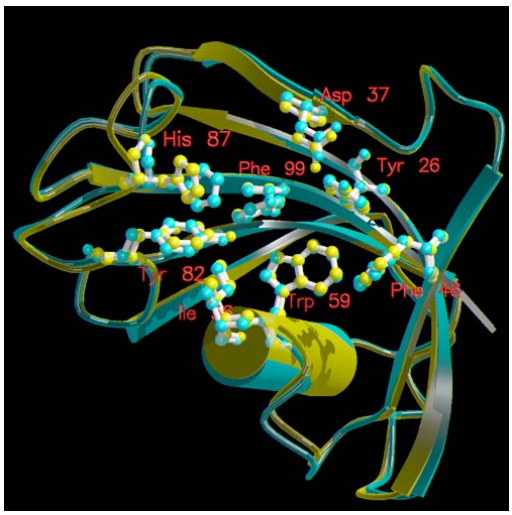
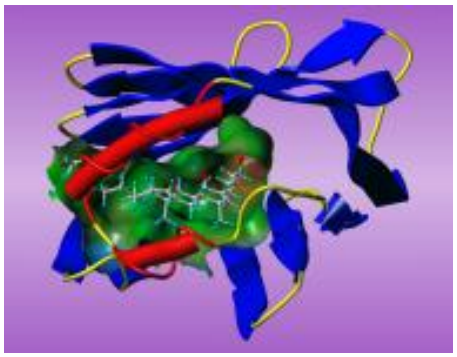
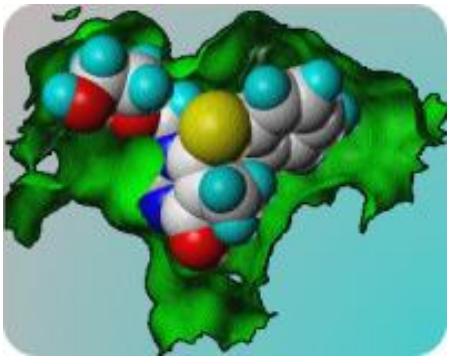


IV KONWERSATORIUM CHEMII MEDYCZNEJ

LUBLIN

08-10 września 2011





Polskie Towarzystwo Chemii Medycznej

Uniwersytet Medyczny w Lublinie

Marszałek Województwa Lubelskiego

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

Lublin, 2011

Komitet Naukowy:

Prof. dr hab. Andrzej Bojarski

Prof. dr hab. Zdzisław Chilmonczyk

Prof. dr hab. Bożenna Gutkowska

Prof. dr hab. Janina Karolak-Wojciechowska

Prof. dr hab. Katarzyna Kieć-Kononowicz

Prof. dr hab. Dariusz Matosiuk

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Dr hab. Krzysztof Jóźwiak

Dr hab. Monika Wujec

oraz

dr Monika Aletańska-Kozak

dr Marzena Rządkowska

dr Elzbieta Szacoń

mgr Marcin Hus

mgr Daniel Kupryciuk

mgr Tomasz Wróbel

Plan Konwersatorium

Czwartek, 08.09.2011

15.00-17.00 – Rejestracja Uczestników

17.00-17.15 - Otwarcie Konwersatorium

Prof. dr hab. Dariusz Matosiuk
Przedstawiciel JM Rektora Uniwersytet Medyczny w Lublinie Prof. dr hab. Andrzeja Książka;

17.15-18.00 – Wykład Inauguracyjny

Prof.Holger Stark, University of Frankfurt, Germany
„ Selectivity or promiscuity in drug development?."

18.30-22.00 – Spotkanie powitalne

Piątek, 09.09.2011

9.30-11.00 – Sesja wykładowa – International Sesion

Prowadzący sesję – prof. dr hab. Katarzyna Kieć-Kononowicz
prof. dr hab. Dariusz Matosiuk

L-1
Prof. Gilles Subra,IBMM, Universite de Montpellier 1, France
„ Chemical tools for protein structural study and peptide quantification in complex mixtures."

L-2
Prof. Adolfo Rivero-Muller, Turun Yliopisto, Finland
„ Understanding physiology by molecular biology."

L-3
Prof. Leonard Amaral, Universidade Nova de Lisboa, Portugal
„ Over-expressed efflux pumps cause multi-drug resistance of pathogenic bacteria and cancer making therapy problematic. Can we develop non-toxic compounds that inhibit their activity thereby rendering these cells susceptible to current therapies?."

11.00-11.30 – przerwa na kawę

11.30-13.00 – Komunikaty – New Active Compounds.

Prowadzący sesję – prof. dr hab. Barbara Malawska
prof. dr hab. Jan Mazerski

K-1
Dr hab.Anna Bielawska,Uniwersytet Medyczny w Białymstoku
„The effect of platinum(II) berenil complexes on apoptosis induction in human breast cancer cells."

K-2
Dr Maciej Dawidowski, Uniwersytet Medyczny, Warszawa
„ Application of Ugi (U-5C-4CR) multicomponent reaction as a key step in synthesis of 2,6-diketopiperazine derivatives with potential antiseizure activity in animal models of epilepsy."

K-3
Mgr Piotr Bujak, Uniwersytet Śląski, Katowice
„ Synthesis of functionalized 4,5-dihydroisoxazoles via tandem isomerization - 1,3-dipolar cycloaddition and studies on their antifungal activity."

K-4

Dr Beata Morak-Młodawska, Śląski Uniwersytet Medyczny, Katowice

„Selected properties of new analogues of phenothiazines of the dipyrido-1,4-thiazine type. “

K-5

Mgr Patrycja Kleczkowska, CMDK im. Mossakowskiego, PAN, Warszawa

„ New drug – new hope? PK20 opioid-neurotensin hybrid peptide as a new potent analgesic in acute pain treatment.“

13.00-14.00 – Lunch

14.00-15.30 – Sesja wykładowa – Structure Effects

Prowadzący sesję – prof. dr hab. Marek Cegła
prof. dr hab. Krzysztof Bielawski

L-4

Prof. dr hab. Marek Główka, Politechnika Łódzka

„ Geometry of thesSpacer in LCAPs: a crystallographic approach.”

L-5

Prof. dr hab. Barbara Malawska,CMUJ,Kraków

„ Is multifunctional drug able to combat Alzheimer's disease ? “

L-6

Prof. dr hab. Zdzisław Chilmonczyk,NIL, Warszawa

„ Participation of dimers in GPCRs signal transduction pathway. “

15.30-16.00 – Przerwa na kawę

16.00-17.30 – Sesja posterowa i prezentacje ustne posterów

Prowadzący sesję – dr hab. Anna Bielawska
dr hab. Andrzej Bojarski

PP-1

Dr Joanna Cytarska, CMUMK, Bydgoszcz

„ Synthesis and properties of new potential prodrugs for melanocyte-directed enzyme prodrug therapy.”

PP-2

Mgr Maciej Serda, Uniwersytet Śląski, Katowice

„ Quinoline based thiosemicarbazones and their antitumor properties.”

PP-3

Mgr Maria Żądło, Uniwersytet Śląski, Katowice

„The application of spectroscopic methods for determination of Ethoposide closed in liposomals vesicles.”

PP-4

Mgr Dawid Warszycki, Instytut Farmakologii PAN, Kraków

„ Linear combination of pharmacophore hypotheses as a new tool in search of new 5-HT_{1A} receptor ligands.”

PP-5

Dr Andrzej Chodkowski, Uniwersytet Medyczny, Warszawa

„Synthesis of new 3-(1H-indol-3-yl)pyrrolidine-2,5-dione derivatives with dual SSRI and 5-HT_{1A} activity.”

PP-6

Mgr Anna Chorąży-Jakubowska, CMUJ, Kraków

„ Application of nuclear magnetic resonance to determine the absolute configuration of stereoisomers of spiro derivatives of 6-tert-butyl-5-methoxy-6-methyl-3,6-dihydro-2H-1,4-oxazin-2-one.”

Sobota, 10.09.2011

9.30-11.00 – Sesja wykładowa – New Methodologies

Prowadzący sesję – prof. dr hab. Janina Karolak-Wojciechowska
prof. dr hab. Zdzisław Chilmonczyk

L-7
Prof. dr hab. Sławomir Filipek, Uniwersytet Warszawski
„The structure of presenilin-1 and the influence of Alzheimer's Disease mutations on binding of amyloid precursor protein."

L-8
Dr Agnieszka Kaczor, Uniwersytet Medyczny, Lublin
"Application of fractal dimension for identification of ligand-protein binding interfaces – a methodological study."

L-9
Prof. dr hab. Piotr Paneth, Poltechnika Łódzka
„ Distinguishing isoforms of lactic dehydrogenase using binding isotope effects."

11.00-11.30 – przerwa na kawę

11.30-13.00 – Komunikaty – New Active Compounds II

Prowadzący sesję – prof. dr hab. Bożenna Gutkowska
prof. dr hab. Sławomir Filipek

K-6
Mgr Kamil J. Kuder, CMUJ, Kraków
„ Search for novel histamine H_3 receptor ligands."

K-7
Dr Robert Musioł, Uniwersytet Śląski, Katowice
" Quinoline based antifungals."

K-8
Mgr Janina Witowska-Jarosz, Narodowy Instytut Leków, Warszawa
" Mass spectrometry of new serotonin transporter inhibitors."

K-9
Dr Wojciech Płaziński, IKFP PAN, Kraków
„Interactions between CD44 protein and hyaluronan: insights from the molecular modeling study."

K-10
Dr Jadwiga Turło, Uniwersytet Medyczny, Warszawa
„Selenium-enriched polysaccharides – biosynthesis, structure, biological activity."

13.00-14.00 – Lunch

14.00-15.30 – Sesja posterowa i prezentacje posterowe

Prowadzący sesję – dr hab. Monika Wujec
dr hab. Krzysztof Jóźwiak

PP-7
Mgr Katarzyna Grychowska, CMUJ, Kraków
„ Solid-phase synthesis of long-chain arylpiperazines modified with triazinone derivatives as potential 5-HT receptor ligands."

PP-8
Mgr Magdalena Knaś, Uniwersytet Śląski, Katowice
„ Profen as chiral rotors in TLC."

PP-9
Mgr Paula Kowalczyk, CMUJ, Kraków

„ Search for new GABA-uptake inhibitors among the derivatives of 2-substituted N-benzylamides of 4-hydroxybutyric acid."

PP-10

Mgr Magdalena Kulma, Uniwersytet Medyczny, Lublin

„ Application of SPR technique in ligand – nicotinic receptor interaction studies."

PP-11

Mgr Tomasz Plech, Uniwersytet Medyczny, Lublin

„ Novel 3,6-disubstituted 1,2,4-triazolo[3,4-b]1,3,4-thiadiazoles as highly potent anti-MRSA and anti-MSSA agents."

PP-12

Dr Jolanta Sochacka, Uniwersytet Medyczny, Katowice/Sosnowiec

" Binding of 6-mercaptopurine to site I on human serum albumin: prediction by molecular docking."

17.30-23.00 – Wieczór pożegnalny „Nad Zalewem"

Lista prezentacji posterowych:

PP-1 Cytarska Joanna, dr
Synthesis and properties of new potential prodrugs for melanocyte-directed enzyme prodrug therapy.

PP-2 Serda Maciej, mgr
Quinoline based thiosemicarbazones and their antitumor properties.

PP-3 Żądło Maria, mgr
The application of spectroscopic methods for determination of *Ethoposide* closed in liposomals vesicles.

PP-4 Warszycki Dawid, mgr
Linear combination of pharmacophore hypotheses as a new tool in search of new 5-HT_{1A} receptor ligands.

PP-5 Chodkowski Andrzej, dr
Synthesis of new 3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione derivatives with dual SSRI and 5-HT_{1A} activity.

PP-6 Chorąży-Jakubowska Anna, mgr.
Application of nuclear magnetic resonance to determine the absolute configuration of stereoisomers of spiro derivatives of 6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-*2H*-1,4-oxazin-2-one.

PP-7 Grychowska Katarzyna, mgr
Solid-phase synthesis of long-chain arylpiperazines modified with triazinone derivatives as potential 5-HT receptor ligands.

PP-8 Knaś Magdalena, mgr
Profen as chiral rotors in TLC.

PP-9 Kowalczyk Paula, mgr
Search for new GABA-uptake inhibitors among the derivatives of 2-substituted *N*-benzylamides of 4-hydroxybutyric acid.

PP-10 Kulma Magdalena, mgr
Application of SPR technique in ligand – nicotinic receptor interaction studies.

PP-11 Plech Tomasz, mgr
Novel 3,6-disubstituted 1,2,4-triazolo[3,4-b]1,3,4-thiadiazoles as highly potent anti-MRSA and anti-MSSA agents.

PP-12 Sochacka Jolanta, dr
Binding of 6-mercaptopurine to site I on human serum albumin: prediction by molecular docking.

P-1 Aletańska-Kozak Monika, dr
Synthesis and antibacterial activity of new 5-substituted 4-benzyl-2,4-dihydro-3H-1,2,4-triazole-3-thiones.

P-2 Baran Marzena, mgr
Evaluation of mutagenic and antimutagenic activity of benzimidazole and pyridone derivatives.

P-3 Bartuzi Damian, mgr
Theoretical investigation of opioid receptors by homology modelling based on diverse templates.

P-4 Bielawski Krzysztof, prof. dr hab.
Activity of G3 PAMAM-NH_2 dendrimer-chlorambucil conjugate on metabolism and growth of human breast cancer cells.

P-5 Bugno Ryszard, dr
New Serotonin 5-HT_7 Receptor Ligands with 1,2,4-Oxadiazole Fragment - Molecular Modeling Studies.

P-6 Czopek Anna, dr
Determination of the lipophilicity of arylpiperazinylalkyl derivatives of imidazolidne-2,4-dione and imidazo[2,1-f]theophylline by RP HPLC.

P-7 Czopek Izabela, mgr
Application of Liposomes to Encapsulate Anticancer Drugs for Chemoterapy of Lung Cancer.

P-8 Dela Anna, mgr
Influence of the substituent(s) at aromatic rings at arylidene phenylpiperazine hydantoin on affinity to 5-HT_6 and 5-HT_7 serotonine receptors.

P-9 Dołowy Małgorzata, dr
Densitometric estimation of the detection manners of acetylsalcylic acid and salicylic acid in thin-layer chromatography.

P-10 Dołowy Małgorzata, mdr
Determination of lipophilicity of ursodeoxycholic acid by TLC and computational methods.

P-11 Gomółka Anna, mgr
Synthesis of novel 4-aryl-pyrido[1,2-*c*]pyrimidine derivatives as potential antidepressants.

P-12 Handzlik Jadwiga, dr
5-Arylidene(thio)hydantoin derivatives as modulators of cancer efflux pump inhibitors.

P-13 Jarończyk Małgorzata, dr
The study of buspirone analogues docking to serotonin transporter.

P-14 Kaczor Agnieszka, dr
Studies on the mechanism of anticancer activity of 4-benzyl-3-[(1-methylpyrrol-2-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-one.

P-15 Kamiński Krzysztof, dr
Synthesis and anticonvulsant activity of new 1-[2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]pyrrolidine-2,5-diones and 1-[2-oxo-2-(4-phenylpiperazin-1-yl)ethyl]-3-methylpyrrolidine-2,5-diones.

P-16 Karcz Tadeusz, mgr
Modulation of adenosine A_1 and A_{2A} receptors affinities in the group of phenol derivatives of 1,3-dialkyl-pyrimido[2,1-f]purinediones.

P-17 Karczmarzyk Zbigniew, dr hab
The synthesis and structural characterization of 1-(1-arylimidazolidin-2-ylidene)-4-substituted-thiosemicarbazides, new potential analgesic agents.

P-18 Karolak-Wojciechowska Janina, prof. dr hab.
Impact of N-substitution on hydrogen bonds architecture in urea-hydantoins.

P-19 Karolak-Wojciechowska Janina, prof. dr hab.
X-ray studies of histamine H_3 receptor ligands from the group of piperidine derivatives.

P-20 Karolak-Wojciechowska Janina, prof. dr hab.
Search for intermolecular interactions in histamine H_4 receptor ligands in the group of 4-(4-methylpiperazino) derivatives of 1,3,5-triazine.

P-21 Kijkowska-Murak Urszula, mgr
Structural determinants of high affinity agonists of the histamine H4 receptor activity - construction of the pharmacophore model.

P-22 Klimaszewska Marzenna, dr
Isolation of polysaccharides fraction from the mycelial culture of *Lentinula edodes*.

P-23 Kos Agnieszka, mgr
The effect of humic substances on blood coagulation and fibrinolysis.

P-24 Kos Agnieszka, mgr
The application of spectroscopic methods for determination of *Vinorelbine* closed in liposomals vesicles.

P-25 Kowalczyk Wioleta, mgr
Antifungal properties of quinoline derivatives.

P-26 Kryjewski Michał, mgr
Synthesis and photophysical properties of phthalocyanine possessing adamantanylsulfanyl substituent.

P-27 Kubowicz Paulina, mgr
Cunninghamella as a microbiological model for metabolism of DL76 which is H_3R antagonist.

P-28 Kujawski Jacek, mgr
New indazole derivatives – synthesis, ion complexation, experimental and theoretical NMR studies.

P-29 Kurczab Rafał, mgr
Development and validation of methodology for designing and analysis of virtual combinatorial libraries based on defined reaction pathways.

P-30 Kurczyk Agata, mgr
Probing pharmacological space for the analysis of fragmental drug-likeness topology: application to mono- and diazanaphthalene compounds.

P-31 Latacz Gniewomir, dr
Microbiological models in study of H3R histamine receptor ligands metabolizm.

P-32 Lijewski Sebastian, stud.
Photochemistry and biological activity of novel porphyrazines endowed with peripheral thiol functionality.

P-33 Łażewska Dorota, dr
Amide derivatives of 4-methylpiperazine as histamine H_4 receptor antagonists.

P-34 Łączkowski Krzysztof Z., dr
Synthesis of the novel terpene based 2,4-disubstituted 1,3-thiazoles as potential antifungal agents.

P-35 Maiejewski Marcin, mgr inż.
Comparison of docking procedures for the set β-adrenergic receptor models complexed with their ligands.

P-36 Maniukiewicz Waldemar, dr inż.
Analysis of molecular structure and crystal packing of perindopril *tert*-butylamine salt and perindoprilat.

P-37 Maniukiewicz Waldemar, dr inż.
Synthesis and characterization of new co-crystals of tadalafil.

P-38 Maniukiewicz Waldemar, dr inż.
Structural study of Merthiolate and its derivatives.

P-39 Mazurkiewicz Jakub, mgr
5-naphthyl derivatives of hydantoin as potential efflux pump inhibitors.

P-40 Mączyński Marcin, dr
Looking for new isoxazole derivatives with potential immunorestoring activity.

P-41 Mojzych Mariusz, dr
Synthesis and biological evaluation of new pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*b*][1,2,4]triazines.

P-42 Morak-Młodawska Beata, dr
Synthesis of new 1,8-diazaphenothiazines and prediction of their biological activities.

P-43 Morak-Młodawska Beata, dr
TLC detection of new azaphenothiazines.

P-44 Morak-Młodawska Beata, dr
Synthesis and anticancer activity of quinobenzo-1,4-thiazines.

P-45 Mordalski Stefan, mgr
A system for automated validation of GPCRs homology models against mutational data.

P-46 Obniska Jolanta, dr hab.
Lipophilicity characterization of new 3,3-disubstituted Pyrrolidine-2,5-dione derivatives as potential anticonvulsant agents.

P-47 Oracz Monika, mgr inż.
Crystal and molecular structure of Baclofen hydrogen sulfate hemihydrate.

P-48 Otrebska Ewa, mgr
Search for new compounds inhibiting bacterial multidrug resistance among amine derivatives of imidazolone.

P-49 Pachuta-Stec Anna, dr
Antimicrobial activity of new derivatives of *N*-substituted amides of 1-(5-methylthio-1,2,4-triazol-3-yl)cyclohexane-2-carboxylic acid.

P-50 Pachuta-Stec Anna, dr
RP-TLC study of biologically active *N*-substituted 3-amino-5-hydroxy-4-phenyl-1*H*-pyrazole-1-carboxamides.

P-51 Piskorz Jarosław, mgr
Synthesis and photochemical characteristics of novel styryldiazepinotribenzo-porphyrazine.

P-52 Rataj Krzysztof, mgr
Comparison of homology models of 5-HT6R created with different crystal templates.

P-53 Rutkowska Ewelina, stud.
Use of HPLC method with spectrophotometric and fluorescent detection for bi… pharmaceutical preparation analyses.

P-54 Satała Grzegorz, mgr
Exploring the effect of radioligand depletion on affinity determinations in the dopamine D2 binding assay.

P-55 Serafin Katarzyna, mgr
The inhibition of HIV-I integrase by ethyl malonate amides and nalidixic acid derivatives - analogue drug design and molecular modelling.

P-56 Siwek Agata, dr
Does dehydrocyclization of 4-benzoylthiosemicarbazides in acetic acid lead to *s*-triazoles or thiadiazoles?.

P-57 Smusz Sabina, mgr
Meta-learning as an improvement of machine learning methods performance in virtual screening.

P-58 Sochacka Aleksandra, mgr
The study of reactivity of 5-amino-3-methyl-4-isoxazolecarboxylic acid azide with N-substituted hydrazines.

P-59 Sochacka Jolanta, dr
Characterization of thiopurine derivates binding site on human α_1-acid glycoprotein (Orosomucoid) using molecular docking.

P-60 Stefanowicz Jacek, mgr
Synthesis of novel 3β-Aacylamine derivatives of tropane with potential antipsychotic activity.

P-61 Stefański Tomasz, mgr, mgr inż.
A convenient methods for conversion of phenols to thiophenols and/or alkylated thiophenols.

P-62 Struga Marta, dr hab.
Synthesis, structure analyze and microbilogical evaluation of the novel tryptamine thiourea derivatives.

P-63 Szacoń Elżbieta, dr
Synthesis of new cyclic arylsulfonylurea derivatives with potential pharmacological activity.

P-64 Szczesio Małgorzata, dr
Planarity of derivatives of dithiocarbonate esters showing tuberculostatic activity.

P-65 Szczołko Wojciech, mgr
Synthesis and physicalchemical properties of porphyrazines possessing bulky peripheral substituents.

P-66 Szkaradek Natalia, mgr
Preliminary evaluation of anti-*Helicobacter pylori* activity of some new xanthone aminoalkanol derivatives.

P-67 Szymańska Ewa, dr
Studies on phenylalanine-based AMPA/KA receptor ligands.

P-68 Targowska-Duda Katarzyna, mgr
Structure Activity Relationship analysis of ibogaine analogs with the use of molecular descriptors and docking simulations.

P-69 Tylińska Beata, mgr
Synthesis of new 1-pyridin-6*H*-pyrido[4,3-*b*]carbazole derivatives and their cytostatic activity.

P-70 Urniaż Rafał, mgr
Molecular modeling study of interaction between the AMPA receptor and selected positive modulators.

P-71 Waszkielewicz Anna, dr
Preclinical evaluation of antiepileptic drugs for analgesic properties.

P-72 Więcek Małgorzata, dr
Search for histamine H_4 receptor ligands in the group of 1,3,5-triazine derivatives.

P-73 Witek Jagna, mgr
Application of interaction patterns to discriminate ligand preference to target/antitarget protein.

P-74 Wróbel Tomasz, mgr
Pitfalls of Flash purification using built-in detector.

P-75 Wróbel Tomasz, mgr
Using microwave to speed up synthesis of novel N-alkyl derivatives of dextrometorphan.

P-76 Wysocki Waldemar, mgr
Synthesis and X-ray crystallographic studies of 1,2,4-triazolin-5-thione derivatives.

P-77 Zagórska Agnieszka, dr
The synthesis and pharmacological *in vitro* screening of new imidazo- and pyrimido[2,1-f]theophylline derivatives.

