, dr
Mono and bicyclic heterocycles aromaticity of izothiazolopyridines.

P-51 Szczesio Małgorzata, dr
Crystallographic structure of arylopiperazines.

P-52 Jarończyk Małgorzata, mgr
The study of ligand-serotonin transporter interactions.

P-52 Żelaszczyk Dorota, mgr
Aminolysis of chiral phenyl glycidyl ethers.

P-54 Gajec Maciej, stud.
Msh2/3 involvement in trinucleotide expansions leading to huntington’s disease.

WYKŁADY

L-1

Usefulness and Restrictions of the Computer Aided Drug Design: Leucylaminopeptidase Inhibitors.

Paweł Kafarski

Department of Bioorganic Chemistry, Faculty of Chemistry, Wroclaw Technical University, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław
e-mail: pawel.kafarski@pwr.wroc.pl

It was not until the 1960's that some understanding began to develop about the quantitative relationship between chemical structure and biological activity. A fundamental assumption for rational drug design is that drug activity is obtained through the molecular binding of one molecule (the ligand) to the specific portion of another, usually larger, molecule (the receptor, commonly a protein). In their active conformations, the molecules exhibit geometric and chemical complementarities, both of which are essential for successful drug action. Knowledge of biomolecular structures, which is increasing at an explosive rate enables to apply computer-aided methods for *de novo* drug design (so called *in silico* drug design). Computer-aided drug design is a comprehensive subject based on the knowledge of chemistry, biology and computer science. With the help of computer and the structural information of drugs and their macromolecular targets, this methodology can guide and assist the design of new therapeutic agents by means of molecular modeling, theoretical calculation and prediction methods. In a course of nearly 30 years' development, computer-aided drug design has shown its potential advantages, and play more and more important role in current pharmaceutical industry. However, modeling of molecular structure is a complex task, in particular because most molecules are flexible, being able to adopt a number of different conformations that are of similar energy.
Leucine aminopeptidase (LAP, E.C.3.4.11.1) is one of the first discovered and the most widely studied aminopeptidasea with respect to sequence, structure and mechanism of action. It is also an enzyme for which the most systematic and detailed computational studies regarding enzyme-inhibitor interactions have been performed. This results both from the availability of the crystal structure of LAP with bound inhibitors, including phosphonic acid analogue of leucine - LeuP (structure encoded as 1lcp ib PDB), and from the existence of binding data for many LAP inhibitors. Such a set of experimental results enabled to evaluate the effectiveness of theoretical methods: both empirical and quantum chemical in designing and activity prediction of LAP inhibitors.

L-2

Protein Crystallography in Drug Discovery.

Grzegorz Bujacz

Institute of Technical Biochemistry, Faculty of Biotechnology and Food Sciences, Technical University, Stefanowskiego 4/10, 90-924 Łódź
e-mail: gdbujacz@p.lodz.pl

Protein crystallography is a discipline based on three facts not widely known to the general scientific community. The first is that proteins and nucleic acids can be crystallized. The second is phenomenon of X-ray diffraction by macromolecular crystals. The third one is the mathematical operation, known as the Fourier transformation, which enables one to calculate the atom positions inside the crystal from the amplitudes of the measured intensities of the diffracted X-ray beams, also known as "X-ray reflections". These three facts allow crystallographers to obtain experimental atomic models of medicinally important proteins, nucleic acids, and their complexes.

In the early age of protein crystallography, skeptics wondered if protein conformation in a crystal corresponds to the physiological one. The enormous volume of data accumulated over the past fifty years of protein crystallography has proven that interactions responsible for protein fold are much stronger than the tenuous forces responsible for crystal formation, and that protein molecules retain their natural form also in their crystals. A number of additional experiments confirm the active protein conformation in their crystals.

Macromolecules involved in all physiological processes, including pathological, can be used as targets for drug design, based on their crystal structure information. Protein crystallography has now been involved in drug discovery for two decades and thanks to structural data, drugs that precisely interact with specific target enzymes involved in various diseases are now available. The process of structure-guided drug design begins with the identification of the target protein and it's role in the pathological process. The initial “hit compounds” capable of interaction with the active site of the target protein can be identified by analysis of physiological ligands, random screening, computer modeling or structural analysis of the active-site pocket. Crystalline complex of the target protein with the "hit compound" can be obtained on two ways: by co-crystallization and by soaking. The crystal structure of such a complex provides very precise information about the nature of the protein-ligand interactions and allows optimization of the drug compounds. Structure-activity correlation for a series of ligands allows then to evaluate the role of each structural "module" in the activity. The process of synthesis of new ligands is repeated until one obtains a molecule with optimal activity, which is suitable for clinical trials.

Although protein crystallography is a relatively new tool in drug discovery, it has already helped to create a number of very powerful drugs for combating the most fatal diseases, such as AIDS or cancer.

L-3

Homology Modelling of Ionotropic GluR5/6 Receptors and Theoretical Studies of Novel GluR5/6 Non-Competitive Antagonists.

Agnieszka Kaczor [a], *Urszula Kijkowska-Murak* [a], *Christiane Kronbach* [b], *Klaus Unverferth* [b], *Dariusz Matosiuk* [a]

[a] *Department of Synthesis and Chemical Technology of Pharmaceutical Substances, Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin,*
[b] *elbion AG, Meissner Str. 191, 01445 Radebul, Germany*
e-mail: agnieszka.kaczor@am.lublin.pl

As glutamate and aspartate, together with their few analogs, mediate most of the excitatory transmission in the brain, the physiological relevance of iGluRs and possible therapeutic applications of their ligands are difficult to overestimate. Indeed, glutamate is involved in aetiology of several neurodegenerative disease such as stroke, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and neuropathic pain. Glutamate receptors are also engaged in pathomechanisms of schizophrenia, mood disorders, alcoholism and epilepsy. Among all the ionotropic glutamate receptors, kainate receptors are the least investigated. However, it is proved that they play an important role in the process of epileptogenesis and that they are engaged in inducing the synaptic plasticity. Although their therapeutic potential is underestimated, the ligands of kainate receptors seem to lack undesirable psychotropic side effects traditionally linked with NMDA receptor ligands.

The aim of the presented work was construction of GluR5 and GluR6 receptor models in the closed form with the application of homology modelling with Modeller 9v2 and theoretical studies of novel indole-derived non-competitive GluR5/6 antagonists [1-3]. The obtained receptor models were the first complete models of any ionotropic glutamatergic receptor. They displayed the correct symmetry: two-fold in N-terminal domain, ligand binding domain and the extracellular part of transmembrane domain and four-fold in the main part of a channel which is in agreement with single-particle electron microscopy images of iGluR and with the results of the studies by Sobolevsky et al. The constructed models were applied to investigate interactions of novel indole derivatives with these receptors. Taking into account experimental studies by Balannik et al. it was stated, that binding pocket for kainic acid receptors non-competitive antagonists is situated in the transduction domain, between two subunits in the receptor dimer. The following residues were recognized as crucial for interactions: Arg663A, Arg663B (M3-S2 linker), Ser809B (S2-M4 linker) and Phe553A (S1-M1 linker).

As novel indole derivatives were active *in vitro*, but not *in vivo*, estimation of drug-likeness of considered indole derivatives was carried out, applying Lipinski's rule and calculating constitutional, geometrical, physicochemical and topological descriptors and subsequently placing novel compounds in chemical space determined by chemical compounds collected in known databases of medicinal substances. The investigated indole derivatives were characterized with favourable values of many parameters, but have borderline values of lipophilicity. Furthermore, the elements of ADMET analysis were performed and skin permeation, crossing blood-brain barrier, bioavailability after oral administration, intestinal absorption according to Caco-2 and MDCK models as well as % of absorption were calculated. Most of them easily cross blood-brain barrier. One of the unfavourable parameter turned out to be the high degree of binding with plasma proteins.

The characteristics of the binding pocket as well as the constructed pharmacophore model allowed to suggest further modifications of the lead compound.

[1] Kaczor, A.; Kijkowska-Murak, U.; Matosiuk, D. *Curr. Pharm. Des. 2008*, accepted
[2] Kaczor, A.; Kijkowska-Murak, U.; Matosiuk,D. *J. Med. Chem. 2008*, in press
[3] Kaczor, A.; Kijkowska-Murak, U.; Matosiuk,D. *J. Med. Chem.*, submitted

This work was funded by the Polish Ministry of Science and Higher Education, grant number 405 021 31/1121. Computations were performed in the framework of computational grant by Interdisciplinary Centre for Mathematical and Computational Modelling, Warsaw, Poland, grant number G30-18.

L-4

Protein Kinases and Phosphatases as Cellular Substrates of Addiction and Memory.

Grażyna Biała

Department of Pharmacology and Pharmacodynamics,
Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin
e-mail: grazyna.biala@am.lublin.pl

In the recent years, it became apparent that learning and memory processes and drug addiction share intracellular signaling cascades and are associated with similar changes in synaptic plasticity. Moreover the brain regions involved in learning and memory and those underlying drug addiction may overlap. Several lines of evidence indicate that the dynamic balance between phosphorylation and dephosphorylation of specific target proteins mediated by kinases and phosphatases, respectively, determines the long-term processes of memory formation [2]. In the hippocampus, a calcium/calmoduline-dependent protein phosphatase calcineurin has been shown to play an important role in synaptic plasticity and memory storage [4]. As transgenic mice that express an active form of calcineurin specifically in forebrain structures have previously been shown to have a deficit in the transition from short- to long-term memory [3], in collaboration with INSERM U-513 (Paris, France, director: dr Bruno Giros) and Prof. Isabelle Mansuy (Swiss Federal Institute of Technology, Zurich, Switzerland) we investigated the involvement of calcineurin in amphetamine and morphine motivational effects using this line of transgenic mice (CN98 wild type and mutant mice) [3].
Our results [1] show that d-amphetamine and morphine induced conditioned place preference in wild type littermates but failed to produce any response in mutant mice. This effect was drug-specific, as food-induced place preference was not affected in mutant animals. Behavioural sensitization to these two drugs after chronic exposure was also disturbed in the transgenic mice. In contrast, neither the locomotor response to acute dose of d-amphetamine or morphine nor the somatic signs of morphine withdrawal differed between the two genotypes.
Our data indicate that calcineurin-mediated protein dephosphorylation in the hippocampus is involved in the long-term effects of drug without influencing the motivational response to a natural reward or the physical component of opioid withdrawal. The present results emphasis the essential role of hippocampal-dependent memory in development of the drug addiction.

[1] Biała G., Betancur C., Mansuy I. M., Giros B.: The reinforcing effects of chronic d-amphetamine and morphine are impaired in the line of memory-deficient mice overexpressing calcineurin. *Eur. J. Neurosci. 2005, 21, 3089-3096*.
[2] Malenko R. C., Nicoll R. A.: Long-term potentiation – a decade of progress? *Science 1999, 285, 1870-1874*.
[3] Mansuy I. M., Mayford M., Jacob B., Kandel E. R., Bach M. E.: Restricted and regulated overexpression reveals caclineurin as a key component in the transition from short-term to long-term memory. *Cell 1998, 92, 39-49*.
[4] Yakel J. L.: Calcineurin regulation of synaptic function: from ion channels to transmitter release and gene transcription. *Trends Pharmacol. Sci. 1997, 18, 124-134*.

L-5

Prolidase-Convertible Prodrugs.

Krzysztof Bielawski

Department of Medicinal Chemistry and Drug Technology, Medical University of Białystok, Kilińskiego 1, 15-089 Białystok
e-mail: kbiel@umwb.edu.pl

One approach to overcome the toxicity of alkylating agents to normal tissue is to construct a prodrug with lower hydrophobicity and cytotoxicity but preferentially activated in cancer cells. Prodrugs have been traditionally used to increase oral bioavailability, but recently prodrug strategies have also been employed to achieve drug targeting. Enzymes that are differentially expressed in disease states are possible targets since enzymes comprise 30% of all drug targets. Of several possible enzymes that were so identified, prolidase was found to be overexpressed in breast cancer MDA-MB 231 cells, lung adenocarcinomas and melanoma cancer cell lines.

We synthesized proline prodrugs of chlorambucil and melphalan. Proline analogue of melphalan shows susceptibility to the action of breast cancer MDA-MB 231 cells prolidase, compared to standard prolidase substrate glycyl-L-proline (Gly-L-Pro) and about sixfold higher susceptibility, compared to another its substrate glycyl-L-hydroxyproline (Gly-L-Hyp). Proline analogues of chlorambucil and melphalan evoked slightly higher cytotoxicity for MDA-MB 231 cells, compared to the parent drugs.

It is known that IGF-I is the main stimulator of collagen biosynthesis. Its actions is regulated by IGF-I receptor expression that induces downstream signaling through MAP kinase pathway. Interestingly, melphalan did not affect the expression of both IGF-I receptor and MAP kinases, while proline analogue of melphalan distinctly reduced the expression of these proteins. Although, the mechanism of this process is unknown it suggests that this feature of proline analogue of melphalan may be of benefit from the point of its potential application in pharmacotherapy of neoplastic diseases, since IGF-I receptor is also involved in stimulation of cell division.

The results of these studies support the proposition that prolidase could serve as a target enzyme for the selective action of anticancer agents. However, in order to demonstrate selective delivery of the prodrugs to tumor tissues, it would be necessary to examine potential bioactivation of the prodrugs by prolidase expressed in normal tissues and in organs such as the liver and kidney.

L-6

In Search for Novel Endothelium-Targeted Therapeutics.

Stefan Chłopicki

Department of Experimental Pharmacology, Faculty of Medicine, CM UJ,
Grzegórzecka 16, 31-531 Kraków
e-mail: mfschlop@cyf-kr.edu.pl

Healthy endothelium is essential for undisturbed functioning of the cardiovascular system, while endothelial dysfunction leads to pathologies of the cardiovascular system. Indeed, endothelial dysfunction is the key event in the development of atherosclerosis, heart failure and other cardiovascular diseases. Endothelial dysfunction is characterized by the deficiency of NO and robust activation of pro-inflammatory and pro-thrombotic endothelial mediators. Pharmacology of endothelium is aimed to halt or inhibit the progression of various cardiovascular diseases by treating endothelial dysfunction. Many cardiovascular drugs display endothelial action that contributes to their clinical efficacy and there is a unmet need for novel endothelium-targeted treatments. 1-methylnicotinamide (MNA), a major metabolite of nicotinamide (vitamin PP, vitamin B_3) that has been for a long time considered to be inactive, seems to represent an interesting candidate for an endothelial drug. In 2003 Gebicki et al, described that MNA applied topically displayed beneficial effects in various skin diseases [1]. Recently we described anti-thrombotic, anti-inflammatory and vasoprotective activity of MNA *in vivo* [2-4].

Antithrombotic action of MNA was demonstrated in normotensive rats with extracorporeal thrombus formation [2], anti-inflammatory activity in the model of the contact sensitivity reaction (CS) to oxazolone (OX) in CBA/J inbred mice [3] and the ability of MNA to reverse endothelial dysfunction was shown in hypertriglicerydemic and diabetic rats [4]. Using various experimental models we demonstrated that MNA, displays a unique profile of vasoprotective activity that is linked to the activation of vascular COX-2/PGI_2 pathway. Furthermore, endogenous MNA, produced in the liver from nicotinamide by NNMT (N-nicotinamide-methyl-transferase), appears to be an endogenous activator of COX2/PGI_2 pathway and may play an important regulatory role in the cardiovascular system providing anti-thrombotic, anti-inflammatory and vasoprotective activity. There results open a new avenue for understanding of vascular effects of nicotinic acid, nicotinamide (both may be metabolized to MNA) and may foster the development of novel vasoprotective agents based on NA/MNA/COX-2/PGI_2 pathway.

[1] Gebicki et al.: *Pol. J. Pharmacol. 2003, 55 (1), 109-112*.
[2] Chlopicki et al.: *Br. J. Pharmacol. 2007, 152 (2), 232-239*.
[3] Bryniarski et al.: *Eur. J. Pharmacol. 2008, 578 (2-3);332-338*.
[4] Bartus et al.: *Pharmacol. Rep. 2008, 60(1),127-138*.

L-7

Applications of Affinity Chromatography in Drug-Binding Determination and Medicinal Chemistry Projects.

Krzysztof Jóźwiak

Laboratory of Drug-Receptor Interactions, Department of Analytical Chemistry, Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin
e-mail: krzysztof.jozwiak@am.lublin.pl

Affinity chromatography (AF) was initially developed for bioanalytical application in chemistry and molecular biology. But scientists soon recognized it as a promising tool to investigate drug – receptor interactions in many pharmacologically relevant systems. It allows measuring the relative affinity of the series of ligands to immobilized target protein in quick and simple chromatographic experiments. Usual the frame of experiments include the following procedures:

1. immobilization of intact or pretreated protein target on the surface of the stationary phase;
2. packing of affinity stationary phase into the chromatographic column;
3. validation of immobilization process in test experiments with well known marker ligands;
4. actual measurements of retention of tested ligands on the AF column (both zonal elution and frontal experiments find application here);
5. data analysis and control experiments;

The relative retention of tested ligands in experiments can be transformed into the relative trend of their affinities. More sophisticated processing of chromatographic data allows determination of the actual equilibrium constants of ligand – receptor interaction, kinetics and thermodynamics of this process and in some cases the IC_{50} values of tested inhibitors.

Currently this technique proved to generate pharmacologically relevant information in many different systems. A vast number of immobilization methods were developed for both cytoplasmic and embedded membrane proteins for use in AF. Many different classes of drug targets (carriers, membrane transporters, receptors and enzymes) were successfully studied using this technique.

The review of several recent projects when AF lead to successful elucidation of ligand – receptor interactions will be presented. These projects allowed determining cooperative and anticooperative allosteric action of ligands on serum albumin [1], affinity of channel blockers towards the nicotinic acetylcholine receptor [2] and inhibitory activity of ligands of acetylcholinesterase [3].

[1] Chen J., Hage D. S.: Quantitative analysis of allosteric drug-protein binding by biointeraction chromatography. *Nat. Biotechnol. 2004, 22 (11), 1445-8*.

[2] Jozwiak K., Moaddel R., Wainer I. W.: Allosteric modifiers of neuronal nicotinic acetylcholine receptors: new methods, new opportunities. *Med. Res. Rev. 2007, 27 (5), 723-753*.

[3] Bartolini M., Cavrini V., Andrisano V.: Monolithic micro-immobilized-enzyme reactor with human recombinant acetylcholinesterase for on-line inhibition studies. *J. Chromatogr. A 2004, 1031 (1-2), 27-34*.

L-8

Quantitative Structure-Retention Relationships (QSRR) as an Objective Tool for Characterization of HPLC Columns.

Michał Markuszewski, Roman Kaliszan

Department of Biopharmacy and Pharmacokinetics, Faculty of Pharmacy, Medical University, al. Gen. Hallera 107, 80-416 Gdańsk
e-mail: markusz@farmacja.amg.gda.pl

Quantitative structure-chromatographic retention relationships (QSRR) are one of the most extensively studied manifestations of linear free-energy relationships (LFER). These are the statistically derived relationships between the structure of solutes and their chromatographic retention. Using the tools of QSRR the chromatographic column could be regarded as a „free-energy transducer", translating differences in chemical potential of solutes resulting from differences in their structure, to chromatographic retention. If statistically significant QSRR are derived and if these equations approximate the experimental retention data for a structurally representative set of model solutes, it is possible to define the dominant factors which determine the interactions of solute molecules with the chemical entities forming the chromatographic system. In other words, QSRR analysis can provide an insight into the molecular mechanism of chromatographic retention in a given HPLC system.

Few main approaches to QSRR can be distinguished. One employs as independent variables in QSRR equations the structural descriptors provided solely by the calculation chemistry. Having good QSRR equations with such descriptors one can predict retention for any given structural formula. It is also possible to assign physical sense to the more commonly used theoretical descriptors. This, in turn, facilitates interpretation of the mechanism of separation operating in a given HPLC system.

Another approach to QSRR employs the LFER-based empirical (semiempirical) solute parameters based on spectroscopic, complexation and dissolution scales proposed by Abraham.

It has been demonstrated that the *clogP* based model, the Abraham model and the molecular modeling descriptors-based model provide generally similar classification of the HPLC columns studied. All the approaches allow a quantitative, although multidimensional, characteristic of HPLC columns. However, the non-empirical QSRR based approach is the simplest and requires less labor.

All the QSRR equations derived appeared clearly interpretable in physical terms. Due to that it was possible to identify specific types of intermolecular interactions which determine retention on individual separation systems.

L-9

Supramolecular Structures Formed by N-lipidated Peptides Immobilized on Cellulose Support.

Zbigniew J. Kamiński

Institut of Organic Chemistry,
Technical University, Stefanowskiego 4/10, 90-924 Łódź
e-mail: zbigniew.kaminski@p.lodz.pl

The supramolecular structures were prepared from N-acylated peptides attached on the a regular basis to the CH_2OH groups on the surface of cellulose support via aminophenylamino-1,3,5-triazine. Due to regular pattern of microcrystalline regions dominated in the cellulose matrix N-lipidated peptides created highly ordered composition of ”holes” and “pockets” in dynamic equilibrium, which very efficiently recognized the structure (shape, size and polarity) of small guests molecules, thus resembling artificial receptors.
The supramolecular structures are highly flexible, thus an adjustement of their shape to fit the guests molecules the most efficiently is expected. Thus, even in the case, when the single receptor in a differential array does not necessarily have selectivity for a particular analyte, the combined fingerprint response can be extracted as a diagnostic pattern visually, or using chemometric tools [1], or diagnostic fields can be selected as characteristic markers.
The selectivity of binding was studied by using triphenylmethyl dyes. The interactions of colorless guest with the array were visualized by the subsequent processes of competitive adsorption-desorption of appropriate reporter dye. We found that the selectivity of binding depends on the structure of peptide and lipidic fragment of the receptor and vary with the analyte structure.
The previous studies confirmed that alternation of the binding pattern could detect even tiny structural changes of guest molecules and therefore offer a new tool for SAR studies. An assay of physiological fluids and tissue homogenates has been found useful for tissue differentiation.
It has been found, that under favorable circumstances the supramolecular structures could operate as catalysts if suitable molecular fragment are included inside the binding pocket. Thus, incorporation of triade His Asp(Glu) Ser into the binding pocket gave library of supramolecular hosts with catalytic activity. The most active catalyst were selected from the library and their stability, selectivity and ability for re-use was studied.
The mechanism of molecular recognition by artificial receptors formed from N-lipidated peptides was studied. The complex nature of the host-guest interactions will be discussed.

Acknowledgements: This work was supported by the Ministry of Science and Higher Education, Grant 2 P05F 031 30.

[1] Wright A.T. Anslyn, E.V.; Differential receptor arrays and assays for solution-based molecular recognition, *Chem. Soc. Rev., 2006, 35(1), 14-28*.

L-10

Death Receptors as Molecular Target of Anticancer Drugs.

Zdzisław Chilmonczyk

National Institute for Public Health,
Chełmska 30/34, 00-725 Warszawa
e-mail: chilmon@il.waw.pl

Apoptosis, a programmed cell death, plays a crucial role in such processes as embriogenesis, metamorphosis, cellular homeostasis, tissue atrophy or cancer regression. There are two main routs of apoptosis initiation: death receptors activation and mitochondrial pathway. Death receptors belong to the superfamily of tumor necrosis factor receptors (TNF-Rs). In the cytosolic part they contain highly conservative domains – so called death domains.- necessary for the direct activation of cell apoptotic program. Thus receptors possessing death domains, in the presence of cytosolic adaptor proteins, may initiate apoptosis. Ligands activating death receptors - TNF-α, Fas-ligand, TRAIL (TNF-receptor apoptosis inducing ligand) - belong to the family of cytokins and possess an ability to activate apoptic program and may be used in cancer treatment. TNF-α is one the few cytokins that has found clinical application as a cancer therapeutic. Its use is, however, very restricted due to its pronounced systemic toxicity and has been only approved and registered for melanomas and soft tissue sarcomas confined to the limbs. Fas-ligand, but not TRAIL, exhibits similar systemic toxicity. There are, however, several tumors that exhibit pronounced TRAIL resistance. Therefore for all three groups of death receptors (TNF-R, Fas, TRAIL-R) modified and conjugated ligands, as well as agonistic monoclonal antibodies, are being tested as compounds possessing lower normal cell toxicity as well as higher efficacy and broader tumor spectrum. Since inhibition of cellular pathways promoting cell survival and proliferation together with death receptors activation appeared favourable, synergistic properties of death receptor ligands and conventional chemotherapeutics are also being tested. Death receptors are thus promising target for new and effective antitumor therapy.

L-11

Structure-activity Relationship of Antitumor 1-Aminoacridinones and Triazoloacridinones.

Jerzy Konopa

Department of Pharmaceutical Technology and Biochemistry, Faculty of Chemistry, Gdansk University of Technology, Narutowicza 11/12, 80-952 Gdańsk
e-mail: konopa@chem.pg.gda.pl

Several series of acridinones and triazoloacridinones with aminoalkylamino side chains, synthesized in our Department, exhibit divergent antitumor activity against leukemia P388 in mice. Numerous structure activity relationship studies have shown that there are some strict structural requirements crucial for biological activity of both group of acridines. We discovered that the presence of aminoalkylamino group in side chains attached to acridine core is the most important of such requirements. Blocking or removing one of the amino group in the side chain led to the loss of biological activity of tested compounds. In case of 1-aminoacridinones, another strict condition is the presence of proper substituents (methyl or nitro group) in position 4 (para to proximal amino group in the side chain). Several other structure-activity relationship studies further revealed that e.g.: a) compared to triazoloacridinones, the presence of hydroxyl group in position 7 (para to heterocyclic nitrogen) in acridinones does not play important role for biological activity of latter compounds b) modification of hydroxyl group in triazoloacridinones have significant impact on their biological activity – alkylation leads to the loss of activity while estrification entails loss, preserved or alternately increased activity of triazoloacridinones. Estimated SAR allows to hypothesize the possible pathways of metabolic activation of both group of acridines, which are required for their biological activity.