P-78 Zajdel Paweł, dr
Synthesis and pharmacological evaluation of quinolone- and isoquinoline-sulfonamides of long-chain arylpiperazines as 5-HT_7 antagonists.

P-79 Zavyalova Olga, dr
The study of processes initiated by gamma radiation effect on pyrimidine nucleosides.

P-80 Żądło Maria, mgr
Use of humic substances in the medicine.


BRUKER


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IL-1

Selectivity or Promiscuity in Drug Development?

Holger Stark

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The traditional therapeutic approach “one disease – one target” has been overcome in several aspects. Many diseases have numerous reasons which reflect different disease states and different reasons for the same effects. Despite the necessity for compounds which influence only one target for basic pharmacological investigations, most drugs possess an affinity profile for numerous targets. In addition to highly selective ligands many compounds with multiple targeting purposes have been developed by design or by serendipity acting simultaneously on a number of different targets. This is especially true for complex central diseases like cognitive impairment or schizophrenia. Numerous approaches have been described and some of them have been introduced into market. Indeed, a thorough inspection of most compounds reflect that more than one target is addressed leading to an optimized profile but in the same way to undesired side effects. Not only affinity has been taken into account but also efficacy and distribution for the evaluation of the quality and quantity of drug effects. Extended knowledge on the targets, their structures and the biochemical organization as well as on structure-activity relationships are essential for the design of suitable ligands.
With emphasis on dopamine $D_{2/3}$ receptor, histamine H_3 and H_4 receptor subtypes some recent developments from our own lab will be described. New hybrid compounds with a designed profile which may be optimized for a potential therapeutic indications (e.g. schizophrenia, Parkinson´s disease, cognitive impairment). Mainly some pharmacophore substitutions on the piperazino(alkyloxy)-aryl moiety led to compounds which do have some antagonist properties at dopamine D_2, D_3 and mainly histamine H_3 receptor subtypes, while the affinity at histamine H_1 receptor as off-target has been reduced.

This work has been kindly supported by the Hesse Schwerpunkte OSF and NeFF as well as the COST Action BM0860.

L-1

Chemical Tools for Protein Structural Study and Peptide Quantification in Complex Mixtures.

Gilles Subra, David Paramelle, Christine Enjalbal, Muriel Amblard, Lubomir Vezenkov, Marcel Garcia, Marie Maynadier, Sonia Cantel, Jean Martinez

Department of Aminoacids, Peptides and Proteins, Institute of Biomolecules Max Mousseron, UMR CNRS 5247, Av. Ch. Flahault 15, 34093 Montpellier, France
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Chemistry allied with mass spectrometry can afford valuable tools to study the biological systems at the molecular level and give information on structure, function, in a qualitative but also quantitative way. Herein will be reported some applications developed the Institute of Biomolecules Max Mousseron in Montpellier.

1) Crosslinkers for protein structure determination

The technique of chemical cross-linking followed by mass spectrometry analysis has proven to bring valuable information about protein structure when NMR or X-ray crystallography data are lacking. Crosslinkers react with protein then the modified proteins are digested of chemically cleaved to afford a mixture of shorter peptides. Some of them are covalently modified by chemical reagents and the size of the crosslinker can give interesting information about the distance between the targeted residues. Analysis by a special dedicated software of MS data can facilitate this step. However, the detection of a significantly large number of cross-linked peptides in protein lysates represents the real bottleneck of this method. To address this issue we developed two families of mono and bifunctional reagents able to selectively react with accessible side chains of a protein in aqueous solution [1,2].

The first strategy involves relative enhancement and discrimination of the MALDI-MS signals by using cross-linkers bearing an UV light-absorbing label [α-cyano-4-hydroxycinnamic acid (HCCA)] and preparing samples in a neutral matrix such as a-cyano-4-hydroxycinnamic methyl ester (HCCE). This combination (HCCA tag and HCCE matrix) enable us to discriminate signal induced by tagged compounds from over-represented untagged materials avoiding chromatography separation [3]. The second methodology is based on solid supported cross-linkers. The originality resides in the fact that the whole process is realized on solid support including synthesis of the cross-linkers, reaction with the protein and enzymatic digestion. All undesired soluble materials including unreacted protein and non-covalently linked peptides are easily removed by simple washings avoiding chromatography or purification steps. Mild acidic treatment results in the cleavage of the cross-linked peptides from the solid support. Structural data are obtained straightforward as only modified peptide fragments are released and analysed by mass spectrometry. The technology was validated using horse hearth cytochrome c and apomyoglobine as an examples. The data obtained were in full accordance with those available from the NMR and X-Ray data of these proteins [4].

2) Cell penetrating compound Intracellular uptake measurement

Estimation of cell penetrating peptides (CPPs) cellular uptake relies often on radioactivity or fluorescence measurement. Results strongly differ from one study to another depending of the protocol used and in particular inaccurate distinction between membrane trapped and internalised CPP. The pioneer work of Burlina et al. set a great improvement in proposing a highly reproducible quantification method based on MALDI-TOF MS to measure the concentration of the internalised peptides. Here we describe and validate a new method to absolutely quantify CPP internalised by MDA-MB-231 breast cancer cells. Contrary to the existing protocols, this sensitive strategy does not require any purification or separation steps thanks to matrix discrimination effect induced by HCCA/HCCE Matrix/tag combination. At least, we will describe the first series of non peptidic, non cationic, cell penetrating compounds based of short oligomeric sequences of benzothiazepine scaffold [5].

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Understanding Physiology by Molecular Biology.

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Even the simplest of organisms is awfully complex, so how can we understand such complexity? One simple approach to this question is to modify one player (gene, protein, enzyme, receptor, etc.) and observe the resulting phenotype. Yet only until the advent of Molecular Biology techniques like gene modification, RNA silencing, and protein manipulation were just unfeasible. These tools allow us not only to study living systems in vitro or as cell cultures but to understand physiological processes using animal models.

We share with other animals not just similar organs but also carry many homologous genes, which play similar function too. Thus, by analyzing animals, in particular those with closer evolutionary ties e.g. mammals, we can recapitulate many of the molecular events of human physiology in health and disease, and study them in detailes. Animal models allow us to experiment new molecular and therapeutic approaches to them, something that ethically is impossible with humans. While these models are far from perfect, Molecular Biology keeps innovating tools to render them closer to the human archetype.

Nowadays, using these techniques we are able to delete, modify, insert and repair genes, control proteins, use enzymes as “reporters” and even follow the growth and migration of cells throughout an animal’s body, all with the goal of understanding physiology, and maybe to create into beneficial action for humankind. Such need for creating better models brings new challenges to molecular biology and also new opportunities to integrate novel sciences such bioinformatics and system biology.

This lecture will focus in the old and new techniques available in Molecular Medicine (Molecular Biology and Animal models) with a personal account on the experiences and limitations of the current systems and their promises that newer and future systems must fulfil.

L-3

Over-Expressed Efflux Pumps Cause Multi-Drug Resistance of Pathogenic Bacteria and Cancer Making Therapy Problematic. Can we Develop non-Toxic Compounds that Inhibit their Activity thereby Rendering these Cells Susceptible to Current Therapies?

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The major reason why longevity of the human has increased during the past 50 years is due to the reduction of infectious diseases as a consequence of effective antibiotics and vaccination. In contrast, the advent of cancer continues to rise mainly as a consequence of extended life span, although the role of cancer inducing agents in the environment cannot be ignored. Therapy of infectious diseases has become increasingly more problematic as a consequence of the use and misuse of antibiotics rendering what were previously antibiotic susceptible infections. Therapy of cancer also results in the development of resistance to anti-cancer drugs. For both bacteria and cancer cells that become resistant to the agent used for therapy, resistance to many other therapeutic agents takes place even though the bacterial or cancer cell has never been in contact with those agents. The means by which resistance takes place to two or more antibiotics, termed multi-drug resistance (MDR), involves the over-expression of genes that code for transporters (efflux pumps) that extrude the antibiotic or anti-cancer drug from the cell prior to it reaching its intended target. If drugs can be developed that can inhibit the activity of these efflux pumps, then the activity of the antibiotic or anticancer agent is possible as a consequence of their increased intracellular concentration. The presentation today will focus on the structure of efflux pumps of bacteria and cancer cells in general, the physical chemistry involved in their mechanism of action, the means by which these efflux pumps arise (induced) in the treated patient, and the types of compounds that have potential as inhibitors of the efflux pump by either direct inhibition, by competition with the antibiotic/anti-cancer agent for extrusion and indirectly, by interfering with sources of energy required for their activity.

L-4

Geometry of the Spacer in LCAPs: a Crystallographic Approach.

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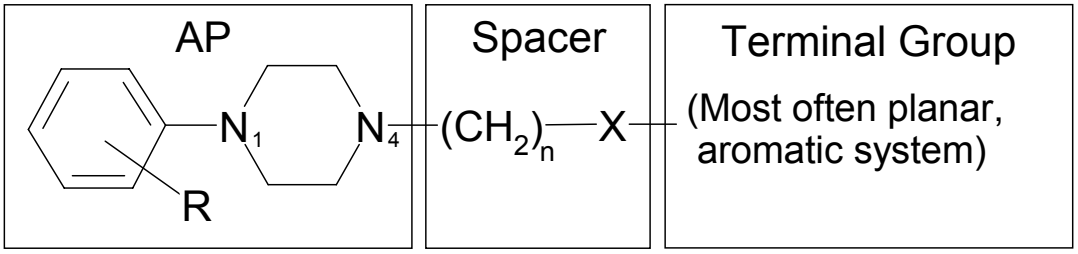
Long-Chain Aryl-Piperazines (LCAPs) are well known serotonin receptor ligands used as active ingredients of several marketed drugs. LCAPs consists of three structural units: a terminal group, an aryl at N1 atom of the piperazine ring and an aliphatic chain (called either spacer or linker) at N4 atom joining the two former units. Both arylpiperazine and terminal groups have rather rigid structures and thus their conformational freedom is very limited. The opposite is true in case of the aliphatic spacer, which allows practically any orientation of the terminal group in relation to the piperazine rings and, within specific limits, any distance between them. As a result there is a significant diversity of the conformations observed in the crystals of LCAPs (Figure), which shows possibility of their spatial adjustment to many types of serotonin receptors.



There is a vast literature concerning SAR of LCAPs ligands, particularly those showing high affinity to 5-HT1A receptor. Due to the studies several qualitative observations helpful in designing new ligands were drawn. However, due to flexible spacer and diversity of the terminal group, the scores of such approach were never high.
The latest work on new LCAPs, synthesized by dr W. Lewgowd of Medical University of Łódź [1] and our study on their crystal structures (16 compounds) have drawn our attention to the subject of the spacer flexibility. This issue has been neglected despite as much as 121 other crystal structures of arylpiperazines deposited in CSD. Our study showed two important factors not considered earlier, which has to be taken into account. One is the presence of heteroatoms or groups (depending on their chemical built some of them should be included into the terminal group). The second factor is parity of the number of atoms in the spacer chain.

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L-5

Is Multifunctional Drug Able to Combat Alzheimer's Disease ?

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Novel strategy for design more effective drugs bases on designing dual or multiple ligands. Its goal is to create a single molecule which can act simultaneously on multiple targets of therapeutic interest. This approach has been developed especially for drugs aimed at treatment of disorders with multiple pathogenic factors such as neurodegenerative disorders, cancer, hypertension, metabolic disease and allergic disease [1-3]. One such disorder is Alzheimer's disease (AD), currently the most common multifactorial, irreversible, progressive, neurodegenerative disease of the brain. AD is complex and many processes are involved in neuropathological changes leading to neuron death. The presence of cerebral plaques containing the neurotoxic □-amyloid peptide is a major pathological feature of AD. On a molecular level, the most important event is accumulation of misfolded protein in the aging brain which in turn leads to energy failure and synaptic dysfunction [4]. Many potential targets for the development of anti-AD drugs have been identified, and the multi-factorial nature of this disease requires multifunctional agents, which can be beneficial for AD treatment [5]. Successful outcomes of applying the multi-target-directed ligand methodology will be presented. These include examples of new compounds obtained via combination of structurally active moieties interacting with different targets. Our study concerned on the synthesis and investigation of new hybrid molecules interacting with multiple targets. One series of compounds represent hybrid molecules bearing two moieties linked by alkyl chain as potential AChE dual binding site and (butyrylcholinesterase) BuChE inhibitors. These compounds acted as dual binding site cholinesterases inhibitors interacting with catalytic and peripheral anionic binding site of acetylcholinesterase as well as weak inhibitors of b-amyloid fibril formation. Other example are dual-acting compounds, that act as histamine H_3 receptor antagonists/inverse agonists combined with anti-cholinesterases properties.

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Participation of Dimers in GPCRs Signal Transduction Pathway.

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In the present paper G protein-coupled receptors (GCPRs) dimers formation and activation will be discussed. GPCRs represent the largest cell surface receptor superfamily, and the largest class of drug targets with about 50% of the existing drugs currently targeting these receptors for their therapeutic action. Accumulating evidence indicates that GPCRs can assembly as dimmer/oligomers. However, the functional significance of this phenomenon in G-protein coupling and signaling is not yet clear [1, 2, 3]. A number of open questions about the functional mechanisms of GPCRs center on the interaction between particular protomers as well the role of dimerization and its pharmacological significance.

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L-7

The Structure of Presenilin-1 and the Influence of Alzheimer's Disease Mutations on Binding of Amyloid Precursor Protein.

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Presenilin-1 (PS1) is a major protein of membranous γ-secretase complex. This complex is composed of four membrane proteins PS1, APH-1, PEN-2 and nicastrin. They differ greatly in size and also in number of transmembranous (TM) domains having 1, 2, 7 and 9 TM domains for nicastrin, PEN-2, APH-1 and PS1, respectively. The γ-secretase complex performs the last cut of Amyloid Precursor Protein (APP) and generates β-amyloid peptide which aggregates in the brain of the Alzheimer's Disease patients. Diminishing of the production of β-amyloid is one of the most promising ways to stop progression of Alzheimer's Disease. However, there are also other substrates of this protease like Notch receptor which is involved in cell signaling. Therefore, the prospective γ-secretase inhibitors should be selective enough for reducing a production of β-amyloid only. Among all components of γ-secretase complex the PS1 is populated with largest number of Alzheimer's Disease mutations (over 180). This is because it contains two catalytic aspartic acid residues which perform cleavage so the structure of PS1 must be sensitive to contact with substrates and also other protein components of the proteolitic complex.

During maturation of the PS1 it is cleaved into N-terminal (NTF) and C-terminal fragments (CTF) each containing one catalytic aspartate residue. Although the topology of the NTF is well accepted as it contains six TMs, it is somewhat controversial for CTF. NMR studies provided the first glimpse on the structure of CTF in SDS micelles. The structure consisted of half-TM helix containing an aspartate, one full TM and kinked terminal TM helix as well as soluble helix. Subsequent molecular dynamics simulations of this structure in detergent micelles and also in lipid bilayers altered this structure and made it more elongated. For these investigations we used all-atom as well as coarse-grain simulations – the latter one especially for simulation of dynamics of CTF in detergent micelles starting from random mixture of detergent and water molecules. The CTF structures obtained in molecular dynamics simulations in bilayers (both coarse-grain and all-atom) showed dependence of the structure on the bilayer thickness. The rearrangement of PS1 was visible especially in extracellular loop region. The angles between TM helices stayed similar to those in NMR structure indicating that this part is stable in micelle environment. We also simulated the interactions of APP with catalytic part of γ-secretase and studied the influence of Alzheimer's Disease mutations on APP binding. Revealing of the whole mechanism of cleavage and substrate recognition by γ-secretase still requires high-resolution structures which could lead to efficient drug design.

L-8

Application of Fractal Dimension for Identification of Ligand-Protein Binding Interfaces – a Methodological Study.

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The objects in nature cannot be properly described using the Euclidean geometry. They can be better represented, however, in terms of fractal geometry, a theory elaborated by Mandelbrot. The extension of the concepts of fractal geometry towards the life science has led to significant progress in understanding complex structural and functional features characterizing tissues, cells and molecules. In particular, the concepts of fractal geometry have been applied to the description of structure and function of proteins[1-3].
The fractal nature of proteins manifests itself in the way proteins vibrate and in the manner they fill space. This is described by the spectral dimension d_s and the fractal dimension d_f, respectively. Fractal dimension, d_f, denotes the rate of change in the protein's surface area with respect to the yardstick or probe size used to measure it. The surface of proteins determines the first level of communication with its surroundings and the global and local roughness of the protein surface affects this communication in terms of diffusion, molecule recognition, and physical properties. Thus, fractal dimension, proportional to surface roughness, may be applied to description of protein-protein and ligand-protein interactions. In particular, it can be used for identification of small molecule binding sites as well as protein-protein interaction interface but even qualitative data on the relative roughness of binding sites (both small molecules and in protein-protein complexes) contain many discrepancies [4].
The aim of this study is elaboration and extensive testing of novel methodology for detection of small molecule binding sites, based on the fractal dimension. The fractal dimension d_f can be calculated according to the following formula:

$$d_f = 2 - \frac{d\,\log SES}{d\,\log r}$$

where SES denotes solvent excluded surface and r denotes a probe size. The fractal dimension is calculated per residue and "smoothened" over the neighborhood of the radius of 5Å.The methodology is tested on a set of protein-ligand complexes of known 3D structure. The studies revealed that the fractal dimension of all binding sites is significantly higher than the average for the whole protein. The differences are checked with Student t-test and are statistically significant. In conclusion, the method constitutes a valuable tool to detect ligand-protein binding interfaces.

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L-9

Distinguishing isoforms of lactic dehydrogenase using binding isotope effects.

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Details of a ligand binding in the active site of an enzyme are of great interest in many areas of chemistry, biochemistry and enzymology. Especially in drug design information about interactions between a reactant and/or inhibitor and their host molecules is of crucial importance to the design process. We have, therefore, focused our studies on specific interactions of ligands in the active sites of enzymes. In particular, we have tested if isotope effects (IEs) can shed some light on the modes of binding of ligands to different isoforms of lactic dehydrogenase (LDH).
There are a few reasons why LDH is a good model system; firstly, the experimental value of binding IE for [1-^{18}O]-oxamate bounded in LDH from rabbit muscle has been measured by us some years ago, and thus theoretical predictions can be validated. Secondly, LDH has 5 different isoforms which differ in their biophysical properties and in the molecular structures. Thus there should be subtle differences in binding modes between them. Thirdly, LDH became an important marker in the diagnosis of a large variety of diseases thus understanding differences in binding ligands by different isoforms might have practical applications.
We will discuss results of QM/MM molecular modeling of binding IEs which show that it is possible to pinpoint the origins of differences in the interactions between ligands and two different isoforms of LDH from human skeletal and heart muscles. The results of these studies have been published in the articles listed below:

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PREZENTACJE USTNE
KOMUNIKATY

K-1

The effect of platinum(II) berenil complexes on apoptosis induction in human breast cancer cells.

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The aim of the study was to compare capabilities of platinum(II) berenil complexes and cisplatin of forming inter-chain bonds, netting DNA, in MCF-7 and MDA-MB-231cells [1]. The influence of dinuclear platinum complexes on apoptosis induction was compared in breast cancer cells MCF-7 and MDA–MB-231 and in skin fibroblasts. The examinations performed by means of a flow cytometer and a fluorescent microscope indicated that the studied compounds induced apoptosis stronger than cisplatin. Additionally, the effects of platinum(II) berenil complexes and cisplatin on biosynthesis of collagen as well as on the processes of signal transmission were estimated. It was proved that these compounds were characterized by the higher capability of netting DNA both in breast cancer MCF-7 and MDA–MB-231 cells. A high cytotoxicity of berenil platinum(II) derivatives was associated with their higher capability of binding DNA of cancerous cells, compared to cisplatin. The impaired metabolism of collagen, the main component of extracellular matrix, constituting a barrier that makes it impossible for invasive cells to spread was observed in the course of various neoplastic diseases. A higher ability of platinum(II) berenil derivatives to inhibit collagen biosynthesis in comparison with cisplatin was demonstrated in breast cancer cells of MCF-7 and MDA – MB-231 [2].
An increase in protein p53 expression blocked a cell cycle and induced apoptosis. In both normal and cancerous cells, cisplatin and the studied platinum(II) berenil complexes had no influence on the content of proapoptic protein p53, which might suggest other stimulatory mechanism of a signal transmission pathway leading to apoptosis. A special attention were paid to insulin-like growth factor, IGF-I. It has been proved that platinum(II) berenil complexes caused an increase in IGF–IR expression contrary to cisplatin in both normal and breast cancer cells. Both berenil derivatives of platinum(II) and cisplatin caused no changes in the expression of a phosphorylated forms of kinase Akt. This may explain lack of the antiapoptic activity of the studied compounds, despite the high stimulation of the IGF-IR receptor [2, 3].

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K-2

Application of Ugi (U-5C-4CR) Multicomponent Reaction as a Key Step in Synthesis of 2,6-Diketopiperazine Derivatives with Potential Antiseizure Activity in Animal Models of Epilepsy.

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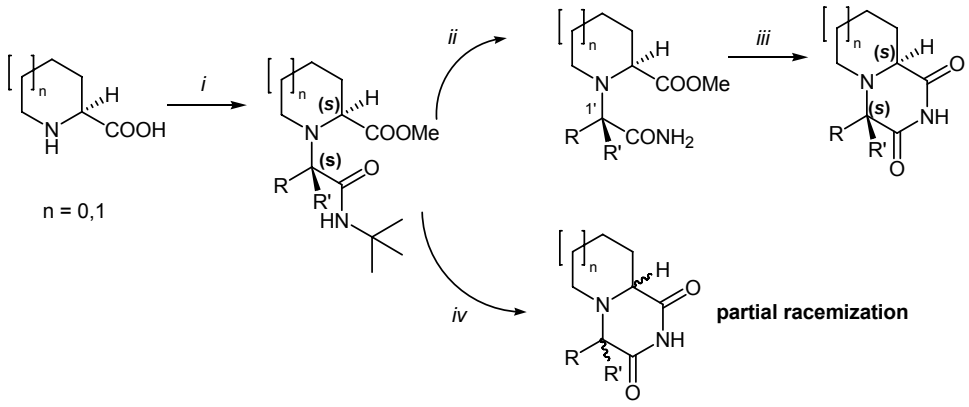
A multicomponent reaction (MCR) is a process, in which three or more starting materials react to form a single product, usually in a one-pot operation. Among the great variety of known MRCs, the isocyanide-based Ugi reaction has proven to deliver a quick access to structurally diverse intermediates for small-sized 'drug-like' molecules. The reaction is accompanied by the formation of at least one stereogenic center, and as long as a chiral substrate is used, it proceeds with high diastereoselectivity [1].
The aim of the presented work was to examine the usefulness of the U-5C-4CR (*Ugi-five-center-four-component reaction*) variant of the Ugi reaction for synthesis of chiral, bicyclic 2,6-diketopiperazine derivatives of potential anticonvulsant activity [2]. The U-5C-4CR → amide *N*-de-tertbutylation → intramolecular cyclocondensation synthetic strategy was examined, as depicted below.



Reagents and conditions: *i*. (a) RCOR', *t*Bu-NC, $FeCl_{3(cat.)}$, MeOH, rt., (b) column chromatography; *ii*. BF_3*$2CH_3COOH$, rt; *iii*. NaOH, EtOH, rt; *iv*. BF_3*$2CH_3COOH$, 90 ºC

In the U-5C-4CR step, various aromatic aldehydes or arylaliphatic/simple ketones were coupled with cyclic aminoacid (proline or homoproline), to give the Ugi products with moderate to high yields. In the majority of cases the sense of diastereoinduction was (*SS*). The subsequent reactions proceeded with retention of configuration, to furnish the biologically active (SS) stereoisomers of the final products.

K-3

Synthesis of Functionalized 4,5-Dihydroisoxazoles *via* Tandem Isomerization - 1,3-Dipolar Cycloaddition and Studies on Their Antifungal Activity.

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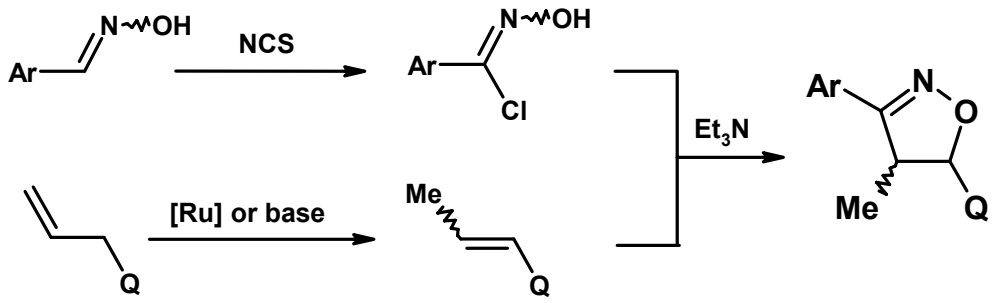
A novel, effective method for the synthesis of new isoxazolines *via* tandem isomerization of allyl compounds to 1-propenyl derivatives catalyzed by ruthenium complexes (or 18-crown-6/KOH system) and 1,3-dipolar cycloaddition of the latter compounds to arenenitrile oxides is presented [1,2]. Many of the 1-propenyl systems are difficult to obtain by methods other than isomerization of allylic precursors. Transition metal complexes and 18-crown-6/KOH system are both particularly attractive catalysts for double bond migration in allylic systems. Dipolar cycloaddition of relatively stable nitrile oxides to 1-propenyl systems allows simple and convenient synthesis of a series of functionalized 4,5-dihydroisoxazoles containing the Q group (e.g., R_2N, RO) connected with the heterocyclic ring (Scheme). Dihydroisoxazoles of this type are very difficult to obtain by other methods. All reactions are strictly regioselective, the cycloaddition product is 5-*O*-substituted (4,5-dihydroisoxazole) or 5-*N*-substituted (4,5-dihydroisoxazole) only.

The broth microdilution test was used for the assessment of *in vitro* antifungal activity of the synthesized compounds against *Candida albicans* ATCC 44859, *Candida tropicalis* 156, *Candida krusei* ATCC 6258, *Candida glabrata* 20/I, *Trichosporon beigelii* 1188, *Aspergillus fumigatus* 231, *Absidia corymbifera* 272 and *Trichophyton mentagrophytes* 445. Fluconazole was used as the standard.



Ar = 2,6-dichlorophenyl-, 2,4,6-trimethylphenyl-, 2,4,6-trimethoxyphenyl-
Q = Me_2N, H_2NCONH, MeCONH, MeC(O)NAr, 4-MeOPhCH=N, *N*-phtaloimidolyl, *N*-imidazolyl, HOC_2H_4O, HOC_4H_8O

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K-4

Selected Properties of New Analogues of Phenothiazines of the Dipyrido-1,4-thiazine Type.

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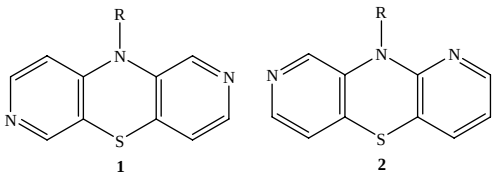
Phenothiazines are significant class of heterocyclic compounds for their interesting chemical properties and widely recognized pharmacological activity (neuroleptic, antihistaminic, antitussive and antiemetic). Recent reports demonstrated promising anticancer, antiplasmid and antibacterial activities, reversal of multidrug resistance (MDR) and potential treatment in Alzheimer's, Creutzfeldt-Jakob and AIDS diseases of classical and newly synthesized phenothiazines [1]. Chemical modification of the phenothiazine structure was carried out by replacing the benzene ring with the pyridine ring and by introduction of new substituents in position 10 [1].
Up till now in the world chemical literature, there were described only four dipyrido-1,4-thiazines: 1,6-, 1,9-, 3,6-, 3,7-diazaphenothiazines [2]. In our search we modified the phenothiazine structure with the pyridine rings to form new azaphenotiazines being 10-substituted 2,7-diazaphenothiazines **1** [3,4] and 10-substituted 1,8-diazaphenothiazines **2**.



1 **2**

R = H, alkyl, aryl, heteroaryl, alkyloaminoalkyl

In our study we determined the spectroscopic, chromatographic, lipophilic and biological properties. Some compounds exhibited very significant anticancer activity against human tumor cell lines deriving from the colon, lung, breast, renals, ovaries, prostate and CNS, and against melanoma and leukemia cell lines determined in National Cancer Institute in Bethesda, USA [4]. Some selected 10-substituted 2,7-diazaphenothiazines exhibited immunosuppressive activity *in vitro* and *in vivo*. The compounds were found to strongly suppress the humoral immune response even at low concentrations and inhibited the delayed-type hypersensitivity lipopolysaccharide-induced production of tumor necrosis factor and interleukin-6 in cultures of human blood cells. The suppressive effect could be associated with the ability to inhibit activities of TNF-α and IL-6 [5].
Several of 2,7-diazaphenothiazines exhibit significant antioxidant activity with IC_{50} values in the range of 64-125 μM [6].

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K-5

New drug – New Hope?
PK20 Opioid-Neurotensin Hybrid Peptide as a New Potent Analgesic in Acute Pain Treatment.

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Acute pain is commonly defined as “the normal, predicted physiological response to an adverse chemical, thermal or mechanical stimulus . . . associated with surgery, trauma and acute illness” [1]. There are numbers of methods to control acute pain, which have progressed as a result of the discovery that early control of pain can shape its subsequent evolution. However most of used methods rely upon opioid analgesics, which – apart from desired pain relief – produce several side effects such as development of dependence and addiction as well as sedation, dysphoria, and constipation. One of the solution to this problem is creating new drugs characterized by their specific structure in which two (or more) potent analgesics are hybridized in one.
Neurotensin (NT) as well as opioids exert analgesia. Opioid drugs block pain signals by interacting especially with mu-opioid receptors [2], whereas NT or its analogs act independently of the opioid pathways [3]. Therefore, by combining these two elements, the antinociceptive effect might be obtained either by the opioid or neurotensin part alone, or by synergism of two interacting parts, thus acting much stronger than in case of separate administration of each of them.
Indeed, presented here PK20 opioid-neurotensin hybrid peptide exerts high time- and dose-dependent analgesic effect when administered centrally as well as peripherally [4]. Its antinociceptive potency is significantly intensified when compare to saline and morphine. This growing analgesia mediated by the peptide suggests of possible PK20’s stability in the plasma and implies a delayed enzymatic degradation.Additionally, by blocking the PK20’s antinocisponsive action with either naltrexone or SR48692, used as selective antagonists of each pharmacophore receptor, a synergistic interaction between both parts of this novel chimera has been shown.

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K-6

Search for Novel Histamine H_3 Receptor Ligands.

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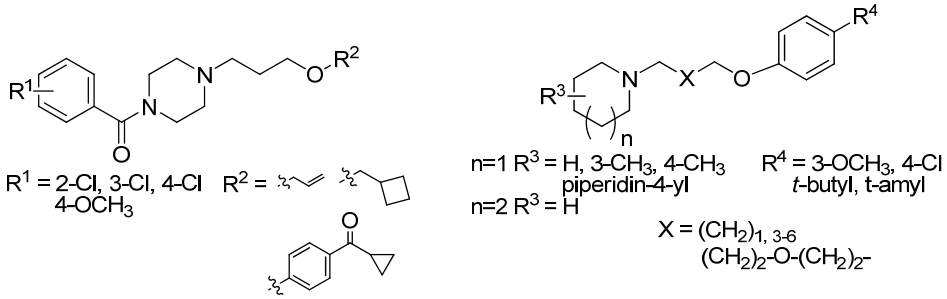
Histamine H_3 receptors are constitutively active G_i-protein coupled receptors mostly expressed in central nervous system (CNS), described as presynaptically located auto- and heteroreceptors. Activation of these receptors results in modulation of histamine levels as well as that of other neurotransmitters like ACh, NA, 5-HT. Therefore, blockade of these receptors could be useful in the treatment of different CNS disorders [1].
First known histamine H_3 receptor antagonists contained an imidazole group, which may be connected to a number of side effects, due to its potential interaction with cytochrome P_{450}. Among others, one of the first successful imidazole replacements has been performed by piperidine moieties. According the proposed pharmacophore for histamine H_3 receptors, heterocyclic residue should be connected via the aliphatic linker with polar moiety, connected itself by other linker with the lipophilic residue.



Scheme 1 General structure of the obtained derivatives

In this study we obtained histamine H_3 receptor ligands that fit to the general histamine H_3 receptor core proposed by Lipp et al.[2]. Compounds could be divided in two groups: piperazine and piperidine derivatives (**Scheme 1**). All of the obtained derivatives were tested *in vitro* for desired histamine receptor activity showing weak (piperazine derivatives) and moderate to very high (piperidine derivatives) histamine H_3 receptor activity. Moreover fluorescent compound was also obtained and showed very high, picomolar affinity at histamine H_3 receptor *in vitro* (hH_3K_i = 0.11 nM).
For the group of piperidine derivatives lipophilicity studies were provided, using reversed phase planar chromatography method. Experimental values were then compared with values obtained by various computational programs. Fluorescent properties of one of the compounds were also studied. Computational approaches allowed the *in silico* visualization of binding to histamine H_3 receptor model described by Levoin *et al* [3].

Acknowledgements:
This work was partly supported by the Polish Ministry of Science and Higher Education Grants No: K/PBP/000264, K/ZDS/001915, DAAD/55/2007and the COST Action BM8006.

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K-7

Quinoline Based Antifungals.

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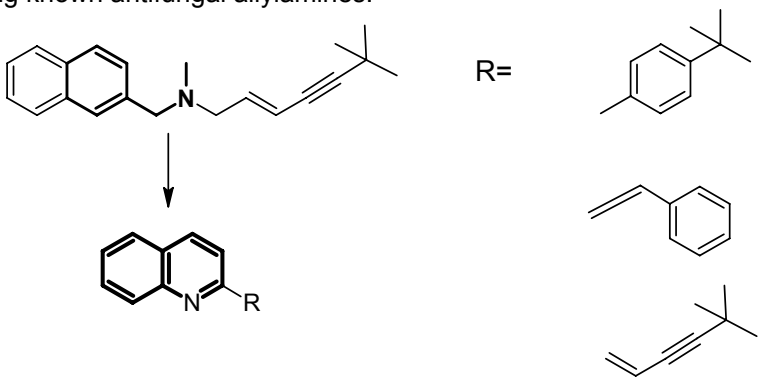
Modern antifungal therapy have to deal with number of issues associated with broad but inadequate arsenal of drugs. The most commonly used agents have serious drawbacks as toxicity and resistance. On the other hand new drugs and drug candidates under clinical trials do not guarantee better overall performance. This is not the only reason of strong need for new antifungals. The other is – observed during last four decades – steadily growth of the fungal infections. Especially in patients with compromised immune system[1]. Morbidity and mortality of some endemic and opportunistic mycoses is still very high[2]. Thus we strongly need new drugs acting through new mechanisms on new targets. Lack of expected success form established methodology like combinatorial chemistry and high throughput screening we turn on fragment based design and search for privileged structures. Quinoline moiety by its abundant presence in various natural and bioactive compounds may be considered as such structure [3-6]. We wish to introduce here the fragment based approach to quinolines mimicking known antifungal allylamines.



This approach lead to well known for their biological activity styrylquinolines as naftifine analogues. Styrylquinolines were broadly studied for their anticancer and antiviral activity and FZ-41 is an example of HIV integrase inhibitor under clinical trials. We explored the styrylquinolines finding some highly active antifungals.

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K-8

Mass Spectrometry of New Serotonin Transporter Inhibitors.

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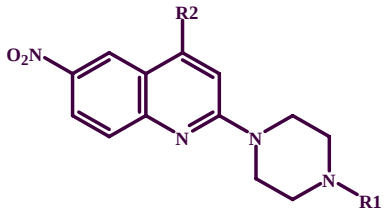
The serotonin (5-HT) transporter (SERT) is the main molecular target for the selective serotonin reuptake inhibitors (SSRIs), currently the most prescribed antidepressant drugs. We obtained several new potential SERT and 5-HT_{1A} receptor ligands of the general formula **1**. The compounds were evaluated in SERT affinity tests and appeared to possess high (nanomolar) affinity to SERT.



1

We examined a fragmentation of some new SSRI's (active in *in vitro* and *in vivo* tests) in MS sources and found exceptional stability of negative ions.

This study was supported by a grant PNRF-103-AI-1/07 through the Norwegian Financial Mechanism.

K-9

Interactions Between CD44 Protein and Hyaluronan: Insights From the Molecular Modeling Study.

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CD44 is a major cell surface receptor for hyaluronan (HA), i.e. a high–molecular weight copolymer of N-acetyl-D-glucosamine (GlcNAc) and D-glucuronic acid (GlcUA), $(\beta\text{-}1,3\text{-GlcNAc-}\beta\text{-}1,4\text{-GlcUA})_n$. The molecular dynamics study was focused on the dynamic and thermodynamic aspects of HA-CD44 interactions. The extracellular part of the CD44 (link module) immersed in explicit water solution was considered. In summary, the interactions between hyaluronan and CD44 protein are mainly of the hydrogen bonding type; HBs are usually formed involving the central part of the HA chain (i.e. residues from GlcUA5 to GlcUA7). Hydrophobic interactions (involving Ile 92, Ile 100, Leu 111) and salt bridges are of secondary importance. Structures corresponding to the two crystal forms ('A' and 'B', according to ref. [1]) can be distinguished only in some cases when considering the values of dihedral angle φ at Y46 residue. The free energy barrier associated with the Arg56-HA distance can be easily overcome and both 'A' and 'B' states reduce to some average, dynamic structure. The simulated values of the Gibbs free energy changes accompanying the formation of CD44-hyaluronan complexes remain in (qualitative) agreement with the available experimental data [1].

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K-10

Selenium-enriched polysaccharides – biosynthesis, structure, biological activity.

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Lentinula edodes (Berk.) Pegl. is a source of two well-studied and widely approved polysaccharide medicines: LEM (an acronym for *Lentinula edodes* mycelia), a protein-bound polysaccharide derived only from the mycelium, and lentinan – a cell-wall branched β-D-glucan extracted from both the fruiting body and mycelium. Both compounds are immune system enhancers that demonstrate anticancer activity.

In our previous studies we demonstrated that submerged cultivated mycelium of *L. edodes* accumulated selenium from the cultivation medium very effectively, more effectively than yeast [1]. Selenium was well bioavailable from the mycelial preparations in *in vitro* and *in vivo* tests [2]. Selenium-containing compounds present in water and alcohol mycelial extracts enhanced antioxidant and reducing power, and free radical scavenging effect in *in vitro* tests for almost 100- 400% [3]. The first goal of the present study was to test if selenium combines to the cell wall polysaccharides in *L. edodes*. The next was to isolate Se-enriched polysaccharide fractions from *L. edodes* mycelium cultivated under the submerged conditions in selenium-enriched medium. Ng and Yap and Chihara's methods of isolation were used. The second objective was to determine the structure of Se-enriched polysaccharides. The monosaccharide composition was determined after hydrolysis performed with trifluoroacetic acid, by reversed-phase high-performance liquid chromatography (RP HPLC) with UV detection. The total concentration of Se was determined by RP-HPLC with fluorimetric detection. X-ray absorption spectroscopy (XAFS) was used to probe the oxidation state of selenium. The molar weight of Se-enriched fractions was determined by the ***gel permeation chromatography*** (GPC). IR and NMR spectra were used to determine the type of glycosidic bonds. Finally, Se-enriched polysaccharides were tested for its antioxidant, cytotoxic and immunomodulating properties. All results regarding Se-enriched polysaccharides were compared with that of reference polysaccharide fraction, extracted from mycelium not enriched in Se.

Results: Approximately 13% of total mycelial selenium was combined to the polysaccharide fractions. Concentration of selenium in tested polysaccharides was in range 210 - 67μg/g. Se-enriched fractions contained mainly glucose, mannose and galactose. The molecular weight of the polysaccharides was 200-400 KDa. Isolated fractions contained 3-10% of protein. The type of glycosidic bounds was mainly β. XAFS analysis showed that the degree of Se oxidation in the polysaccharide was equal to –II and 0. The comparison of cytotoxic profiles of tested fractions revealed that polysaccharide was not toxic toward HeLa (cervix carcinoma) and HUVEC (normal) cells. However, the Se-enriched mycelial polysaccharide fraction of high molecular weight significantly enhances viability of cells; that may be effect of the enhanced antioxidant activity. When assayed *in vitro* Se-enriched fractions caused significant inhibition of human lymphocyte activation induced by mitogens.

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Acknowledgments:

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PREZENTACJE USTNE
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PP-1

Synthesis and Properties of New Potential Prodrugs for Melanocyte-Directed Enzyme Prodrug Therapy.

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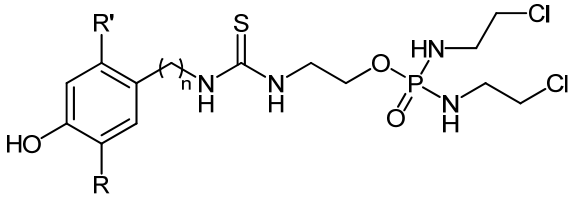
Melanocyte-directed enzyme prodrug therapy (MDEPT) has been proposed as a selective strategy for the treatment of malignant melanoma [1]. This therapy takes advantage of the unique occurrence of over expression of the enzyme tyrosinase gene in melanocytes and melanoma cells [2]. When melanocytes become malignant, the genes responsible for expression of tyrosinase upregulate causing a significant increase in the level of tyrosinase within the cancer cells [3]. Melanoma tissue have a sufficiently high concentration of this enzyme to activate prodrugs. Using tyrosinase as a prodrug-activating enzyme, allowing cancerous cells to locally activate prodrugs, raising anticancer activity without a corresponding increase in overall toxicity and minimization of side effects. There is an assumption that the best substrates for tyrosinase are phenol derivatives, which can be activated by several mechanisms leading to the formation of active form of quinine [4].
The problem to be solved is to design prodrugs that are not undergone activation by cytochrome P450 in the liver to the activation of tyrosinase in melanoma. According to recent studies DNA alkylating agents are promising in the cancer chemotherapy. Among many of the agents isophosphoramide mustard (iPAM) was selected, which is active, cytotoxic metabolite of ifosfamide (IF), a widely used anticancer alkilating drug [5].
Our reaserch concentrated on the synthesis, the selected chemical properties, stability, antitumor activity and toxicity of new compounds, potential prodrug for MDEPT therapy. The aim of research was to find a potential prodrug, which is minimally metabolized by liver enzymes, and eventually will be able to generate reactive quinone metabolites in melanoma cells due to bioactivation by tyrosinase. We designed and synthesized such prodrugs, which contain a unit sensitive to the activation of tyrosinase coupled with isophosphoramide mustard, a DNA alkylating agent, by means of thiourea group:



n = 0, 2
R = H, OH
R'= H, OH, $CH_2CH_2NH_2$

Prodrugs should have a good stability under phisiological conditions. Solubility and hydrolytical stability of our potential prodrugs was examined. Further studies on the susceptibility to activation of tyrosinase of the obtained compounds are in progress.

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PP-2

Quinoline Based Thiosemicarbazones and Their Antitumor Properties.

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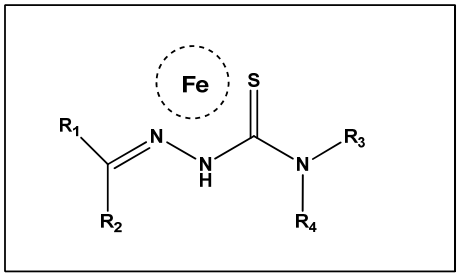
Iron, due to its unique biochemical and biophysical properties is present in the most important processes within human cells. The transportation of oxygen and its presence in complex proteins, such as transferrin and ferritin, can be used to highlight the role of iron [1]. Despite of iron importance in living cells, high levels of this bioelement have been identified as a risk factor for the development of cancer.

Since early 1950s thiosemicarbazones (**TSC**) are described as a class of compounds with a wide spectrum of biological properties. Due to their easy preparation and purification heterocyclic thiosemicarbazones are an interesting medicaments with a pharmaceutical applications (antibacterial, antiviral, antifungal activities). Furthermore TSC can be perceived as a convenient *N*,*N*,*S*- donor ligands, creating various metal complexes.

Novel iron chelators based on quinoline scaffold have been synthesized and tested for antiproliferative activity. They were found to be active against **HCT116** p53 positive and p53 negative and **SK-N-MC** cancer cells. Clonogenicity of the most active compounds was also examined and revealed that these compounds induce mitotic catastrophe in malignant cells.

Fig.1
Iron chelator based on thiosemicarbazone scaffold.



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PP-3

The application of spectroscopic methods for determination of *Ethoposide* closed in liposomals vesicles.

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The main characteristic of liposomes is the spontaneous creation of bubbles, in which various solutions can be closed. This explains the usage of liposomes in medicine. They are used to incorporate drugs, antibodies, antigens, nucleic acids. This method of drug delivery, or another substance, it is much safer for the body and protects the material against rapid degradation. The latest technologies are designed to create a method of drug delivery that is of most appropriate dosage, is non-toxic to the body, while maintaining high efficacy. The objective of the study was research on incorporation of drugs into liposomes, obtained by dry film method and a modified reverse-phase drug etoposide (ETO) used in the therapy and to investigate multidrug the incorporation of the liposomes. UV-Vis spectroscopy and ^{1}H-NMR was used to characterize the system liposome/drug. Based on the curves calibration study medications the concentration and the percentage of encapsulation (% E) of individual drug contained in liposomes obtained by both methods has been determined.

PP-4

Linear Combination of Pharmacophore Hypotheses as a New Tool in Search of New 5-HT$_{1A}$ Receptor Ligands.

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Matthews correlation coefficient (MCC) is a measure of the quality of binary classifications which is often used in evaluation of prediction models. The range of MCC is from -1 to 1, where value of 1 represents perfect prediction; 0 random, and -1 an inverse prediction. Here, MCC was used to discus efficiency of 5-HT1AR pharmacophore models and their linear combinations.
Generation of pharmacophore hypotheses was based on three different approaches of 5-HT1AR ligands clustering: (i) using 3D pharmacophore, (ii) MOLPRINT 2D fingerprints (as implemented in Canvas software [1]), or (iii) manually, based on a common core, containing two basic pharmacophore features. Next, for the obtained clusters (27, 36 and 28, respectively) representative compounds were selected (diversity-based selection tool, Canvas [1]), to be used for final models production (Phase, [2]). The best hypothesis for each cluster was then tested on different test sets, consisting of 200 active compounds (not used in pharmacophore development), 200 decoys (extracted from ChEMBL database [3]) and 200 assumed inactives (already used drugs lacking data for 5-HT1A receptor).
Statistics for all possible linear combinations of hypotheses were calculated by an in-house script. Finally, the best linear combination from each approach was validated on test set consisting of compounds extracted from an updated ChEMBL version (May 2011) which were not present in previously used release. The linear combination of pharmacophore models created on automatically clustered ligands by using MOLPRINT2D approach was the most efficient. Moreover, in all the cases efficiency of single hypotheses was much worse than their linear combinations. The created pharmacophore models will be used in further studies in multistep virtual screening in order to search for new compounds acting on 5-HT1A receptor.

Acknowledgments
This study was partly supported by grant PNRF-103-AI-1/07 from Norway through Norwegian Financial Mechanism; http://www.cns-platform.eu/

[1] Canvas, version 1.4, Schrödinger, LLC, New York, NY, 2011.
[2] Phase, version 2.2, Schrödinger, LLC, New York, NY, 2011
[3] https://www.abi.ac.uk/chembl/

PP-5

Synthesis of New 3-(1*H*-indol-3-yl)pyrrolidine-2,5-dione Derivatives with Dual SSRI and 5-HT$_{1A}$ Activity.