L-12

Metabolism *in vitro* of a New Antitumor 9-Amino-1-Nitroacridine Derivative, C-1748, in Respect of its Diminished General Toxicity.

Zofia Mazerska

Department of Pharmaceutical Technology and Biochemistry, Faculty of Chemistry, Gdansk University of Technology, Narutowicza 11/12, 80-952 Gdańsk
e-mail: mazerska@chem.pg.gda.pl

Drug molecules are typically subjected to a variety of biotransformation reactions. The formation of each metabolite is a specific point of the balance between activation and deactivation pathway, between the stable and reactive metabolite, between activity and toxicity of the studied drug. Such a balance is particularly crucial in the case of antitumor compounds characterized by extremely narrow "therapeutic window".

Antitumor agent 9-amino-4-methyl-1-nitroacridine derivative, C-1748, belongs to a new set of antitumor derivatives developed in our laboratory and was selected to preclinical studies. It was shown to be less toxic in animals than other 9-amino-1-nitroacridines without 4-methyl substituent. We hypothesized that diminished susceptibility of C-1748 to metabolic transformations might be a reason of its reduced toxicity. Therefore, we present here the results of our studies, which aimed to find out the specificity in metabolism of less toxic C-1748 in comparison to its close analog C-857, which expressed higher toxicity. Metabolic transformations *in vitro* were performed with enzymes of rat and human liver microsomes and with recombinant P450 isoenzymes [..]. There was also applied NADPH:cytochrome P450-reductase, CPR, the enzyme that is responsible for electron transport to cytochrome P-450 [..]. Furthermore, studies on metabolism of both compounds were carried out in human hepatoma line HepG2 cells [..]. Analysis of metabolites formed in all experiments were done by means of RP HPLC with UV-Vis multidiode array detection and with ESI-MS spectra.

The obtained results showed that less toxic compound C-1748 expressed lower than C-857 metabolic reactivity in all studied systems and metabolites of C-1748 were much more stable than those of C-857. Several new metabolites of the studied compounds were formed after HepG2 metabolism in comparison to model enzymatic systems. However, at least one common metabolite was found in the cell as well as with all simple enzymatic systems. It is a derivative with additional pyrazole ring closed between nitrogen atoms at positions 1 and 9 of acridine ring. In conclusion, compound C-1748 expressed higher selectivity in metabolic pathway observed in all studied systems in comparison to other highly toxic 9-amino-1-nitroacridines.

PREZENTACJE USTNE

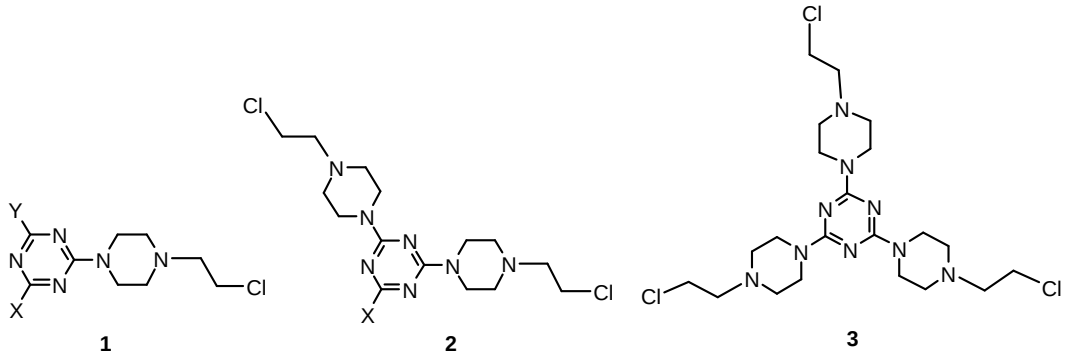
PU-1

N-Triazinylammonium Salts as Pro-drugs Convertible into the New Analogues of Nitrogen Mustard With One, Two or Three 2-Chloroethylamino Fragments.

Beata Kolesińska [a], *Danuta Drozdowska* [b], *Zbigniew J. Kamiński* [a]

[a]*Institute of Organic Chemistry, Technical University of Łódź, 90-924 Łódź;*
[b]*Department of Organic Chemistry, Medical University, Białystok*
e-mail: dbartule@umwb.edu.pl

Nitrogen mustards (NM) with 2-chloroethylamino fragment are used as classic group of antineoplastic agents in therapy of cancer as nonspecific DNA alkylating agents. NM drugs don't operate selectivity, causing high levels of inadvertent DNA damage in normal cells, toxic and mutagenic side effects, and in some cases, leading to secondary malignancies Therefore, the search for the new analogues is continued expecting improvement of therapeutic index by modification of NM structure, designing a pro-drug form, and supplementary mode of pharmacological activity [1].
In our studies, triazines **1-3** substituted with one, two or three 2-chloroethylamine moiety were prepared and apoptotic index and cell viability on the standard cell line of mammalian tumor MCF-7 by the compounds obtained has been determined.



1 **2** **3**

Herein, we present studies on the basic reactivity pathways including an alkylation of broad range of nucleophiles with triazine NM **1-3** and designing of their new, stable, water soluble pro-drug form [2].

References:
[1] Just recently, it has been found that relatively simple triazines substituted with nitrogen heterocyclic group are potent inhibitors of topoisomerase, telomerase, histone deacetylase, phosphatidiloinositol kinase, protein kinase CK2 etc.
[2] Kolesińska, B.; Kamiński Z.J.; Wąsikowska, K.; Drozdowska, D. „A New Method of Nitrogen Mustards Synthesis", Patent Appl. nr **P-385126** from 08. 05. 2008.

PU-2

Theoretical Studies on the Bioactive Conformation of Long-Chain Arylpiperazine Ligands of 5-HT_{1A} Receptor.

Urszula Kijkowska-Murak, Agnieszka Kaczor, Dariusz Matosiuk

Department of Synthesis and Chemical Technology of Pharmaceutical Substances, Faculty of Pharmacy, Medical University, Staszica6, 20-081 Lublin
e-mail: urszula.kijkowska@am.lublin.pl

Arylpiperazine derivatives represent one of the most relevant classes of 5-HT_{1A} receptor ligands [1]. However, because of the significant conformational freedom of the alkyl linker between arylpiperazine moiety and second pharmacophoric group, the problem of bioactive conformation for this group of medicinal substances has not been solved yet [2-3].
The aim of presented work was to estimate bioactive conformation of arylpiperazine ligands of 5-HT_{1A} receptor, especially to decide if biological activity is ensured by extended or "bent" conformation.
The key point in the methodology was the proper modeling of 5-HT_{1A} receptor as well as the fact that to eliminate mistakes resulting from the methodology of ligands preparations, only compounds of experimentally solved structures were applied in all the stages of the studies.
To estimate the bioactive conformation of long-chain arylpiperazine ligands, an active conformation of 5-HT_{1A} receptor was studied. To achieve it, several ligands active both on 5-HT_{1A} and adrenergic β_2 receptor of known structure were identified. However, in the experimentally solved structure adrenergic β_2 receptor exists in the conformation to interact with one of the antagonists (carazolol). Thus, molecular docking of ergoline derivatives (lisuride, terguride, bromocriptine) followed by molecular dynamics simulations were performed to elaborate better the receptor binding pocket. In the next step of studies homology modeling with Modeller9v2 was applied to generate a population of 100 5-HT_{1A} receptor models, using the solved adrenergic β_2 receptor as a template. Subsequently, docking procedure of ergoline derivatives was carried out to find a receptor bioactive conformation which corresponded with bioactive conformation of earlier modeled adrenergic β_2 receptor. The best 5-HT_{1A} receptor model was applied for docking procedure of 8-OH-DPAT and WAY100635 (selective 5-HT_{1A} receptor ligands) to confirm the correctness of the receptor model. Finally, long-chain arylpiperazines, both rigid and with conformational freedom, were docked to the 5-HT_{1A} receptor model. The obtained high values of all the scoring functions allowed to state that the applied procedure was correct and to formulate final conclusions.

[1] López-Rodríguez, M.L.; Ayala, D.; Benhamú, B.; Morcillo, M.J.; Viso, A. *Curr. Med. Chem. 2002, 9, 443-469.*
[2] Chilmończyk, Z.; Szelejewska-Woźniakowska, A.; Cybulski, J.; Cybulski, M.; Kozioł, A.E.; Daniec, M. *Arch. Pharm. Pharm. Med. Chem. 1997, 330, 146-160.*
[3] Paluchowska, M.H.; Bojarski, A.J.; Charakchieva-Minol, S.; Wesołowska, A. *Eur. J. Med. Chem. 2002, 273-283.*

Computations were performed in the framework of computational grant by Interdisciplinary Centre for Mathematical and Computational Modelling, Warsaw, Poland, grant number G30-18.

PU-3

Binding of Fenoterol Derivatives and Stereoisomers of Fenoterol to the β_2-Adrenergic Receptor. A Molecular Modeling Study.

Anita Plazinska, Krzysztof Jozwiak, Joanna Kozak

Laboratory of Drug-Receptor Interactions, Department of Analitycal Chemistry, Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin
e-mail: anita.plazinska@am.lublin.pl

Molecular modeling is very attractive and promising tool used by chemists to predict structure and properties of chiral compounds, while some mathematical models are assumed. In particular, it can be applied to molecular drug design where enantioselectivity plays a crucial role. Binding of the stereoisomers of fenoterol and fenoterol derivatives to the β2 adrenergic receptor has been analyzed. The binding of 26 agonists (fenoterol and its derivatives) has been studied using comparative molecular field analysis (CoMFA). Results indicate that several electrostatic and steric fields exist on the pseudoreceptor and are responsible for binding of tested ligands. Docking analysis has also been performed using determined binding zones and the template ligand TA2005. Both CoMFA and docking analysis demonstrate that (R,R) stereoisomers have generally higher affinities relative to their (R,S), (S,R) and (S,S) stereoisomers.

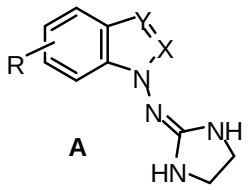
PU-4

Synthesis and Structure of 1-[(Imidazolidin-2-yl)imino]azoles with Cardiovascular Activity.

Anita Kornicka [a], *Franciszek Sączewski* [a], *Apolonia Rybczyńska* [b], *Alan L. Hudson* [c], *Shu Sean Miao* [c], *Maria Gdaniec* [d], *Konrad Boblewski* [b], *Artur Lehmann* [b]

[a] *Department of Chemical Technology of Drugs,* [b] *Department of Pathophysiology, Faculty of Pharmacy, Medical University, Al. Gen. J. Hallera 107, 80-416Gdańsk*
[c] *Department of Pharmacology, University of Alberta, Edmonton, T6G 2R3 Canada*
[d] *Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań*
e-mail: a.kornicka@amg.gda.pl

Our extensive study on novel imidazoline compounds with α_2-adrenoceptor and/or imidazoline I_1/I_2 receptor affinity [1-3] prompted us to synthesize analogues of type **A** bearing (imidazolidin-2-yl)imino moiety at position 1 or 2 [4].



A

X, **Y** = CH or N

The *in vitro* assays involving investigation of the affinity and selectivity of the newly synthesized imidazoline ligands for α_2-adrenoceptors, imidazoline I_1 and imidazoline I_2 binding sites showed very low or no affinity for imidazoline I_2 receptors. 1-[(Imidazolidin-2-yl)imino]indazole (**X** = N, **Y** = CH, **R** = H, *marsanidine*), the most active agent at α_2-adrenoceptors (K_i = 14 nM), displayed a very high α_2/I_1 selectivity ratio = 3879.

The *in vivo* cardiovascular properties of the selected indazole derivatives (**X** = N, **Y** = CH, **R** = H, Me, Cl, OMe, Ph) were evaluated after intravenous infusion in anaesthetized male Wistar rats. Among the tested compounds the highest hypotensive activity was found for 7-methyl analogue of *marsanidine* (Δ MAP = - 43.5 mmHg at dose 10 μg/kg, ED_{50} = 0.6 μg/kg), which also exhibited a good affinity for α_2-adrenoceptors (K_i = 53.5 nM) and moderate affinity for imidazoline I_1 receptors (K_i = 387 nM).

These results suggest that *marsanidine* may find a variety of medical uses ascribed for α_2-adrenoceptor agonists especially in anaesthesiology, while its 7-methyl derivative is a good candidate for further development as a centrally acting antihypertensive drug.

[1] Sączewski F., Kobierska E., Dębowski T., Charakchieva-Minol S., Mokrosz M., Gdaniec M., Nowak E.: *Arch. Pharm*. (*Weinheim, Ger.*) *2000, 333, 425-430.*
[2] Sączewski F., Hudson A.L., Tyacke R.J., Nutt D.J., Man J., Tabin P., Sączewski J.: *Eur. J. Pharm. Sci. 2003, 20, 201-208.*
[3] Sączewski F., Tabin P., Tyacke R.J., Maconie A., Sączewski J., Kornicka A., Nutt D.J., Hudson A.L.: *Bioorg. Med. Chem. 2006, 14, 6679-6685*.
[4] Sączewski F., Kornicka A., Rybczyńska A., Hudson A.L., Miao S.S., Gdaniec M., Boblewski K., Lehmann A.: *J. Med. Chem*. *2008, 51, 3599-3608*.
This research was supported by the Polish Ministry of Science and Higher Education (Grant N40500532/0458).

PU-5

NBD-labeled 3-Methyl-1-(3-phenoxypropyl)piperidine as a Novel, Active Histamine H_3 Receptor Fluorescent Ligand.

Kamil Kuder [a], *Holger Stark* [b], *Xavier Ligneau* [c], *Jean-Charles Schwartz* [c], *Katarzyna Kieć-Kononowicz* [a]

[a] *Department of Technology and Biotechnology of Drugs, Jagiellonian University Medical College, Faculty of Pharmacy, Medyczna 9, 30-688 Krakow*
[b] *Institut für Pharmazeutische Chemie, Johann Wolfgang Goethe-Universität, Biozentrum, ZAFES/CMP, Frankfurt am Main, Germany*
[c] *Bioprojet-Biotech, Saint-Gregorie, France*
e-mail: kkuder@cm-uj.krakow.pl

Fluorescent ligands have been in use since the mid-70's, mainly used as a biological markers [1], and also for the identification of the biogenic amines in tissues [2. Generally the fluorescent moieties have been used more as labels, than as ligands. Recent years bring the new application for such ligands and the burst of literature in this area. One of the largest groups in therapeutics in this field are G-protein coupled receptors ligands [3].

In comparison to radioligands fluorescent compounds possess a variety of advantages. First of all, fluorescent methods are relatively safe, and cheap in comparison to traditional radioligand methods. The tests could be performed on live or fixed tissues, using small amounts of tissue, or single cells. Immediate results could be obtained. Moreover fluorescent ligands could be replaced by non-fluorescent ones. With the correct drugs and the state-of-the-art technique one can see single molecule binding and also appropriate displacement.

In our research on drug for the central nervous system we focus on non-imidazole histamine H_3 receptor ligands. Basing on the results described by Amon *et al.* [4] we obtained novel histamine H_3 receptor fluorescent ligand, using 4-nitrobenzo[c][1,2,5]oxadiazole (NBD) as a fluorescent marker. Pharmacological *in vitro* assays proved its high affinity at histamine H_3 receptors stably expressed in CHO-K1 cells. Fluorescent studies showed excellent fluorescent properties concerning absorption and emission maxima in wave length.

The novel ligand obtained may provide a useful pharmacological tool for further in vitro and in vivo studies on histamine H_3 receptors.

This work was partly supported by the Ministry of Science and Higher Education – grant No. DAAD/55/2007

[1[McGrath J. C., Arribas S., Daly C. J.: *J. Trends Pharmacol. Sci. 1996, 17, 393*; and literature cited there.
[2] Falck B., Hillarp N. A. Torp A.: *J. Histochem. Cytochem. 1962, 12, 348.*
[3] Kuder K., Kieć-Kononowicz K.: *Curr. Med. Chem., in press.*
[4] Amon M., Ligneau X., Camelin J.-C., Berrebi-Bertrand I., Schwartz J.-C., Stark H.: *ChemMedChem 2007, 14, 708.*

PU-6

Synthesis and Antibacterial Activity of 1-{[(4-Phenyl-4*h*-1,2,4-triazol-3-yl)sulfanyl]acetyl}thiosemicarbazide Derivatives

Łukasz Popiołek [a], *Maria Dobosz* [a], *Urszula Kosikowska* [b], *Monika Pitucha* [a], *Monika Wujec* [a], *Anna Malm* [b]

[a] *Department of Organic Chemistry, Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin*
[b] *Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Medical University, Chodźki 1, 20-093 Lublin*
e-mail: lukasz.popiolek@um.lub.pl

Reaction of 4-phenyl-4*H*-1,2,4-triazole-5-thione with ethyl bromoacetate led to ethyl [(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetate. In the next reaction with 80% hydrazide hydrate appropriate hydrazide was obtained, which in reactions with isothiocyanates was converted to new acyl derivatives of thiosemicarbazides. These compounds were used further for synthesis new heterocyclic compounds with 1,2,4-triazole system. The structure of the compounds was confirmed by elemental and spectra analysis.

The compounds were screened for *in vitro* antibacterial activity against 6 Gram-positive and 4 Gram-negative reference strains by the agar well diffusion method. The results of the qualitative screening were presented as the average diameter of the growth inhibition zone surrounding the well containing the test compound at 5000 mg/L concentration. Antimicrobial activity was monitored by an appearance of zone of growth inhibition around a well. All compounds had activity only against Gram-positive bacteria, especially against *Micrococcus luteus* ATCC 10240. The growth of *Staphylococcus aureus* ATCC 25923, *S. aureus* ATCC 6538 and *S. epidermidis* ATCC 12220 were inhibited by compounds: 4-ethyl-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}thiosemicarbazide, 4-(4-bromophenyl)-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}thiosemicarbazide, 4-ethoxycarbonylmethyl-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}thiosemicarbazide. The growth of *Bacillus subtilis* ATCC 6633 and *B. cereus* ATCC 10876 were inhibited by compounds: 4-benzyl-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl}thiosemicarbazide, 4-ethyl-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl} thiosemicarbazide and 4-ethoxycarbonylmethyl-1-{[(4-phenyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]acetyl} thiosemicarbazide.

PU-7

Physicochemical properties of (thio)carbonyl groups in (thio)barbiturates.

Anna Stasiewicz-Urban, Grzegorz Żuchowski, Marek Żylewski, Jerzy Bojarski

Department of Organic Chemistry, Faculty of Pharmacy,
Jagiellonian University, Medical College, Medyczna 9, 30-688 Kraków
e-mail: mfurban@kinga.cyf-kr.edu.pl

The first barbiturate was introduced to the therapy over hundred years ago, therefore we can suppose that this class of drugs were accurately examined in this time. Numerous papers are devoted to barbiturates, indeed [1]. But when we observe data on physical properties of their carbonyl group, obtained in different analytical methods, the picture is not coherent. Physicochemical parameters, as bond length [2,3] and chemical shift in ^{13}C NMR spectra [4,5] seem to be inconsistent with theoretically calculated charge density for appropriate carbon atoms. Similar lack of clarity is observed in the reactions with carbonyl groups, which are described in literature [1], also in a case of the thionation reactions [6,7].

This presentation is an attempt to clarification the knowledge about the physicochemical properties of carbonyl groups of 2,4,6(1H,3H,5H)-pyrimidinetrione ring, which is structural framework of the barbiturates.

The experiment of tionation of barbiturates with different substituents was run using the Lawesson reagent [5,8]. These reactions prove significant influence of steric hidrance of substituents in the C(5) position on results of thionation reaction, which is at variance with theoretical calculations suggesting, that the carbonyl group in the 2 position is the most polarized part of barbiturate molecule. Therefore, the hypothesis was formulated, that in barbiturates the largest electropositive charge is located on carbon of carbonyl groups in position 4,6. This hypothesis was proved by the desulfurization reactions of 2,4-ditio- and tritiobarbiturates using nucleophilic agent (NH_3) [6,8] and electrophilic agent (NO^+) [9,8].

[1] CrossFire Beilstein Database, www.mdl.com.
[2] Craven B. M., Vizzini E. A., Rodrigues M. M.: *Acta Cryst. B, 1969, B25, 1978*.
[3] Williams P. P.: *Acta Cryst. B, 1973, B29, 1572.*
[4] Okada J., Esaki T.: *Yakugaku Zasshi 1973, 93), 1014.*
[5] Stasiewicz-Urban A., Kubaszek M., Żylewski M., Cegła M., Bojarski J.: *Pol. J. Chem. 2004, 78, 2105*.
[6] Carrington H.: *J. Chem. Soc. 1944, 124*.
[7] Stratmann J.: *Pharm. Acta Helv. 1989, 64, 252.*
[8] Stasiewicz-Urban A.: *PhD Thesis (2007).*
[9] Joergensen K. A., Ghattas A.-B. A. G., Lawesson S.-O.: *Tetrahedron 1982, 38, 1163.*

PU-8

Novel cholinesterases inhibitors with carbamoyloxyphenyl and *N*-benzylpiperidine moieties.

Anna Więckowska, Barbara Malawska

Department of Physicochemical Drug Analysis, Chair of Pharmaceutical Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków
e-mail: musialanna@op.pl

Alzheimer's disease (AD), a progressive, degenerative disorder of the brain is associated with the deficits of neurotransmitters, particularly the deficits in cholinergic system in the brain areas related to memory and learning. Hence, the most important drugs approved for the treatment of AD include a group of indirect cholinomimetic agents which enhance central cholinergic neurotransmission by inhibiting the acetylcholinesterase (AChE) – the enzyme that hydrolyses acetylcholine. Lately there has been a growing number of evidence that butyrylcholinesterase (BuChE) plays an important role in the patogenesis of AD. Significant decline of AChE during the AD is accompanied by an increase in BuChE levels suggesting that BuChE can partly compensate for action of AChE in AD. Apart from their enzymatic function cholinesterases exert secondary functions among which mediating processing and deposition of A-β peptide seems to be crucial for development of AD. Identification of the peripheral binding site of AChE as a fragment responsible for binding with A-β and resulting fibrillogenesis caused interest in synthesis of dual binding site AChE inhibitors.

The study concentrated on the synthesis of new carbamate and alkylarylpiperazine and piperidine derivatives as AChE dual binding site and BuChE inhibitors. Activity of the obtained products was tested *in vitro* with the spectrometric method of Ellman. Among all tested compounds the most interesting inhibitors of both AChE and BuChE as well as the derivatives characterized by a selective mode of action against BuChE were chosen for further investigation. The IC_{50} values of the most potent inhibitors were calculated and they were similar to rivastigmine.

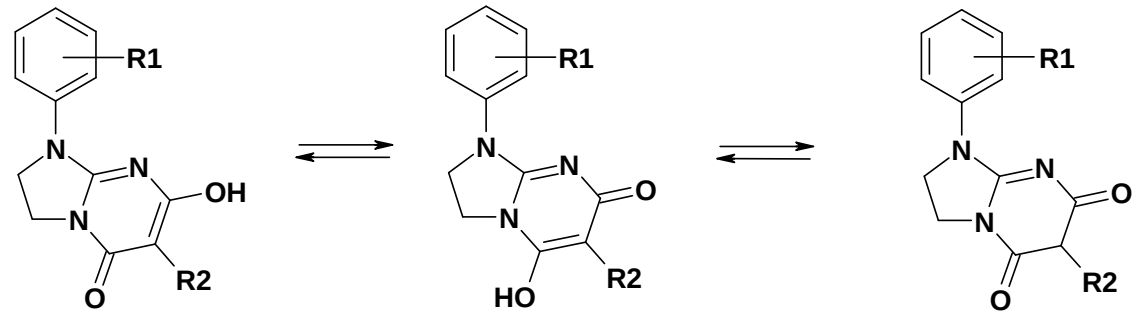
PU-9

x-Ray and Theoretical Studies on the Keto-Enol Tautomerism of the Selected Dioxo Imidazopyrimidine Derivatives.

Waldemar Wysocki [a], *Dariusz Matosiuk* [b], *Zbigniew Karczmarzyk* [a], *Marzena Rządkowska* [b], *Elżbieta Szacoń* [b]

[a] *Department of Chemistry, University of Podlasie, 3-go Maja 54, 08-110 Siedlce*
[b] *Department of Synthesis and Chemical Technology of Pharmaceutical Substances, Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin*
e-mail: wwysocki@ap.siedlce.pl

Aminoimidazoline and their anologues have been widely used as medicines against a broad range of diseases because of their significant pharmacological activities. Dioxo derivatives of fused imidazoline ring systems have been found to have significant anelgesic opioid-like action but without the typical narcotic analgestic side-effects [1].



A **B** **C**

R1 = H; 2-CH_3; 2-OCH_3; 2-Cl; 4-Cl; 3,4-Cl; 2,6-Cl
R2 = H; Ph; $PhCH_2$; 2-$ClPhCH_2$

The tauthomeric equilibrium of **A<=>B<=>C** forms for the fused imidazopyrimidine system was investigated using quantum chemical calculation in the gas phase and in solutions. For the crystalline state the X-ray analysis was used. The tauthomerism of the oxo groups may be responsible for the pharmacological action of the analyzed compounds.

[1] Matosiuk D., Fidecka S., Antkiewicz-Michaluk L., Lipkowski J., Dybała I., Kozioł A. E.: *Eur. J. Med.. Chem. 2002, 37, 845.*

PU-10

The 1-[3-(4-Arylpiperazin-1-yl)-2-hydroxy-propyl]pyrrolidin-2-one Derivatives as α-Adrenocoptor Antagonist and Antiarrythmic Agents: a SAR Studies.