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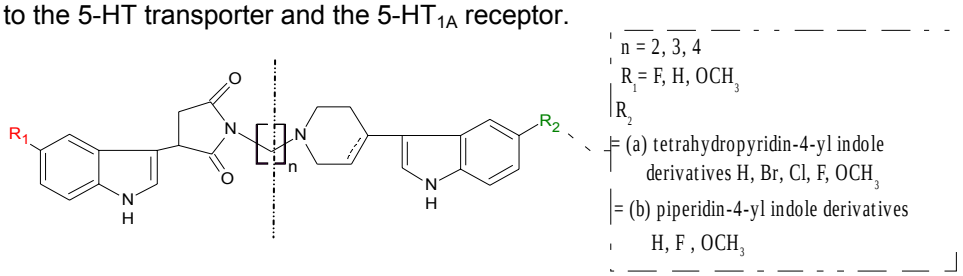
It is well known that selective serotonin reuptake inhibitors are effective in treatment of depression. It has been proposed that the addition of a 5-HT$_{1A}$ agonist component to the action of a SSRI can limit the side effects including delayed onset of action. In this way it is possible to obtain a new generation of antidepressants in the SSRI + group.
We report the synthesis of a new set of compounds of general structure as below with structural modification in pharmacophoric and terminal moiety. Many of our derivatives showed a high/very high affinity to the 5-HT transporter and the 5-HT$_{1A}$ receptor.



Currently, several compounds of SSRI+ group are in various stages of clinical trials (OPC-14523 II phase, MN-305 II/III phase, AP-521 II phase, Vilazodon III phase, Gepiron III phase), which confirms the potential of these compounds as a new generation of drugs [1-2].
We synthesized a series of compounds (their structure was confirmed by ^{1}H and ^{13}C NMR spectra) of which the highest affinity show:

Compound	n	R_1	R_2	Receptor 5-HT$_{1A}$ [^{3}H]8-OH-DPAT		SERT [^{3}H]citalopram	
				Ki [nM]	IC50 [nM]	Ki [nM]	IC50 [nM]
F1*	4	H	H	15,7 ± 2,0	28,2 ± 4,1	5,7 ± 0,5	15,3 ± 0,9
MF101	4	H	H	12,5 ± 1,7	21,3 ± 2,1	11,3 ± 0,6	30,2 ± 0,95
MF104	4	H	F	17,6 ± 2,9	30 ± 3,5	20,0 ± 0,7	53,3 ± 12,3
MF109	4	OCH_3	H	30,4 ± 1,8	54,8 ± 5,5	2,6 ± 0,3	6,8 ± 0,7
MF112	4	OCH_3	F	32,2 ± 1,5	57,9 ± 4,3	6,3 ± 0,6	16,8 ± 2,3
F15	4	H	OCH_3	3,2 ± 0,2	5,8 ± 0,5	46,2 ± 2,5	123,0 ± 7,0

* piperidin-4-yl derivative, other derivatives are 1,2,3,6-tetrahydro-pyridin-4-yl

Preliminary results of in vitro studies showed high affinity of 3-(1*H*-indol-3-yl) pyrrolidine-2,5-dione to 5-HT$_{1A}$ receptor and SERT, due to which these compounds can be considered a good entry point for future biological investigations.

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PP-6

Application of Nuclear Magnetic Resonance to Determine the Absolute Configuration of Stereoisomers of Spiro Derivatives of 6-*tert*-Butyl-5-methoxy-6-methyl-3,6-dihydro-*2H*-1,4-oxazin-2-one.

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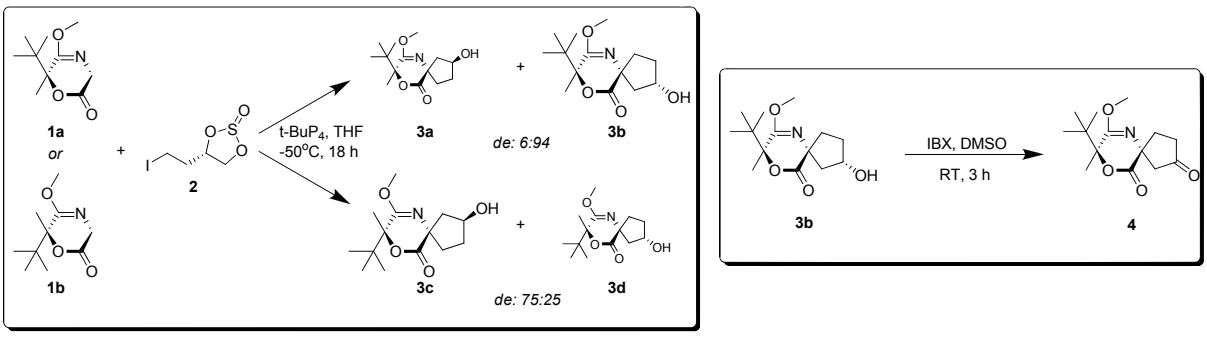
One of the most challenging goals in biomimetic research is the construction of new peptide sequences characterized by improved pharmacokinetic and pharmacodynamic properties compared with natural active peptides and proteins. Among the many non-coded amino acids, quaternary α-amino acids play a key role in these studies [1].
The aim of our study was the synthesis of chiral aminocyclopentanecarboxylic acids using glicyne equivalent (**1**) and cyclic sulfite (**2**) derivatives as nucleophilic reagent In our research we used glycine equivalent (**1**) described by *Wanner and coworkers*. Compound **1** is a very useful tool for the construction of α,α-disubstituted amino acids, as its chirality raises from a quaternary carbon atom and so it may be subjected repeatedly to deprotonation for alkylation reactions without the risk of racemization [2].
We obtained four stereoisomers (**3a-d**) of the spiro derivatives of 6-*tert*-butyl-5-methoxy-6-methyl-3,6-dihydro-*2H*-1,4-oxazin-2-one with high stereoselectivity. The structure of compounds obtained were determined using NMR studies. Due to high complexity of the spectra caused by strong signal overlapping proper spectral assignment was done through the analysis of 2D spectroscopy. Apart of chemical structure confirmation it was of great importance to elucidate stereochemistry of obtained products. Unfortunately, previously mentioned strong signal overlapping did not allow us to accomplish this from direct measurement. To fulfill this task various experiment were performed. Chemical shift reagents, chiral solvating agents and finally derivatization of investigated compound were used to differentiate important for stereochemistry studies signals.



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Acknowledge:
The study is supported from the Polish Minister of Higher Education research project no. N N405 620938

PP-7

Solid-Phase Synthesis of Long-Chain Arylpiperazines Modified with Triazinone Derivatives as Potential 5-HT Receptor Ligands.

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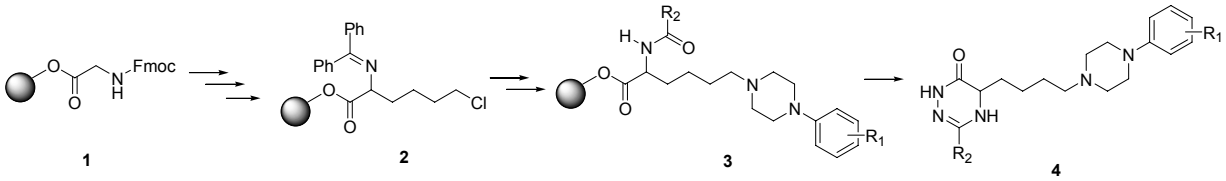
Long-chain arylpiperazine derivatives exert a high affinity for G-protein coupled receptors (such as serotoninergic, dopaminergic and adrenergic receptors) and constitute an important class of CNS acting agents . The general chemical structure of long-chain arylpiperazine derivatives consists of a piperazine moiety with a substituted phenyl ring, a so-called tail of the molecule, which is separated by an alkylen linker from a heterocyclic terminal fragment (a head).[1] According to many SAR studies, all those substructures highly influence the receptor affinity, selectivity and intrinsic activity.[2]
As a part of our ongoing studies to identify novel multi receptor ligands in a group of arylpiperazine derivatives, we proposed an introduction of a triazinone moiety as a new heterocyclic terminal fragment.



1 2 3 4

The designed compounds were synthesized starting from Fmoc-protected glycine attached to the Wang resin (**1**). The novelty of the presented approach involves manipulating with different protecting groups to enable the monoalkylation of the α-carbon of glycine with α-ω-dihalogene alkane,[3,4] followed by nucleophilic substitution with arylpiperazine derivatives and acylation of glycine moiety with respective carboxylic acid to give intermediate (**3**). The final products (**4**) were prepared by conversion of an amide bond into tioamide and subsequent one-pot cleavage-cyclisation process yielding 1,2,4-triazin-6-one fragment.[5,6]

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PP-8

Profen as Chiral Rotors in TLC.

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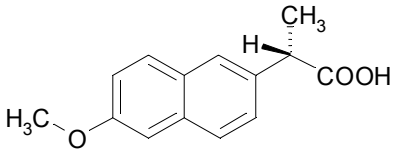
Molecular and chiral rotors are molecules able to produce a variety of special effects, due to their ability for the specific rotational motion, however, these effects are not well recognized.
In this work we present that in the thin-layer chromatography (TLC) systems, the chiral rotors can deviate their migration route from the expected straight-line direction. Although lateral relocation have been theoretically predicted for the fluxes of rotating molecules, such phenomena have never been observed in the experiment.
Profen drugs investigating by means of TLC show lateral relocation of the analyte spots in planar chromatograms. The investigated chiral propionic acid derivatives, i.e., ibuprofen, naproxen, katoprofen or flurbiprofen, and variety of other compounds, while migrating with the solvent on the vertical and horizontal TLC plates, deviated from the straight-line route.



naproxen

We have also showed an influence of molecular chirality of impregnates (L- and DL-arginine) on RF values and chromatographic spots' deviation.
TLC systems used in these experiments were composed of the different stationary and mobile phases. The credibility of the experiment was tested by the blind samples, which don't deviate their migration routes in TLC.

PP-9

Search for New GABA-uptake Inhibitors Among the Derivatives of 2-Substituted *N*-Benzylamides of 4-Hydroxybutyric Acid.

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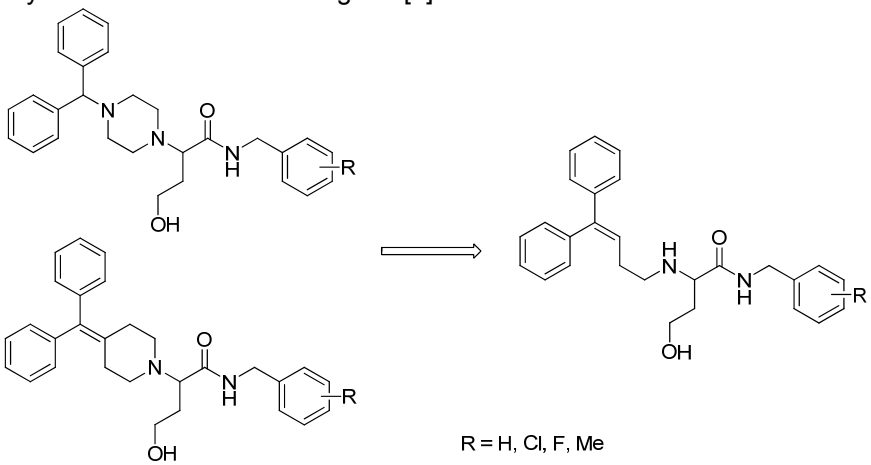
4-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system [1]. It is believed that many neurological disorders such as epilepsy, anxiety, neuropathic pain, Huntington Chorea, Morbus Parkinson and some forms of schizophrenia are associated with a reduced neurotransmission in the GABAergic system [2]. One of the many ways of controlling GABAergic disorders is inhibition of GABA-uptake [3]. Although many GABA uptake inhibitors possess antiepileptic properties only Tiagabine is GAT inhibitor currently available for the treatment of epilepsy. This work is a continuation of research which aim is synthesis of new GAT inhibitors among amide derivatives of butanoic acid. Based on obtained results of chemical and pharmacological studies, new series of *N*-benzylamides of GHB was designed [4].



The obtained compounds were tested for the inhibitory activity at the four murine GABA uptake transporters mGAT1 – mGAT4 expressed in HEK cells. The determined for them pIC_{50} values are in range 4.15-4.54 (GAT-1), 4.32-4.69 (GAT-2), 4.49-4.73 (GAT3) and 4.72-4.96 (GAT-4). Among the compounds investigated *ortho*-chloro-*N*-benzylamid 2-(4,4-diphenyl-3-butenylamin)-4-hydroxybutyric acid showed the highest affinity at mGAT4 (IC_{50} = 4,96).
In order to defined structure-activity relationship within group of compounds tested their lipophilicity was determined using reversed phase thin layer chromatography.

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Acknowledgements
Financial support of this work by the Jagiellonian University Medical College K/ZDS/001919 grant is gratefully acknowledged.

PP-10

Application of SPR Technique in Ligand – Nicotinic Receptor Interaction Studies.

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Physostygmine and galanthamine are low molecular weight alkaloids that act as a competitive and reversible acetylcholinesterase inhibitors but also as a positive allosteric modulators (PAMs) of the activity of nicotinic acetylcholine receptor (nAChR) by increasing the concentration of acetylcholine in the brain [1]. For this reason they play significant role in allosteric modulation of the nAChR, thereby enhance gating of the receptor in the presence of agonists.
Since 1990, Surface Plasmon Resonance (SPR) method have been used to study protein interaction without labeling [2] and application for small-molecule analysis, which generates high-resolution information about a wide range of binding interaction. We will measure directly binding of PAMs to the α7 and α3β4 nAChR using the *SPRimager II System*. For this purpose the plasma membrane with nicotinic acetylcholine receptors on the surface will be isolated from transfected HEK293 cell lines and will be immobilized on the gold surface of *SpotReady*™ chip. The sensor surface will be captured by receptors in the presence of membrane environment because nAChRs need to be in membrane containing specific lipids to display native properties [3]. After that the analyte will be injected on nAChRs captured sensor surface and association/dissociation will be monitored in the time intervals. These experiments will allow us to determine a kinetic of receptor- ligand interaction.
We expect that SPR technology will become a common method for characterizing the interaction of positive allosteric modulators with different subtypes of the nicotinic acetylcholine receptors.

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PP-11

Novel 3,6-Disubstituted 1,2,4-Triazolo[3,4-b]1,3,4-thiadiazoles as Highly Potent anti-MRSA and anti-MSSA Agents.

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Treating infections caused by drug-resistant bacterial strains constitutes one of the most essential challenges for medicine nowadays. Methicillin- and vancomycin-resistant strains of *Staphylococcus aureus* are responsible for most infections of this type. As a response to the more and more significant problem of drug-resistance, new substances are synthesized aiming at efficient inhibition of the growth of bacteria dangerous to human life. Two derivatives of 1,2,4-triazolo[3,4-b]1,3,4-thiadiazole substituted at position 3 with an aryl group, and at position 6 with arylamino group have been obtained. Their structures were confirmed on the basis of spectral data (MS, IR, ^{1}H NMR) and elemental analyses. Compounds **1**, **2** indicated high activity towards Gram-positive bacteria, which was up to 16 times more than currently used antibiotics. Two new derivatives were as effective towards the MRSA strain as vancomycin. High activity of compounds **1**, **2** in conjunction with their good bioavailability (calculated theoretically), indicates that there is a possibility of using 3-aryl-6-arylamino-1,2,4-triazolo[3,4-b]1,3,4-thiadiazoles as a potential drugs for Gram-positive bacteria.

Acknowledgements:
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PP-12

Binding of 6-Mercaptopurine to Site I on Human Serum Albumin: Prediction by Molecular Docking.

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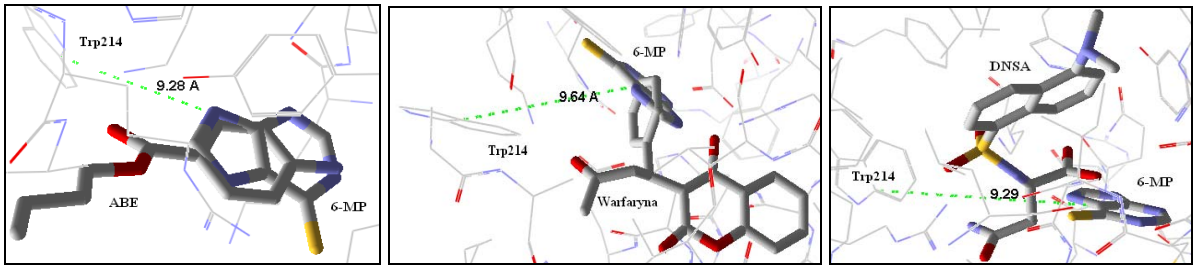
HSA consists of three homologous domains (I, II and III) and each domain is formed by two subdomains (A and B) [1]. The principal drugs–binding regions of albumin were located in subdomain IIA and IIIA, which are structurally characterized by the presence of the hydrophobic interior and the polar exterior. The binding cavity in subdomain IIIA possesses the primary binding activity whereas the cavity in subdomain IIA is more specialized and binds generally bulky heterocyclic compounds with a negative charge [2, 3]. Sudlow et al. [4] classified the two clearly separate binding sites for drugs: site I (warfarin binding site) and site II (benzodiazepine binding site). Moreover, Yamasaki et al. [5] proposed concept that site I in HSA consists of three partially overlapping binding regions, i.e. subsites Ia, Ib and Ic. Regions Ia and Ib correspond to the warfarin and azapropazon, respectively, and region Ic corresponds to n-alkyl-p-aminobenzoates (ABE). The alone Trp214 residue is located in the hydrophobic pocket in the binding subdomain IIA within the non-overlaping part of the warfarin region [6].

In the present work, we studied the interaction between HSA and 6-Mercaptopurine (6-MP) used in medicine as anticancer and immunosuppressive drug. Computer simulation of molecular docking was employed to improve the understanding of this interaction. The warfarin, phenylbutazone and dansyl-L-asparagine as subsite Ia, Ib and Ic markers were used.

The two dimensional (2D) structures of ligands were obtained using the ChemDraw Std computer program. Cambridge Soft 2002 v.7.0.1. 2D to three dimensional (3D) representations were converted by the use of CS Chem3D Ultra Molecular Modeling and Analysis 2001 CambridgeSoft v.7.0.0 software. The 3D structures were energy–minimized using semiempirical (AM1) method implemented in the same software. The X-ray structure of HSA (PDB ID: 1AO6) was retrieved from the Protein Data Bank (PDB) [20]. The ligand and HSA molecules were imported to the Molegro Virtual Docker (MVD v.2010. 4.2.0) computer program [7].

The identification of potential binding sites (cavities) was performed automatically using the grid-based (MolDock Score [Grid]) cavity prediction algorithm. The 6-MP and markers (as a 3D energy-minimized structures) were docked one at a time. The resulting conformations (poses) were clustered and only the lowest-energy representation from each cluster was returned when the docking run was completed. The cluster was ranked in order of increasing binding energy of the lowest binding energy conformation in each cluster. The population of the first five poses representing the estimated lowest binding free energy was selected for further analysis.



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PREZENTACJE POSTEROWE

P-1

Synthesis and Antibacterial Activity of New 5-Substituted 4-Benzyl-2,4-dihydro-3H-1,2,4-triazole-3-thiones

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In recent years, resistance of pathogenic or opportunistic bacteria to various antimicrobial agents, including antibiotics and chemotherapeutics or disinfectants has been growing increasingly. Although control of bacterial infections has been remarkably effective since the discovery of antimicrobial drugs, widespread drug resistance among bacteria, because of inappropriate use of antimicrobials and the occurrence of their undesirable side effects has led to a search for new antibacterial agents.
An effort has been undertaken to obtain novel 5-substituted 4-benzyl-2,4-dihydro-3H-1,2,4-triazole-3-thiones. In order to achieve this 1-(1-arylimidazolidyn-2-yliden)-4-phenylthiosemicarbazides were heated in excess of NaOH solution under reflux conditions. A precipitate was formed after cooling down the mixture and treating it with diluted HCl.
A structure of 3-amino-1,2,4-triazole-5-thiol is known in the literature however new compounds were synthesised using different methods.
Structure of the novel compounds was described on the basis of elementary, spectral and crystallographic analysis. Newly synthesized compounds were further assessed toward antimicrobial activity.
On the basis of our results, the most active compound 4-benzyl-5-({2-[(2,3-dimethylphenyl)amino]ethyl}amino)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione appears to be a promising precursor of agents with bactericidal activity against pathogenic (e.g. *Staphylococcus aureus*) or opportunistic (e.g. *Bacillus subtilis*, *B. cereus*, *S. epidermidis* or *Micrococcus luteus*) Gram-positive bacteria (MIC = 125 mg/L, MBC = 250 – 1000 mg/L). This compound may be also useful as precursor of compounds active against MRSA (methicillin resistant *S. aureus*) species (MIC = 62,5 – 250 mg/L, MBC = 500 – 1000 mg/L), very important bacteria in invasive infections especially in hospital environment.

P-2

Evaluation of Mutagenic and Antimutagenic Activity of Benzimidazole and Pyridone Derivatives.

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The Vibrio harveyi assay was used to assess mutagenic and antimutagenic activity of some benzimidazole and pyridone derivatives which are potential inhibitors of phosphodiesterase. These compounds were synthesized by the reaction of 2-bromobenzimidazole or 6-bromo-2-pyridone with N-substituted 2,3-epoxypropylo-1-amine. Two types of products were obtained. One of them was fused dihydrooxazole and second product contained three carbon open-chain with hydroxyl group [1].
A series of strains used in the V. harveyi mutagenicity and antimutagenicity assay consist of four strains: BB7 (natural isolate), BB7X bearing the cgtA::Tn5TpMSC mutation and strains analogous to BB7 and BB7X but bearing plasmid pAB91273 (containing mucA and mucB genes), called BB7M and BB7XM, respectively [2].
The obtained preliminary results showed that tested compounds did not have mutagenic activity with the exception of one compound which elicited a mutagenic response only in BB7X strain. Results from the antimutagenicity studies demonstrated that these compounds were highly (more than 40%) or moderately (30-40%) effective against BB7 strain. For the remaining strains the antimutagenic effects was considered weak or absent (less than 30%).

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Acknowledgements
The authors would like to thank prof. G. Węgrzyn from Department of Molecular Biology, University of Gdańsk for strains of V. harveyi.

P-3

Theoretical Investigation of Opioid Receptors by Homology Modelling Based on Diverse Templates.

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Knowledge of exact protein structure is very useful. It helps to understand protein's function, and gives a clue about it's subtle mechanisms. Unfortunately, cognition of high resolution structures require long and laborious study, that includes obtaining concentrated solution or crystal of the investigated biopolymer. This process is particularly difficult in case of transmembrane proteins, which contain large hydrophobic areas, and thus require very specific conditions for crystallisation. The largest family of transmembrane proteins are G-Protein Coupled Receptors. As they constitute about 45% of potential drug targets[1], it is crucial to learn their structure and mode of action in order to elaborate new, efficient drugs. Due to difficulties in obtaining experimental data, computational modelling may be used instead to get rough models. At the moment, the best method is homology modelling, that consists in computing estimated protein structures on the basis of template – experimentally solved protein structure, related to investigated one.
The aim of work was analysis of main differences between μ and δ opioid receptors' models, based on diverse templates: human β_2-adrenergic receptor in it's active[2] and inactive[3] state and human A_{2A} adenosine receptor[4], in order to identify the best template for modelling of these receptors. Attention was focused on the orthosteric binding site in the transmembrane helical bundle, as well as on the ECL2 region, which is suspected to be responsible for hypothetical allosteric modulation. Analysis of the results shows difference between models obtained by using different templates, and appears to be useful in further study on opioid receptors.

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P-4

Activity of G3 PAMAM-NH_2 Dendrimer-Chlorambucil Conjugate on Metabolism and Growth of Human Breast Cancer Cells.

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Chlorambucil, a lipophilic anticancer agent, has been used clinically against chronic lymphocytic leukemia, lymphomas, advanced ovarian and breast cancer. However, chlorambucil use is limited by its toxic side effects, including myelotoxicity, and neurotoxicity. A promising approach to circumvent the toxic effects and to improve therapeutic efficacy is connection of chlorambucil with a suitable nanosized carrier. PAMAM dendrimers are synthetic polymer-based nanoparticles, which are widely recognized as important quantized nanoscale building blocks in biomedical research. They offer particular advantages including their nanoscale spherical architecture, narrow polydispersity and the multifunctional surface offering the possibility to tailor-make their surface chemistry. The terminal functional groups of dendrimers show higher chemical reactivity compared to that when present in other classes of polymers. In the present study, chlorambucil was conjugated to G3 PAMAM dendrimer (with 32 surface primary amino groups) *via* amide linkage, and the effects of PAMAM-NH_2 dendrimer-chlorambucil conjugate on the cytotoxicity and antiproliferative activity in both MDA-MB-231 and MCF-7 breast cancer cells were examined.
Evaluation of the cytotoxicity of a novel G3 PAMAM-NH_2 dendrimer-chlorambucil conjugate employing a MTT assay and inhibition of [^{3}H]thymidine incorporation into DNA in both MDA-MB-231 and MCF-7 breast cancer cells demonstrated that the conjugate was more potent antiproliferative agent than chlorambucil. The effects of dendrimer-chlorambucil conjugate on collagen biosynthesis, β_1-integrin receptor, IGF-I receptor and the expression of several proteins in the signal generated through these receptors like: phosphorylated MAP-kinases and phospho Akt, NFκB in human breast cancer cells were compared to those evoked by chlorambucil. It was found that dendrimer-chlorambucil conjugate was more active inhibitor of collagen biosynthesis than chlorambucil. The expression of IGF-I and β_1 integrin receptor, as well as phosphorylated MAPK kinases was significantly increased in cells incubated for 24 h with 20 μM dendrimer-chlorambucil conjugate compared to chlorambucil. The phenomenon was related to the increase expresion of NFκB by dendrimer-chlorambucil conjugate as shown by Western immunoblot analysis. The presented data suggest that PAMAM-CH conjugate impair more efficiently growth and metabolism of MCF-7 breast cancer cells than chlorambucil.

P-5

New Serotonin 5-HT$_7$ Receptor Ligands with 1,2,4-Oxadiazole Fragment - Molecular Modeling Studies.

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The 5-HT$_7$ receptor is the most recently discovered G-protein-coupled receptor for serotonin. Through the combined use of modern molecular biology, knockout animal models, and other more traditional research methods of medicinal chemistry and classical pharmacology, a clearer picture of the pathophysiological role of the 5-HT$_7$ receptor has emerged. Studies so far suggest the involvement of brain 5-HT$_7$ receptors in different neurological and psychiatric diseases, e.g. anxiety, obsessive compulsive disorder, migraine headaches, chronic pain conditions, schizophrenia. Moreover, recent studies indicate that 5-HT$_7$ receptor may be involved in the regulation of mood, suggesting that 5-HT$_7$ receptor is the goal in the effective treatment of depression [1-3].
As part of research program for discovering new 5-HT$_7$ receptor ligands, a short series of compounds with 1,2,4-oxadiazole fragment was synthesized. All the new compounds were tested for their affinity for 5-HT$_7$ receptors. The structures-affinity relationship studies of these compounds revealed two structural features influencing *in vitro* activity, i.e. type of methylenearomatic substituent at position 3 of central 5-phenyl-1,2,4-oxadiazole fragment, and the length of aliphatic linker between central core and terminal dimethylamine group.
All the new molecules were automatically docked into homology model of 5-HT$_7$ receptor. Correlation between computational results and experimental *in vitro* affinity data are discussed.

Acknowledgments
This study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism; http://www.cns-platform.eu/

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P-6

Determination of the Lipophilicity of Arylpiperazinylalkyl Derivatives of Imidazolidne-2,4-dione and Imidazo[2,1-f]theophylline by RP HPLC.

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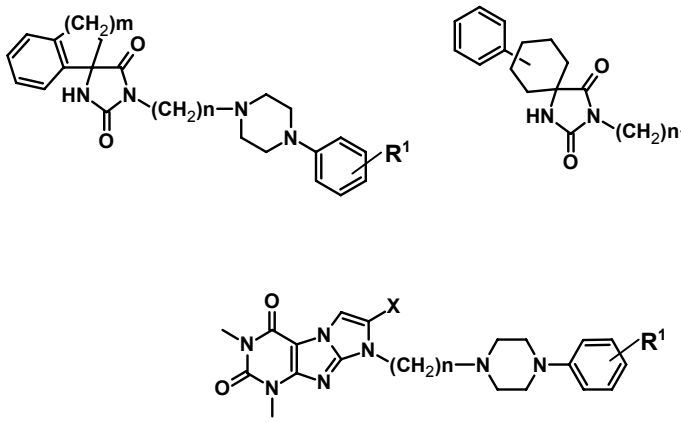
Lipophilicity as a physicochemical factor, particularly crucial for compounds with potential CNS activity, is often used in quantitative structure-activity relationship studies [1]. It has been observed that the maximum potency of drugs which act on the central nervous system are obtained with compounds having an optimum lipophilicity, log P near two [2].
In aim to evaluate the structure-activity relationship in a group of imidazolidine-2,4-dione and imidazo[2,1-f]theophylline (fig. 1), we estimated their chromatographic logk' parameters, using the reversed – phase high-performance liquid chromatography (RP-HPLC) method and discussed influence of lipophilicity parameters on serotonin receptor affinities. Then the experimental logk' values were compared with the theoretical partition coefficient calculated by a module of the Pallas and Marvin programs [3].



X = -H, -CH_3, -Ph
m = 1, 2
n = 3, 4
R^1 = H, 2-OCH_3, 3-Cl, 2,3-diCl, 3-CF_3

Fig. 1

The tested compounds exhibit multireceptor profile as potent 5-HT_{1A} and 5-HT_{2A} receptor ligands and diversified affinity for the serotonin transporter [4,5].

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P-7

Application of Liposomes to Encapsulate Anticancer Drugs for Chemoterapy of Lung Cancer.

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Research on the possibility of using liposomes as carriers of therapeutic substances concern mainly cancer therapy, diabetes, rheumatic diseases.

The use of liposomes has great importance when it comes to treatment of cancer and it is associated with high cytotoxicity of drugs. Drugs used in cancer therapy generally have narrow therapeutic index (TI) and can be very toxic to healthy organs. Toxic effects of anticancer drugs can be greatly reduced by reducing the dose of drug.

For many years there has been extensive research on embedding with liposomal drugs etoposide (ETO) and vinorelbine (VIN). However, there is no literature data on their joint incorporation into liposomes, despite the effectiveness of a combination of these two drugs may indicate the fact of their common use in the treatment of lung cancer.

The objective of the study is research on incorporation of liposomes obtained by dry film modified drugs: vinorelbine, including etoposide used in therapies and to investigate their multidrug the incorporation of the liposomes. UV-Vis spectroscopy and 1H-NMR was used to characterize the system liposome / drug. Based on the curves calibration of studied medications it has been determined the concentration and the percentage of encapsulation (% E) of individual drug contained in liposomes.

P-8

Influence of the Substituent(s) at Aromatic Rings at Arylidene Phenylpiperazine Hydantoin on Affinity to 5-HT_6 and 5-HT_7 Serotonine Receptors.

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Text was removed due to the patent proprietary rights.

P-9

Densitometric Estimation of the Detection Manners of Acetylsalcylic Acid and Salicylic acid in Thin-Layer Chromatography.

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This work is continuation of our previous studies about application of new reagents visualizing the selected drugs [1-3].

The objective of this research was a mixture of acids: acetylsalicylic and salicylic, which were analyzed by adsorption thin-layer chromatography on silica gel $60F_{254}$ (#15554, E. Merck) and using mobile phase *n*-hexane – diethyl ether – acetic acid (80%) in volume fraction 7:2:1. In this work the following visualizing reagents were applied: methyl green, gentian violet, brilliant green, malachite green, alkali blue, aniline blue, neutral red, crystal violet, fuchsin, Janus blue, bromothymol blue, thymol blue, phenol red, helasol green, bromocresyl green, brilliant-cresyl blue, bromophenol blue, NaOH and H_2O_2 (3%). After complete separation of examined compounds, detection by the use of individual visualizing reagent from the mentioned above reagents was performed. The visualizing effect were estimated by: dipping chromatographic plate in solution of respective visualizing reagent for 15 seconds or the plate was sprayed with proper visualizing reagent solution. After drying, the obtained chromatographic bands were subjected to densitometric and spectrodensitometric analysis.

The spectra obtained by means of exactly defined visualizing reagents indicate ability to apply them in wide qualitative and quantitative analysis. Of all visualizing reagents tested, for detection of examined acids by spraying: Janus blue, bromopenol blue, bromocresyl green, H_2O_2 (3%) and NaOH are noteworthy.

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P-10

Determination of Lipophilicity of Ursodeoxycholic Acid by TLC and Computational Methods.

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Ursodeoxycholic acid (UDCA) is a bile acid having hepatoprotective action. The pharmaceutical formulations of ursodeoxycholic acid (*Ursopol, Ursocam, Ursofalk, Proursan*) are widely used in the therapy of liver and biliary duct diseases [1].
In this paper, the lipophilicity of ursodeoxycholic acid (UDCA) was determined. To estimate the lipophilic character of UDCA, thin-layer chromatography in reversed phase system: RP-TLC and RP-HPTLC was applied. Chromatographic analysis was performed on different glass and aluminum plates from E. Merck: RP-18F_{254}, RP-18WF_{254}, RP-2F_{254} with the use of mobile phases: organic modifier (methanol, acetone or dioxane) – water mixed in respective volume compositions. Results of chromatographic parameter of lipophilicity expressed as R_{MW} values were compared with partition coefficient (logP) values determined by different computer programs: AlogPs, logP_{KOWWIN}, xlogP2, xlogP3, milogP, AlogP, MlogP and with experimental logP value (logP_{exp}) respectively [2].
Good correlation observed between chromatographically determined and computational calculated lipophilicity parameters of examined UDCA shows the usefulness of both methods: chromatographic and theoretical to predict the lipophilicity of ursodeoxycholic acid.
Presented in this paper lipophilicity parameters can be used in further UDCA research type structure – activity relationships (SAR study).

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Acknowledgments

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P-11

Synthesis of Novel 4-Aryl-Pyrido[1,2-*c*]pyrimidine Derivatives as Potential Antidepressants.

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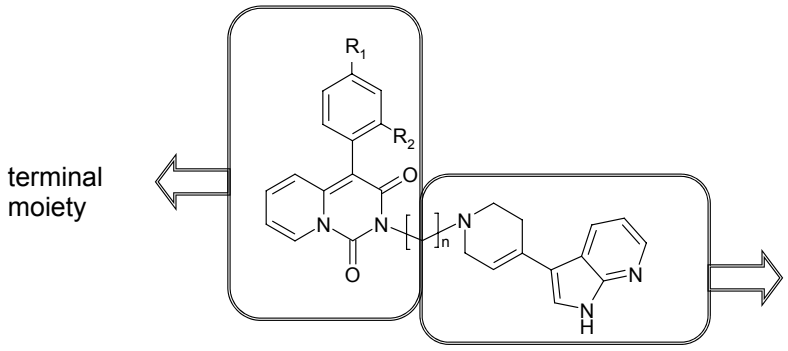
Methods of synthesis and biological properties of 4-aryl-pyrido[1,2-*c*]pyrimidine derivatives have been the subject of the research carried out in the Department of Drug Technology and Pharmaceutical Biotechnology for the recent years. Many of the synthesized compounds possess high/very high affinity to 5-HT_{1A} receptors and 5-HT transporter (SERT). They combine presynaptic 5-HT_{1A} receptor agonistic activity with SERT inhibitor properties, which makes them potential novel antidepressants [1-3]. Dual 5-HT_{1A}/SERT activity may contribute to a faster desensitization of 5-HT_{1A} autoreceptors, which leads to shortening of the latency period in treatment of mood disorders.
Further modification of 4-aryl-pyrido[1,2-c]pyrimidine derivatives led us to obtain a series of novel compounds containing 1*H*-pyrrolo[2,3-*b*]pyridine moiety.



R_1=H, R_2=Cl, F, CH_3, OCH_3
R_1=Cl, F, CH_3, OCH_3, R_2=H
n = 2,3,4

The biological activity of the compounds outlined above will be tested in *in vitro* and *in vivo* studies. The results of biological investigations will enable us to draw conclusions regarding the influence of the substituents in phenyl ring and the length of carbon linker between terminal and pharmacophoric moiety on the affinity to 5-HT_{1A} and serotonin transporter.

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P-12

5-Arylidene(thio)hydantoin Derivatives as Modulators of Cancer Efflux Pump Inhibitors.

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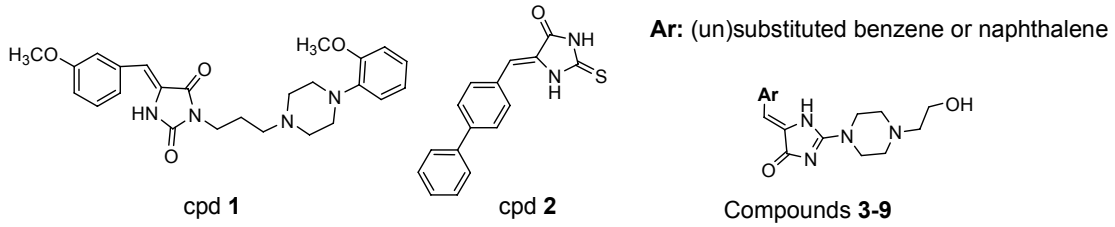
Multidrug resistance has become a factor seriously limiting treatment of various diseases, including therapy of bacterial and fungal infections and cancer [1]. The major mechanism for multi-drug resistance (MDR) of cancer is the over-expression of ATP-dependent drug-efflux pumps (drug transporters), which reduce the accumulation of the antitumor agents. The main role in cancer-MDR is played by the P-glycoprotein (P-gp, ABCB-1) transporter. Various chemical groups possessing efflux pump inhibitor (EPI) properties in *P-gp* have been described, including three generations of P-gp modulators, but none have passed clinical trials because of undesirable side effects. Consequently, it is a major challenge to search for new successful P-gp inhibitors active for chemotherapy of MDR cancer with minimal side effects. In this context, our interest has been focused on the EPI activity of arylidene(thio)hydantoin derivatives. Our previous studies [2] indicated that arylidene(thio)hydantoin derivatives (Fig.1, **1** and **2**) possessed P-gp modulating properties in cancer cells in the range of Verapamil or higher (Fig. 1).



cpd **1** cpd **2** **Ar:** (un)substituted benzene or naphthalene Compounds **3-9**

Fig.1

Within present studies, a series of new arylidene imidazolinone derivatives (**3-9**), possessing hydroxypropylpiperazine fragment at position 2 (Fig 1) were synthesized within a 3-step synthesis. The compounds were tested for their efflux modulating effects in T-lymphoma cancer cells using fluorescence activated cell sorting and real-time fluorimetry. The modification of intracellular drug accumulation was evaluated by flow cytometry using rhodamine 123 accumulation assay. As reference, the P-gp modulator, verapamil was used. Structure-activity relationship analysis was performed based on present and previous results [2] of pharmacological assays. Results indicated that compounds possessing, both hydantoin or thiohydantoin, moieties are more potent cancer EPIs than those possessing an imidazolone fragment (**3-9**). Piperazine alkyl substituent at position 3 and an aromatic substituent at the piperazine ring possessed for high activity whereas hydroxyethylpiperazine substituent at position were less active. All hydroxyethylpiperazine derivatives (**3-9**) promoted the retention of rhodamine 123 above than that of Verapamil as opposed to compounds **1** and **2**. Among compounds **3-9**, the most promising one included 2,4-dichlorobenzylidene moiety.

This work was partly supported by Program K/ZDS/001915

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P-13

The study of buspirone analogues docking to serotonin transporter

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It is well known that 6-nitroquipazine exhibits about 150-fold higher affinity for the serotonin transporter (SERT) than does quipazine and recently we showed quipazine buspirone analogues with high to moderate SERT affinity. Now we have designed and synthesized several 6-nitroquipazine buspirone derivatives. Unexpectedly, their SERT binding affinities were moderate, and much lower than that of the previously studied quipazine buspirone analogues. To explain these findings, docking studies of both groups of compounds into two different homology models of human SERT, was performed using a flexible target-ligand docking approach (4D-docking). The crystal structures of leucine transporters from Aquifex aeolicus in complex with leucine and with tryptophan were used as templates for the SERT models in closed and outward-facing conformations [1, 2], respectively. We found that the latter conformation represents the most reliable model for binding of buspirone analogues. Docking into that model showed that the nitrated compounds acquire a rod like shape in the binding pocket with polar groups (nitro- and imido-) at the ends of the rod. 6-Nitro substituents gave steric clashes with amino acids located at the extracellular loop 4, which may explain their lower affinity than corresponding quipazine buspirone analogues. The results from the present study may suggest chemical design strategies to improve the SERT modulators.

This study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism.

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P-14

Studies on the Mechanism of Anticancer Activity of 4-Benzyl-3-[(1-methylpyrrol-2-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-one.

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The 1,2,4-triazoles are an important group of medicinal substances which exhibit a wide range of activity, such as analgesic, antibacterial, fungicidal, anti-inflammatory, antiviral and anticancer. Among many 1,2,4-triazole derivatives which were synthesized in the Department of Organic Chemistry of Medical University of Lublin, 4-benzyl-3-[(1-methylpyrrol-2-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-one is characterized with anticancer activity [1].
The aim of studies is extensive experimental and theoretical investigation of the structure of 4-benzyl-3-[(1-methylpyrrol-2-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-one, complemented by searching for the molecular target responsible for its anticancer activity. The structural studies include X-ray analysis, experimental and computed spectral analysis (^{1}H and ^{13}C NMR, IR) as well as conformational analysis and the frontal molecular orbitals (FMO) analysis. In order to inspect the mechanism of anticancer activity of the investigated compound, its similarity to the compounds from the in-house set of compounds with different mechanisms of anticancer activity was evaluated. This analysis revealed that the most probable molecular target for 4-benzyl-3-[(1-methylpyrrol-2-yl)methyl]-4,5-dihydro-1*H*-1,2,4-triazol-5-one is the epidermal growth factor receptor (EGFR). This hypothesis is supported by molecular docking. Moreover, we find that formation of the respective ligand-protein complex is conditioned by the keto-enol tautomerism of the ligand, i.e. the energetic prevalence of the keto form [1,2].

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Acknowledgments
This work was partially founded by Foundation for Polish Science (FNP, outgoing fellowship for postdoctoral researchers – Agnieszka A. Kaczor). Calculations with Gaussian03 were performed under a computational grant by Interdisciplinary Center for Mathematical and Computational Modeling (ICM), Warsaw, Poland, grant number G30-18.

P-15

Synthesis and Anticonvulsant Activity of New 1-[2-Oxo-2-(4-phenylpiperazin-1-yl)ethyl]pyrrolidine-2,5-diones and 1-[2-Oxo-2-(4-phenylpiperazin-1-yl)ethyl]-3-methylpyrrolidine-2,5-diones.

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Numerous compounds are synthesized and screened for their anticonvulsant activity each year. To make the discovery of new anticonvulsants more rational many investigators identified structural fragments essential for anticonvulsant properties. One of the structural features that plays a significant role for antiepileptic activity is an amide function [1,2]. In the course of developing new anticonvulsant agents as well as taking into consideration the above and vital influence of 4-arylpiperazine moieties on anticonvulsant activity of pyrrolidine-2,5-diones differently substituted at 3-positon of succinimide ring [3,4]. In the present studies we have synthesized a library of (2,5-dioxopyrrolidin-1-yl)- and (3-methyl-2,5-dioxopyrrolidin-1-yl)- acetamides with differently substituted piperazines as an amide function. These molecules were designed as analogues of levetiracetam and brivaracetam which are known as the newest antiepileptic drugs. The structures of compounds obtained are shown on Figure 1.

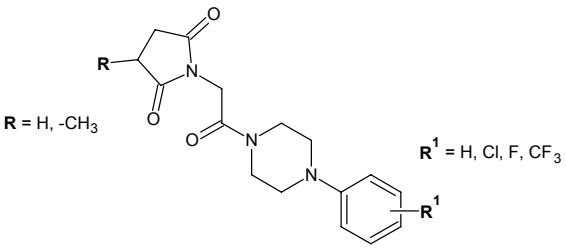

Figure 1.

The desired compounds were prepared by condensation of previously obtained 2,5-dioxopyrrolidin-1-yl- and 3-methyl-2,5-dioxopyrrolidin-1-yl-acetic acids with the appropriately substituted piperazines, in the presence of the *N,N*-carbonyldiimidazole (CDI) reagent.
The compounds were evaluated for their anticonvulsant activity and neurotoxic properties within the Antiepileptic Drug Development (ADD) Program (Epilepsy Branch, Neurological Disorders Program, National Institute of the Neurological and Communicative Disorders and Stroke (NINCDS), Rockville, USA) [5].

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P-16

Modulation of Adenosine A_1 and A_{2A} Receptors Affinities in the Group of Phenol Derivatives of 1,3-Dialkyl-pyrimido[2,1-f]purinediones.

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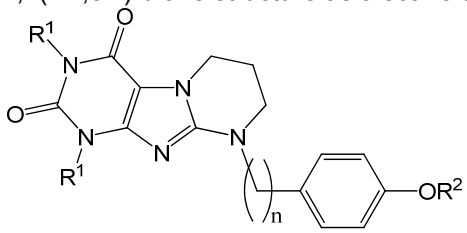
The adenosine receptor (AR) family consists of four G protein-coupled receptor subtypes: A_1 (A_1 AR), A_{2A} (A_{2A} AR), A_{2B} and A_3. Adenosine A_1 or A_{2A} receptor antagonists may be useful for the treatment of acute and chronic neurodegenerative disorders including cerebral ischemia, Parkinson's and Huntington's diseases, cognitive deficits and Alzheimer's disease as well as for the treatment of peripheral diseases, such as cardiac failure [1, 2].
The goal of current work was to develop novel adenosine receptor ligands with selectivity either for A_1 or A_{2A} receptors. Basing on our previous studies we considered phenol-substituted 1,3-dialkyl-6,7,8,9-tetrahydropyrimido[1,2-f]purine-2,4(1H,3H)-dione structure as a scaffold for further modification [3, 4].



n = 0, 2
R^1 - methyl-, ethyl-, propyl- or butyl-

Structure to affinity relationship studies were driven in two stages for both phenyl- and phenethyl-substituted derivatives. In the first stage phenol ring substituent R^2 was kept constant and an influence of alkyl groups elongation in positions 1 and 3 (R^1) on adenosine receptors affinity was investigated. In the second stage we kept the alkyl moieties unchanged and a role of various polar substitutions of phenol ring (R^2) was tested.
Affinity for A_1 and A_{2A} adenosine receptors was investigated for 53 compounds. In tested group we found both A_1 AR and A_{2A} AR selective ligands with affinity in nanomolar and submicromolar concentration range. The obtained results allow for determination of main modifications responsible for modulation of A_1 AR and A_{2A} AR affinity. Further analysis of other adenosine receptors subtypes affinities is planned in future experiments.

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P-17

The Synthesis and Structural Characterization of 1-(1-Arylimidazolidin-2-ylidene)-4-substituted-thiosemicarbazides, New Potential Analgesic Agents.