Alicja Nowaczyk [a], *Katarzyna Kulig* [b], *Barbara Malawska* [b], *Bożena Modzelewska-Banachiewicz* [a]

[a] *Department of Organic Chemistry, Faculty of Pharmacy, Collegium Medicum, Nicolaus Copernicus University, Skłodowskiej-Curie 9, 85-094 Bydgoszcz*
[b] *Department of Physicochemical Drug Analysis, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków*
e-mail: alicja@cm.umk.pl

α-Adrenergic receptors (α -ARs) are members of the G-protein coupled superfamily of receptors, which modulate intercellular biochemical processes in response to changes in extracellular concentration of the neurotransmitter norepinephrine and circulating hormone epinephrine, leading to widespread physiological actions.The arylpiperazines represent one of the most studied class of α_1-AR receptor antagonists (α_1-AR). The typical α_1-AR contains arylpiperazine moiety, substituted with one or two additional molecular fragments. The pharmacological results suggest that the antiarrhythmic effects of these compounds are related to their adrenolytic properties [1]. According to this an arylpiperazine derivatives are currently the most widely studied class of antiarrhythmic agents. The exact crystal structures of α-adrenolitic and antiarrhythmic receptors are not known, for this reason the pharmacophore model that gives indirect information concerning the topology of protein active site was derived [2]. In the absence of detailed structural information on the target for antiarrythmic drug we can make an assumption, that the topology of this target is similar to the α_1-AR pharmacophore[3]. The synthesis of a series of 1-[3-(4-arylpiperazin-1-yl)-2-hydroxy]propyl-pyrrolidin-2-one derivatives were previously reported. Some of these compounds shows high affinity for α-AR, and in *in vivo* research displayed antiarrhythmic activity [1-4].
In order to better define the structure-activity relationship of investigated compounds, a molecular modelling study was undertaken. The three-dimensional structures of the pyrrolidin-2-ones derivatives at their neutral state were obtained through full optimization based on the AM1 quantum chemical procedure. This work was based on the earlier described pharmacophore model for α_1-AR, which includes three features: an aromatic region, a positively ionisable group, and a hydrogen-bond acceptor. The structures were compared to the early proposed pharmacophore features by measurements of the appropriate distances and angels. The preliminary analysis of these geometrical quantities for the set of title compounds revealed that the distances are comparable, while the angel values are appreciably different. In order to check applied pharmacophore model more precisely, we have extended our molecular modelling study with the MEP of electrostatic potential calculation experiment and geometrical similarity analysis.

[1] Malawska B., Kulig K., Filipek B., Sapa J., Maciąg D., Zygmunt M., Antkiewicz-Michaluk L.: *Eur. J. Med. Chem. 2002, 37, 183*.
[2] Kulig K., Sapa J., Maciąg D., Filipek B., Malawska B.: *Arch. Pharm. Chem. Life Sci. 2007, 340, 466*.
[3] Kulig K., Sapa J., Nowaczyk A., Filipek B., Malawska, B.: *in press 2008*.
[4] Malawska B., Kulig K., Gippert A., Filipek B., Sapa J., Maciąg D.: *Il Farmaco 2005, 60, 793*.

PREZENTACJE POSTEROWE

P-1

Synthesis, DNA-binding Affinity and Cytotoxicity of the Dinuclear Platinum(ii) Complexes with Berenil and Amines Ligands.

Anna Bielawska, Krzysztof Bielawski, Bożena Popławska, Arkadiusz Surażyński, Urszula Bołkun-Skórnicka

Department of Medicinal Chemistry and Drug Technology, Medical University of Białystok, Kilińskiego 1, 15-089 Białystok
e-mail: aniabiel@umwb.edu.pl

Despite its success, the clinical usefulness of cisplatin is limited by its severe side effects such as dose-dependent nephrotoxicity, nausea and vomiting, ototoxicity, neurotoxicity, and myelosuppression. Some strategies have been applied during synthesis of new platinum drugs, such as the use of different ligands, in order to reduce side effects or increase the cytotoxicity potential of the drug. Another strategy is the synthesis of dinuclear or trinuclear platinum complexes which may decrease the action of the cellular repair machinery by forming different types of complex-DNA adducts. A series of platinium(II) complexes of formula $[Pt_2L_4(berenil)_2]Cl_4$•4HCl where L is piperidine (**1**), 4-picoline (**2**), 3-picoline (**3**), 2-picoline (**4**) or isopropylamine (**5**) was prepared and their cytotoxicity have been tested against the growth of human breast cancer cells and MOL4 human lymphoblastic leukemia cells. The mechanism of action of compounds **1**-**5** was studied employing the topoisomerase I/II inhibition assay, and ethidium displacement assay using calf thymus DNA, T4 coliphage DNA, poly(dA-dT)$_2$ and poly(dG-dC)$_2$. Evaluation of the cytotoxicity of these compounds employing a MTT assay and inhibition of [^{3}H]thymidine incorporation into DNA in both MOL4 human lymphoblastic leukemia cells and human breast cancer cells demonstrated that these compounds were more active than cisplatin. The result of DNA binding studies, reveal that **1** does have a greater DNA binding affinity, which correlates with its greater potency relative to **2** - **5** as a topoisomerase II inhibitor. In $[Pt_2(amine)_4(berenil)_2]Cl_4$ complexes, berenil rather than platinum may dominate the DNA sequence specificity and ultimately dictate the sites of covalent attachment of the metal on DNA. It is probable that deregulation of DNA replication and transcription by inhibition of topoisomerase II activity contribute significantly to the cytotoxicity of $[Pt_2(amine)_4(berenil)_2]Cl_4$ complexes in addition to primary drug-DNA reaction products.

P-2

Synthesis and Biological Evaluation of Amidine Analogs of Chlorambucil and Melphalan.

Krzysztof Bielawski, Anna Bielawska, Grażyna Gryciuk, Arkadiusz Surażyński, Bożena Popławska

Department of Medicinal Chemistry and Drug Technology, Medical University of Białystok, Kilińskiego 1, 15-089 Białystok
e-mail: kbiel@umwb.edu.pl

A drawback common to the nitrogen mustards is their high chemical reactivity. This can result in loss of drug by reaction with other cellular nucleophiles, particularly proteins and low molecular weight thiols. For these reasons there has been much interest in the concept of specifically targeting “simple” mustards and other alkylators to DNA by attaching them to DNA affine carrier molecules, since this could in principle address these limitations. Additionally, the use of DNA-affine carriers with their own defined binding geometry makes it possible to alter both the region and sequence specificity of alkylation compared with that of the “simple” mustards [1-3]. We synthesized compounds that have two moieties in the structure. One is a aromatic amidine moiety to acquire DNA minor groove binding activity, and another is an *N,N*-bis(2-chloroethyl)amino residue for DNA alkylation. These compounds are able to bind to double stranded DNA preferentially at AT base pairs along the minor groove by formation of hydrogen bonds. Evaluation of the cytotoxicity of these compounds in both MOL4 human lymphoblastic leukemia cells and human breast cancer cells demonstrated that these compounds were more active than melphalan and chlorambucil. DNA binding suggests that the combined effect resulting from alkylation and DNA minor groove binding might be in part responsible for the cytotoxic activity of these compounds. An attempt has also been made to correlate the observed biological activity with topoisomerases inhibitory properties and the DNA-binding properties of these compounds. The cytotoxic properties of the amidine analogs of melphalan and chlorambucil towards MOL4 human lymphoblastic leukemia cells correlate with topoisomerase II inhibitory properties but not with DNA-binding properties.

[1] Bielawski K, Bielawska A.: *ChemMedChem. 2008, 3, 536-542.*
[2] Bielawski K, Bielawska A, Sosnowska K, Miltyk W, Winnicka K, Pałka J.: *Biochem. Pharmaco. 2006, 72, 320-331.*
[3] Bielawska A., Bielawski K., Anchim T.: *Arch. Pharm. Chem. Life Sci. 2007, 340, 251-257.*

P-3

Formation and Pro/-Antioxidative Activity of Oxazolo[3,2-a]-Benzimidazoles.

Marzena Baran, Marek Żylewski, Renata Francik, Marek Cegła

Department of Organic Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków
e-mail: marzena_baran@wp.pl

New 7-(substituted amino)-2,3-dihydrooxazolobenzimidazoles have been synthezised from 2-bromobenzimidazole and the oxirane derivatives. The substrates containing oxirane ring were N-(2,3-epoxypropyl)indoline and N-(2,3-epoxypropyl)morpholine. In both reactions two products were obtained. One of them contained three-carbon chain which was formed during the process of opening oxirane ring and its addition to NH group of heterocyclic system. The second product was a threecyclic compound with oxazolic ring. The structure of obtained compounds was confirmed by NMR spectra (^{1}H, ^{13}C, COSY, NOESY, HSQC, HMBC) and MS spectra. The derivatives with oxazine ring were not formed although they were obtained in previous studies on synthesis of compound of analogical structure.
In future further reactions of oxazolidyne derivatives with ammonium and amines will be carried out. They should allow to investigate if oxazolic ring opens simultaneously with forming of hydroxylic group in aliphatic chain and addition of amine group in C2 position of benzimidazole.
Analysis of antioxidative capacity as indication of oxidative stress was based on ability to scavenge free radicals by DPPH test. Outcome was compared to pattern substances like vitamin C, trolox, quercetin, curcumin.
Obtained results shows that benzimidazole derivatives indicate weak antioxidative properties in higher concentrations, but prooxidative in low concentrations.

[1] Cegła M.T., Potaczek J., Żylewski M., Strekowski L.: *Tetrahedron Lett*. 2005, 46, 3561-3563.
[2] K. Schlesier, M. Harwat, V. Bohm, R. Bitsch.: Assessment of Antioxidant Activity by Using Different In Vitro Methods. *Free Radical Research 2002, 36 (2), 177–187.*

P-4

Low-molecular-weight Inhibitors of Gingipains – Alternative Approach to the Treatment of Periodontitis.

Arkadiusz Białas, Artur Mucha

Department of Bioorganic Chemistry, Faculty of Chemistry, Wroclaw University of Technology, Wybrzeże Wyspiańskiego 29, 50-370 Wrocław
e-mail: arkadiusz.bialas@pwr.wroc.pl

Gingipains are cysteine proteases expressed in large amounts by Gramm-negative anaerobic bacterium *Porphyromonas gingivalis*. They were recognized as key virulence factors in human periodontitis. Selective inhibition of the protease crucial for the development, survival and spread of pathogenic bacteria is one of possible approaches to the treatment of infectious diseases. Such therapeutic strategy seems to be competitive against approved medical procedures based on administration of broad-spectrum antibiotics. Using of a drug directed toward protease specific for selected bacterial species could be a solution to the problems accompanying antibioticotherapy, such as secondary fungal and bacterial infections and increasing bacterial resistance.
Gingipains with their specific substrate preferences (hydrolysis of peptide bond Arg-Xaa or Lys-Xaa, gingipain R and K, respectively) and their proven role in pathogenesis of periodontitis are attractive targets for development of potential, highly selective antibiotic-like inhibitors. Availability of the crystal structure of gingipain R complexed with the covalent inhibitor D-Phe-Phe-Lys-CH_2Cl (1CVR code in PDB) encouraged to apply molecular modeling methodology to the development of new low-molecular-weight inhibitors of this protease. Initial studies on structure-activity relationship of designed and synthesized series of chloromethyl ketones of lysine and arginine provided data useful for detailed characterization of binding pockets of the Sn site of both gingipains. [1] The R2 residues (S2 pockets-directed fragments) of the most active chloromethyl ketones were selected as conservative structural elements of more advanced inhibitors bearing less reactive warhead and S1'-directed 1,4-phenylenediamine residue (Fig. 1).

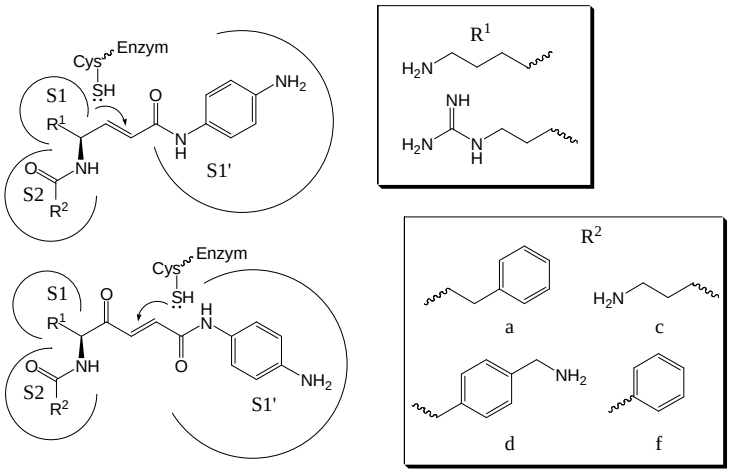


Fig. 1 General structures of two classes of the synthesized Michael acceptors.

[1] Białas A., Grembecka, J., Krowarsch, D., Otlewski, J., Potempa, J., Mucha, A.: *J. Med. Chem. 2006, 49, 1744-1753.*

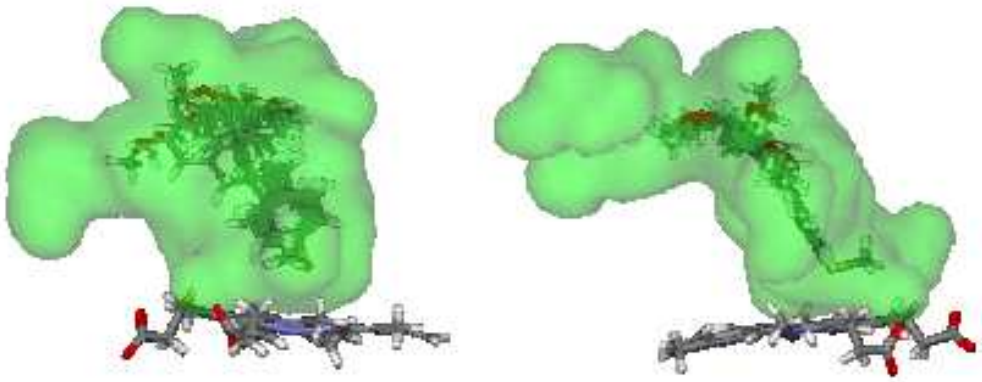
P-5

Molecular Docking Study on Thiomethylstilbenes as CYP1A2 Inhibitors.

Zbigniew Dutkiewicz, Renata Mikstacka, Stanisław Sobiak, Marcin Wieczorek

Department of Chemical Technology of Drugs, Faculty of Pharmacy, University of Medical Sciences, Grunwaldzka 6, 60-780 Poznań
e-mail: zdutkie@ump.edu.pl

Cytochroms P450 (CYPs) are a superfamily of hemoproteins, which play a pivotal role in the metabolism of many endogenous and exogenous compounds, including drugs, environmental pollutants and microcomponents of human diet. Specific CYP1- dependent enzymes that activate procarcinogenes, are considered to be potential targets for cancer chemoprevention strategy.
The inhibitory potency of a series of 4'-thiomethy-*trans*-stilbene toward human recombinant CYPs (CYP1A1, CYP1A2 and CYP1B1) has been demonstrated previously [1]. Based on these results, molecular docking methods were applied to investigate ligand-enzyme interactions and the affinities of 4'-thiomethylstilbenes toward CYP1A2 active site.
To find possible binding modes (poses of ligand inside the binding site) a series of 4'-thiomethyl-*trans*-stilbene derivatives molecules were docked into the binding site of the human CYP1A2 enzyme (PDB code: 2hi4). Autodock 4.0.1 with the Lamarckian genetic algorithm and Discovery Studio 2.0 with LigandFit procedure were used in automated docking experiment. Both programs predicted that preferred orientation of these molecules inside the CYP1A2 binding site are poses with SCH_3 substituent pointed toward the hem prosthetic group. Correlation between the docking score (values of scoring functions) and compound affinity expressed as IC_{50} was examined and compared with the corresponding correlation for *trans*-resveratrol and 7,8-benzoflavone, known as a very potent CYP1A2 inhibitors. Applicability of 12 scoring functions for inhibitor affinity estimation was also assessed.



Visual representation of the CYP1A2 binding cavity with ten top scored poses of the 3,5-dimethoxy-4'-methylthio-*trans*-stilbene (hem molecule at the bottom; DS 2.0, LigandFit procedure).

[1] Mikstacka R., Baer-Dubowska W., Wieczorek M., Sobiak S.: Thiomethylstilbenes as inhibitors of CYP1A1, CYP1A2 and CYP1B1 activities. *Mol. Nutr. Food Res. 2007, 52, 77-83.*

This study was supported by grant from the University of Medical Sciences in Poznań, 501-01-3313427-08295 (ZD). Discovery Studio calculations were performed at Poznań Supercomputind and Networking Center.

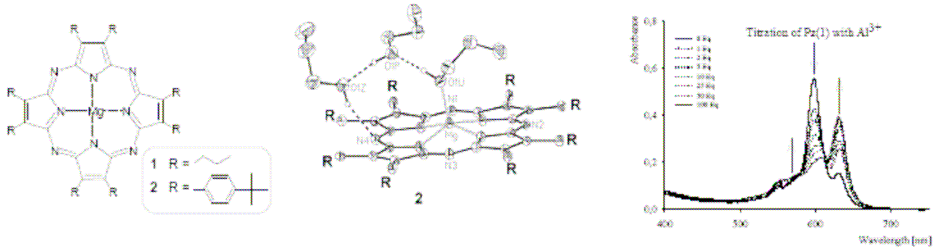
P-6

Peripherally Modified Porphyrazines as Spectroscopic Chemosensors for Aluminium Ions.

Tomasz Gośliński [a], *Ewa Tykarska* [a], *Michał Krajewski* [a], *Tomasz Osmałek* [b], *Jadwiga Mielcarek* [b], *Maria Gdaniec* [c], *Zbigniew Dutkiewicz* [a], *Stanisław Sobiak* [a]

[a] *Department of Chemical Technology of Drugs,* [b] *Department of Inorganic and Analytical Chemistry, Faculty of Pharmacy, University of Medical Sciences,*
[c] *Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań*
e-mail: tgoslin@ump.edu.pl

Quantitative detection of aluminum is of great interest due to its adverse health effects, such as neurotoxicity, amyotrophic lateral sclerosis, Alzheimer's disease, its possible role in Parkinson's disease in elders. De detecting of Al^{3+} has always been problematic due to its ph-dependence in aqueous solution and poor coordination ability comparing to transition metals. Porphyrazines are compounds regarded as porphyrin analogues. They have many medical and technical applications, especially in photodynamic therapy and diagnosis, as gas and metal sensors, molecular semiconductors and non-linear optical materials.



Porphyrazines bearing propyl (**1**) and *tert*-buthylphenyl (**2**) groups in the periphery and Mg(II) in the core were titrated with a wide range of mono-, di- and tri-valent cations: Na(I), K(I), Ag(I), Ca(II), Mg(II), Cu(II), Zn(II), Co(II), Mn(II), Pd(II), Al(III), Ru(III). The UV-vis spectroscopy was employed to evaluate the ability of poprphyrazines to coordinate metal cations. It turned out that addition of Al^{3+} and Pd^{2+} to the solution of poprphyrazine **1** and **2** leads to explicit changes in the shape of the UV-vis spectrum. In case of poprhyrazine **1** fading of absorption intensity in the range of 580-620 nm with simultaneous increase of 550-580 nm and 620-660 nm bands was observed. Such phenomenon can be explained by strong ability of the nitrogen-*meso* atoms in porphyrazine ring to coordinate these ions. However, no optical changes were observed during the titration of the complexes with Na^{+}, K^{+}, Ag^{+}, Ca^{2+}, Mg^{2+}, Cu^{2+}, Co^{2+}, Mn^{2+} and Ru^{3+}.

Some electronic properties of both poprphyrazines were calculated using density functional theory (DFT) methods. All calculations were performed at the B3LYP/6-31G(d,p) level. For the D_2 **1** and D_4 **2** symmetry energy-minimized structures obtained in the first step, the electrostatic potential (MEP) and MEP derived charges were calculated. Results of the normal mode analyses showed that computed IR frequencies are in good agreement with the experimental ones.

X-Ray structural characterization of **2**, revealed that the C_8N_8 poprphyrazine core is planar to within 0.088(1) Å and the magnesium center adopt slightly distorted square pyramidal geometry, in which the metal atom is displaced out of the N_4 coordination plane toward the apical 1-propanol oxygen atom by 0.4204(9) Å. Three connected by hydrogen bond solvent molecules (1-propanol) were found over the porphyrazine core from which the first one is coordinated to magnesium atom and the last one is attached by the hydrogen bond to the *meso* nitrogen (N4). The eight *tert*-buthylphenyl substituents are arranged in propeller-like architecture with six bladed oriented in the same way in three units. The two blades of the fourth unit are rotated in the opposite direction to make *meso* nitrogen open for the hydrogen bonding from the third solvent molecule.

This study was supported by grants from the University of Medical Sciences in Poznań, 501-01-3313427-08870 (TG) i 501-01-3313427-08891 (ET).

P-7

Lipophilicty and Antioxidative Activity of Some β-Carboline Derivatives.

Renata Francik, Elżbieta Kępczyńska, Halina Winnicka, Maria Czarnecka, Marek Cegła

Department of Organic Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków
e-mail: mfrfranc@cyf-kr.edu.pl

Compounds containing a carboline ring system belong to a large family of biological active indoles which are very important to the function of the central nervous system [1]. The investigated β-carboline derivatives were synthesized in our department due to elucidate their activity as 5-HT_{1A} and 5-HT_{2A} receptor ligands. The paper shows results of investigations of lipophilicity and pro/-antyoxidative activity of some β-carboline derivatives [2].
Lipophilicity is a predominant descriptor of pharmacodynamic, pharmacokinetic and toxic aspects of drug activity [3]. The lipophilicity was estimated by the method of planar chromatography on reversed phases. The chromatographic data were determined on the aluminium sheets covered with modified silica gel RP-18 F_{254s} (Merck). Buffer (pH 9.5) – methanol mixtures were applied as mobile phases. The lipophilicity was also estimated theoretically by computing the values of logarithm of partition coefficient (log P) and correlating them with chromatographic parameter R_{M0}.
One of the conditions of the homeostasis state is the balance between the rate of producing reactive oxygen species (ROS) and the antioxidant system activity. Analysis of antioxidative capacity as indication of oxidative stress of β-carboline based on ability of derivatives to scavenge free radicals by DPPH test (*free radical scavenging activity test)*. The outcome was compared to pattern substances like vitamin C, trolox, quercetin, curcumin. Based on the research it was admitted that derivatives of β-carbolins shows weak antioxidative activity.

[1] Saxton J. E.; *The Chemistry of Heterocyclic Compounds*.; A Wiley-Interscience Publication, New York, 1994.
[2] Schlesier K. , Harwat M., Bohm V., Bitsch R.; Assessment of Antioxidant Activity by Using Different In Vitro Methods. *Free Radical Research 2002, 36 (2), 177–187.*
[3] Mannhold R. (Ed). *Molecular Drug Properties. Measurement and Prediction*. Wiley-VCH: Weinheim, 2008.

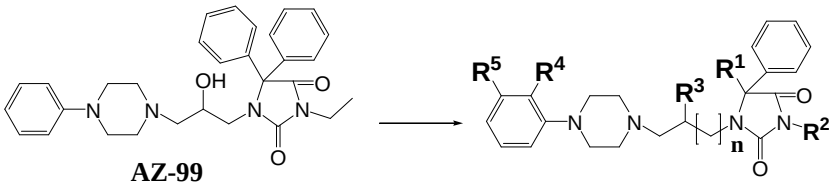
P-8

Synthesis, SAR-study and Drugability Prediction for Phenylpiperazine Derivatives of Hydantoin with Affinity for α_1-Adrenoceptors.

Jadwiga Handzlik, Magdalena Jastrzębska, Małgorzata Dybała, Agata Siwek, Barbara Filipek, Katarzyna Kieć-Kononowicz

Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków
e-mail: jhandzli@cm-uj.krakow.pl

The α_1-adrenoceptors are involved in many important physiological functions resulting from their SNS- and CNS-activity. Recent studies have marked the increasing role for α_1-AR in arrhythmias mechanism, especially in the case of ischemic arrhythmia [1]. In this context, the search for cardioselective α_1-adrenoceptor antagonists is an important topic in medicinal chemistry. Analysis of a number of chemical structures of selective α_1-adrenoceptor antagonists indicates that a presence of arylpiperazine moieties is distinctly profitable for α_1-adrenoceptor affinity [2]. Our previous studies allowed to define the lead structure, compound **AZ-99**, for a search for new α_1-adrenoceptor antagonists with potential antiarrhythmic activity among phenylpiperazine derivatives of hydantoin [3,4]. In the present work, further modifications of the lead have been performed. The investigations, including synthesis, receptor affinity evaluation, drugability prediction and SAR-study, were carried out for twelve compounds. The modifications of lead (**Fig. 1**) were focused on four important areas (hydantoin positions 5 (R^1) and 3 (R^2), alkyl chain (R^3, n), phenylpiperazine phenyl ring (R^4,R^5)). The new compounds were obtained in four different synthesis ways.



R^1= Ph, CH_3
R^2 = H, CH_3
R^3 = H, OH
R^4 = H, CH_3O, Cl
R^5 = H, CH_3O, Cl
n = 1,2

The affinity for α_1-adrenoceptors were evaluated in radioligand binding assays using [^{3}H]-prazosin as a selective radioligand. The antagonistic properties at α_1-adrenoceptors were assessed in functional bioassays. Compounds were evaluated on their drugability in respect to Lipinski's- and Ghose's rules and their BBB-permission were theoretically investigated, too. The key parameters were calculated using several computer programs (Pallas, Chemaxon). The obtained results showed the best pharmacological properties for 5-phenyl-5-methylhydantoin derivative possessing 2-methoxyphenylpiperazine moiety.

The work was partly supported by grants: K/ZBW/000209 and 501/G/519.

[1] Bremner J. H., Coban B., Griffith R., Groenewoud K. M., Yates B. F.: *Bioorg. Med. Chem. 2000, 8, 201*.

[2] Kurz T., Schneider I., Tolg R., Richardt G.: *Cardiovasc. Res. 1999, 42, 48-56.*

[3] Dyląg T., Zygmunt M., Maciąg D., Handzlik J., Bednarski M., Filipek B., Kieć-Kononowicz K.: *Eur. J. Med. Chem*. 2004, *39, 1013.*

[4] Handzlik J., Maciąg D., Kubacka M., Mogilski S., Filipek B., Kieć-Kononowicz K.: *Bioorg. Med. Chem*., 2008, *16, 5982-5998.*

P-9

Designing of New Potential Acetylcholinesterase Inhibitors Based on Computer Modeling Elements.

Paweł Szymański, Agnieszka Janik, Elżbieta Mikiciuk-Olasik

Department Pharmaceutical Chemistry and Drug Analyses, Faculty of Pharmacy, Medical University, Muszyńskiego 1, 90-151 Łódź
e-mail: agajanik_24@o2.pl

Alzheimer's disease is the most often occurring ailment among dementia syndromes. It is a progressing neurodegenerative illness, incurable at the current state of the medical knowledge. A considerable decrease in cholinergic neurotransmission associated with the loss of neurons in some parts of the brain has been found in this disorder. Therapy of Alzheimer's disease involves only alleviation of symptoms. At present, acetylcholinesterase inhibitors are the only group of drugs applied in treatment. The aim of the study was to work out new derivatives of acetylcholinesterase inhibitors that would be used in therapy and/or diagnostics of the Alzheimer's disease.
The study comprised the analysis of literature data, the results of which were applied in molecular modeling computation. On the basis of the gathered information, the series of acetylcholinesterase inhibitors were designed. The selected structures are the derivatives of the aromatic-heterocyclic system substituted by primary and secondary arylaliphatic amines. These structures contain pharmacofore groups, which occur in currently used drugs. Next, the synthesis of chosen compounds and the method of their cleaning were worked out. Identification of the chosen derivatives was confirmed with NMR, IR, MS and MS- HR analyses.
Activity of synthetized derivatives was measured with colorimetric method (Ellman's method), which depends on measurement of absorbance of yellowish solutions. The analysis was conducted by using two enzymes; butyryl and acetylcholinesterase. Iodide butyryl and acetylthiocholine were applied as a substratum for enzymatic reactions. On the basis of the obtained results, the selectivity of the chosen derivatives in relation to individual enzymes and the activity of new connections in comparison to the pattern of tacrine were determined.

Acknowledgements:
The autors thanks Medical University of Lodz for financial support of this work (Grant No 502-13-625)

P-10

Involvement of Opioid Receptors in the Antinociceptive Activity of the New Derivatives of 1-Aryl-2-iminoimidazolidine in the Writhing Test in Mice.

Ewa Kędzierska [a], *Sylwia Fidecka* [a], *Dariusz Matosiuk* [b]

[a] *Department of Pharmacology and Pharmacodynamics,*
[b] *Department of Synthesis and Chemical Technology of Pharmaceutical Substances, Faculty of Pharmacy, Medical University, Staszica 4/6, 20-081 Lublin*
e-mail: epirogowicz@poczta.onet.pl

Seven new derivatives of 1-aryl-2-iminoimidazolidine, named DM-1, DM-6, DM12, DM13, ZT-12, ZT-30 and ZT-31 have been synthesized and evaluated for antinociceptive properties using the writhing test and the hot-plate in mice [1-3]
In this study, the antinociceptive effect of the new compounds and their interactions with various opioid receptor subtypes were evaluated. The strong antinociceptive activity of the compounds was observed in the writhing test in mice. Compounds induced an antinociceptive effect following s.c. administration and this effect was significantly inhibited by naloxone, an opioid receptor antagonist, suggesting some connections with endogenous opioid system. Moreover binding assays were performed showing moderate affinity (on the micromolar level) of the compounds toward opioid receptors [1-3]. So, in this study, the effect of opioid selective antagonists was examined as to their ability to block observed antinociception.
In most cases the antinociceptive effect of the compounds was significantly inhibited by cyprodime (selective μ-opioid receptor antagonist) and naltrindole (selective δ-opioid receptor antagonist), but not by nor-binaltorphimine (selective κ -opioid receptor antagonist), implying the involvement of μ and δ-, but not κ-opioid receptors. When the compounds tested were injected together with morphine – an opioid agonist, they significantly potentiated (except DM-13 and ZT-31 compound) antinociception induced by morphine.
Together, these data suggest, that the antinociceptive effect of some of the compounds under study is mainly influenced by the μ and δ-, but not κ-opioid receptor mechanism.

[1] Matosiuk D., Fidecka S., Antkiewicz-Michaluk L., Dybała I., Kozioł A.E.: *Eur. J. Med. Chem. 2001, 36, 783-797.*
[2] Matosiuk D., Fidecka S., Antkiewicz-Michaluk L., Lipkowski J., Dybała I., Kozioł A.E.: *Eur. J. Med. Chem. 2002, 37, 761-772.*
[3] Matosiuk D., Fidecka S., Antkiewicz-Michaluk L., Dybała I., Kozioł A.E.: *Eur. J. Med. Chem. 2002, 37, 845-853.*

P-11

Synthesis and Lipophilicity Determination of Some Derivatives of a Natural Triterpene Betulin.

Elżbieta Kępczyńska [a], *Jacek Achrem-Achremowicz* [b], *Marek Żylewski* [a]

[a] *Department of Organic Chemistry,* [b] *Department of Pharmacognosy, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków*
e-mail: mfepotoc@cyf-kr.edu.pl

Betulin, or lup-20(29)-en-3,28-diol, is a natural triterpene compound found in large amounts in the bark of white birch trees. The triterpene and its derivatives display many biological activities which are reported in recent literature. These are: antiinflammatory, antiviral (HIV-1), hepatoprotective, etc. One of the major features, however, is the selective cytotoxicity of lupane derivatives to many human cancer cell lines. This is why lupane derivatives have become lead structures in many cancer reserches.

For the exact structure—activity—relationship (SAR) studies lipophilicity is one of the most often used parameters, as the predominant descriptor of pharmacodynamic, pharmacokinetic, and cytotoxic aspects of a drug activity.

Most of the reported synthesized betulin derivatives are highly hydrophobic which limits the number of methods used for their lipophilicity measurement. In this study we applied reversed-phase thin-layer chromatography (RP-TLC) using 1,4-dioxane—acetate buffer mixtures as mobile phase for a series of prepared semisynthetic betulin derivatives. Cholesterol was used as a reference compound in this specific case of steroid-like structures.

Linear relationship was found between R_M values and 1,4-dioxane concentrations in the mobile phase. The retention parameters (R_{M0}) were related to computed partition coefficients (logP), calculated by means of theoretical procedures with Pallas 3.2.1.4 (CompuDrug Chemistry Ltd. 1994, 95) and ACD/LogP DB (ChemSketch 10.0, Advanced Chemistry Development, Inc.) programs.

P-12

Lipophilic Derivatives of Glucosamine-6-phosphate Synthase Inhibitors.

Dominik Koszel, Ryszard Andruszkiewicz

Department of Pharmaceutical Technology and Biochemistry, Gdańsk University of Technology, 80-952 Gdańsk, Poland
e-mail: merlin16@op.pl

Glucosamine-6-phosphate synthase (GlcN-6-P) plays a key role in the biosynthesis of glucosamine-containing microbial cell wall structures: lipopolisaccharides, peptidoglycan and chitin. Inactivation of GlcN-6-P synthase in fungal cells induces morphological changes, agglutination and lysis while in mammals temporary depletion of enzyme activity is acceptable, due to slow turnover of macromolecules containing aminosugers [1]. Therefore, GlcN-6-P is considered to be a target for potential antimicrobial drugs.

There are many potent and selective inhibitors of GlcN-6-P. One of the most strong and specific inhibitor is N^3-(4-methoxy-fumaroyl)-L-2,3-diaminopropanoic acid (FMDP). FMDP is non-peptide amino acid and it is poorly transported by amino acid permeases into the cells. Consequently FMDP exhibits relatively poor anticandidal activity.

In order to overcome this problem we have synthesized latent and lipophilic derivatives of FMDP, which could be transported into cells by diffusion [2]. That kind of approach is called ‘pro-drug’ strategy and it is very common in the penicillin group [3]. Recently, using ‘pro-drug’ approach we synthesized latent and lipophilic derivatives of FMDP with different structures and lipophilic properties. Those analogues of FMDP penetrate the fungal cell membrane by free diffusion and then are rapidly hydrolysed by cytoplasmic enzymes to release free FMDP.

[1] Milewski S.: *Biochim. Biophys. Acta* 2002, *1597, 173-192.*
[2] Zgódka D., Milewski S., Borowski E.: *Microbiology* 2001, *147, 1955-1959.*
[3] Daehne v. W., Frederiksen E., Gundersen E., Lunch F., Morch P., Petersen H, J., Roholt K., Tybring L., Dodtfredsen W. O.: *J. Med. Chem*. 1970, *13, 607-612.*

P-13

Molecular Modeling of Interactions Between Selected Ligands and the Torpedo Model of Nicotinic Acetylcholine Receptor.

Joanna Kozak [a], Katarzyna Targowska [a], Anita Płazińska [a], Hugo Arias [b], Krzysztof Jóźwiak [a]

[a] Laboratory of Drug-Receptor Interactions, Department of Analytical Chemistry, Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin
[b] Department of Pharmaceutical Sciences, College of Pharmacy, Midwestern University, Glendale, Arizona, USA
e-mail: joanna.kozak@am.lublin.pl

Nicotinic acetylcholine receptors are promising targets for its allosteric modulators in the treatment of such disorders as cognition deficits, nicotine addiction, depression or schizophrenia. Most of these ligands interact with the inner surface of the ion channel and disturb the flux of ions through the channel during the receptor open state.

In our investigations we used the molecular model of the nAChR obtained from the electric organ of *Torpedo marmorata* (2BG9.pdb) for simulations of molecular interactions between the ion channel of the receptor and several allosteric channel blockers. Docking of the flexible ligand into the rigid model of the receptor was performed, which was followed by extensive molecular dynamics simulation of obtained ligand – receptor complex. The simulations allowed to assess the energy of interaction and specific mechanism of the ligand interaction with particular residues.

Analysis of the results indicates that the ligand stably interact with the inner surface of the channel formed by 5 M2 transmembrane helices. The binding site is predominantly located between the serine ring and the valine ring within the channel. And ligands interact evenly with M2 residues contributed by each subunit. The binding energy estimated in MD simulations for such compounds as imipramine, bupropion and phencyclidine (PCP) can be related to experimental values determined in radiolabeled ligand displacement.

The *Torpedo* version of the nAChR shows high level of amino acid homology with mammalian receptors including human neuronal nAChR. We build homologous models of nAChR originated from other species and subject them to the same simulations in order to determine species specific and subtype specific aspects of ligand binding.

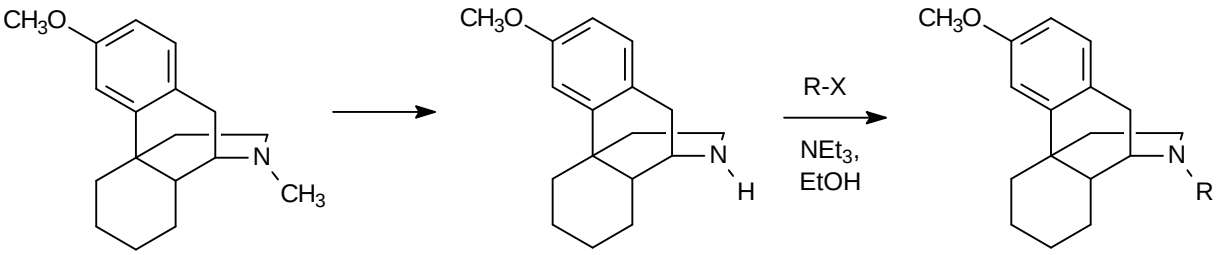
P-14

Synthesis of N-alkyl Derivatives of Dextromethorphan.

Agnieszka Ligęza [a], *Dariusz Matosiuk* [a], *Krzysztof Jóźwiak* [b]

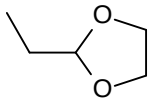
[a] *Department of Synthesis and Chemical Technology of Pharmaceutical Substances,*
[b] *Laboratory of Drug-Receptor Interactions, Department of Analytical Chemistry,*
Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin
e-mail: agnieszka.ligenza@am.lublin.pl

New derivatives of dextromethorphan had been synthesized as potential, noncompetitive antagonists of nicotinic receptor. The derivatives were synthesized from nordextromethorphan, resulting from N-demethylation of dextromethorphan with 2,2,2-trichloroethyl chloroformate. Next, dextromethorphan was alkylated with respective alkyl halides. Final alkyl derivatives were isolated as salts (hydrochlorides or hydrobromides). Some of the compounds investigated exhibited activity similar or higher than dextromethorphan.



X = Cl, Br;

R = -CH_2-CH_2-OH;
R = -CH_2-CH_2-CH_2-OH;
R = -CH_2-CO-NH_2;
R = -CH_2-CN;
R = -CH_2-CH_2-CN;
R = -CH_2-CH_2-CH_2-CN;

R = 

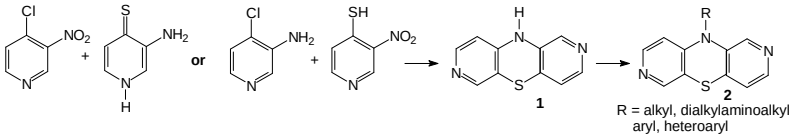
P-15

Recent Syntheses and Properties of Novel Azaphenothiazines.

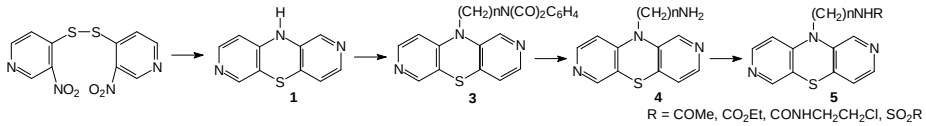
Beata Morak-Młodawska, Małgorzata Jeleń, Krystian Pluta

Department of Organic Chemistry, School of Pharmacy, Medical University of Silesia, Jagiellonska 4, Sosnowiec
e-mail: bmlodawska@sum.edu.pl

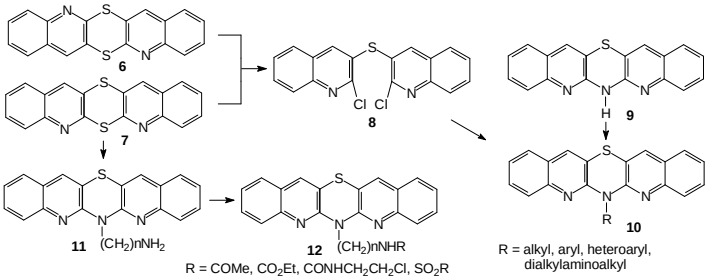
Phenothiazines are the oldest and the largest group of neuroleptic drugs. They exhibit valuable antiemetic, antihistaminic and antitussive properties. There have appeared numerous articles for last ten years on new biological properties of phenothiazines, among them anticancer and multidrug resistance activity [1,2]. Chemical modification of the phenothiazine structure was carried out by replacing the benzene ring with the azine ring and by introduction of new substituents in position 10. In continuation of our search for pharmacoactive pyridine and quinoline derivatives we modified the phenothiazine structure to form new type of the linear tri- and pentacyclic azaphenothiazines. Recently we described the synthesis of novel 2,7-diazaphenothiazines **1** and **2** in the reactions of disubstituted pyridines followed by N-alkylation [1,2].



This time we discuss reaction of 3,3'-dinitro-4,4'-dipyridinyl disulfide with sodium hydroxide in DMF to give thiazine **1** which was further alkylated to give phthalimidoalkyl derivatives **3** and hydrolysed to aminoalkyl derivatives **4**. The last compounds were transformed into acyl and sulfonyl derivatives **5**.



Reactions of the 1,4-dithiin ring opening in diquinodithiins **6** and **7** led to sulfide **8** which underwent annulation reactions with divalent reagents (acetamide, aliphatic, aromatic and heteroaromatic amines) to 6H- and 6-substituted diquino-1,4-thiazines **9** and **10**, being dibenzo-1,9-diazaphenothiazines [3,4]. Reactions of the 1,4-dithiin ring opening in diquinodithiin **7** with diaminoalkanes led to aminoalkyldiquinothiazines **11** which were further transformed into acyl and sulfonyl derivatives **12** [5].



We calculated and determined experimentally (using *RP-TLC*) lipophilic parameters for these compounds [6,7]. Some selected diazaphenothiazines exhibited *in vitro* promising anticancer activity, determined in National Cancer Institute in Bethesda in USA in *Development Therapeutics Program.*

[1] Morak B., Pluta K., Suwińska K.: *Heterocyclic Commun. 2002, 8, 331.* [2] Morak B., Pluta K.: *Heterocycles,2007, 71,1347.* [3] Nowak M., Pluta K., Suwińska K.: *New J. Chem. 2002, 26, 1216*. [4] Nowak M., Pluta K., Suwińska K., Straver L.: *J. Heterocycl. Chem*. *2007, 44, 543*. [5] Jeleń M., Pluta K.: *Heterocycles 2008, 73,*. [6] Morak B., Nowak M., Pluta K.: *J. Liq. Chromatogr. & Rel. Technol. 2007, 30, 1845*. [7] Morak-Młodawska B., Pluta K.: *J. Liq. Chromatogr. & Rel. Technol.* 2008, 31, 611.

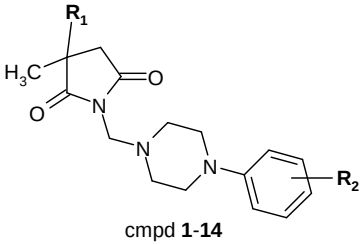
P-16

Synthesis and Physicochemical and Anticonvulsant Properties of New N-[(4-Arylpiperazin-1-yl)-methyl]-3,3-dialkyl-pyrrolidine-2,5-diones.

Jolanta Obniska, Krzysztof Kamiński, Alicja Orman

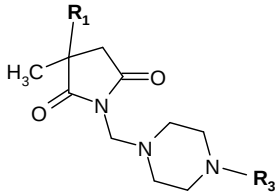
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków
e-mail: mfobnisk@cyf-kr.edu.pl

Previous studies from our laboratory have demonstrated the potent anticonvulsant activity among the 3-aryl-pyrrolidine-2,5-diones with differently substituted piperazine, piperidine or morpholine moieties at the imide nitrogen atom. The most active were compounds with the methylene spacer (Mannich bases), which revealed the anti-seizure protection especially in the maximal electroshock test (MES). Following these results, as part of our efforts to design new anticonvulsant agents which would be active both in MES and subcutaneous metrazole tests (*sc*Met) and according to the foregoing effective in different types of seizures, in the present study we have synthesized a library of analogues with two methyl or one methyl and ethyl substituents at the 3-position of the succinimide ring. This modification approximate the designed molecules to the structure of ethosuximide (3-ethyl-3-methyl-pyrrolidine-2,5-dione), the antiepileptic drug which is active in *sc*Met screen (**Fig**. **1**).

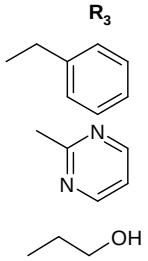


cmpd **1**-**14**

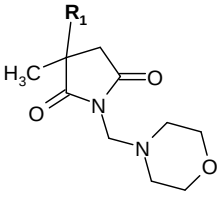
R$_2$ = H, 2-F, 4-F, 2-Cl, 3-Cl, 4-Cl, 3-CF_3



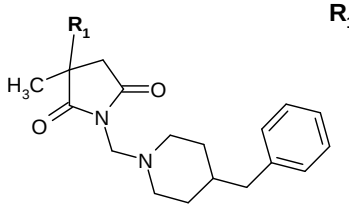
cmpd **15**-**20**



R$_1$ = CH_3, C_2H_5



cmpd **21**-**22**



cmpd **23**-**24**

All the compounds synthesized were pharmacologically pre-evaluated within the Antiepileptic Drug Development (ADD) Program, Epilepsy Branch, Neurological Disorders Program, National Institute of the Neurological and Communicative Disorders and Stroke (NINCDS), Bethesda, using procedures described elsewhere.

P-17

Binding of Fenoterol Derivatives and Stereoisomers of Fenoterol to the β_2-Adrenergic Receptor. A Molecular Modeling Study.

Anita Plazinska, Krzysztof Jozwiak, Joanna Kozak

Laboratory of Drug-Receptor Interactions, Department of Analitycal Chemistry, Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin
e-mail: anita.plazinska@am.lublin.pl

Molecular modeling is very attractive and promising tool used by chemists to predict structure and properties of chiral compounds, while some mathematical models are assumed. In particular, it can be applied to molecular drug design where enantioselectivity plays a crucial role. Binding of the stereoisomers of fenoterol and fenoterol derivatives to the β2 adrenergic receptor has been analyzed. The binding of 26 agonists (fenoterol and its derivatives) has been studied using comparative molecular field analysis (CoMFA). Results indicate that several electrostatic and steric fields exist on the pseudoreceptor and are responsible for binding of tested ligands. Docking analysis has also been performed using determined binding zones and the template ligand TA2005. Both CoMFA and docking analysis demonstrate that (R,R) stereoisomers have generally higher affinities relative to their (R,S), (S,R) and (S,S) stereoisomers.

P-18

Heterocyclic Phosphonates as Potential Therapeutics in Parkinson's Disease Therapy.

Monika Prokopowicz, Piotr Młynarz, Paweł Kafarski

Department of Bioorganic Chemistry, Faculty of Chemistry, Wroclaw Technical University, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław
e-mail: monika.prokopowicz@pwr.wroc.pl

Parkinson's disease is characterized by a loss of dopamine producing neurons. Main path of therapy is based on natural precursor of dopamine – L-DOPA administration with combination of aromatic acid decarboxylase and monoaminooxydase inhibitors.
Unfortunately, in these conditions, only a small amount of L-DOPA reaches a target receptor in the brain, because of catechol-O-methyltransferase (COMT) activity. Thus, COMT inhibition is a required approach in parkinsonism treatment. The inhibitors prolong the effectiveness of a dose of L-DOPA by preventing its breakdown. They help to provide a more stable, constant supply of L-DOPA, which makes its beneficial effects lasting longer. The inhibitors increase "on" time and decrease "off" time, reduce motor fluctuations caused by the wearing-off effect of L-DOPA and improve motor function and the ability to do daily activities.
Currently applied in standard therapy COMT inhibitors possess several shortcomings such as low potency, necessity of application of high doses and toxicity. So, there is an urgent therapeutic need to discover new catechol-O-methyltransferase inhibitors.
Using molecular modeling tools we stated that phosphonic acids based on indol, benzothiazol and other heterocycles could be good potential enzyme inhibitors. We proved that theoretically hydroxyl groups in phosphonic unit good be as good pharmacophors as hydroxyls in nitrocatechol-based inhibitors used in therapy.
We also made an effort to assess the ability of modeled structures to inhibit COMT activity. The enzyme assay was based on UV/VIS spectroscopy with 3,4-dihydroxyacetophenone or phosphonic analogue of DOPA used as substrates.
Obtained results suggested that heterocyclic phosphonates could be theoretically new, potent class of catechol-O-methyltransferase inhibitors.

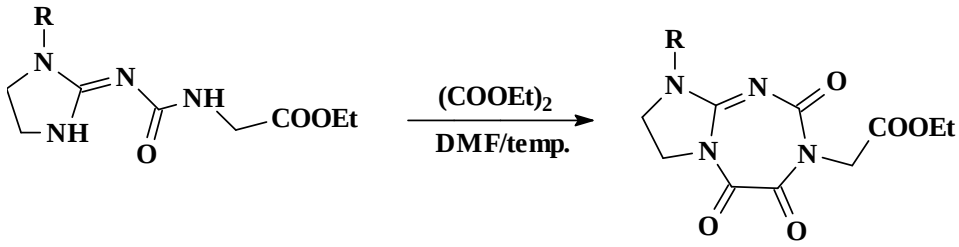
P-19

Synthesis of New Imidazo[1,2-a][1,3,5]triazepines.

Marzena Rządkowska, Elżbieta Szacoń, Dariusz Matosiuk

Department of Synthesis and Chemical Technology of Pharmaceutical Substances, Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin
e-mail: ela.szacon@am.lublin.pl

The aminocarbonyl derivatives of 1-aryl-2-imidazolidine-2 have significant antinociceptive activity connected with activation of the MOP (mu opioid peptide) receptor [1-3].
The synthetic derivatives of triazepine form also a various and important group of medicine.
In the search for new derivatives with potential pharmacological activity we obtained group of new imidazo[1,2-a][1,3,5]triazepines.
New 1-aryl-7-etoxykarbonylomethylo-5,6,8(1H)-dioxo-2,3-dihydroimidazo[1,2-a][1,3,5]triazepines were synthesized in reaction of 1-(1-arylimidazolidine-2-ylidene)-3-ethylocarbonylurea with diethyl oxalate.



R = C_6H_5, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$, 3-Cl- C_6H_4, 4-Cl- C_6H_4,

The structure of all new compounds was confirmed by elemental analysis, as well as by the ^{1}H NMR.

[1] Matosiuk D., Fidecka S., Antkiewicz-Michaluk L., Dybała I., Kozioł A. E.: *Eur. J. Med.. Chem. 2001, 36, 783.*
[2] Matosiuk D., Fidecka S., Antkiewicz-Michaluk L., Lipkowski J., Dybała I., Kozioł A. E.: *Eur. J. Med.. Chem. 2002, 37, 761.*
[3] Sztanke K., Fidecka S., Kędzierska E., Karczmarzyk Z., Pihlaja K., Matosiuk D.: *Eur. J. Med. Chem. 2002, 45, 127.*

P-20

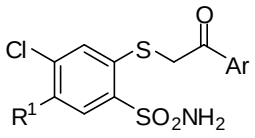
Carbonic Anhydrase Inhibitors.