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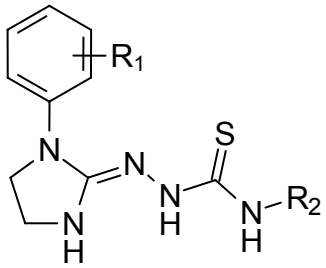
Aminoimidazoline and their analogues have been widely used as medicines against a broad range of diseases because of their significant pharmacological activities. The title 1-(1-arylimidazolidin-2-ylidene)-4-substituted-thiosemicarbazides were synthesized as the potential analgesic agents.



These compounds were obtained in the reaction of respective 1-aryl-2-hydrazinoimidazolines-2 with isothiocyanates. The synthesis pathway and structure of the compounds were unambiguously confirmed by X-ray analysis, taken 1-[1-(4-metoxyphenyl)imidazolidin-2-ylidene]-4-(4-chlorophenyl)-thiosemicarbazide (R_1=OMe, R_2=4-Cl-Ph) and 1-[1-(4-metoxyphenyl)imidazolidin-2-ylidene]-4-benzyl-thiosemicarbazide (R_1=OMe, R_2=CH_2-Ph) as model compounds.
In order to determine the tautomeric equilibrium within a series of investigated thiosemicarbazides, the theoretical calculations at DFT/B3LYP/6-311++G(d,p) level in the gaseous phase and solution were undertaken.

P-18

Impact of N-Substitution on Hydrogen Bonds Architecture in Urea-Hydantoins.

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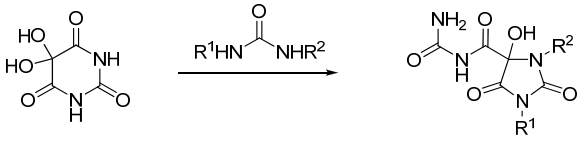
The hydrogen bond network and various motifs of multiple hydrogen bonded pattern seen in the crystals of derivatives of imidazolidine-4-one have been studied intensively in our group. At the present work we report crystal structures of four hydantoin analogues (**2-5**) obtained in the reaction of alloxan with urea and its mono- and dialkyl derivatives. Crystallographic studies confirmed the structure of products, that are presented below on Scheme 1.

Scheme 1



1

2 $R^1 = R^2 = H$
3 $R^1 = Me$; $R^2 = H$
4 $R^1 = Et$; $R^2 = H$
5 $R^1 = R^2 = Me$
6 $R^1 = R^2 = Et$

Two observed molecules variations

anti
2 and **5**

syn
3 and **4**

In all studied molecules urea fragment is almost perpendicular to planar hydantoin ring. However atoms O5 and O6 accept two different mutual positions – *syn* for non-symmetrically monosubstituted species (**3** and **4)** and *anti* in case of symmetrically substituted ones (**2** and **5**). As main structure motifs are determined by urea residues, for those two observed conformations the arrangement of hydrogen bonds is not identical. In the *anti* mode strong hydrogen bonds create 3D network. Additionally, in case of unsubstituted derivative **2** possessing two H-bond donors in the imidazolone ring, the water molecule is assembled into the crystal. From the other side, *syn* molecules are arranged as 2D layers. It reflects in the properties of crystals which form very thin plates.

P-19

X-ray Studies of Histamine H_3 Receptor Ligands from the Group of Piperidine Derivatives.

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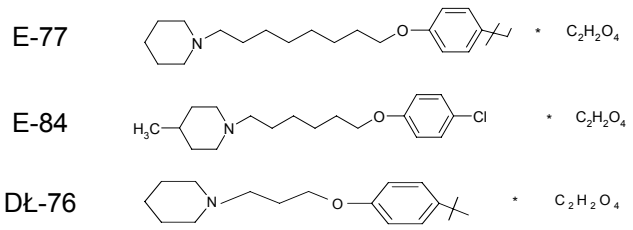
The histamine H_3 receptor belongs to the histamine receptor family. This receptor is preferentially expressed on ADHD, Parkinson's and Alzheimer's disease. Based on the group of imidazolones general structure of H_3R antagonists was created. Recently piperidine derivatives were tested as potential H_3R antagonists. The aim of this work was to study the 3-D structures for the series of new derivatives (scheme 1).



Scheme 1

The obtained substances in the form of bases were strongly insoluble. For this reason X-ray studies were done for respective oxalate monocrystals. The protonated molecules in three studied derivatives adopt extended conformation (see Fig. 1). Based on respective combination of three oxalic acid residues (oxalic acid, mono or di-oxalate ions), in studied crystals dissimilar anionic ribbons were assembled (Fig.2).

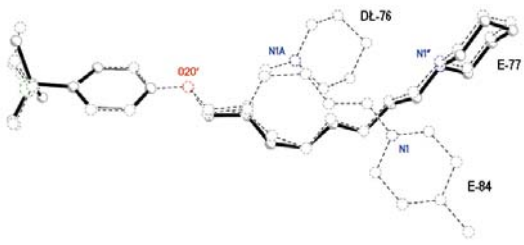


Fig.1. Superimposition of protonated molecules.

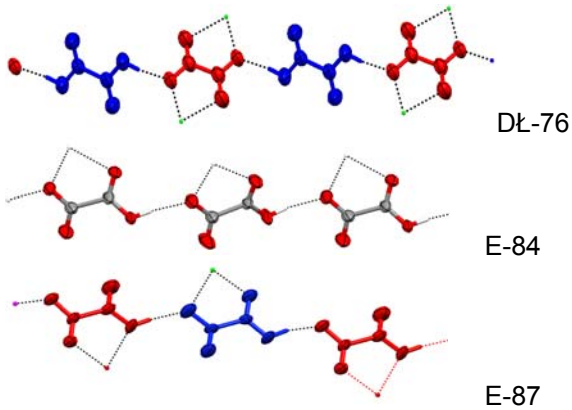


Fig.2. Anionic ribbons.

P-20

Search for Intermolecular Interactions in Histamine H_4 Receptor Ligands in the Group of 4-(4-Methylpiperazino) Derivatives of 1,3,5-Triazine.

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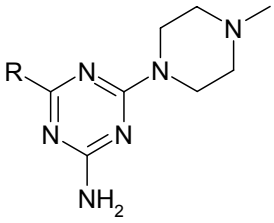
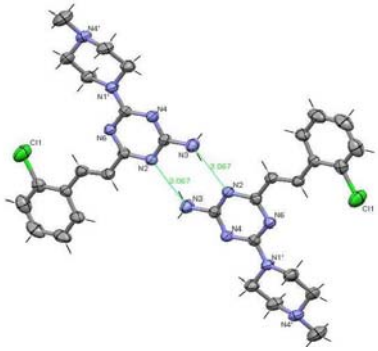
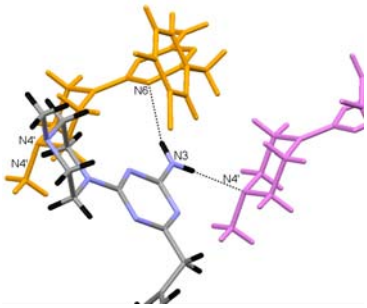
The histamine H_4 receptor (H_4R) is receptor belonging to the histamine receptor family. This receptor is preferentially expressed a role in immunological and inflammatory processes. Lead structures for this receptor were describe with 2-aminopyrimidine as privileged skeleton. By analogies, related 1,3,5-triazine derivatives with modified aromatic group R (see Scheme) were synthesized and searched as histamine H_4 receptor ligands.
The aim of this work was the X-ray studies of species from this family differing in substitution and distance of phenyl from triazine. The structures of four compounds were solved. On that base the impact of various aromatic groups on intermolecular interactions in the crystals were analysed.

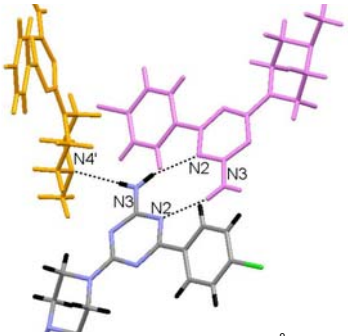


N3-H3B···N2 = 3.067(3) Å
Stacking with distance of 3,398Å

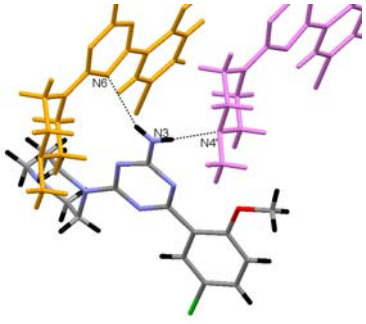


N3-H3A···N6 = 3.195(2)Å
N3-H3B···N4' = 3.089(2)Å





N3-H3A···N4' = 3.069(4)Å
N3-H3B···N2 = 3.097(4) Å



N3-H3A···N6 = 3.223(3) Å
N3-H3B···N4' = 2.946(3) Å

P-21

Structural Determinants of High Affinity Agonists of the Histamine H4 Receptor Activity - Construction of the Pharmacophore Model.

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Histamine receptors (H1 - H4) belong to the GPCR superfamily and are involved in various biological pathways in both central and periphedral systems. Among those receptors, H4 receptor was discovered most recently - in 2000 [1]. The *h*H4R is a topic target in the development of drug candidates in the therapy of chronic inflammatory diseases and immune disorders [2, 3].
Chemical European Molecular Biology Laboratory database ChEMBL [4] contains 311 ligands of the H4 receptor. Majority of them are antagonists with a relatively low affinity to receptor. Only few of them are full agonists with the affinity pKi higher than 7.5 and relatively rigid structure (number of rotatable bonds ≤ 5). Some of this group contains the imidazole fragment, the others comprise piperazine and only one of them has two protonation sites. Interestingly, in the pharmacophore's model obtained for the antagonists of *h*H3 receptor [5] it is postulated that for affinity the beneficial are two protonation sites or one protonation site and the second basic moiety [6], which are equivalent to handle on $Asp^{3.32}$ and $Glu^{5.46}$ - conservative residues in the histamine receptor's group.
Here we would like to propose the pharmacophore's models for H4 receptor which were developed using the GALAHAD program. Obtained results suggested that one of the conservative amino acid takes secondary part in the binding of agonists. This is consistent with the results of researches [7] on the histamine H4 receptor's partial agonists, that confirmed influence of the $Glu^{5.46}$ residue in creating hydrogen bonds with agonist via water molecule. Furthermore the analysis of the low-energy conformers descriptors of the investigated group of agonists generated by the SPARTAN program showed the relevance of the hydrophobic areas in the interaction with the receptor's protein.

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P-22

Isolation of Polysaccharides Fraction from the Mycelial Culture of *Lentinula edodes*.

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Lentinula edodes (Berk.) is a widely cultivated edible mushroom with high nutritional value and excellent medicinal properties [1].
Both, lentinan (an active polysaccharide extracted from fungus) and an extract preparation of the mycelium of *Lentinula edodes* (L.E.M) have shown antitumor and antiviral activity [2].
The polysaccharide fraction from *Lentinula edodes* has been reported to possess anticancer and immunoregulatory activity, and that these effects involve macrophage activation. Lentinan is commonly used for cancer treatment, often in conjunction with chemotherapy [3].
The mycelium of *Lentinula edodes* was grown in submerged conditions on a glucose-peptone nutrient medium. Mycelium of the strain was separated from the medium by means of filtration. The polysaccharide fractions were extracted from mycelium by Chihara`s method [4] and their content was estimated in hydrolysates by means of liquid chromatography following Fu`s and O`Neill`s method [5].
The main component of the investigated exopolysaccharides were glucose and mannose.

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The Effect of Humic Substances on Blood Coagulation and Fibrinolysis.

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The humic substances are major components of organic matter in nature. The humic substances are complex and heterogeneous mixtures of polydispersed materials formed by biochemical and chemical reactions during the decay and transformation of plant and microbial remains (a process called humification). These substances can be divided into three main fractions: humic acids, fulvic acids and humin [1]. In the last decade these substances have been an increasing interest in the employment of humic materials in medicine. For example, the humic substances can affect the blood coagulation and fibrinolysis. The aim of this study was a literature review on the above mentioned processes.
Many authors described the application of humic acids in prophylaxis and therapy of fusions after tubal or ovarian inflammations a well as the postoperative treatment of sterility operations in order to prevent secondary adhesions and repeated occlusions of the ovarian duct. Fusions are caused by postoperatively reduced degradation of fibrin to soluble fibrin degradation products. In laparotomy, the postoperative baths in humic acids have a clear adhesion-inhibiting effect. Probably, the activated fibrin degradation due to the humic acids-induced release of tissue-type plasminogen activator. Tissue-type plasminogen activator is regarded as the regulator of the antithrombotic defense mechanism. It activates plasminogen to plasmin, which splits insoluble fibrin to soluble fibrinogen degradation products. In addition, humic acids inhibit the coagulation enzyme thrombin, thereby syspressing the formation of fibrin monomers from fibrinogen. Compared with other polyanionic substances (heparin, pentosanpolysulfate), the anticoagulant effect of humic acids was found to be less pronounced [2, 3].

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P-24

The Application of Spectroscopic Methods for Determination of *Vinorelbine* Closed in Liposomals Vesicles.

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Liposomes are closed structures obtained during the hydration of phospholipids. They are constructed from the same lipid components as biological membranes. Liposomes can be built from many types of lipids and use them as models to study the properties of biological membranes.
Closure of the drug in liposomes allows the delivery of the drug into the cell in a safe way for the body, and most importantly, the drug has a better pharmacokinetic properties, while preserving the cytotoxic activity. Liposomal form of the drug can provide a greater amount of drug per dose, which is tolerated by the body, the drug persists longer in the body and is not toxic.
The aim of the research was study on incorporation of drugs into liposomes, obtained by dry film and a modified reverse-phase methods, vinorelbine (VIN) drug used in multi-drug therapy, and to investigate of the competition in incorporation to liposomes. UV-Vis and ^{1}H-NMR spectroscopy was used to characterize the system liposome/drug. Based on the calibration curves of studied drug it has been determined the concentration and the percentage of encapsulation (% E) of individual drug contained in liposomes, obtained by both methods.

P-25

Antifungal Properties of Quinoline Derivatives.

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In the last two decades significant changes in the epidemiology of fungal infections can be observed. The number and diversity of new threatening fungal infections increased dramatically during this time [1]. There are some reasons of this phenomenon such as growing population of immunocompromised patients and appearing of new, drug resistant fungal strains. Thus, searching for novel drugs remains to be one of the major challenge for modern science. In spite of, broad arsenal of drugs we have still an urgent need for new, more effective antifungal drugs with less side effects [2].
A large number of natural products and drugs contain a quinoline moiety, the synthesis of this heterocyclic nucleus and derivatives has been of considerable interest to organic and medicinal chemists. Quinoline family compounds possess a wide spectrum of biological activities such as antifungal, antineoplastic and herbicidal activity [3]. For this reason quinoline moiety may be regarded as privileged structure - especially valuable for drug design.
We are exploring the styrylquinoline derivatives as possessing strong antifungal activity, especially derivatives containing 8-hydroxyquinoline were found interesting in our former research. These derivatives show a significant similarity to novel antifungal agents, allylamines, which possess strong antifungal activity. Some of the studied compounds indicated in vitro antifungal activity comparable or higher than Fluconazole [4]. On the basis of analysis of structure-activity relationship we are able to design new analogues of Terbinafine, one of analogs of allylamine.

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P-26

Synthesis and Photophysical Properties of Phthalocyanine Possessing Adamantanylsulfanyl Substituent.

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Phthalocyanines are synthetic aza-analogues of naturally occurring porphyrins. Phthalocyanines are promising candidates for photodynamic therapy (PDT), which is a promising treatment method of various diseases, especially tumors. PDT requires photosensitizer, which after irradiation with light of an appropriate wavelength generates reactive oxygen species (ROS), particularly singlet oxygen. Damage caused by ROS leads to necrotic and/or apoptotic cell death [1].

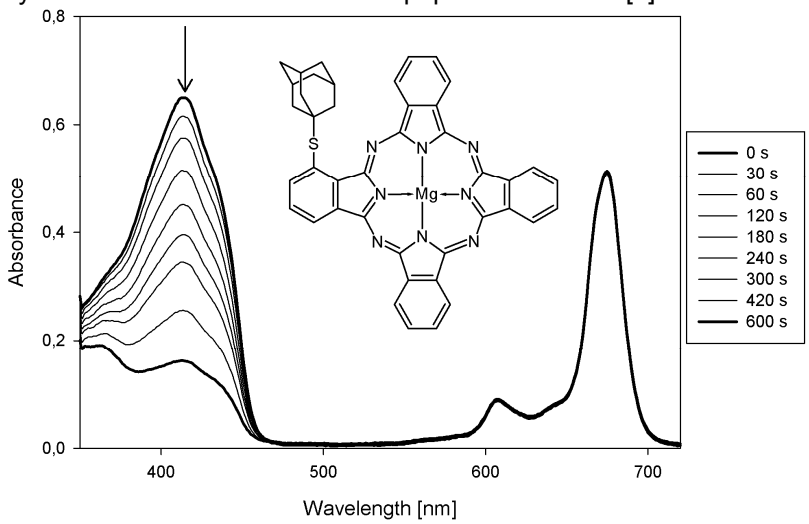

Fig. 1

Magnesium phthalocyanine bearing adamantanylsulfanyl substituent was synthesized by mixed macrocyclization reaction of 3-adamantanylsulfanyl-1,2-dicyanobenzene [2] and 1,2-dicyanobenzene. Structure of resulting compound was confirmed by NMR spectra and its purity by HPLC analysis. Moreover, phthalocyanine was investigated as a singlet oxygen generator, as efficient singlet oxygen production seems to be crucial for efficient photosensitizers. Solution of magnesium phthalocyanine and 1,3-diphenylisobenzofurane (singlet oxygen quencher) was irradiated with monochromatic light at an appropriate long-wavelength maximum and UV-Vis monitored (**Fig. 1**). Zinc phthalocyanine was used as a standard of known singlet oxygen generation yield. Singlet oxygen generation quantum yield of novel phthalocyanine was determined to be 0.32 and 0.25 when measured in DMF and DMSO, respectively.

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P-27

Cunninghamella as a Microbiological Model for Metabolism of DL76 Which is H_3R Antagonist.

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Traditionally *in vivo* drug metabolism studies have relied on the use of model systems which have been used to indicate the probable metabolic pathway. Usually whole animal systems are used, especially small laboratory animal models like rat, dog, cat, guinea pig, rabbit etc. Plasma and urine of these animals are then examined for the presence of metabolites. Next step is to identify the chemical structure of these metabolites. *In vitro* studies are generally used to complement and specify the data obtained using perfused organs, tissue or cell cultures and microsomal preparations. These methods have several limitations such as cost of experimental animals, ethical aspects and interspecies differences. Moreover, the toxicity of drugs limits the amount of substance that can be administered and therefore only small quantities of metabolites can be isolated. Despite the benefits of currently available analytical techniques, identification of the chemical structure of substances with its small amount is extremely difficult. Use of microbial model offers a number of advantages over the use of animals in metabolism studies, mainly simplicity and financial advantage. Last but not least is ethical aspect.

The hydrolytic and reductive capabilities of microorganisms, especially fungi, have been well known for a long time and are used in preparative reactions. Among the fungi, *Cunninghamella* species have the ability to metabolize a wide variety of xenobiotics in regio- and stereoselective manners that are similar to those in mammalian enzyme systems (1,2). The genus *Cunninghamella* contains species of importance in medical mycology and in biotechnological processes. The genus C*unninghamella* currently contains 14 species. *C. bertholletiae, C. elegans and C. echinulata* are the most common species.

The histamine H_3 receptor (H_3R) has been identified in the central nervous system (CNS) and peripheral nervous system as a pre-synaptic receptor controlling the release of histamine and numerous other neurotransmitters. The first histamine H_3R ligands (agonists, partial agonists and antagonists) were described in 1987. At the beginning, histamine H_3R antagonists were imidazole containing compounds. imperfection of these structures appeared in unwanted hepatic cytochrome P450 inhibition and potential drug–drug interactions. Therefore a new class of non-imidazole histamine H_3R antagonists were designed and synthesized. Potential therapeutic use of histamine receptor ligands involve treatment of CNS diseases. In our Department for many years we were looking for a new ligands of the H_3R in a group of imidazole and non-imidazole derivatives. One of the newly synthesized compounds, DL-76 (1-[3-(4-*tert*-butylphenoxy)propyl]piperidine) (3), DL76 proved to be highly potent and orally available histamine H_3 receptor antagonist ($h$$H_3R$ K_i = 22 ± 3 nM - affinity for the recombinant human H_3R, stably expressed in CHO; ED_{50}: 2.8 ± 0.4 mg/kg).

The aim of this study was to analyze the ability of microorganism *Cunninghamella* to carry out the biotransformation of DL76. Biotransformation was carried out by using three strains of filamentous fungus: *Cunninghamella echinulata* NRRL 1348, *Cunninghamella blakesleeana* DSM 1906, *Cunninghamella elegans* DSM 1908. All of these strains were able to carry out the biotransformation of DL76. Compound which was introduced into the culture was dissolved in an organic solvent (DMSO). The use of co-solvent was dictated by the poor solubility of the substance in water.

Most probable direction of metabolic transition of DL76 was the oxidation of the methyl group in the *tertbutyl* moiety leading to formation of a metabolit which had alocohol I° properties. This kind of reaction was biocatalised by all three strains. However only in the case of strain *Cunninghamella blakesleeana* biotransformation product had a structure of carboxylic acid.

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P-28

New Indazole Derivatives – Synthesis, Ion Complexation, Experimental and Theoretical NMR Studies.

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A series of dimeric derivatives of indazole **5** was obtained by a few-step synthesis involving nucleophilic aromatic substitution and *vicarious substitution of hydrogen* (VNS) (**Scheme 1**). The VNS products were hydrogenated and the obtained amines **4** were cyclized to the indazole derivatives **5**. Due to low solubility of amines **4** in water medium, the cyclization was carried out using *phase-transfer catalysis* or *microwave-assisted organic synthesis*. The analysis using the *PASS* program as well as preliminary cytotoxic studies have shown the dimeric indazoles **5** to be potential anticancer agents.[1] Additionally, a possibility of complexation of metal ions, such as magnesium (**Fig.1**), was investigated using the DFT/B3LYP method and 6-31G (d/p) basis set (**Fig.3**) as well as experimental NMR techniques (**Fig.2**). The theoretical studies showed good correlation with the experimental investigations. Moreover, log *P* was calculated using *ALOGPS* and *ACD Lab/ChemSketch* programs.

Scheme 1.

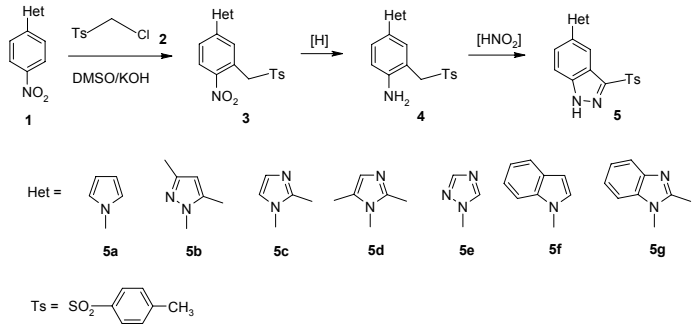


Fig.1.

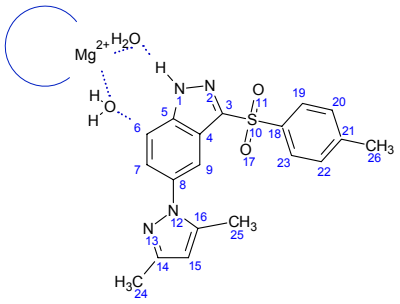


Fig.2.