Franciszek Sączewski [a], Zdzisław Brzozowski [a], Jarosław Sławiński [a], Anita Kornicka [a], Elżbieta Pomarnacka [a], Alessio Innocenti [b], Andrea Scozzafava [b], Claudia Temperini [b], Claudiu T. Supuran [b]

[a] Department of Chemical Technology of Drugs, Faculty of Pharmacy, Medical University, Al. Gen. J. Hallera 107, 80-416 Gdańsk
[b] Dipartimento di Chimica, Universita degli Studi di Firenze, Italy
e-mail: saczew@farmacja.amg.gda.pl

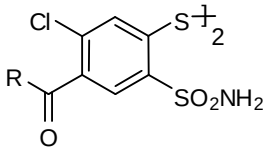
Carbonic anhydrases (CA, EC 4.2.1.1), also known as carbonate dehydratases, are metallo-enzymes present in both prokaryotes and eukaryotes. Thus far 16 different □-carbonic anhydrase isoforms have been isolated in mammals, 13 of which possess catalytic activity for the reversible hydration of carbon dioxide to bicarbonate. These enzymes are responsible for acid-base homeostasis, secretion of electrolytes, transport of ions, biosynthetic reactions and tumourigenesis, and therefore, they are suitable targets for the drug design. Pharmacological applications of CA activators include the treatment of Alzheimer's disease, ageing and other conditions in which spatial learning and memory has to be enhanced. On the other hand, inhibitors of different isoforms of CA are potential drugs for glaucoma, obesity, osteoporosis and cancer.

It is well known that certain aryl- and heteroaryl-sulfonamides such as dichlorphenamide, acetazolamide, mathazolamide or ethoxzolamide inhibit tumor-associated isozymes CA IX and CA XII [1]. Therefore, our continuing interest in the synthesis of the potential anticancer agents prompted us to synthesize two series of benzenesulfonamides (**I**) and aryldisulfides (**II**) for biological tests[2-4].



R = H, alkyl
R^1 = H, CH_3, COOH

benzenesulfonamides **I**



R = alkyl, alkoxyl, aminoalkyl

aryldisulfides **II**

We found that compounds of type **I** inhibited cytosolic isozymes CA I and CA II as well as tumor-associated isozymes CA IX and CA XII, while disulfides of general structure **II** proved to be potent and selective inhibitors of CA IX and CA XII activatable in hypoxic tumors.

[1] Supuran C. T.: *Nature Reviews (Drug Discovery) 2008, 7, 1-15.*
[2] Sączewski F., Innocenti A., Brzozowski Z., Sławiński J., Pomarnacka E., Kornicka A., Scozzafava A., Supuran C. T.: *J. Enz. Inhibit. Med. Chem*. 2006, *21, 563-568.*
[3] Saczewski F., Sławiński J., Kornicka A., Brzozowski Z.. Pomarnacka E., Innocenti A., Scozzafava A., Supuran C. T.: *Bioorg. Med. Chem. Lett*. 2006, *16, 4846-4851.*
[4] Saczewski F., Innocenti A., Sławiński J., Kornicka A., Brzozowski Z., Pomarnacka E., Scozzafava A., Supuran C. T.: *Bioorg. Med. Chem*. 2008, *16, 3933-3940.*

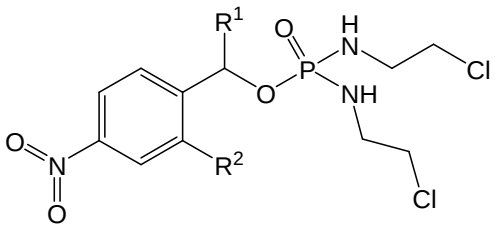
P-21

Nitrobenzyl Isophosphoramide Mustard Analogues as Prodrugs for GDEPT.

Krzysztof Skowerski, Konrad Misiura

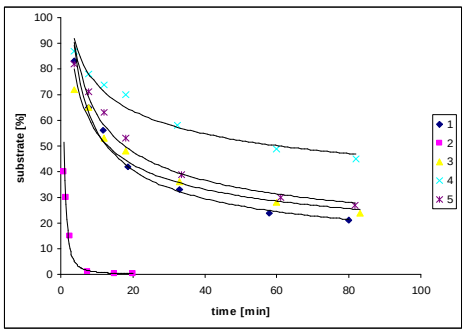
Department of Chemical Technology of Pharmaceuticals, Faculty of Pharmacy, Collegium Medicum NCU, M. Sklodowskiej-Curie 9, 85-094 Bydgoszcz
e-mail:

Gene–Directed Enzyme Prodrug Therapy (GDEPT) is an anticancer therapy, consist of three components: the prodrug to be activated, the enzyme to activate – usually non human, and the delivery system for the corresponding gene. After activation prodrug should be able to release cytotoxin, but only in cells transfected with the gene of the appropriate enzyme. High selectivity is the most important factor required in GDEPT. A several prodrug–enzyme systems were developed for GDEPT, among which the nitroaromatic prodrugs–nitroreductase system seems to be one of the most attractive. *E. coli* nitroreductase reduce nitroaromatic group to corresponding hydroxylamine or to amine with large electronic effect. Dramatic change in electron distribution in the prodrug can be exploited to ensure that one of the possible metabolites is potent cytotoxin [1].
Our research were based on the employment of isophosphoramide mustard, an active metabolite of ifosfamide, widely used anticancer drug [2]. A series of *p*–nitrobenzyl phosphoramide mustard (**1** – **5**), potent anticancer prodrugs for GDEPT, were synthesized and activated using *E. coli* nitroreductase.



Nr	R^1	R^2
1	H	H
2	H	Cl
3	H	OMe
4	Me	H
5	CH_2Br	H

All analogues were stable in phosphate buffer pH 7,0 and 37 ºC for 120 hours and undergo reductive activation in the presence of nitroreductase. The halflives of **1** – **5** were in the range of 1 to 60 min and, as was expected, an analog **2** was the best substrate for *E. coli* nitroreductase. The results of activation process are presented in figure below.



This research was supported by Nicolaus Copernicus University, Rector Grant, 1/CM.

[1] Denny W. A.: *Curr. Pharm. Design 2002, 8, 1349-1361.*
[2] Misiura K.: *Mini-Rev. Med. Chem. 2006, 6, 325-400.*

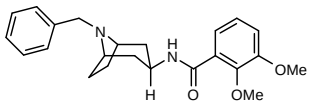
P-22

Synthesis of 1-Phenylpiperazine Derivatives of 3β-Aminotropane with Potential Antipsychotic Activity.

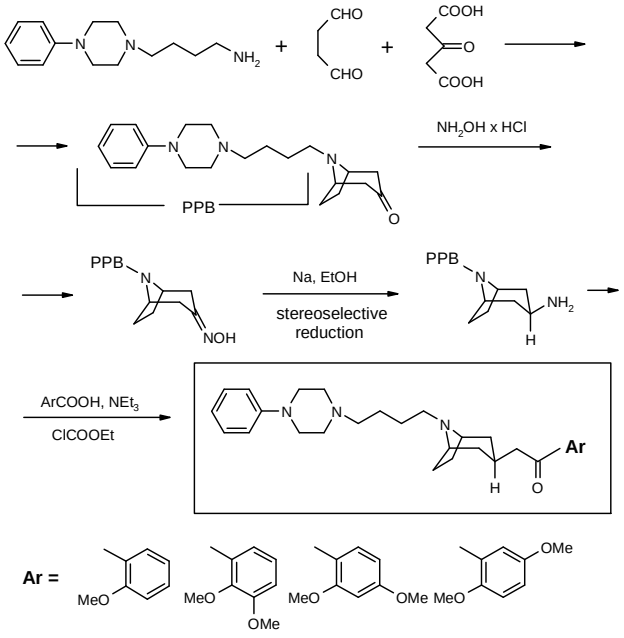
Jacek Stefanowicz , Damian Siepietowski, Tomasz Słowiński, Franciszek Herold

Department of Drug Technology, Faculty of Pharmacy, Medical University, Banacha 1a, 02-097 Warszawa
e-mail:

A lot of N-arylpiperazine derivatives are ligands of serotonin and dopamine receptors [1-3]. Some of them are active as anxiolytics (Buspirone), antidepressants (Nephazodone) and antipsychotics (Ziprasidrone, Aripirazole). The aim of our work was to introduce 4-(4-phenylpiperazin-1-yl)butyl (PPB) substituent to Tropapride molecule. Tropapride is an antagonist of postsinaptic dopamine D_2 receptor [4]. This modification may give compounds which could be ligands of dopamine and serotonin receptors as atypical antipsychotic drugs.



Tropapride



The structure of new molecules was confirmed by elemental analysis IR , ^{1}H and ^{13}C-NMR spectra.

[1] Tomić M., et al.: *Bioorg. Med. Chem. 2004, 14, 4263-4266.*
[2] Hackling A., et al.: *J. Med. Chem. 2003, 46, 3883-3889.*
[3] Herold F., et al.: *Eur. J. Med. Chem. 2006, 41, 125-134.*
[4] Jalfre M., et al.: *Arch. Int. Pharmacodyn. Ther, 1983, 264, 232-256.*

P-23

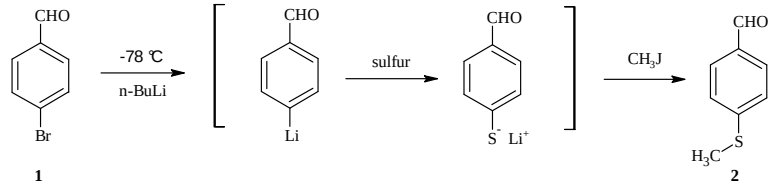
Synthesis of Methoxy- and Methylthiostilbene Derivatives.

Tomasz Stefański, Stanisław Sobiak

Department of Chemical Technology of Drugs, Faculty of Pharmacy, University of Medical Sciences, Grunwaldzka 6, 60-780 Poznań
e-mail: farmakolog@wp.pl

Numerous synthetic methods have been used for the preparation of stilbene derivatives so far. Among them Wittig reaction has been one of the most useful with their versatility and high optimization possibilities. The aim of our study was to find efficient and possible most simple methods for the synthesis of wide range stilbene derivatives.
Optimization of the whole process starting with the phosphonium salt synthesis through modification of the Wittig reaction in aqueous solution and under unconventional conditions by using microwave irradiation methods has been made possible to prepare effective methods of the stilbene derivative synthesis.
Moreover we used a convenient one-pot synthetic method for the formation of methyl phenyl sulfides from the corresponding aryl bromides in the presence of n-BuLi, sulfur and methyl iodide which is a interesting technique compared with classical methods required much more reagents (**scheme 1**).

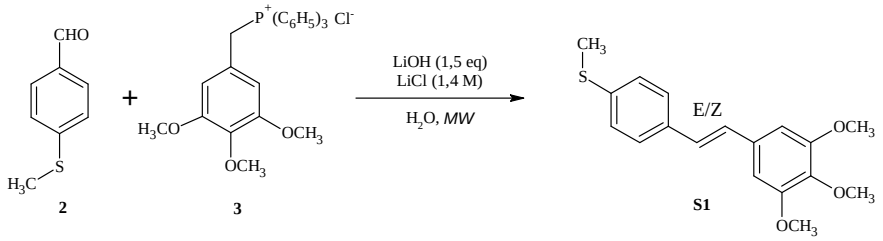
Scheme 1. Preparation of 4-methylthiobenzaldehyde (2) from 4-bromobenzaldehyde (1)



1 **2**

That was the starting point for the preparation of methylthiostilbene derivatives (**scheme 2**).

Scheme 2. Preparation of (E/Z)-4'-methylthio-3,4,5-trimethoxystilbene (S1) from 4-methylthiobenzaldehyde (2) and 3,4,5-trimethoxybenzyltriphenylphosphonium chloride (3)



2 **3** **S1**

It seems that this technique made be a good way to obtain both (E)- and (Z)-stilbene derivatives.

P-24

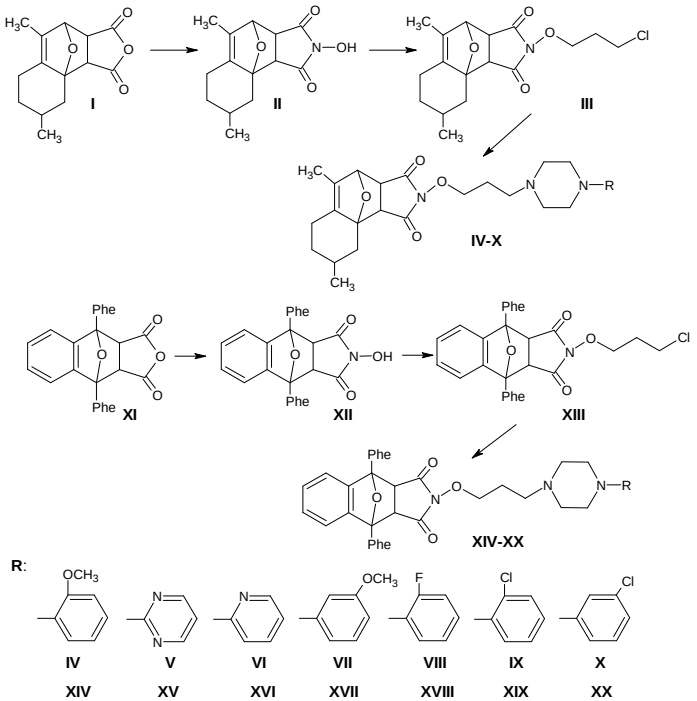
Synthesis of New N-Substituted Derivatives of 2-Hydroxy-4,9-diphenyl-4,9-epoxy-3a,4,9,9a-tetrahydro-1*H*-benzo[f]isoindole-1,3(2*H*)-dione and 2-Hydroxy-5,8-dimethyl-3b,9-epoxy-3a,4,5,6,7,8,9,9a-octahydro-1*H*-benzo[e]isoindole-1,3(2*H*)-dione with an Expected Anxiolytic Activity.

Jerzy Kossakowski, Bożena Kuran, Mariola Krawiecka

Department of Medical Chemistry, Faculty of Medicine,
Medical University, Oczki 3, 02-007 Warsaw
e-mail: bozena.kuran@wum.edu.pl

The aim of the present study is the synthesis of new LCAPs derivatives with an expected anxiolytic activity. This work is a continuation of our previous studies in searching for compounds with anxiolytic and antidepressant activity.

The starting compounds were 3,6-dimethyl-4,5,6,7-tetrahydrobenzo[b]furan and 1,3-diphenylisobenzofuran which were heated with maleic anhydride in Diels-Alder reaction. The obtained anhydride (**I**, **XI**) were converted to N-hydroxy derivatives with using of a hydroxylamine solution. The obtained products (**II**, **XII**) were reacted in acetonitrile in the presence of anhydrous K_2CO_3 and KI with 1-bromo-3-chloropropane to give propoxy derivatives (**III, XIII**). Finally, the resulting N-substituted derivatives were condensed with appropriate aryl-/heteroarylpiperazinylamines in acetone, in the presence of anhydrous K_2CO_3 and KI as well. All new piperazinyl derivatives (Scheme) were converted into their corresponding hydrochlorides. The structures of the all compounds obtained were confirmed by ^{1}H NMR and ESI MS.



P-25

Synthesis of New 2-Aminobezimidazole Derivatives with an Expected Antimicrobial Activity.

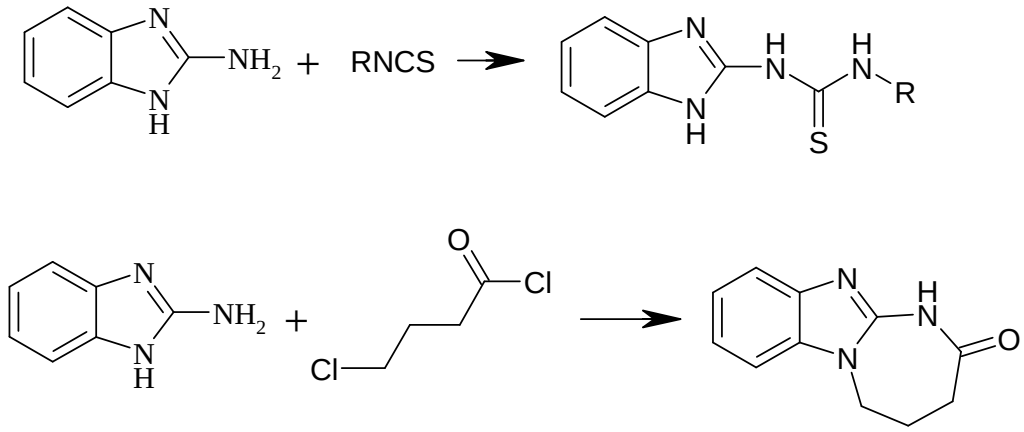
Marta Struga, Jerzy Kossakowski

Department of Medical Chemistry, Faculty of Medicine,
Medical University Oczki 3, 02-007 Warsaw
e-mail: marta.struga@wum.edu.pl.

The rapid emergence of multidrug resistant pathogenic bacteria has become a serious health treat worldwide. It has been postulated that the development of resistance to known antibiotics could be overcome by identifying new drug targets via genomics, improving existing antibiotics and by identifying new antibacterial agents with novel structures and modes of action [1]. A survey of the existing literature indicated that there were reports, which described the use of 2-aminobenzimidazole derivatives as antibacterial agents [2].

Synthesis of new derivatives was started by reaction of 2-aminobenzamidazole with isotiocyanetes. In this reaction thiourea derivatives were obtained. The second route of synthesis was cyclization 2-aminobenzimidazole with 4-chlorobutyryl chloride to 4,5-dihydro-1*H*-[1,3]diazepino[1,2-*a*]benzimidazol-2(3*H*)-one. All final compounds were characterized by ^{1}H NMR spectra which corresponded with the proposed structures.

The general synthetic pathway is given in Scheme.



[1] Walsh C.: *Nature 2000, 406, 775.*
[2] Seth P. P., Jefferson A., Risen L. M., Osgood S. A.: *Bioorg. Med. Chem. Lett. 2003, 13, 1669.*

P-26

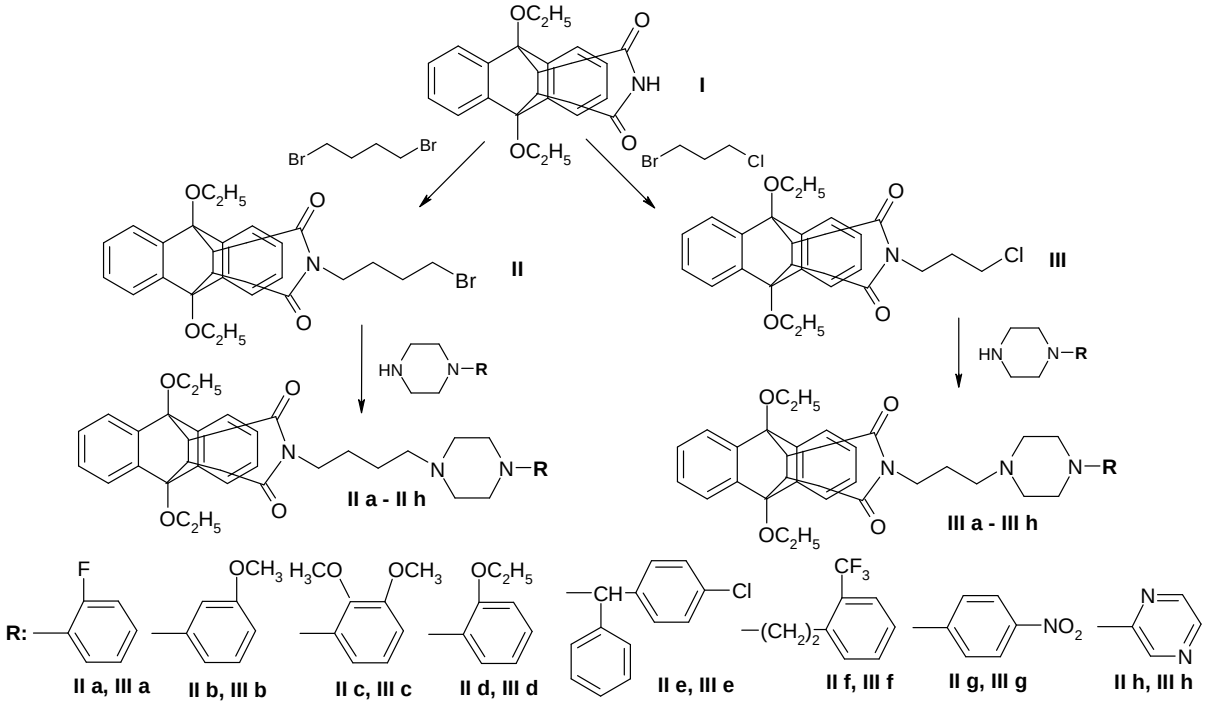
Synthesis of Some N-Substituted Derivatives of 1,8-Dietoxy-17-azapentacyclo[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadec-2,4,6,9,11,13-hexaen-16,18-dione with a Potential Pharmacological Activity.

Jerzy Kossakowski, Magdalena Pakosińska-Parys

Department of Medical Chemistry, Medical University of Warsaw,
3 Oczki Street, 02-007 Warsaw, Poland
e-mail: mparys@wp.pl

It is known that most anxiolytics and hypnotic-sedative drugs such as benzodiazepines and barbiturates exert their pharmacological actions *via* interactions with a discrete neuronal site on the $GABA_A$ receptor. Suriclone and zopiclone are examples of non benzodiazepine structures binding to this receptor and acting as agonists. Non-benzodiazepine anxiolytics have also been developed that appear to act by modulating the serotonergic, histaminergic and non-aminergic systems. It prompted us to continue our search for potential anxiolytics within arylpiperazine derivatives of **II** and **III**, analogues of suriclone. Synthesized compounds posses an alkyl-(*N*-aryl) substituted piperazine moiety, that is the pharmacophore of 5-HT_{1A} receptor and is believed to give high potency in the treatment of anxiety and depression.

The structure of all derivatives of compounds **II** and **III** has been established on the basis of elemental analysis or MS and ^{1}H NMR spectra. The activities of the synthesized compounds were evaluated for their cytotoxicity and anti-HIV-1 activity in MT-4 cells.



P-27

Synthesis of New N-Substituted Aminoalkanol and Aminoalkyl Derivatives of 1,7,8,9-Tetrachloro-10,10-dimethoxy-4-azatricyclo-[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione as Potential β-Adrenolytic and/or Psychotropic Drugs.

Jerzy Kossakowski, Magdalena Pakosińska-Parys

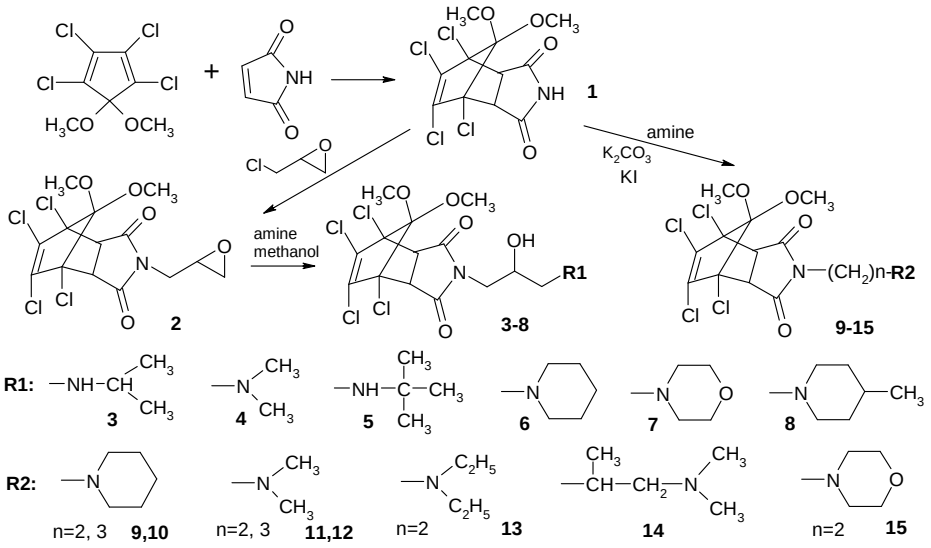
Department of Medical Chemistry, Faculty of Medicine,
Medical University of Warsaw, Oczki 3, 02-007 Warsaw
e-mail: mparys@wp.pl

Antipsychotics are a group of drugs that are used to treat a handful of psychiatric disorders characterized by disturbed thought and behaviour, most notably schizophrenia. Although they are not curative, they relieve some of the debilitating symptoms of this group of disorders. They are indicated clinically for patients with both acute and chronic schizophrenic symptoms.

It is also known that for typical antipsychotics (e.g. chlorpromazine, acepromazine, dibenzepin, diethazine, clomipramine) a 2-carbon or 3-carbon alkyl connection between a heterocyclic ring and a terminal aminoalkyl or piperidine part is optimal for dopamine-receptor blockade and antipsychotics activity.

Unfortunately, the therapeutic effects of classical neuroleptics frequently come with severe extrapyramidal side effects, therefore new drugs are still requested. Searching for compounds with predictable neuroleptic activity, as a continuation of our previous investigations, our attention was focused on amino derivatives of 1,7,8,9-tetrachloro-10,10-dimethoxy-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-3,5-dione.

ß-adrenoreceptor antagonists, like propranolol, befunolol and pindolol, contain 2-hydroxypropyl group that corresponds with their antiarrhytmic and hypotensive activity. Considering that, we designed and synthesized derivatives with an expected pharmacological activity. The activities of the synthesized compounds were evaluated for their cytotoxicity and anti-HIV-1 activity in MT-4 cells. The structure of all derivatives have been established on the basis of elemental analysis or MS and ^{1}HNMR.



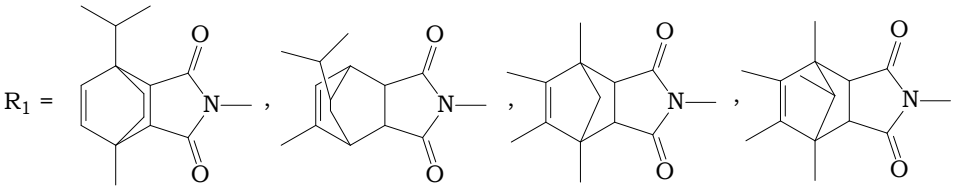
P-28

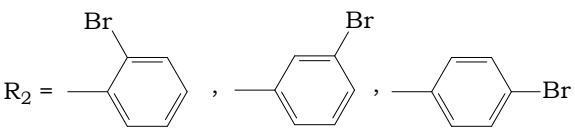
Synthesis of New Thiourea Derivatives of Tricyclic Imides with an Expected Antimicrobial Activity.

Marta Struga [a], *Jerzy Kossakowski* [a], *Joanna Stefańska* [b], *Martyna Kulas* [c]

[a] *Department of Medical Chemistry, Faculty of Medicine,*
e-mail: marta.struga@wum.edu.pl
[b] *Department of Pharmaceutical Microbiology,* [c] *Student Scientific Society at Department of Pharmaceutical Microbiology, Faculty of Pharmacy,*
Medical University, Oczki 3, 02-007 Warsaw
e-mail: joanna.stefanska@wum.edu.pl

Thourea and urea derivatives show a broad spectrum of biological activities as anti-HIV, antiviral, HDL-elevating, antibacterial, anaglesic properties. Numerous compounds containing thiourea group are selective ligands for 5-HT family receptors, including 5-$HT_{2A,}$ 5-HT_{2B} and 5-HT_{2C}.
The preparation of new nine thiourea derivatives of tricyclic imide (Scheme) is described.
Imides obtained in Diels-Alder reaction were used as starting materials and reacted with hydrazine (80% aqueous solution). Afterwards the compounds were subjected to the reaction with phenyl, 4-bromophenyl, 3-bromophenyl and 2-bromophenyl isothiocyanate to be transformed into the corresponding urea or thiourea derivatives.
All final compounds were characterized by ^{1}H NMR spectra which corresponded with the proposed structures.
The general synthetic pathway is given in Scheme.
All newly synthesized compounds were tested for their antibacterial and antifungal activities. Gram-negative and Gram-positive bacterial strains and *Candida albicans* used in this study, have common application in the antimicrobial activity tests for many substances like antibiotics, disinfections and antiseptic drugs or in research on new antimicrobial agent. Part of tested compounds was active using disc diffusion method against Gram-negative bacterial strains and *Candida albicans*
.





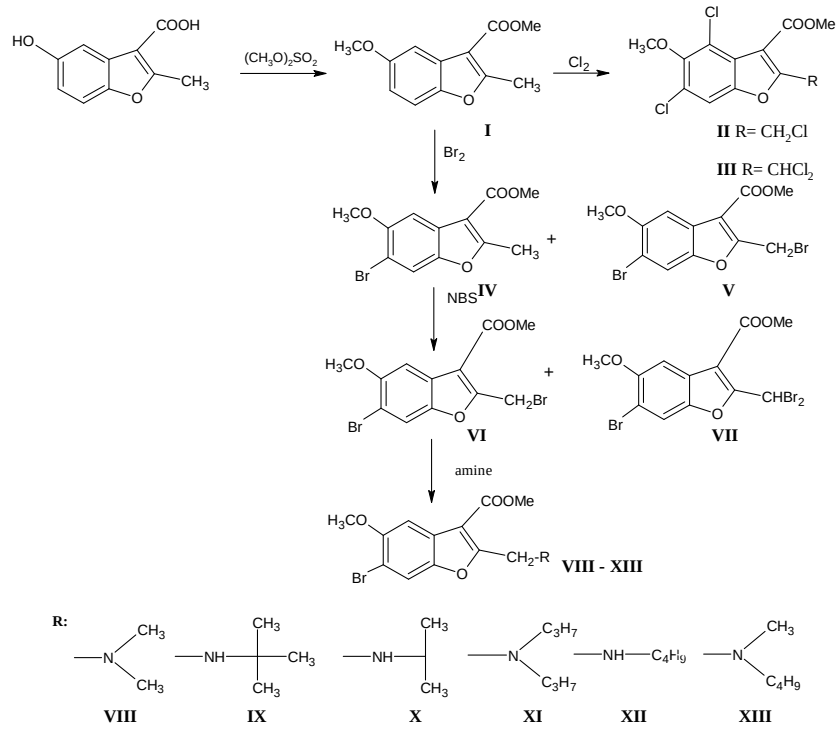
P-29

Synthesis of New Derivatives of 5-Methoxy-2-methyl-benzo[b]furan-3-carboxylic Acid with an Expected Biological Activity.

Jerzy Kossakowski [a], Mariola Krawiecka [a], Bożena Kuran [a], Irena Wolska [b]

[a] Department of Medical Chemistry, Faculty of Medicine, Medical University of Warsaw, Oczki 3, 02-007 Warsaw
[b] Department of Crystallography, Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań
e-mail: mariola.krawiecka@wum.edu.pl

It is widely know that a lot of compounds with the benzo[b]furan system show biological activity[1-2]. Inspired by these we designed and synthesized new derivatives of 5-methoxy-2-methyl-benzo[b]furan-3-carboxylic acid (Scheme) in order to find new compounds with biological activity.
The starting compound was 5-methoxy-2-methyl-benzo[b]furan-3-carboxylic acid which in the reaction with $(CH_3)_2SO_2$ gave compound (**I**) used for further reactions. Next in the reaction with Br_2 or Cl_2 halogeno derivatives (**II**-**V**) were obtained. The obtained 6-bromo-5-methoxy-2-methyl-benzo[b]furan-3-carboxylic acid methyl esther (**IV**) was reacted with NBS to give two derivatives (**VI**) and (**VII**). Finally, compound (**VI**) obtained with high yield was condensed with appropriate amines (Scheme). The structures of new derivatives were established by elemental analysis and ^{1}H NMR spectra.
In order to confirm the structures of compounds (**I**) and (**IV**) the X-ray crystallographic structure were solved.



[1] Kodama I., Kamiya K., Toyama J.: *Am. J. Cardiol. 1999, 84, 20R-28R.*
[2] Sun W., Sarma J.S.M, Singh B.N.: *Circulation* 1999, *100, 2276-2281.*

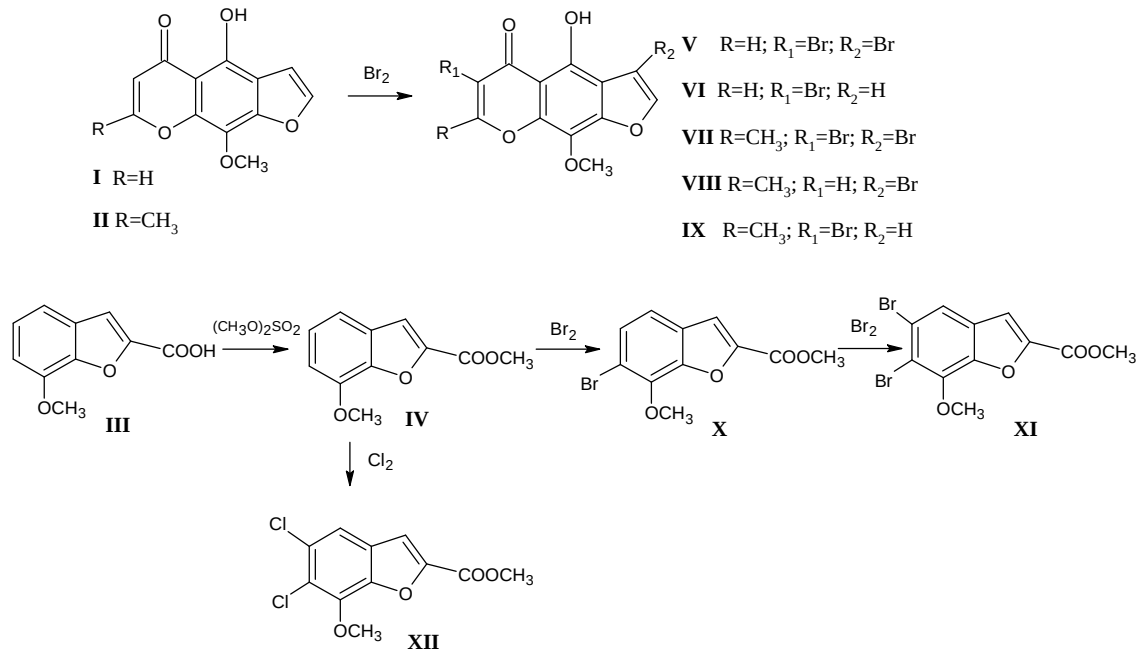
P-30

Synthesis of Halogen Derivatives of Selected Furobenzopiran-4-one and Benzo[b]furan-2-carboxylic Acid with an Expected Biological Activity.

Jerzy Kossakowski, Mariola Krawiecka, Bożena Kuran

Department of Medical Chemistry, Faculty of Medicine,
Medical University, Oczki 3, 02-007 Warsaw
e-mail: mariola.krawiecka@wum.edu.pl

Well-known derivatives of furobenzopirane and benzofuran show high biological activity. This work is a continuation of our studies in searching for compounds with an expected biological activity (1-3).
The starting compounds were 4-hydroxy-9-methoxy-5H-furo[3,2g]chromen-5-one (**I**), 4-hydroxy-9-methoxy-7-methyl-5H-furo[3,2g]chromen-5-one (**II**) and 7-methoxybenzo[b]furan-2-carboxylic acid (**III**) (Scheme). Compound **III** in the reaction with $(CH_3O)_2SO_2$ gave compound **IV** used for further reactions. Next in the reaction of compounds **I**, **II** and derivative **III** with Br_2 or Cl_2 halogeno derivatives (**V-XII**) were obtained (Scheme). The structures of the derivatives were established by elemental analysis and ^{1}H NMR spectra.



[1] Samochowiec L., Kadłubowska D., Bohdziewicz J., Wójcicki J., Zawadowski T,: *Pol. J. Pharmacol. Pharm. 1978, 30, 767.*
[2] Kossakowski J., Zawadowski T.: *Acta. Polon. Phar. 1987, 5, 400.*
[3] Kossakowski J.: *Pol. J. Chem. 1984, 52, 157.*

P-31

A Phytochemical Studies of *Heracleum dissectum* Ledeb. Aboveground Parts.

Katarzyna Targowska–Duda [a], *Anita Płazińska* [a], *Magdalena Bartnik* [b]

[a] *Laboratory of Drug-Receptor Interactions, Department of Analytical Chemistry, Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin*
[b] *Department of Pharmacognosy, Faculty of Pharmacy, Medical University, Chodźki 1, 20-093 Lublin*
e-mail: katarzyna.targowska@gmail.com

Plants belonging to the *Heracleum* Ledeb. (*Apiacae*) family are the rich source of coumarin compounds. These compounds are widely used in therapeutics but unfortunately, they also can cause phytodermatoses. It seems to result in lesser interesting in searching the other groups of active compounds in biological materials originating from these species. *Heracleum dissectum* Ledeb. Which can be found in east Asia countries is often used as a fodder or utilitarian plant. It is a vegetable which, when added to food, improves digestion and reveals diastolic properties. Only young, aboveground parts of this plant are used in these purposes. The aim of the performed study was to perform a phytochemical analysis of the plant material originating from the Ulaanbaatar region in Mongolia. The research was performed by using the adsorption liquid chromatography method (TLC, HPLC). Of particular interest was the group of secondary metabolites which can be taken into account as biologically active compounds, i.e. phenolic acids, phenolic compounds and substances included in essential oils.

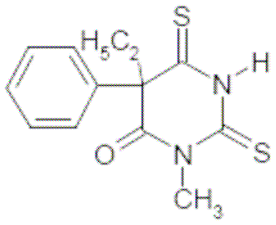
P-32

Investigation of the N-methyl-2,4-dithiophenobarbital Stability, as a Function of pH and Temperature.

Monika Tarsa, Grzegorz Żuchowski

Department of Organic Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków
e-mail: mftarsa@cyf-kr.edu.pl

The topic is a continuation of former investigations carried on in Department of Organic Chemistry CM UJ [1-7]. The subject is N-methyl-2,5-dithiophenobarbital.



This compounds was synthesized by direct sulphurization of N-methylbarbital with Lawesson reagent [4].

The concept of compound stability is connected to elucidation to rate of its change during storage in proper conditions. The rate of degradation depends on external conditions like temperature, light, pH and chemical properties of substance. Kinetics of degradation process of N-methyl-2,4-dithiophenobarbital was carried on by UV-spectrometry after checking usability of Lambert-Beer law in ethanol and buffer (pH=9) solutions.

Investigations were carried on in buffer solutions (pH 3-12), temperature 40^0C. Starting concentration of N-methyl-2,4-dithiophenobarbitalo was 4 x 10^{-5} M. Absorbance was measured at λmax. Kinetic investigations covered elucidation of reaction order, rate constant k, pKa, activation energy Ea.

Obtained results were compared to phenobarbital, 2-thiophenobarbital and 2,4-dithiophenobarbital [5,6]. On that basis one can assume that N-methyl-2,4-dithiophenobarbital is less stable than phenobarbital and 2-thiophenobarbital but more stable than 2,4-dithiophenobarbital.

[1] Tarsa M., Bojarski J.: *Bull. Pol. Acad. Sci., Chemistry 1997, 45, 63.*
[2] Tarsa M., Żuchowski G., Bojarski J.: *Acta Poln. Pharm. 2003, 60, 247.*
[3] Tarsa M., Żuchowski G., Bojarski J.: *Acta Polon. Pharm. 2003, 60, 253.*
[4] Stasiewicz-Urban A., Kubaszek M., Żylewski M., Cegła M., Bojarski J.: *Pol. J. Chem. 2004, 78, 2105.*
[5] Garret E. R., Bojarski J., Yakatan C. J.: *J. Pharm. Sci. 1971, 60, 1145.*
[6] Tarsa M., Żuchowski G., Bojarski J.: Zastosowanie chromatografii cienkowarstwowej do badania hydrolizy 2,4-ditiofenobarbitalu – poster, Szczyrk, 2005.
[7] Żuchowski G., Tarsa M., Stasiewicz-Urban A., Bojarski J.: *Acta Polon. Pharm. 2005, 62, 355.*

P-33

Implementation of Thin Layer Chromatography for Investigations of N-Methyl-2,4-dithiophenobarbital Hydrolyses.

Monika Tarsa, Grzegorz Żuchowski

Department of Organic Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków
e-mail: mftarsa@cyf-kr.edu.pl

The concept of compound stability is connected to elucidation to rate of its change during storage in proper conditions. The rate of degradation depends on external conditions like temperature, light, pH and chemical properties of substance. Continuing studies on stability of barbiturates [1-6] N-methyl-2,4-dithiophenobarbital was investigated. The aim was to obtain the way of degradation. Initial analyses was carried on by TLC. For this purpose the solution containing 1% of N-methyl-2,4-dithiophenobarbital in buffer pH=10 was made. This solution was immersed in oil bath at 60^0C and after defined amount of time samples of 5 µL were acquired and applied on TLC plates.
Plates were developed using: cyclohexane : ethyl acetate (2:1 vv), chloroform : ethyl acetate (1:1 vv), chloroform : hexane (2:1 vv), hexane : ethanol : triethylamine (7:1:1 vv) eluents. Spots were visualized using UV light. In the next stage of investigations, products of hydrolyses were separated and identified. Obtained results show that in the first stage of degradation ring decomposition occurs yielding malonuric acid derivative. Simultaneously desulphurization reaction is running, which gives N-methyl-2-thiophenobarbital. After that during decarboxylation process, ureid appears, which after breaking C-N bond yields N-methyl-2-thiourea.

[1] Tarsa M., Bojarski J.: *Bull. Pol. Acad. Sci., Chemistry 1997, 45, 63.*
[2] Tarsa M., Żuchowski G., Bojarski J.: *Acta Poln. Pharm. 2003, 60, 247.*
[3] Tarsa M., Żuchowski G., Bojarski J.: *Acta Polon. Pharm. 2003, 60, 253.*
[4] Stasiewicz-Urban A., Kubaszek M., Żylewski M., Cegła M., Bojarski J.: *Pol. J. Chem. 2004, 78, 2105.*
[5] Tarsa M., Żuchowski G., Bojarski J.: Zastosowanie chromatografii cienkowarstwowej do badania hydrolizy 2,4-ditiofenobarbitalu – poster, Szczyrk, 2005.
[6] Żuchowski G., Tarsa M., Stasiewicz-Urban A., Bojarski J.: *Acta Polon. Pharm. 2005, 62, 355.*

P-34

Synthesis and Antitumor Activity of N-substituted Amides of 3-(3-Ethylothio-1,2,4-triazol-5-yl)propenoic Acid.

Anna Pachuta-Stec [a], Jolanta Rzymowska [b], Monika Wujec [a], Monika Pitucha [a]

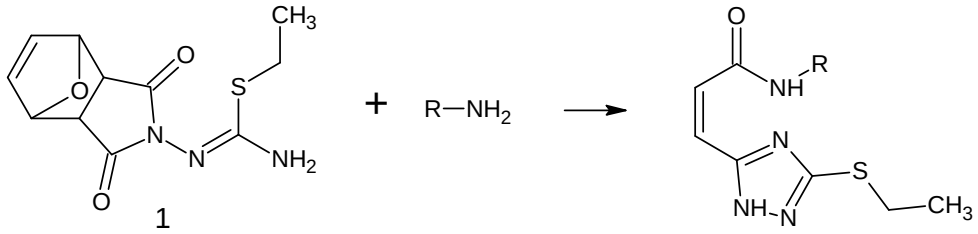
[a] Departament of Organic Chemistry,
[b] Department of Biology and Genetics,
Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin
e-mail:

Derivatives of 1,2,4-triazole show a wide range of pharmacological activities. Many of them possess antifungal, antimicrobial, anti-inflammatory, anticonvulsant and antitumor activity. Vorozole, Letrozole and Anastrozole having triazole moieties are very effective nonsteroidal aromatase inhibitors. They are useful for preventing breast cancer.

We present here synthesis and testing results of possible anticancer activity of N-substituted amides of 3-(3-ethylothio-1,2,4-triazol-5-yl) propenoic acid **2-4**.

These compounds were prepared by heating S-ethyl-7-oxabicyclo-[2.2.1]-hept-5-ene-2,3-dicarbonyl isothiosemicarbazide **1** with primary amines in glacial acetic acid.

Compounds **2-4** were evaluated for their antyproliferative and anticancer activity in two human cell lines derived from breast and lung –A549 human epithelial lung cancer cells (ECACC 86012804) and T47D – human epithelial breast cancer cells (ECACC 85102201). One normal cell line was included in the cytotoxicity study – primary cell line of human skin fibroblasts (HSF).



R= 4-BrC_6H_4 , 2-ClC_6H_4 , 3-$CH_3C_6H_4$

P-35

Synthesis and Antibacterial Activity of 4-Substituted-3-nitromethyl-1,2,4-triazoline-5-thione Derivatives.

Nazar Trotsko [a], Maria Dobosz [a], Urszula Kosikowska [b], Jakub Król [a], Monika Pitucha [a], Monika Wujec [a], Anna Malm [b]

[a] Department of Organic Chemistry, Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin
[b] Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Medical University, Chodźki 1, 20-093 Lublin
e-mail: nazar.trotsko@umlub.pl

Depending of the nature of substitutents, the 1,2,4-triazole derivatives can show various biological activity, such as analgesic, anti-inflammatory, anti-cancer, antibacterial and virusostatic action.
These derivatives can be synthesized by the cyclization of thiosemicarbazide derivatives in alkaline medium. By the reaction of hydrazide of nitroacetic acid with appropriate isothiocyanate thiosemicarbazide derivatives were obtained, which were cyclized to 1,2,4-triazoline derivatives in alkaline medium. Structure of new compounds was confirmed by elemental analysis and IR, ^{1}H NMR spectra. New derivatives were investigated for their antimicrobial activity.
Antimicrobial activity tests were carried out against the reference strains of bacteria (*S. aureus* ATCC 25923, *S. aureus* ATCC 6538, *S. epidermidis* ATCC 12220, *B. subtilis* ATCC 6633, *B. cereus* ATCC 10876, *M. luteus* ATCC 10240, *E. coli* ATCC 25922, *K. pneumoniae* ATCC 13883, *P. mirabilis* ATCC 12453 and *P. aeruginosa* ATCC 9027) and fungi (*C. albicans* ATCC 10231, *C. albicans* ATCC 2091, *C. parapsilosis* ATCC 22019). The agar well diffusion method was used to determine *in vitro* antimicrobial activity of tested compounds. The results of the qualitative screening were presented as the average diameter of the growth inhibition zone surrounding the well containing the test compound at 5000 mg/L concentration. The best antibacterial activity had 3-nitromethyl-4-phenyl-1,2,4-triazoline-5-thione and 4-(4-methoxyphenyl)-3-nitromethyl-1,2,4-triazoline-5-thione against reference strains belonging to *Staphylococcus* or *Bacillus* species and N-phenyl thiosemicarbazide of nitroacetic acid, 3-nitromethyl-4-phenyl-1,2,4-triazoline-5-thione or 4-(4-methoxyphenyl)-3-nitromethyl-1,2,4-triazoline-5-thione against *M. luteus* ATCC 10240. None of the tested compounds had influence on the growth of reference strains of Gram-negative bacteria or fungi.

P-36

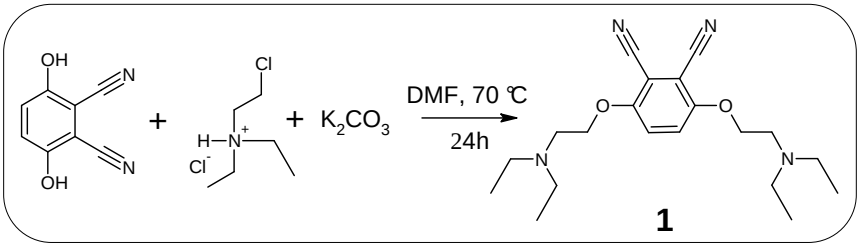
Synthesis and Molecular Modeling Study on Cationic Phthalocyanines Derived from 3,6-bis[2-(Dimethylamino)-ethoxy]benzene-1,2-dicarbonitrile.

Marcin Wierzchowski, Tomasz Gośliński, Stanisław Sobiak

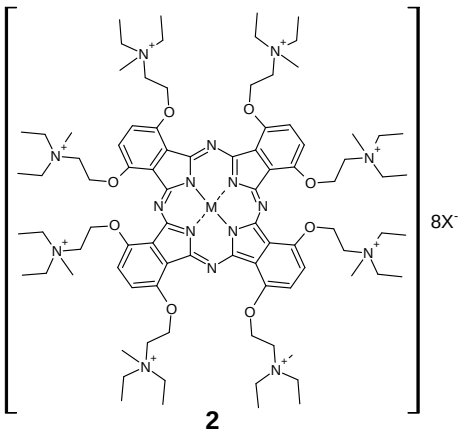
Department of Chemical Technology of Drugs, Faculty of Pharmacy, University of Medical Sciences, Grunwaldzka 6, 60-780 Poznań
e-mail: mwierzch@ump.edu.pl

Photodynamic therapy (PDT) and photodynamic antimicrobial chemotherapy (PACT) constitute alternative successful approaches to both cancer and antibiotic therapy including bacterial, viral, protozoal infections and psoriasis. In order to perform photodynamic therapy three essential elements are necessary: special source of light, oxygen and photosensitizer. The transfer of energy from the activated photosensitizer to available oxygen results in the formation of toxic oxygen species such as singlet oxygen ($^1\Delta_g$) and free radicals causing cell damage. Synthetic dyes, especially phthalocyanines and their derivatives, have been intensively studied due to their applications in nanotechnology as building blocks and in medicinal chemistry as photosensitizers.

Our main goal in this work was to synthesize the starting dinitrile: 3,6-bis[2-(dimethylamino) ethoxy]benzene-1,2-dicarbonitrile (**1**) and examine its usefulness in phthalocyanine synthesis. We have planned to synthesize cationic, soluble in water phthalocyanines bearing various d-block metals in the core. The synthesis of dinitrile was carried out in DMF at 70℃ and under nitrogen using 2-chloro-N,N-diethylamine, 2,3-dicyanohydroquinone in the presence of K_2CO_3 as a base. The structure of the novel dinitrile **1** was confirmed by ^1H, ^{13}C NMR, mass spectra and combustion analysis.



1



2

Next steps include macrocyclization of **1** in basic conditions in the presence of metal salts of general formula MX_2 (M = Cu, Co, Mg, X = Cl, OAc) with following alkylation using iodoethane or iodomethane to obtain octacationic phthalocyanine metal complexes (**2**). Zinc cationic complex of **2** and its non-alkylated precursor were used as representatives for *in silico* calculations. Conformational analysis was performed using Hartree-Fock and Density Functional Theory (functional B3LYP) methods implemented in PCGamess 7.1 program with basis set 6-31G(d,p). The elaborated global minima resulted in structures for which further simulations of Raman and IR spectra were performed. The geometrical and electronic molecular parameters like total energy, orbital energies, HOMO, LUMO, bond orders, dipole moment, chemical hardness and chemical softness were determined.

This study was supported by the grant from the University of Medical Sciences in Poznań № 501-01-3313427-08062 .

[1] Scalise I., Durantini E. N.: *Bioorg. Med. Chem. 2005, 13, 3037-3045.*
[2] Kusanaga K., Hayashi H., Handa M.: *Chem. Lett.1991, 1877-1890.*

P-37

The Attempt to Use NMR Spectroscopy in Observation of Ligand – Micelle Interactions.

Małgorzata Kaleta, Marek Żylewski

NMR Laboratory, Department of Organic Chemistry, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków
e-mail: mfzylews@cyf-kr.edu.pl

The aim of studies was to investigate interaction between insoluble in water molecules and sodium dodecyl sulfate micelles. In this work betulin, and its synthetic derivatives (betulin diacetate, betulin dipropionate, betulin diphthalate) and cholesterol were examined. All these compounds are similar in their chemical constitution.
The studies were made by means of NMR spectroscopy, which is a powerful tool for examining surfactant environment. Apart of chemical structure investigations one can obtain information about molecular dynamics, what is essential for an examination of micelization process and a determination of CMC.
^{1}H NMR spectra of SDS water solution and SDS solution with addition of investigated molecules was aquired. There weren't observed any additional signals of added compounds.
In the next stage of investigation CMC of SDS solution and solution of SDS with analyzed molecules were determined. Chemical shift and spin-lattice relaxation time of two peaks in the proton NMR spectrum of SDS: α CH_2 and the ending CH_3 were measured as well. The results of the chemical shift and relaxation time measurements were plotted versus the reciprocal concentration of SDS.
Obtained results shows that hydrophobic compounds are encapsulated inside SDS micelles, what was impossible to confirm with earlier observation of simple proton NMR spectra.