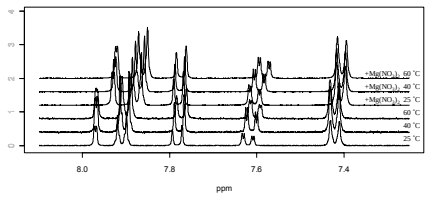
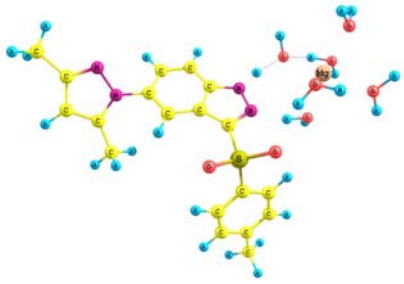


Fig.3.



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Theoretical calculations were supported by PCSS grant No. 92/2011, and polish National Science Centre (NCN) grant No. N N401 642340.
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P-29

Development and Validation of Methodology for Designing and Analysis of Virtual Combinatorial Libraries Based on Defined Reaction Pathways.

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New synthetic methods in combinatorial chemistry, such as parallel solid-phase synthesis, enable preparation of large number of compounds for drug development screening campaigns in a very fast and efficient way. Large libraries of compounds are usually synthesized as combinations of different building blocks (BB's) [1,2]. However, the number of compounds that can be synthesized using elaborated synthesis protocol, and tested for biological activity (even in HTS) is often limited by the project's budget. In that case, methodology enabling prioritization and helping in decision making of which compound, from the available synthetic space, should be obtained first, would be very useful.
Herein we present a new approach to generating and ranking of the virtual combinatorial library based on defined chemical reactions [3]. For searching a specified type of substrates, the biggest 26 vendors building blocks databases were used. All the possible combinations of the selected building blocks with core substructures resulted in approx. 15×106 synthetically available compounds. By applying a modified protocol of multistep Virtual Screening the ranking list of the best derivatives was obtained.
In collaboration with medicinal chemists, several compounds were selected, synthesized and biologically evaluated in order to verify the effectiveness of the methodology applied.

Acknowledgements
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P-30

Probing Pharmacological Space for the Analysis of Fragmental Drug-Likeness Topology: Application to Mono- and Diazanaphthalene Compounds.

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The determination of the relation between chemical, biological and pharmacological space is one of the challenges of drug discovery nowadays. The use of molecular fragments that enables a widespread examination of chemical space is one of the approaches that can be employed to investigate more profitable paths to discovery. Chemoinformatics is of particular interest to pharmaceutical research and medicinal chemistry. Effective modeling work is relative to the availability of essential structural and experimental data, and yet a number of molecular databases are publicly available and can be used in drug design.
Here we report an application of a novel and unique molecular and structural database managing system, MoStBioDat [1] for the massive *in silico* protocols parallely analyzing small molecule ligand and protein data. In this study, a compilation of various publicly available databases of small molecules has been analyzed to map fragmental drug-likeness topology.
Mining small molecule databases relevant to drug discovery could be also a fruitful method for classifying chemical compounds as being drug-like and/or lead-like. In some case it is possible to identify common molecular fragments, so-called privileged motifs, which ease ligand binding to an individual receptor or particular receptor family. The term privileged structure was indeed first applied to the benzodiazepine nucleus by Evans et al. in their search for CCK-A antagonists derived from the natural product asperlicin [2]. Although privileged substructures are intended to be target class-specific it has been shown that this separated molecular subunits also appeared in compounds active against other target families [3]. Frequency of occurrences of that kind generic drug-like molecular fragment among drug populations and bioactive compounds ensembles could be a valuable index of privileged structures estimation. By screening databases we can estimate the population of privileged (sub)structural motifs [4]. This forced us to perform comprehensive exploration of azanaphthalene polypharmacology to designate privileged structural drug architecture and fragmental drug-likeness topology in this class of compounds.
Quinoline scaffold is frequently used in drug design [5]. One would wonder how it compares to other possible “fragmental” azanaphthalens. We attempted to test the attractiveness of the different azanaphhthalene scaffolds in chemical space. Hence, we analyzed a number of the PubChem registered compounds having a given azanaphthalene scaffold. Quinoline appeared the most frequent hit. What is the origin of this popularity: practical applications, synthetic availability or else? To test the different possibilities, we considered two parameters: range of interest and b-value, representing respectively the number of compounds tested to all hits and active to tested ratio (b-value), which are the simplest measures of attractiveness and drug-likeness.

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P-31

Microbiological Models in Study of H3R Histamine Receptor Ligands Metabolizm.

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Major reasons for the increasing significance of metabolism in drug discovery and development are its pharmacodynamic and pharmacokinetic consequences. As a result, many aspects of drug biotransformation are of interest to medicinal chemists, including: active metabolites from active drugs, active metabolites from prodrugs (activation), inactive metabolites (inactivation), toxic metabolites - particularly reactive metabolites able to form covalent adducts with critical biomolecules (toxification), metabolites capable of inhibiting a metabolic pathway and finally, metabolites having different physicochemical properties resulting for example in tissue accumulation and residue retention [1].
It has been estimated that 5 human cytochrome P450 enzymes are involved in the metabolism of ~90% of drugs – CYP3A4, CYP2C9, CYP2C19, CYP2D6 and CYP1A2. CYP3A4 is one of the most important cytochrome P450 isoforms responsible for about half of all drugs metabolism by humans.
There are many microorganisms which can imitate the metabolism of various drugs and xenobiotics that is observed in animal species. The fungus *Cunninghamella echinulata*, which possesses a cytochrome P450 system analogous to that found in humans, is used successfully for years as a suitable *in vitro* model of drug metabolism [2]. Morover, molecular biology techniques are very usuful for obtain genetically modified microorganisms which are able to overexpress enzymes involved in metabolic pathways.
In the present study we used the fungus *Cunninghamella echinulata* 1908 and the bacteria *Escherichia coli* DH5α transformed with pCW3A4 plasmid, overexpressing human P450 CYP3A4 cytochrome, to determine metabolites of H3R histamine receptor ligands [3][4].

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P-32

Photochemistry and Biological Activity of Novel Porphyrazines Endowed with Peripheral Thiol Functionality.

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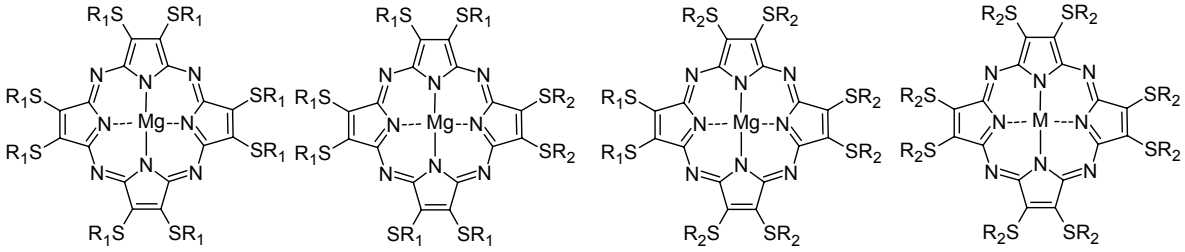
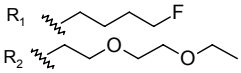
Porphyrazines (pzs) are aromatic macrocyclic compounds consisting of four pyrrole rings linked together with azide groups. After excitation with light of an appropriate wavelength, they demonstrate the ability to generate singlet oxygen. Pzs possess numerous potential applications in industry, technology and medicine, especially photodynamic therapy (PDT). PDT has been used to treat effectively tumors or lesions by destroying cells with singlet oxygen [1]. Sulfur atoms introduced into the macrocyclic core periphery of pzs have significantly improved their physical-chemical properties such as solubility in various solvents and ability to generate singlet oxygen [2, 3].



1 **2** **3** **4 M = Mg** **5 M = 2H**



Novel thiol derived pzs (**1** – **5**) were synthesized and widely characterized using UV-Vis spectroscopy, MS MALDI spectrometry and NMR spectroscopy, including two–dimensional HMBC and HMQC spectra. Moreover, they were subjected to photochemical and biological studies. Sensor properties of synthesized compounds were evaluated by monitoring changes in their UV–Vis spectra in the presence of increasing concentration of palladium cations. Additionally, solvatochromic effects were studied by measuring UV–Vis spectra in different solvents. In order to determine the utility of synthesized macrocycles in PDT, the ability to generate singlet oxygen by pzs **1** and **5** was tested. Although both compounds turned out to be poor singlet oxygen producers, they were subjected to biological tests using squamous carcinoma cell lines derived from the tongue and from the buccal mucosa. Compound **1** showed selectivity and moderate activity towards buccal mucosa derived cancer cell line.

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P-33

Amide Derivatives of 4-Methylpiperazine as Histamine H_4 Receptor Antagonists.

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Histamine H_4 receptor (H_4R) was identified in 2000 by several research groups independently. H_4R is widely expressed in cells and tissues of the immune system (mast cells, dendritic cells, eosinophils, monocytes, basophils and T cells), suggesting its role in the immunological and inflammatory process (1). Anti-H_4R ligands were evaluated in animals models of some diseases (e.g. allergic rhinitis, airway inflammation, pruritus, itch or pain) and showed positive effects (2).
In 2003 Jablonowski *et al.* published a series of selective histamine H_4R antagonists with JNJ 7777120 the first orally active, potent and selective non-imidazole H_4R compound (3). Since that time many other potent and selective H_4R ligands (antagonists/inverse agonists) have been synthesized by pharmaceutical companies and academic researchers (4). Recently, for the first H_4R antagonist (UR-63325, Palau Pharma) the phase I first-in-man clinical trial has been finished with promising interim data (treatment for allergic rhinitis) (5).
As our research group is involved in the search for histamine H_4R ligands (6) we have synthesized a series of JNJ7777120 analogues, with an 4-methylpiperazine amide motif. The compounds were tested for their affinities at recombinant human H_4R transiently expressed in insect *Sf*9 cells. The evaluated compounds showed weak to moderate affinities. The most promising structure is a 3,5-dichlorobenzo[b]thiophene-2-carboxylic acid derivative with K_i = 1 μM.

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This work was partly supported by grant No. 501/N-COST/2009/0 and COST Action BM0806 (Recent advances in histamine receptor H_4R research).

P-34

Synthesis of the Novel Terpene Based 2,4-Disubstituted 1,3-Thiazoles as Potential Antifungal Agents.

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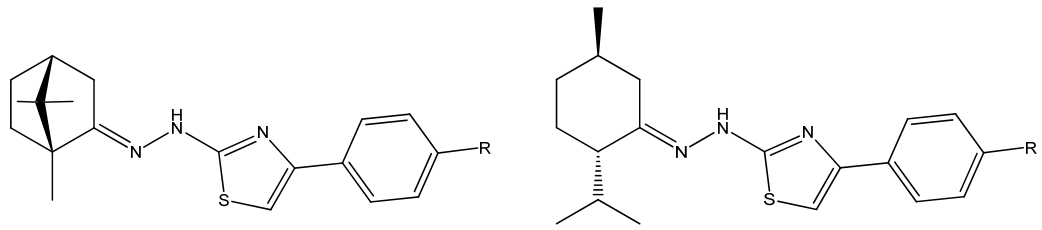
In the recent years, thiazoles and their derivatives are widely studies in medicinal chemistry because of their varied biological activities such as antibacterial [1], antifungal [2], antitumor [3] and ani-HIV [4]. For several years the emergence of multi-drug resistance bacteria and also resistant fungi is reported worldwide. Therefore novel, effective antibacterial and antifungal drugs are required.
Since the thiazole moiety seems to be a possible pharmacophore in various pharmacologically active agents we developed several novel terpene based 2,4-disubstituted 1,3-thiazoles as potential antifungal agents.



R = H, Br, OMe, CN, NO_2, F, $NHCOCH_3$, $NHSO_2CH_3$, $NHCOCH_2Cl$, Ph.

In the first step were synthesized thiosemicarbazones by condensing of (*1R*,*4R*)-(+)-camphore and (2*S*,5*R*)-(−)-menthone with thiosemicarbazide in the presence of glacial acetic acid as catalyst. In the next step terpene based thiazoles were prepared by cyclization of (*1R*,*4R*)-(+)-camphore and (2*S*,5*R*)-(−)-menthone thiosemicarbazones with *para*-substituted bromo- or chloroacetophenones with high yield and purity.
In our research we are investigating the influence of various substituents in the *para* position in the phenyl ring to identify the most active compounds. The newly obtained compound are currently being tested as antifungal agents.

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P-35

Comparison of Docking Procedures for the Set β-Adrenergic Receptor Models Complexed with Their Ligands.

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Aim of the study
The aim of the study was to assess and compare the output of two different docking algorithms in simulation of ligand-receptor interactions for β-1 and β-2 adrenergic receptors.

Materials and Methods
Thirteen crystallographic models of β-1 and β-2 adrenergic receptors were obtained from the Protein Data Bank. All the protein structures were crystallized with corresponding ligands which were further redocked to their original protein models. Docking was performed using Molegro 2010.4.2.0 and Autodock4.0 procedures. RMSD values and visual analysis were used to compare docking results.

Results
After analysis, significant differences in docking results using both software were observed. In some cases ligand's position was correct but some minor inaccuracies were present. They consisted of rotations around the centre of mass, rotations of the aromatic ring or chain misalignment. The results differed in both software. In some cases the best fit chosen by visual analysis did not agree with the best position chosen by respective scoring functions. Overall RMSD scoring suggests that AUTODOCK 4.0 procedures offers slightly better results.

This work was supported by the Foundation for Polish Science (programme TEAM operated within the Innovative Economy Operational Programme of Economy of European Union 2007-2013)

P-36

Analysis of Molecular Structure and Crystal Packing of Perindopril *tert*-Butylamine Salt and Perindoprilat.

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Perindopril, ((2*S*, 3a*S*, 7a*S*)-1-[(2*S*)-2-[[(2*S*)-1-ethoxy-1-oxopentan-2-yl]amino]propanoyl]-2,3,3a,4,5,6,7,7a-octahydroindole-2-carboxylic acid, $C_{19}H_{32}N_2O_5$, is popular antihypertensive prodrug and acts as an ACE inhibitor and is used in the treatment of cardiovascular diseases, especially in the treatment of high blood pressure and heart failure [1]. Perindopril has several unique properties above other ACE-inhibitors in its class, such as a higher affinity for tissue [2]. Perindopril is desesterified in the liver and plasma, by esterases, to active dicarboxylic metabolit – perindoprilat [3]. Perindopril is using as clinically useful dosage forms of API, as two salts: with *tert*-butylamine (perindopril erbumine) and L-arginine (perindopril L-arginine). The perindopril L-arginine salt is equivalent to perindopril erbumine [4]. In view of the pharmaceutical value of perindopril, it has been of prime importance to obtain it with excellent purity. Unfortunately, synthesis of such product is extremely difficult. Perindopril and its salts are chemically highly sensitive compounds and are susceptible to degradation. The containing of impurities in crude perindopril may constitute an even few percent [5]. The main impurity is diketopiperazine (ethyl(2*S*)-2-[(3*S*,5a*S*,9a*S*,10a*S*)-3-methyl-1,4-dioxodecahydropyrazinol[1,2-a]indol-2(1H)-yl]pentanoate [6].

Perindopril erbumine is known to exist in several polymorphic forms, as well as mono-, di- and sesqui-hydrated forms. The differing solid-state forms of a drug substance may influence the stability, bioavailability, ease of manufacture and/or aesthetic appeal of the drug formulation [7]. Although perindopril was first reported in 1982 [8] and subsequently found many applications [9], there were almost no reported details pertaining to its crystal structure. For the better understanding of the inhibition of ACE by perindopril, it is important to know the structural properties of perindopril erbumine. For this reason, we deemed it appropriate to determine the 3D structural data of perindopril by X-ray diffraction.

We report, for the first time, 3D-structural data of the three perindopril erbumine forms: triclinic, monoclinic [10] and orthorhombic, but also diketopiperazine – the perindopril degradation product. Moreover, we took advantage of analyse of structural features concerning molecular geometry and crystal packing arrangements. We found, inter alia, that triclinic structure is most stable form. We observed also analogies between perindopril conformation and that of perindoprilat, wchich is important from biological point of view.

Preceding investigations may have commercial value in drug design and may be useful in preparation of new dose forms with improved properties.

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P-37

Synthesis and Characterization of New co-Crystals of Tadalafil.

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The pharmaceutical active substances usually exist in many forms like polymorphs, solvates and salts. Apart from these mentioned, active pharmaceutical ingredient compounds can create co-crystals. Co-crystals are normally obtained by evaporating or cooling a saturated solution of the target compound, sublimation or crystallization from melt. Recently, as the screening procedure, some interest achieve mechano-chemical methods of co-crystallization like a solid-state grinding in particular a solvent-drop grinding (SDG) where co-crystallization proceeds in the presence of several drops of a proper solvent.

Tadalafil (Fig. 1) is a approved phosphodiesterase-5 inhibitor indicated in the treatment of erectile dysfunction [1]. It is a selective, potent and reversible competitive inhibitor of the enzyme phosphodiesterase-5 (PDE5), which causes inactivation of cyclic guanosine monophosphate (cGMP) [2]. Due to longer duration of its action and minimum potential to cause vision abnormalities, tadalafil has gained wide clinical acceptance. However, it has very low aqueous solubility (practically insoluble), which leads to its poor dissolution in the gastrointestinal tract, resulting in variable bioavailability.

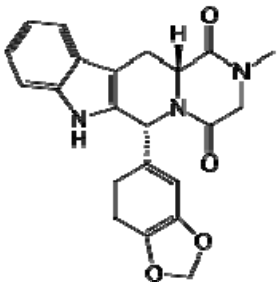

Fig. 1. Chemical structure of Tadalafil.

The aim of this work was to synthesize a new co-crystals of Tadalafil using SDG method. Among 38 esters, sugars, amino acids and other compounds used in synthesis only 3 have formed a new co-crystals. Physicochemical characterization of the prepared systems at molar ratio of 1:1 was studied using X-ray diffractometry (XRD).

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P-38

Structural Study of Merthiolate and Its Derivatives.

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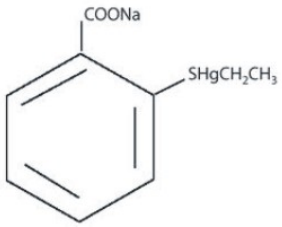
Merthiolate (other common names: thiomersal, thimerosal), sodium ethyl-(2-(carboxylato)phenylthiolato)-mercury, $[(ArCO_2)SHgEt]Na$, see Scheme, and its derivatives are controversial pharmaceutical ingredients due to large content of mercury (up to 49.55%) [1,2]. Nevertheless thimerosal has been marketed as an antimicrobial agent in a range of products, including topical antiseptic solutions for treating cuts, nasal sprays, eye solutions, skin test antigens, contact lens cleaners, soap-free cleansers, diaper rash treatments, cosmetics, tattoo inks, and perhaps most importantly as a preservative in vaccines and other injectable biological products, including Rho(D)-immune globulin preparations [3,5].



Lately flared up discussion on toxicity of merthiolate, which still remains in the drug supply. Organic compounds containing an alkil radical directly attached to a mercury atom, can be more toxic to human than are other kinds of mercury compounds [1]. Despite the fact that the merthiolate was developed in 1927 [6] its three-dimensional structure was uknown until 2008 [7]. In the Cambridge Structural Database published structural data of eight mercury thiosalicylate compounds, and ethylmercury thiosalicylate derivatives to make up half of them [7-11]. Considering growing interest in mercury derivatives, we deemed it appropriate to summarize and compare structural information relating to all mercury thiosalicylate compounds. Discussion of the results will be presented in details.

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P-39

5-Naphthyl Derivatives of Hydantoin as Potential Efflux Pump Inhibitors.

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Despite the development of safe and potent antibiotics serious bacterial infections remain a priority. An increasing concern is the emergence of multi-drug-resistant (MDR) bacteria and their role as opportunistic pathogens. Due to uncontrolled, inappropriate and massive use of antibiotics and chemotherapeutics, the number of drug-resistant strains steadily increases, limiting the effective treatment of many bacterial infections including tuberculosis, as well as fungal diseases or cancer [1, 2].
One of the strategies to overcome MDR is to affect drug delivery systems inhibiting drug efflux proteins, that reduce intracellular drug concentrations and thereby impede accessibility of drugs to their sites of action, ultimately leading to reduced susceptibility [3]. The development of efflux pumps inhibitors (EPIs) could extend the useful lifetime of many antibiotics by improving therapeutic efficacy and by suppressing the emergence of resistant variants that might otherwise arise during treatment. Research carried out in recent years have brought several groups of promising EPIs, like reserpine, verapamil, gemfibrozil, cyclosporine A or PAβN [3, 4].
This work is a continuation of earlier studies on search for bacterial efflux pumps inhibitors, performed by our group in the Department of Technology and Biotechnology of Drugs CM UJ. Based on the previously obtained results and using structural analogies to the known potent EPI, PAβN, we designed and synthesized a series of compounds belonging to the group of aromatic derivatives of hydantoin. In analogy to the structure of PAβN, α- and β-naphthyl fragments were incorporated into 5-position of the hydantoin ring, while alkylamine or alkylguanidine chains were introduced as N3-substituents.
The chemical synthesis of compounds consisted of three steps, involving successively: Bucherer-Berg reaction, two-phase N3-alkylation and the Gabriel synthesis. Four final amines were successfully obtained and characterized. The resulting compounds will be tested, in conjunction with existing antibiotics, on their EPI potency as well as their intrinsic antimicrobial activity, using both susceptible and resistant *E.aerogenes* strains.
In silico calculations of lipophilicity, toxicity and ability for being drug were performed by OSIRIS program and results are presented.

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The project was partly supported by the grant Polonium 757/N-Polonium 2010.

P-40

Looking for New Isoxazole Derivatives with Potential Immunorestoring Activity.

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Our recent investigations of isoxazole derivatives exhibited very interesting immunological activities (immunosupressory, immunostimulatory, immunorestoring). Looking for new active immunomodulators we synthesized a few groups of isoxazole derivatives, which showed significant immunological activity in several *in vitro* and *in vivo* assays in mice and humans. We synthesized and tested monocyclic and bicyclic derivatives, originating from 5-amino-3-methyl-4-isoxazolecarboxylic acid: N'-substituted hydrazides of 5-amino-3-methyl-4-isoxazolecarboxylic acid, semicarbazides and semithiocarbazides of 5-amino-3-methyl-4-isoxazolecarboxylic acid [1], 5-substituted 3-methylisoxazole[5,4-d]-pyrimidin-4-ones [2] and 5-substituted 3-methylisoxazole[5,4-d]-1,2,3-triazin-4-ones [3,4].
As a continuation our study a new series of substituted benzylamides of 5-amino-3-methyl-4-isoxazolecarboxylic acid was synthesized. In reaction of benzylamides with orthoesters or nitrous acid we obtained 5-substituted isoxazolo[5,4-d]-4-pirymidynones and isoxazolo[5,4-d]-1,2,3-triazin-4-ones. This compounds are modified and compare to different isoxazole derivatives with immunostimulatory activity, which immunorestoring activity were described [5-8]. Computational study, molecular modeling and structure/activity relationships is performed.

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Study was supported by grant of Polish National Science Centre nr N N405 682840 and by research fellowship within "Development program of Wroclaw Medical University" funded from European Social Fund, Human Capital, National Cohesion Strategy" (contract no. UDA-POKL.04.01.01-00-010/08-01)".

P-41

Synthesis and Biological Evaluation of New Pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*b*][1,2,4]triazines.