[1] Zhao J., Fung B. M.: *Langmuir* 1993, *9, 1228-1231.*
[2] Néry H., Söderman O., Canet D., Walderhaug H., Lindman B., Orfi L., Lin M., Larive K. C.: *Anal. Chem, 1998, 70, 1339-1345.*

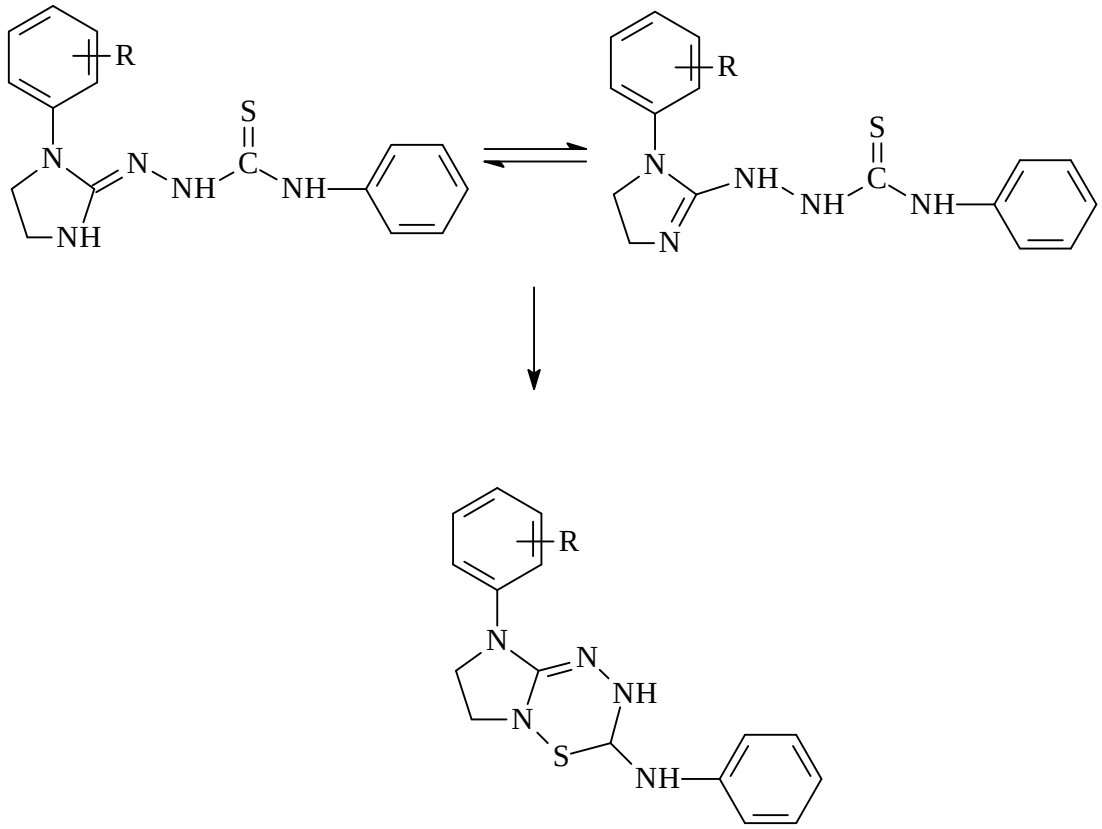
P-38

Synthesis of New Fused Aminoguanidine Derivatives.

Monika Aletańska-Kozak, Dariusz Matosiuk

Department of Synthesis and Chemical Technology of Pharmaceutical Substances
Faculty of Pharmacy, Medical University, Staszica 6, 20-081 Lublin
e-mail: monika.aletanska@am.lublin.pl

In search of new compounds with potential farmacological activity new fused aminoguanidine derivatives were obtained. In order to synthesise derivatives of 1-(1-arylimidazolidyn-2-yliden)-4-phenylthiosemicarbazide (obtained from 1-aryl–2-hydrazinoimidazolines and phenyl isothiocyanate) were cyclized to 6-aryl-6H-2-phenylamine--2,3,7,8-tetrahydroimidazo[2,1-e][1,2,4,5]thiatriazine. Structure of new compounds were described on the basis of spectral analysis.



R= 2,3-diCH_3, 4-Cl, 2,6-diCl

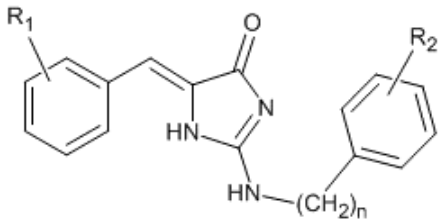
P-39

Antitumor Activity Among 5-Benzylidenehydantoin Derivatives.

Ewa Szymańska, Elżbieta Pękala, Katarzyna Kieć-Kononowicz

Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków
e-mail: mfszyman@cm-uj.krakow.pl

Hydantoin derivatives show a wide range of biological activity. Both natural and synthetic compounds based on imidazolidine-2,4-dione scaffold have been reported to exhibit anticancer, anticonvulsant, antibacterial, antituberculotic or herbicidal properties. Antitumor activity of hydantoin analogs has been intensively studied. In this group a variety of compounds have been identified as both cytostatic and cytotoxic agents, active in various models of cancer, e.g. lung cancer[1].
In the present work a series of benzylidenehydantoin analogs with a structure presented below has been subjected to the screening developed by the National Cancer Institute (NCI, Bethesda, MD). Synthesized 2-phenylamino- and 2-benzylamino- substituted derivatives of 5-benzylidene-1*H*-imidazol-4(5*H*)-one [2] were evaluated for their antitumor activity against 60 human tumor cell lines, including NCI-H460 (non-small lung cancer), MCF7 (breast cancer), and SF268 (CNS cancer).



n = 0, 1

Several analogs proved to possess a broad spectrum of antitumor activity resulting in full panel median growth inhibition (GI50) and total growth inhibition (TGI). On the other hand, compound 5-(2-chlorobenzylidene)-2-(4-methoxybenzylamino)-1*H*-imidazol-4(5*H*)-one showed potential selectivity against prostate cancer cell line PC3 with GI50 = 90.7 nM.
The project was partially supported by Ministtry of Science and Higher Education, grant no. K/ZDS/000727

[1] Cavazzoni A., Alfieri R. R., Carmi C., Zuliani V., Galetti M., Fumarola C., Frazzi R., Bonelli M., Bordi F., Lodola A., Mor M., Petronini P. G.: *Mol. Cancer Ther. 2008, 7, 361*.
[2] Szymanska E., Kiec-Kononowicz K.: *Farmaco 2002, 57, 355*.

P-40

Synthesis and Structure-Activity Relationship Studies on Phenylalanine-Based AMPA/KA Receptor Antagonists.

Ewa Szymańska [a,c], *Tommy N. Johansen* [a], *Darryl Pickering* [b], *Birgitte Nielsen* [a]

[a] *Department of Medicinal Chemistry and* [b] *Department of Pharmacology and Pharmacotherapy, Faculty of Pharmaceutical Sciences, University of Copenhagen, Denmark*

[c] *Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków*

e-mail: mfszyman@cm-uj.krakow.pl

Glutamate- and GABA-releasing neurons form two basic, excitatory and inhibitory systems responsible for neurotransmission in the mammalian central nervous system. Fast excitatory synaptic transmission in the CNS relies almost entirely on the neurotransmitter glutamate and its family of ion ligand-gated channel receptors (iGluRs). The family of iGluRs is divided into three functionally distinct subclasses: NMDA, AMPA and kainate receptors. Structurally, AMPA-receptors are cation-selective tetrameric heterooligomers formed by combinations of the highly homologous subunits GluR1-4, while kainate receptors are tetrameric assemblies of GluR5-7, KA1 and KA2 subunits. There is a clear pharmacological boundary between NMDA and other iGluRs, however, most of AMPA agonists and antagonists activate also kainate receptors and only few compounds discriminate between individual subunits.

The present project is focused on the search for new potent and selective competitive AMPA and/or KA receptors antagonists. On the basis of published crystal structures of the GluR2 and GluR5 binding cores co-crystallized with various ligands, series of compounds with the general structure based on the phenylalanine scaffold was designed and synthesized. Structural modifications, including the substitution of the phenylalanine ring with thiophene, uracil or second phenyl fragments were performed. The influence of changing the nature and the position of the substituent in the distant phenyl ring was also studied.

The whole series of synthesized analogs was pharmacologically characterized on both native (NMDA, AMPA, KA) and cloned (GluR5, GluR6, GluR7) receptors. Structure-activity relationship studies were performed on the group of the obtained compounds, among which several AMPA-prefering as well as GluR5-prefering compounds were identified.

In the present work the synthesis, optimization of chemical conditions and pharmacological results are reported.

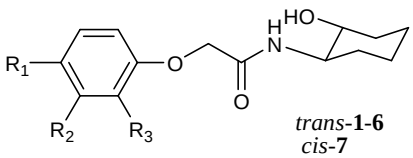
P-41

Anticonvulsant Activity of Some *trans*- and *cis*-2-Amino-1-cyclohexanol Derivatives.

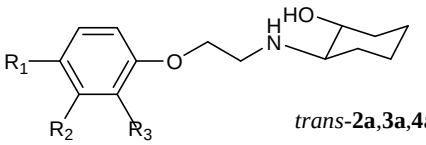
Elżbieta Pękala, Małgorzata Więcek, Henryk Marona, Katarzyna Kieć-Kononowicz

Department Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków
e-mail: mfpekala@cyf-kr.edu.pl

Epilepsy, a common neurological disorders characterized by recurrent spontaneous seizures arising from excessive electrical activity in some portion of the brain, is a major , worldwide, public health problem, which affects approximately 1% of the population.
Antiepileptic drugs (AEDs) can influence the inhibitory or excitatory neurotransmitter systems (GABA or glutamic and aspartic acid, respectively), or the ion transport across cell membranes. Conventional antiepileptic drugs are widely used but exhibit an unfavorable site effect profile and failure to adequately control seizures. In the recent years several new drugs, such as: lamotrigine, gabapentin, tiogabine, vigabatrin or flebamate have been added to the list of therapeutic agents against epilepsy. However, there is a significant group of patients (up to 30%) who are resistant to the available antiepileptic drugs. Hence, there is an urgent need to develop new AEDs with a more selective activity and lower toxicity.
To make the discovery of new anticonvulsants more rational, several investigators identify structural fragments that may enhance anticonvulsant properties and permit also for orientating the synthesis of novel compounds in which some of these active fragments can appear. One of the structural features that play a significant role in relation to antiepileptic activity is an amide function, which may be introduced into a hetrocyclic ring (e.g. ethosuximide, phenytoin) or as an anilide nucleus (e.g. ameltoide).



trans-**1**-**6**
cis-**7**



trans-**2a**,**3a**,**4a**

We herein report synthesis and anticonvulsant activity of the new 2,4-dichloro- and 3-methyl-4-chloro-phenoxyacetyl amide derivatives of *trans*- or *cis*- racemic and enantiomeric forms of 2-amino-1-cyclohexanol (**1-7**). In the few cases we present also synthesis and anticonvulsant evaluation appropriate corresponding *N*-aminoalkyl derivatives (**2a**,**3a**,**4a**). The compounds **1**-**7** and **2a**, **3a** and **4a** were tested *in vivo* by using three screens (mice, rats): the MES, scMet (anticonvulsant tests) and TOX (neurotoxicity). For the six selected compounds: **2**, **2a**, **3**, **3a**, **4a** and **7** were made advanced quantitative test (ED_{50} and TD_{50}) in mice and/or rats). The most interesting were the anticonvulsant results of *cis*-racemic-2-(2,4-dichlorophenoxy)-*N*-((1*S*,2*R*)-2-hydroxycyclohexyl)acetamide (**4a)**, which displayed anti-MES activity with protective index (TD_{50}/ED_{50} of 2.83 (mice, *i.p.*) and 2.51 (rats, *p.o*) corresponding with that for valproate (1.70 and 2.2, respectively) [3].

[1] Marona H., Antkiewicz-Michaluk L.: *Acta Polon. Pharm. Drug-Res*. *1998, 55(6), 487*.
[2] Marona H., Pękala E., Antkiewicz-Michaluk L., Walczak M., Szneler E.: *Bioorg. Med. Chem*. *2008*.
[3] Mulzac D., Scott K. R.: *Epilepsia 1993, 34, 1141*.

The authors are grateful to Professor J. Stables for providing the pharmacological data through the Antiepileptic Drug Development program in National Institutes of Health, Bethesda, USA.

The study was supported by Jagiellonian University Medical College, Cracow, Poland, program research no K/ZDS/000727.

P-42

New Isophosphoramide Mustard Analogues as Prodrugs for Gene Therapy.

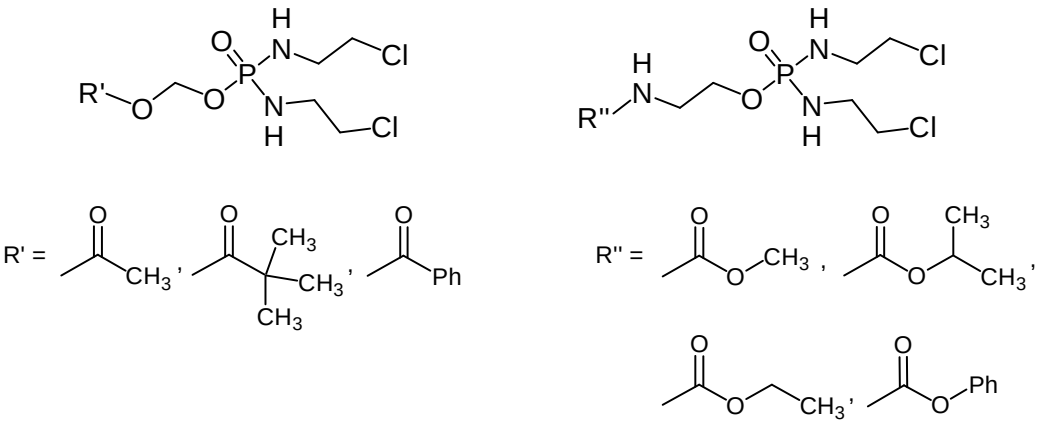
Joanna Cytarska, Konrad Misiura

Department of Chemical Technology of Pharmaceuticals, Faculty of Pharmacy, Collegium Medicum NCU, M. Sklodowskiej-Curie 9, 85–094 Bydgoszcz
e-mail: cytar@cm.umk.pl

Isophosphoramide mustard (iPAM) is active, cytotoxic metabolite of ifosfamide (IF), anticancer alkilating drug widely use in the clinic. Poor selectivity of cytostatic drugs currently used in conventional cancer chemotherapy lead to attempts to employ gene therapy. In Gene-Directed Enzyme Prodrug Therapy (GDEPT)[i] tumor cells are transduced with a prodrug-activating gene, which enables the tumor cells to activate the prodrug locally, leading to enhanced antitumor activity without a corresponding increase in host toxicity.

Prodrugs need to satisfy a number of criteria. They must be efficient and selective substrates for the activating enzyme, and be metabolized to potent cytotoxins preferably able to kill cells at all stages of the cell cycle. Small molecules of prodrugs can be considered as comprised of two major domains, a “trigger” unit that is the substrate for the activating enzyme, and an “effector” unit that is activated or relased by this metabolic process, sometimes joined by a definable linker.

To obtain higher selectivity of cytostatic drugs we synthesized new ester analogs of iPAM with two different linkers, which can be activated by two enzymes, carboxyesterase and amidase. Potential prodrugs, analogs of N,N’-bis(2-chloroethyl)diamidophosphoric acid, were shown in scheme:



Prodrugs for GDEPT should have a good stability under phisiological conditions. Now we are checking if our new potential prodrugs are metabolically stable under *in vivo* conditions and if they are efficient substrates for the activating enzyme.

This research was supported by Nicolaus Copernicus University, Rector grant 1/CM.

[1] Niculescu-Duvaz I., Friedlos F., Niculescu-Duvaz D., Davies L., Springer C.J.: *Anticancer Drug Design, 1999, 14, 517-538.*

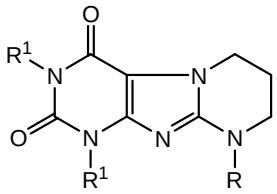
P-43

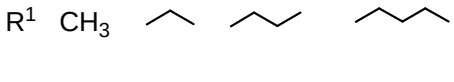
Synthesis and Biological Evaluation of Novel Dialkylpyrimidopurinediones.

Anna Drabczyńska [a], *Christa E.Müller* [b], *Meryem Köse* [b], *Angelica Ziebholz* [b], *Katarzyna Kieć-Kononowicz* [a]

[a] *Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków*
[b] *Pharmaceutical Institute, University of Bonn, An der Immenburg 4, 53121 Bonn, Germany*
e-mail: annadrab@poczta.onet.pl

Xanthines were first and natural ligands for adenosine receptors (AR). In the last ten years many modified xanthine derivatives have been developed as potential therapeutic agents for CNS disorders, inflamation, astma, kidney failure and ischemia [1].
During our search for novel AR antagonists it was found that annelated tricyclic deivatives of xanthine display adenosine A_{2A} eventual A_1 antagonistic properties, some have shown antiepileptic activity [2-4].
In the present work pyrimidopurinediones with alkyl, cyckloalkyl and aryl substituents at annelated ring and elongated (from methyl to butyl) substituents at the purinedione ring were synthesized and their biological activity compared.





The synthesized compounds were evaluated in *in vitro* receptor binding studies for the affinity at A_1 and A_{2A} ARs in assays at rat brain membrane preparations. They were also tested *in vivo* as anticonvulsants according to the Antieplieptic Development Program in the NIH in Bethesda.

This work was partly supported by Grant 2 P05 022 26.

[1] Hess S.: *Exp. Opin. Ther. Patnets 2001, 11, 1533-61*.
[2] Drabczyńska A., Müller C. E., Lacher S. K., Schumacher B., Karolak-Wojciechowska J., Nasal A., Kawczak P., Yuzlenko O., Pękala E., Kieć-Kononowicz K.: *Bioorg. Med. Chem. 2006, 14, 7258-7281*.
[3] Drabczyńska A., Müller C. E., Karolak-Wojciechowska J., Schumacher B., Schiedel A., Yuzlenko O., Kieć-Kononowicz K.: *Bioorg. Med. Chem. 2007, 15, 5003-5017*.
[4] Drabczyńska A., Müller C. E., Schiedel A., Schumacher B., Karolak-Wojciechowska J., Fruziński A., Zobnina W., Yuzlenko O., Kieć-Kononowicz K.: *Bioorg. Med. Chem. 2007, 15, 6956-6974*.

P-44

Antibacterial Activity of the Xanthone Derivatives Against Multidrug-resistant Strains.

Henryk Marona [a], *Natalia Szkaradek* [a], *Budak Alicja* [b], *Karczewska Elżbieta* [b], *Danuta Trojanowska* [b]

[a] *Department of Technology and Biotechnology of Drugs,*
[b] *Department of Pharmaceutical Microbiology, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków*
e-mail: nszkarad@cm-uj.krakow.pl

Searching for structures with potential biologiacal activity, we have directed our attention to the xanthone derivatives. Nowadays, both naturally occurring and synthetic xanthone derivatives showed interesting pharmacological and microbiological properties eg. antimalarial [1], antimycobacterial [2, 3], antibacterial [4] and antifungal [5] effects were described.
The emergence of multidrug-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* have made treatment of infectious diseases difficult and have, over the last decades, become a serious medical problem. As pathogenic bacteria continuously evolve mechanisms of resistance to currently used antibiotics, so the discovery of novel and potent antibacterial drugs is the best way to overcome bacterial resistance and develop effective therapies [6].
Thus, herein we reported the results of study aimed at evaluating the potential antibacterial activity of xanthone derivatives against drug-resistant strains purchased from the MIKROBANK collection or isolated from the nosocomial infections. Some of the examined compounds were previously analyzed and their encouraging antibacterial properties were subject of the conference presentation and manuscript, which is already under review in Archiv der Pharmazie Chemical Life Science.
From the our investigation comes out that Gram-positive strains were more sensitive to the evaluated compounds. According to ours expectations, activity of the tested substances was diversified, determined by the kind and place of substitution in one of the xanthone rings. Thus halogenated structures were more potent than unsubstituted ones, additionally six position in the xanthone moiety was more desired. The most promising results (growth inhibition zones in the disc-diffusion method ranging 15 mm or more) were obtained for the 6-chloro-4-(3-tert-butylamino-2-hydroxypropoxy)-xanthone and 6-chloro-4-(2-hydroxy-3N-(2-amino -2-methyl-1-hydroxy propyl)propoxy)-xanthone.

[1] Portela C., Afonso C. M. M., Pinto M. M. M., Ramos M. J.: *Bioorg. Med. Chem. 2004, 12, 3313-3321.*
[2] Pickert M., Schaper K. J., Frahm A. W.: *Arch. Pharm. (Weinheim) 1998, 331(5), 193-197*.
[3] Szkaradek N., Stachura K., Waszkielewicz A. M., Cegła M., Szeler E., Marona H.: *Acta. Polon. Pharm. – Drug Res. 2008, 65, 21-28*.
[4] Panthong K., Pongcharoen W., Phongpaichit S., Taylor W. C.: *Phytochemistry 2006, 67, 999-1004*.
[5] Salmoiraghi I., Rossi M., Valenti P., Da Re P.: *Arch. Pharm. Pharm. Med. Chem. 1998, 331, 225-227*.
[6] Coleman K.: *Drug Discov. Today, Therapeutic Strategies 2004, 37, 455-460*.

P-45

Homology Modelling as an Aid in Rational Synthesis of Nonclassical Cannabinoids.

Tomasz Kościółek [a], *Karol Dyduch* [a], *Przemysław Szafrański* [a], *Tomasz Wróbel* [a], *Mateusz Nowak* [b]

[a] *Faculty of Chemistry, Jagiellonian University, Ingardena 3, 30-060 Kraków*
[b] *Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, 31-343 Kraków*
e-mail:

In absence of the crystal structure of cannabinoid receptors (CB_1 and CB_2), molecular modelling studies become one of the best sources of structural information on the active site. Providing in-silico predictions on the receptors' structure may facilitate the development of new ligands. In spite of numerous computational studies on cannabinoid ligand binding modes, models constructed so far do not give enough attention to nonclassical cannabinoids (such as CP-55,940).

Our main focus in this work is on constructing a reliable model for nonclassical cannabinoids affinity studies. Homology models of CB_1 and CB_2 based on bovine rhodopsin crystal structure were constructed and evaluated using high-affinity prototype ligands. Modelling involved constructing 7 TM helices, which are the core of the protein and can be modelled reliably, automated docking and further iterative improvements based on torsional restraints imposed on amino acid side chains and pharmacophore constraint to guide the docking procedure.

Further work is planned to examine novel GPCR X-ray structure – human β_2 adrenergic receptor, which shares higher sequence homology with both CB_1 and CB_2 than bovine rhodopsin. This might give further insight into cannabinoid receptors' structure and receptor-ligand interactions.

Thorough examination of obtained results and conclusions concerning SAR provides vital waypoints in designing novel cannabinoid receptors' agonists.

Acknowledgements: Project has been done as a part of students' practice at the Department of Medicinal Chemistry, Institute of Pharmacology, PAS, Smetna 12, 31-343 Krakow, Poland.

P-46

Comparison of FlexX and Surflex Docking Algorithms Based on Astex Diverse Set.

Rafał Kurczab, Mateusz Nowak, Andrzej J. Bojarski

Department of Medicinal Chemistry, Institute of Pharmacology Polish Academy of Sciences, Smętna 12, 31-343 Kraków

e-mail:

Molecular docking is routinely used in lead finding and compound optimization, both for targets with experimental 3D coordinates and for homology-based models. Our study concentrates on comparison of two commercial docking programs: FlexX (BioSolveIT) and Surflex-Dock (Tripos). Their performance was explored using Astex Diverse Set that contains crystal structures of 85 protein-ligand complexes from different drug discovery or agrochemical targets [1]. Docking results were analyzed based on the success rate of producing near-native ligand binding geometries (rmsd < 2.0Å) and usage of different scoring functions (G_Score, D_Score, F_Score, Chem-Score, PMF, C_Score) are discussed. In addition, a number of technical issues and software limitations are described.

References:

[1] Hartshorn M. J., Verdonk M. L., Mortenson P. L., Murray C. W.: *J. Med. Chem. 2007, 50, 726-741*.

P-47

Experimental and Theoretical Studies on Conformations of Arylpiperazines with Pyrimido[5,4-c]quinolin-4(3H)-one Terminal.

Stefan Mordalski [a], *Wiesława Lewgowd* [b], *Andrzej Stańczak* [b], *Małgorzata Szczesio* [c], *Marek L. Główka* [c], *Andrzej J. Bojarski* [a]

[a] *Department of Medicinal Chemistry, Institute of Pharmacology Polish Academy of Sciences, Smętna12, 31-343 Kraków*
[b] *Department of Clinical Pharmacy, Medical University of Lódź, Muszyńskiego 1, 90-151 Łódź*
[c] *Institute of General and Ecological Chemistry, University of Technology, Żeromskiego 116, Łódź*
e-mail:

Arylpiperazine derivatives of cyclic amides and imides are big and intensively investigated group of serotonin receptor ligands. Our study concentrates on pyrimido[5,4-c]quinolin-4(3*H*)-ones connected with arylpiperazine via 2–4 carbon spacer developed as 5-HT_{1A} receptor agents. Conformational behavior of the investigated compounds was studied experimentally in solid state (crystallographic structure), and theoretically in vacuum and in solution (semi-empirical methods) as well as in the rhodopsin-based homology model of 5-HT_{1A} receptor.

Acknowledgments: The study was supported by a grant No. N405 1656 33 from the Ministry of Science and Higher Education.

P-48

Therapeutic Potential, Design and Synthesis of Cannabinoid Drugs.

Przemysław Szafrański, Karol Dyduch, Tomasz Kościółek, Tomasz Wróbel

Faculty of Chemistry, Jagiellonian University, Ingardena 3, 30-060 Kraków
e-mail:

Thanks to their structural diversity and multiple therapeutic applications cannabinoids form an interesting field in medicinal chemistry research and drug design. The therapeutic areas, where cannabinoid drugs are used or researched, include appetite regulation, relieving pain, treating CNS disorders, such as multiple sclerosis, treating cardiovascular and respiratory disorders. Another important element of cannabinoid therapeutic potential is inhibition of tumour growth, giving hope for cannabinoid anti-cancer drugs.

Diverse medical applications of cannabinoids arise from the important role played by the endocannabinoid system (ECS) in the functioning of human organism. This signalling system consists of three cannabinoid receptors: CB_1, CB_2 and GPR55, their endogenous ligands (endocannabinoids like anandamide) and enzymes responsible for their synthesis, transport and breakdown. Currently, the most important pharmacological targets in this system are CB_1 and CB_2 receptors. In absence of their crystal structure, homology modelling based on the structures of other GPCRs becomes the tool of choice in the structure-based drug design approaches.

In our research, we combine information obtained from homology models of cannabinoid receptors with earlier developed structure-activity relationships for nonclassical cannabinoids. This project is meant to design novel, easy to synthesize and displaying high receptor affinity structures. To ensure synthetic accessibility of designed ligands, we pay special attention to simplifying and optimizing the synthetic routes.

Acknowledgements: We wish to thank doc. dr hab. Janusz J. Sepioł and dr Jarosław Wilamowski from Department of Organic Chemistry, Faculty of Chemistry, Jagiellonian University for enabling and supervising synthetic work in our project. We would also like to express our appreciation to doc. dr hab. Andrzej J. Bojarski and dr Mateusz Nowak, Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences for their precious guidelines and enabling computational research on cannabinoid receptors.

P-49

C=O...H-N Interactions - Main Motives in the Crystals of Xanthine Derivatives.

Janina Karolak-Wojciechowska [a], *Małgorzata Szczesio* [a], *Andrzej Fruziński* [a], *Katarzyna Kieć-Kononowicz* [b] , *Anna Drabczyńska* [b]

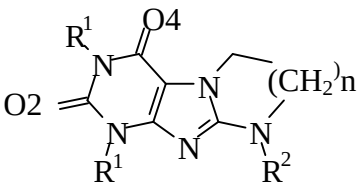
[a] *Institute of General and Ecological Chemistry, Technical University of Łódź, Żeromskiego 116 , 90-924 Łódź*

[b] *Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków*

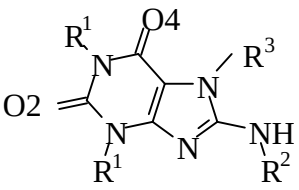
e-mail: Janina.Karolak-Wojciechowska@p.lodz.pl

Hydrogen bonds are most important among all non-covalent intermolecular interactions. They are responsible for molecular recognition and/or self-organization of the molecules. Hydrogen bonds from one site take part in the formation of complexes between biological receptors and respective ligands and from the other, are responsible for packing motive formation in nearly all crystals of organic substances. The most important data about H-bond geometry and topology can be taken directly from crystallographic data. The informations about topology being achieved from these studies concerns building motives and supramolecular synthons formations.

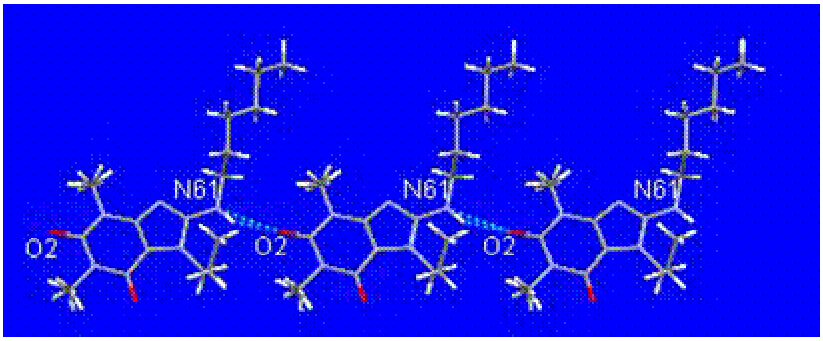
During our studies it was state that xantine derivatives exhibit activity against adenosine receptors [1]. Our contemporary X-ray studies on imidazo-, pyrimido and 1,3-diazepino[2,1-*f*]purinediones (I) have suggested that C-H…O=C interactions are crucial for crystal structure architecture. Recently among derivatives with bicyclic skeletons (II) several structures with were solved. In this structures main motives are construct by N-H…O=C strong H-bonds.



I



II



Research partially finance by project P05F 014 28 of the Polish Cometee for Scierntific Research.

[1] Drabczyńska A., Muller C. E., Schiedel A., Schumacher B., Karolak-Wojciechowska J., Fruziński A., Zobnina W., Yuzlenko O., Kieć-Kononowicz K.: Phenylethyl-substituted pyrimido[2,1-f]purinediones and related compounds: Structure–activity relationships as adenosine A_1 and A_{2A} receptor ligands. Bioorg. Med. Chem. 2007, 15 (22), 6956-6974.

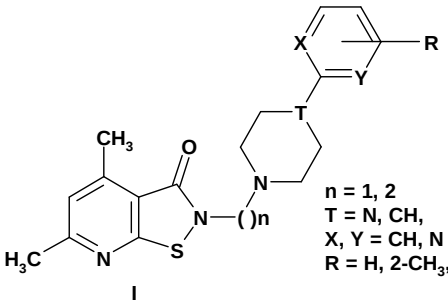
P-50

Mono and Bicyclic Heterocycles Aromaticity of Izothiazolopyridines.

Agnieszka Mrozek [a], *Zbigniew Karczmarzyk* [b]

[a] *Institute of General and Ecological Chemistry, Technical University of Łódź, Żeromskiego 116, 90-924 Łódź*
[b] *Department of Chemistry, University of Podlasie, 3 Maja 54, 08-110 Siedlce*
e-mail: agnieszka.mrozek@p.lodz.pl

Mono- and bicyclic heteroaromatic systems are under our interest since several years. Recently, we have analysed dependencies between heteroring aromaticity and their compostion. We based our discussion on experimental data only – geometrical parameters obtained from CSD and author's own X-ray analysis. As a quantitative measure of aromaticity HOMA index was applicated.
Our last investigations on izothiazolopyridines (scheme below) in which N-S bonds occurs lead us to broaden the application of HOMA index for such bonds.



I

The HOMA index is defined as follows [1]:

$$HOMA=1-\alpha(R_{opt}-R_{av})^2 - \beta/n\sum(R_{av}-R_i)^2=1-EN-GEO$$

where $$R_{opt}=[k_sR_s+k_dR_d]/(k_s+k_d)$$

In order to define empirical constants for the N-S bond, the single and double bonds length are needed (R_s and R_d). The geometrical parameters (bond lengths and angles) for model structures were calculated with NWChem 5.0 at the RHF/6-31G** level. The initial geometries were built from AM1 semiempirical SCF-MO calculations using the program package HYPERCHEM rel. 4.5

[1] Krygowski T.M., *J. Chem. Inf. Comput. Sci. 1993, 33, 70.*

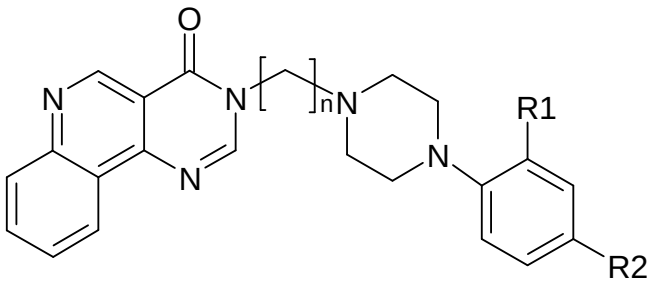
P-51

Crystallographic Structure of Arylopiperazines.

Małgorzata Szczesio

Institute of General and Ecological Chemistry, Technical University of Łódź,
Żeromskiego 116 st., 90-924 Łódź
e-mail: gos3@o2.pl

Most of the arylopiperazine derivatives exhibit biological activity against serotonine receptors: 5-HT1a, 5-HT2a i 5HT7 [1,2].
X-Ray structural analysis for several arylopiperazine derivatives of significant pharmacological activity were done (scheme below). All compounds were synthesized by dr Wiesława Lewgowd (Medical University of Łódź) as a part of our investigations on drug structures modification through their pharmacological parameters improving.



n	R1	R2	Space group	Cell parameters		R_1
2	Cl	H	P-1	7.3735(3) 11.5149(6) 13.2238(7)	103.602(4) 97.836(4) 95.340(4)	3.92
2	OCH_3	H	P2(1)/c	15.3974(6) 21.8072(9) 7.2599(3)	90.00 98.8170(10) 90.00	4.55
3	Cl	H	P2(1)/c	18.8951(17) 16.4124(15) 7.7095(7)	90.00 90.486(7) 90.00	4.86
3	H	OCH_3	Cc	18.0754(15) 18.0111(15) 7.0613(6)	90.00 101.3140(10) 90.00	2.44

The research was carried out under the grant no NN 405165633 from Ministry of Science and Higher Education, Poland.

[1] Hedlund P. B., Sutcliffe J. G.: *Trends Pharmacol. Sci. 2004, 25,481*.
[2] Stańczak A., Lewgowd W., Pakulska W.: *Pharmazie 1998, 53,156.*

P-52

The Study of Ligand-Serotonin Transporter Interactions.

Małgorzata Jarończyk [a], *Zdzisław Chilmonczyk* [a], *Gabriel Nowak* [b], *Ingebrigt Sylte* [c], *Kurt Kristiansen* [c], *Aina W. Ravna* [c]

[a] *National Institut of Drugs,Chełmska 30/34, 00-725 Warszawa*
[b] *Institut of Pharmacology of Polish Academy of Sciences, Smętna 12, 31-343 Kraków*
[c] *Faculty of Medicine, Uniwersity of Tromsø, N-9037 Tromsø, Norwegia.*
e-mail: mjaronczyk@gmail.com

Abnormalities in serotonin levels can lead to depression and anxiety, as well as other mental disorders such as obsessive compulsive disorder. The serotonin transporter (SERT) plays a key role in the regulation of synaptic serotonin (5-hydroxtryptamine, 5-HT) levels and therefore is the major target for antidepressants including both the tricyclic antidepressants and selective serotonin reuptake inhibitors. The antidepressants affect the concentration of the serotonin by inhibiting the reuptake of the 5-HT into nerve cells. To examine the molecular mechanism of their different binding affinities the interactions between ligands and serotonin transporter were studied.
In the present work, a 3D model of SERT based on the bacterial homologue of the Na^+/Cl^- dependent neurotransmitter transporters from *Aquifex aeolicus* ($LeuT_{Aa}$) [1,2] was used. Two possible binding sites for uptake inhibitors and serotonin on SERT are suggested, one site that might correspond to a high affinity binding site, and a second site that might correspond to a low-affinity site. The ligands were docked into the two possible binding sites [2] using the automatic docking module of the ICM molecular modelling software. The docking studies indicated that the ligands interacted strongly with amino acids in transmembrane helix 1, 3, 6 and 8 of SERT at high affinity site. At the possible low-affinity site, we suggest that the ligand interacted with aminoacids in transmembrane helix 1, 6, 10 and aminoacids in the loop connecting transmembrane helix 7 and 8.

[1] Yamashita A., Singh S.K., Kawate T., Jin Y., Gouaux E.: Crystal structure of a bacterial homologoue of Na^+/Cl^- dependent neurotransmitter transporters. *Nature, 2005, 437, 21-29*.
[2] Ravna A.W., Jarończyk M. Sylte I.: A homology model of SERT based on the $LeuT_{Aa}$ template. *Bioorg. Med. Chem. Lett. 2006, 16, 5594-5597*.

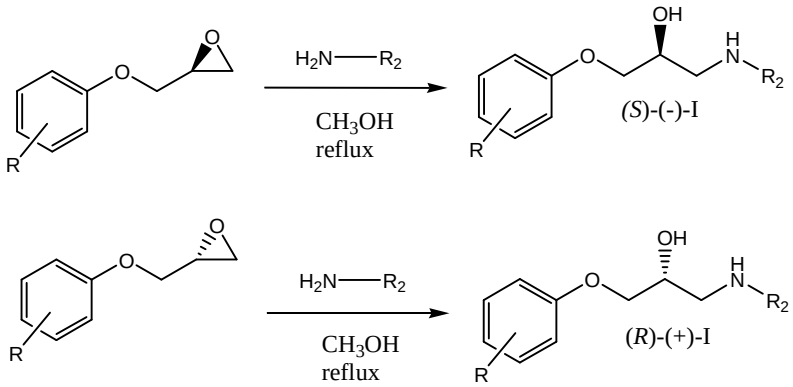
P-53

Aminolysis of Chiral Phenyl Glycidyl Ethers.

Dorota Żelaszczyk[a], Hanna Kozłowska[b], Eberhard Schlicker[c], Barbara Malinowska[b], Katarzyna Kieć-Kononowicz[a]

[a] Department of Technology and Biotechnology of Drugs, Faculty of Pharmacy, Jagiellonian University Medical College, Medyczna 9, 30-688 Kraków
[b] Department of Experimental Physiology, Medical University of Białystok
[c] Department of Pharmacology, University of Bonn, Germany
e-mail: dzelaszc@cm-uj.krakow.pl

Introduction: β-Blockers which are in great commercial demand are still sold mostly as racemates despite the intense desire to change into enantiopure form [1]. Of particular significance, therefore, is the generation of chiral β-amino alcohol moiety involving substituted phenol, the core of the β-blockers. Our interest was focused on one particular β-blocker - bupranolol (BUP), a non-selective antagonist of all known subtypes of β-adrenergic receptor, including so called low-affinity state of β_1-adrenoceptor. Previous study showed that the antagonistic effect of BUP at the cardiostimulant low-affinity state of β_1-ARs in pithed rats is stereoselective [2]. We were interested whether this feature is shared by its analogues, what would be another hint that the low-affinity state of β_1-adrenoceptors in the heart is indeed a receptor.
Aim: Prepare a set of BUP analogues as pairs of enantiomers.
Methods: The modification of classic Sthephenson procedure with commercially available enantiomeric forms of epichlorohydrin was applied. (*S*)-(-)-phenoxypropanolamines ((*S*)-(-)-I) were prepared by aminolysis of chiral phenyl glycidyl ethers derived from (*R*)-(-)-epichlorohydrin. Their antipodes (*R*)-(+)-phenoxypropanolamines ((*R*)-(+)-I) were prepared from (*S*)-(+)-epichlorohydrin. The enantiomeric excess of obtained final compounds was determined using HPLC system equipped with Chiralpak AD column.



Results: The enantiomers of BUP analogues were prepared with very good enantiomeric excess, up to 99%. Interestingly, using as starting material two enantiomers of epichlorohydrin with similar optical purity we obtained (*S*)-(-)-enantiomeric forms of phenoxypropanolamines with higher optical purity comparing to (*R*)-(+)- ones.
Acknowledgment:
This work was partially supported by the Polish Ministry of Science and Higher Education grant No 2 PO2F 019 29

[1] Stinson S. C.: *Chem. Eng. News 1997, 28*.
[2] Malinowska B. *et* al.: *Br. J. Pharmacol. 2003, 139, 1548*.

P-54

Msh2/3 Involvement in Trinucleotide Expansions Leading to Huntington's Disease.

Maciej Gajec, Teresa Wilson, Wiliam F. Morgan

University of Maryland, Baltimore, MD, USA

Trinucleotide repeat diseases such as Huntington's Disease (HD) and Myotonic Dystrophy (DM) are caused by a progressive increase in length of trinucleotide tracts in somatic as well as germ line cells during replication. The encoded proteins misfold or form aggregates *in vivo*, causing dysfunction in proper activity. The mechanisms responsible for expansion are still largely misunderstood, however Methyl Directed Mismatch Repair (MMR) proteins Msh2 and Msh3 have been shown to be responsible for interactions, which allow for trinucleotide expansions. Here, we show that the Msh2/3 complex actively binds to DNA substrates containing insertion loops consisting of trinucleotide repeats *in situ* through Gel Mobility Shift Assays (GMSA), suggesting that the Msh2/3 complex shields secondary structure formations during replication, thereby preventing proper excision and allowing for trinucleotide expansion. Further studies may elucidate the exact mechanism by which shielding occurs, allowing for a better understanding of factors involved, as well as providing date for a possible way of impeding trinucleotide expansions.

The fact that Msh2/3 so strongly binds DNA insertion loops lends evidence to support the claims of previous research done, which states that the presence of Msh2 and Msh3 is required for trinucleotide expansion. In addition, the complex created by both of these proteins is actively involved in binding of secondary structure formations created by CAG repeats.

The results presented here also function to elaborate on a mechanism proposed by McMurray et al., in which Msh2 involvement in gap-repair synthesis acts to stabilize either the loop or gap during the process. Because the mechanism of recognition by Msh proteins involves dimerization and is proposed to act as a sliding-clamp, it is not probable that Msh2 alone acts to stabilize loop structures. Rather, it is much more likely that the Msh2/3 complex, in binding to CAG repeat loops, functions in their shielding, possibly protecting them from proteins which might correct the error.

This possibility of shielding is not unlikely. In previous studies by Manley et al. not only were expansions stopped in mice with the absence of Msh2, but contractions occurred, suggesting that a mechanism does exist for the reduction of trinucleotide repeats. If Msh2/3 binds CAG secondary structure formations so well, then there is a good chance that it sterically impedes other repair pathways from performing their appropriate tasks at the site of expansion.

It appears that because of the lack of specificity to variance at the base of CAG repeat loops, Msh2/3 may possibly bind away from the DNA helix, creating a minor discrepancy with the current sliding-clamp model. Still, this possibility alone does not discredit the sliding-clamp model, but merely proposes an alternate method of mismatch recognition.

The pertinence of this study to HD lies partially in genetic counseling. It is very important to know whether or not an individual is predisposed to HD, but for couples, analysis of predisposition to HD as well as to HNPCC may determine family planning. Despite the drawbacks of Msh2/3 malfunction, progeny of one parent with predisposition to HD and the other parent with a dysfunctional Msh2/3 complex could have children, which will not suffer the detrimental effects of HD, although will still have a predisposition to HNPCC, a much less severe condition.

Furthermore, knowledge of the mechanism by which Msh2/3 allows for expansions, and perhaps even prevents contractions, can potentially lead to gene therapy and specific inhibition of that particular process.

LISTA UCZESTNIKÓW

Achrem-Achremowicz Jacek, dr
Aletańska-Kozak Monika, dr
Andruszkiewicz Ryszard, dr hab., prof. nadzw. UM
Arias Hugo, dr

Bajda Marek, mgr
Baran Marzena, mgr
Bartnik Magdalena, dr
Biała Grażyna, dr hab.
Białas Arkadiusz, dr inż.
Bielawska Anna, dr hab.
Bielawski Krzysztof, dr hab., prof. nadzw. AM
Boblewski Konrad, lek.
Bojarski Andrzej J., dr hab.
Bojarski Jerzy, prof. dr hab.
Bołkun-Skórnicka Urszula, dr
Brzezińska Elżbieta, prof. dr hab.
Brzozowski Zdzisław, prof. dr hab.
Budak Alicja, prof. dr hab.
Bujacz Grzegorz, prof. dr hab.

Cegła Marek, dr hab.
Chilmonczyk Zdzisław, prof. dr hab.
Chłopicki Stefan, prof. dr hab.
Cytarska Joanna, dr
Czarnecka Maria, mgr

Dobosz Maria, prof. dr hab.
Dołowy Małgorzata, dr
Drabczyńska Anna, dr
Drozdowska Danuta, dr
Dutkiewicz Zbigniew, dr
Dybała Małgorzata, mgr
Dyduch Karol, mgr

Fidecka Sylwia, prof. dr hab.
Filipek Barbara, dr
Francik Renata, dr
Fruziński Andrzej, dr

Gajec Maciej, stud.
Gdaniec Maria, prof. dr hab.
Gośliński Tomasz, dr
Gronek Ewa, mgr inż.

Gryciuk Grażyna, dr
Główka Marek L., prof. dr hab.

Handzlik Jadwiga, dr
Harold Franciszek, dr hab.
Hudson Alan L., dr

Innocenti Allesio, dr

Janik Agnieszka, mgr
Jastrzębska Magdalena, mgr
Jarończyk Małgorzata, dr
Jeleń Małgorzata, dr
Johansen Tommy N., dr
Jóźwiak Krzysztof, dr hab.

Kaczor Agnieszka, dr
Kafarski Paweł, prof. dr hab.
Kaleta Małgorzata, mgr
Kaliszan Roman, prof. dr hab.
Kamiński Krzysztof, mgr
Kamiński Zbigniew, prof. dr hab.
Karczewska Elżbieta, dr
Karczmarzyk Zbigniew, dr
Karolak-Wojciechowska Janina, prof. dr hab.
Kędzierska Ewa, dr
Kępczyńska Elżbieta, dr
Kieć-Kononowicz Katarzyna, prof. dr hab.
Kijkowska-Murak Urszula, mgr
Kolesińska Beata, dr
Konopa Jerzy, prof. dr hab. inż.
Kornicka Anita, dr
Kose Meryem, dr
Kosikowska Urszula, dr
Kossakowski Jerzy, prof. dr hab.
Koszel Dominik, mgr inż.
Kościółek Tomasz, mgr
Kozak Joanna, mgr
Kozłowska Hanna, dr
Krajewski Michał, mgr
Krawiecka Mariola, dr
Kristiansen Kurt, dr
Kronbach Christiane, dr
Król Jakub, mgr

Kuder Kamil, mgr
Kuran Bożena, dr
Kurczab Rafał, mgr
Kulas Martyna, dr
Kulig Katarzyna, dr

Lehmann Artur, mgr
Lewgowd Wiesława, dr
Ligneau Xavier, dr
Ligęza Agnieszka, mgr

Malawska Barbara, prof. dr hab.
Malinowska Barbara, prof. dr hab.
Malm Anna, dr hab., prof. nadzw. UM
Markuszewski Michał, dr hab.
Marona Henryk, dr hab.
Matosiuk Dariusz, dr hab., prof. nadzw. UM
Marona Henryk, dr hab.
Mazerska Zofia, dr hab.
Miao Shu Sean, dr
Mielcarek Jadwiga, prof. dr hab.
Mikiciuk-Olasik Elżbieta, prof. dr hab.
Mikstacka Renata, dr
Misiura Konrad, dr hab., prof. nadzw. U
Młynarz Piotr, dr
Modzelewska-Banachiewicz Bożena, dr hab., prof. nadzw. U
Morak-Młodawska Beata, dr
Mordalski Stefan, mgr
Morgan Wiliam F.
Mrozek Agnieszka, dr
Mucha Artur, dr
Muller Christa E., dr

Nielsen Brigitte, dr
Nowaczyk Alicja, dr
Nowak Gabriel, prof. dr hab.
Nowak Mateusz, dr

Obniska Jolanta, dr hab.
Orman Alicja, mgr
Osmałek Tomasz, mgr

Pachuta-Stec Anna, dr
Paluszkiewicz Ewa, dr inż.

Pakosińska-Parys Magdalena, mgr
Pękala Elżbieta, dr
Pickering Darryl, dr
Pitucha Monika, dr
Pluta Krystian, prof. dr hab.
Płazińska Anita, mgr
Pomarnacka Elzbieta, dr hab., prof. nadzw. UM
Popiołek Łukasz, mgr
Popławska Bożena, dr
Prokopowicz Monika, mgr inż.

Ravna Aina W., dr
Rządkowska Marzena, dr
Rzymowska Jolanta, dr hab.
Rybczyńska Apolonia, dr hab., prof. nadzw. UM

Sączewski Franciszek, prof. dr hab.
Scozzafava Andrea, dr
Siepietowski Damian, dr
Siwek Agata, mgr
Schlicker Eberhard, prof. dr
Schwartz Jean-Charles, dr
Skowerski Krzysztof, mgr
Sławiński Jarosław, mgr
Słowiński Tomasz, dr
Sobiak Stanisław, dr hab., prof. nadzw. UM
Stańczak Andrzej, dr hab. prof. nadzw. UM
Stark Holger, dr
Stasiewicz-Urban Anna, dr
Stefanowicz Jacek, dr
Stefańska Joanna, dr
Stefański Tomasz, mgr
Struga Marta, dr
Supuran Claudiu T., prof. dr
Surażyński Arkadiusz, dr
Sylte Ingebrigt, dr
Szacoń Elżbieta, dr
Szafrański Przemysław, dr
Szczesio Małgorzata, dr
Szymańska Ewa, dr
Szymański Paweł, dr

Targowska-Duda Katarzyna, mgr
Tarsa Monika, dr

Temperini Claudia, dr
Trojanowska Danuta, dr
Trotsko Nazar, dr
Tykarska Ewa, mgr

Unverferth Klaus, dr

Wieczorek Marcin, dr
Wierzchowski Marcin, dr
Więcek Małgorzata, dr
Więckowska Anna, dr
Więckowski Marcin, mgr
Wilson Teresa
Winnicka Halina, mgr
Wolska Irena, dr
Wróbel Tomasz, mgr
Wujec Monika, dr
Wysocki Waldemar, mgr

Ziebholz Angelica, dr
Żelaszczyk Dorota, mgr
Żuchowska Grzegorz, dr
Żylewski Marek, dr

Podziękowania

Władzom Uniwersytetu Medycznego w Lublinie za pomoc w organizacji I Konwersatorium Chemii Medycznej oraz za pomoc logistyczną.

Polskiemu Towarzystwu Chemii Medycznej za pomoc organizacyjną.

Urządowi Marszałkowskiemu Województwa Lubelskiego

www.lubelskie.pl

Hurtowniom Elektrycznym Elmax oraz TechPol Medical sp. z o. o.

Za pomoc finansową i logistyczną.

Redakcji Kuriera Lubelskiego oraz Radiu Lublin

Za patronat medialny

Agencji Rekalomowej VIP

Za pomoc organizacyjną

Składają Organizatorzy.