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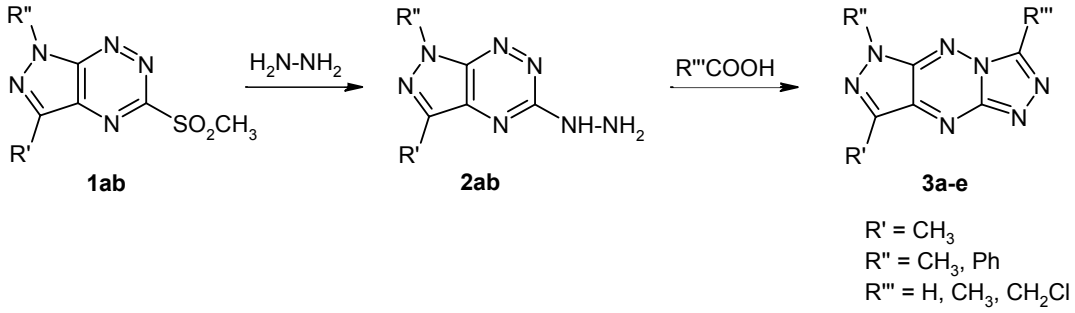
Pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*b*][1,2,4]triazine ring system is a new clas of heterocyclic compounds. Some derivatives of that ring system were prepared and screened against various cancer cell lines. The human cancer cell lines assayed were breast (MCF-7), lung (NCI-H460), prostate (PC-3) and colon (Colo 205). The anulated pyrazolo[4,3-*e*][1,2,4]triazines were afforded by the reaction of 5-hydrazin-1*H*-pyrazolo[4,3-*e*][1,2,4]triazine derivatives **2ab** with appropriate carboxylic acid.



1ab **2ab** **3a-e**

R' = CH_3
R" = CH_3, Ph
R'" = H, CH_3, CH_2Cl

All tested compounds displayed potent promising cytotoxic activity against several cancer cell lines and may be useful as leads for development anticancer compounds.

P-42

Synthesis of New 1,8-Diazaphenothiazines and Prediction of Their Biological Activities.

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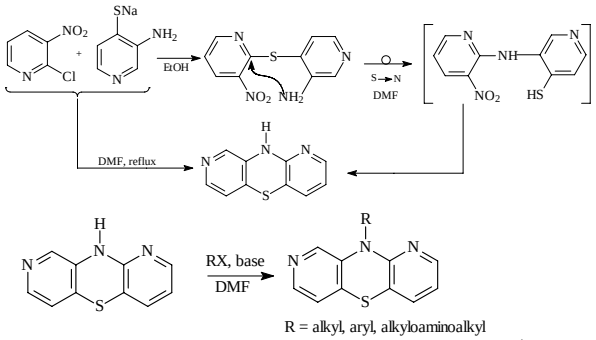
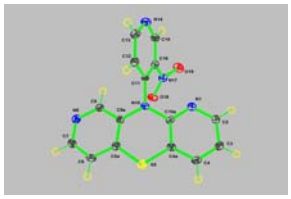
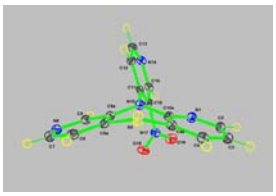
Phenothiazines are the oldest and the largest group of neuroleptic drugs. These compounds are widely used in psychiatry. They exhibit also valuable antiemetic, antihistaminic and antitussive properties. There have appeared numerous articles for last ten years on new biological properties of phenothiazines, among them anticancer, antibacterial, antiprotozoic, antiviral, antiprionic and multidrug resistance reversal activity [1]. Chemical modification of the phenothiazine structure was carried out by replacing the benzene ring with the pyridine ring and by introduction of new substituents in position 10. Some modifications of the phenothiazine structures were directed into azaphenothiazines, where the benzene ring was substituted with the azine ring. In our search we obtained 10-substitued 2,7-diazaphenothiazines with promising anticancer, immunosuppressive and antioxidant activities [2,4].
In continuation of our search for pharmacoactive dipyrido-1,4-thiazines we obtained new 10*H*-1,8-diazaphenothiazine **1** and transformed into 10-substituted derivatives possessing alkyl, aryl, heteroaryl and dialkylaminoalkyl substituents.



The identification of the 1,8-diazaphenothiazine structure was based on ^{1}H NMR, ^{1}H-^{1}H COSY, NOE spectroscopy, mass spectrometry and X-ray analysis of compound with the nitropyridinyl substituent. The X-ray analysis revealed the characteristic features of phenothiazines: the folded structure, the boat conformation of the thiazine ring and the quasi equatorial position of the substituent.All derivatives show promising potential neuroprotective, antipsychotic, anticancer, immunostimulant activity determined by program PASS [5].





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P-43

TLC Detection of New Azaphenothiazines.

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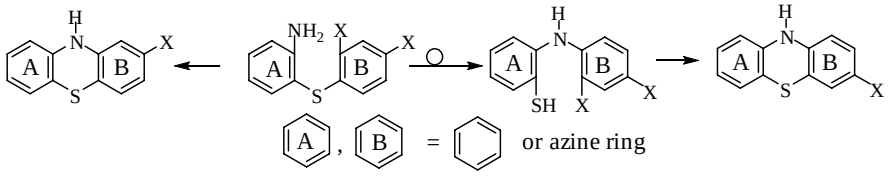
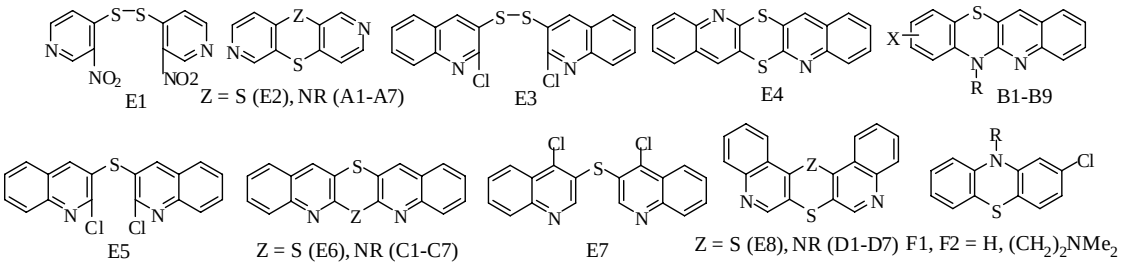
Phenothiazines are known for varied important biological activities. Recent reports deal with anticancer activities, reversal of multidrug resistance and potential treatment in Alzheimer's and Creutzfeldt-Jakob diseases [1]. New phenothiazines are obtained by introduction of new pharmacophoric groups at the thiazine nitrogen atom and by substitution of the benzene ring with the azine rings to form various azaphenothiazines. As the last processes are the most perspective, one can expect synthesis of new azaphenothiazines now and in the future. The synthesis of azaphenotiazines may proceed through a stage of the Smiles rearrangement and may lead to different products: the cyclic compounds as the result of the ring closure processes, most of them of the azaphenothiazine structure (rearranged or not), cyclic side-products of isosteric structure (dithiins) and some acyclic products when the ring-closure processes did not occur [2].



The aim of this study is to find a simple TLC method to follow the synthesis azaphenothiazines [3-5] from various substrates, to detect and to separate the azaphenothiazines from other products and to separate N-substituted azaphenothiazines from NH-azaphenothiazines.



TLC study was performed using new tri- tetra- and pentacyclic azaphenothiazines (10-substituted 2,7-diazaphenothiazines **A**, 6-, 8-, 9- and 10-substituted quinobenzothiazines **B**, 6- and 14-substituted diquinothiazines **C** and **D**, the substrates and side-products **E)** on 2 stationary phases with 8 mobile phases. The separation factors ΔR_F, R_S and α were determined. The spots were detected in the daylight, under the UV lamp and with over 20 visualizing reagents and compared with classical phenothiazines **F**. Under the UV light of 365 nm spectacular color change (natural fluorescence) was detected only for phenothiazines **A-D** and **F**. Combinations of the R_F values and the spot colors (natural fluorescence and after detection with the reagents) facilitated identification of new azaphenothiazines in the reaction mixture.

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P-44

Synthesis and Anticancer Activity of Quinobenzo-1,4-thiazines.

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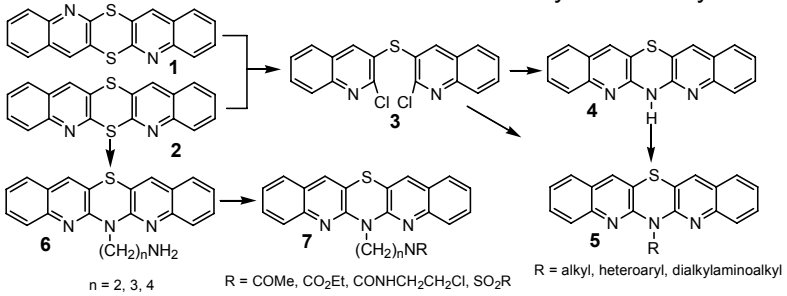
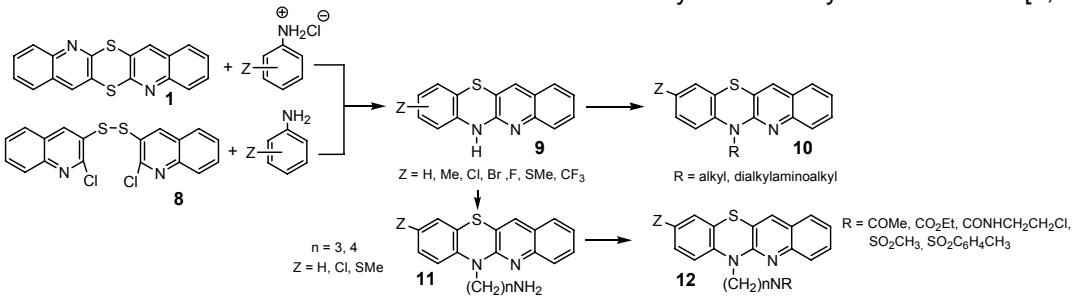
Phenothiazines are known for varied chemical properties and biological activities. Recent reports have focused interests on anticancer activities, reversal of multidrug resistance and potential treatment in Alzheimer's and Creutzfeldt-Jakob diseases [1]. In continuation of our search for pharmacoactive quinoline derivatives we modified the phenothiazine structure to form new type of the linear tetra- and pentacyclic azaphenothiazines. Reactions of the 1,4-dithiin ring opening in diquinodithiins **1** and **2** led to sulfide **3** which underwent annulation reactions with divalent reagents to 6H- and 6-substituted diquino-1,4-thiazines **4** and **5** [2]. Reactions of the 1,4-dithiin ring opening in diquinodithiin **2** with diaminoalkanes led to aminoalkyldiquinothiazines **6** which were further transformed into acyl and sulfonyl derivatives **7** [3].



The novel azaphenothiazines exhibit promising anticancer activities against human cell lines of lung, colon, breast, renal, ovarian, prostate and CNS cancers, melanoma and leukemia determined in National Cancer Institute in Bethesda, in USA [4].

On the other hand, reactions of the 1,4-dithiin ring opening in diquinodithiin **1** with primary aromatic amines led to substituted 6H- and 6-alkylquinobenzo-1,4-thiazines **9** and **10**. Reactions of the 6H-quinobenzo-1,4-thiazines **9** with bromoalkylphthalimides and further hydrolysis led to aminoalkyl-quinobenzothiazines **11** which were further transformed into acyl and sulfonyl derivatives **12** [5, 6].



Selected compounds **12** exhibit significant antiproliferative and anticancer activity, and low toxicity.

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[5] Jeleń M., Pluta K.: *Heterocycles* **78**, (2009), 2325.
[6] This work is supported by Ministry of Science and Higher Education Grant No. N405 101739.

P-45

A System for Automated Validation of GPCRs Homology Models Against Mutational Data.

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Sequence alignment between target and template sequence is the most troublesome stage of homology modeling protocol. Misplacing amino acids responsible for interactions with ligands may lead to improper binding mode of so created model and render it useless. This is the reason of wide usage of mutational data in either aligning sequences or models verification.

In this study we present a tool allowing automated comparison of mutagenesis data retrieved from tinyGRAP [1] database with corresponding residues of the model. tinyGRAP dataset is queried for the investigated sequence and its close homologs (i.e. group members), and substitution mutations are retrieved. Query results are then checked whether appropriate residues face inside of the receptor (with some margin), and if not, the tool produces report in PyMol .pse file pointing amino acids violating mutational „constrains".

Acknowledgments
The study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism; http://www.cns-platform.eu/

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P-46

Lipophilicity Characterization of New 3,3-Disubstituted Pyrrolidine-2,5-dione Derivatives as Potential Anticonvulsant Agents.

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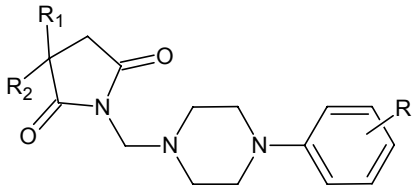
Lipophilicity is one of the most important physicochemical parameters of organic substances related to their biological activity and tendency of molecule to be transported through the biological membranes. Chromatographic approaches (RP-TLC and RP-HPLC) are very important experimental alternatives to octanol/water partisioning and nowadays are the most widely used method to quantifying lipophilicity [1,2].
In the present study we have determined the lipophilicity of library 3,3-disubstituted-N-[(4-phenylpiperazin-1-yl)methyl]-pyrrolidine-2,5-diones using the reserved phase thin layer chromatography (RP-TLC) with n-propanol-Tris buffer (pH 7.4) mixtures as mobile phases. Examination of chromatographic behavior showed a linear correlation between R_M values and the concentration of n-propanol in the mobile phase. An extrapolation method was used for the estimation of relative retention parameters (R_{M0}). The structures of compounds are shown below.



R_1=CH_3, C_6H_5
R_2=CH_3, C_6H_5
R=H, 2-F, 4-F, 3,4-Cl, 2-Cl, 3-Cl, 4-Cl, 3-CF_3, 2-OCH_3, 3-OCH_3, 2-CH_3, 3-CH_3

All the tested compounds were evaluated for their anticonvulsant activity through the Antiepileptic Drug Development (ADD) Program (Epilepsy Branch, Neurological Disorders Program, National Institute of the Neurological Disorders and Stroke, Rockville, USA) by using of the procedures described elsewhere [3].
The result obtained enabled the evaluation of the: relationships between chemical structure and lipophilicity and correlation between the anticonvulsant activity and lipophilicity.

[1] Kerns E. H., Di L., Petusky S., Kleintop T., Huryn D., McConnell O., Carter G.: *J. Chromatogr. B* 791 (2003), 381-382.
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P-47

Crystal and Molecular Structure of Baclofen Hydrogen Sulfate Hemihydrate.

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Baclofen (Fig. 1) is a stereoselective - γ–aminobutyric acid$_B$ ($GABA_B$) receptor agonist used at present to control spasticity [1]. However, recent lines of experimental evidence have suggested the ability of baclofen to suppress alcohol withdrawal signs (AWS) in rats [2] accordingly, recent preliminary data have shown how baclofen rapidly suppressed AWS severity in human alcoholics [3], even when manifested in its severe form complicated by *delirium tremens*.

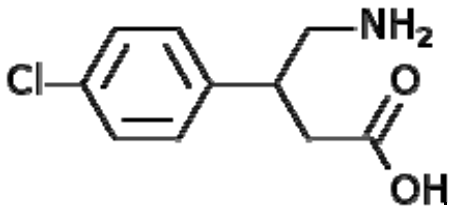

Fig. 1. Chemical structure of Baclofen.

In the course of looking for new forms of Baclofen, the crystal and molecular structure of the Baclofen Hydrogen Sulfate Hemihydrate [$C_{10}H_{13}ClNO_2^+$ HSO_4^- · $0{,}5H_2O$] was solved by single crystal X-ray diffraction analysis. The title compound crystals have a monoclinic symmetry with space group C2/c (a = 35,892(3), b = 7,8510(8), c = 9,9138(10)Å, β = 94,312(2)º). Detailed discussion of the structural features concerning molecular geometry and crystal packing will be presented.

[1] Davidoff R. A.: *Ann. Neurol.* 17 (1985), 107-116.
[2] Colombo G., Agabio R., Carai: *Alcohol Clin. Exp. Res.* 24 (2000), 58-66.
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P-48

Search for New Compounds Inhibiting Bacterial Multidrug Resistance Among Amine Derivatives of Imidazolone.

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The multidrug resistance (MDR) is an element seriously limiting treatment of various bacterial diseases [1-3]. Microbial efflux pumps play a key role in multidrug resistant strains. The Gram- negative bacteria has evolved specialized tripartite AcrAB- TolC and MexAB- OprM efflux systems that transport molecules from the cytoplasm to the extracellular environment in energy dependent processes. One of the strategies to combat MDR is blocking the efflux mechanism of bacterial cell by inhibitors. In our previous studies, a number of hydantoin derivatives were obtained and evaluated on their efflux pumps inhibition (EPIs) properties in *Enterobacter aerogenes* strains. Several compounds displayed moderate EPIs-activities. Basing on the results, new modifications were performed including the conversion of tiohydantoin into imidazolone and an introduction of various arylidene substituents at position 5 and amine moiety at position 2 (Fig. 1).

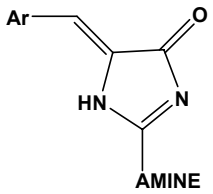

Figure 1. General structure of obtained compounds.

A series of 10 new piperazine derivatives of 5-arylideneimidazolone was obtained within 4-step synthesis including Knoevenagel condensation, S- and N-alkylation and N-deprotection. New compounds were tested in microbiological assays in three *E. aerogenes* strains (ATCC 13048, CM64 and EA-27). Two types of tests were carried out: (1) tests on direct antibacterial activity, (2) tests on the compounds influence of MIC value of antibiotics. SAR-studies were performed. Results indicated that compounds possessing large arylidene substituents displayed slight antibacterial activities, whereas the 4-chlorobenzylidene derivative the best EPIs-properties.

The work was partly supported by grants: 501/N-COST/2009/0 COST action BM0701 and Polonium 757/N-Polonium/2010.

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P-49

Antimicrobial Activity of New Derivatives of *N*-Substituted Amides of 1-(5-Methylthio-1,2,4-triazol-3-yl)cyclohexane-2-carboxylic Acid.

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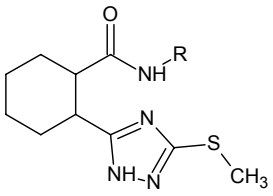
Five-membered heterocyclic compounds containing nitrogen especially 1,2,4-triazole and it's derivatives are highly prevalent in collections of bioactive compounds. Some of them possess antifungal, antimicrobial and antitubercular properties. It is well known that 1,2,4-triazole system is the structural nucleus of many drugs which are used in modern medicine.
We present here antimicrobial activity of new derivatives of *N*-substituted amides of 1-(5-methylthio-1,2,4-triazol-3-yl)cyclohexane-2-carboxylic acid.



I – X

R= $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$, $CH_3CHCH_2CH_3$, cyclo-C_6H_{11}, $CH_2C_6H_5$, $CH_2CH_2C_6H_5$, C_6H_5, o-ClC_6H_4, p-BrC_6H_4, p-$OCH_3C_6H_4$

Compounds (I – X) were screened for their antibacterial activity *in vitro* against the reference strains of 8 species of aerobic Gram-positive and Gram-negative bacteria from American Type Culture Collection (ATCC), routinely used for evaluation of antimicrobials. Microbial suspensions were prepared in sterile saline (0.85% NaCl) with an optical density of McFarland standard 0.5 (150 x 10^6 CFU [Colony Forming Units)/mL]). Antimicrobial activity of the newly synthesized compounds were screened by broth microdilution technique (Mueller-Hinton medium) on the basis of MIC (minimal inhibitory concentration) values. All stock solutions of the tested compounds were dissolved in dimethyl sulfoxide (DMSO).
According to our preliminary results, compounds V and VII showed moderate activity against *Staphylococcus aureus* ATCC 25923 (MIC = 500 µg/mL), while VII - against *Staphylococcus epidermidis* ATCC 12228 (MIC = 500 µg/mL).
Summing up, compounds V and VII may be of value for searching new derivatives showing better antistaphylococcal activity.

P-50

RP-TLC Study of Biologically Active *N*-Substituted 3-Amino-5-hydroxy-4-phenyl-1*H*-pyrazole-1-carboxamides.

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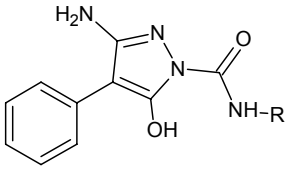
Lipophilicity, in addition to electronic and steric parameters, is a descriptor for determining the effects of all biologically active compounds. This parameter affects the reaction of drugs with receptor in the cell. Due to this it is responsible for e.g. toxicity, solubility or pharmacokinetic processes in living organisms. Particles which possess the appropriate affinity for biological membranes liofilowych will be properly absorbed and distributed in the body.
The title compounds were obtained in the reaction between 1-cyanophenyl acetic acid hydrazide and appropriate isocyanates The chemical structure of compounds is presented below.



R = $CH_3CHC_6H_5$, 4-$C_2H_5OC_6H_4$,$CH_2COOC_2H_5$, C_6H_{11},1-$C_{10}H_7$, C_2H_5, 4-$CH_3OC_6H_4$,C_4H_9, $CH_2C_6H_5$, $CH_2CH{=}CH_2$

The microbiological investigations show that all derivatives possess antibacterial activity. This characteristic for one of derivatives against Gram-positive species is very promising with MIC values 7.81-31.25 μg/mL.
The chromatography in reversed-phase mode plates with methanol as water-organic mobile phase constituent was applied for determination of solutes R_F coefficients. The dependence of concentration of polar modifier on R_F values allowed for calculation of the solute relative lipophilicity (expressed as R_{M0} values). This parameter was in the range 0.51 – 5.33 for investigated solutes. The decrease of this parameter strongly depends on the constituent (R) in the *N*-substituted 3-amino-5-hydroxy-4-phenyl-1*H*-pyrazole-1-carboxamide molecules and it was in the following order:

$$CH_2CH{=}CH_2 < 4\text{-}CH_3OC_6H_4 < C_2H_5 < CH_2C_6H_5 < C_4H_9 < CH_2COOC_2H_5 < 1\text{-}C_{10}H_7 < C_6H_{11} < CH_3CHC_6H_5 < 4\text{-}C_2H_5OC_6H_4$$

The results chromatographic mode of lipophilicity determination can be used in *Quantitative Structure-Activity Relationship (QSAR*) analysis.

P-51

Synthesis and Photochemical Characteristics of Novel Styryldiazepinotribenzoporphyrazine.

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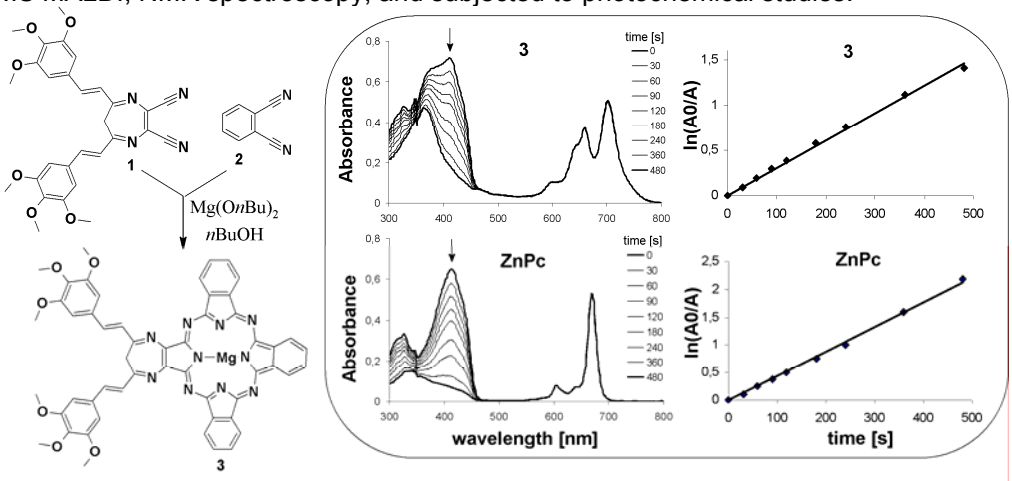
Porphyrazines (pzs) are aromatic macrocyclic compounds consisting of four pyrrolic rings linked together with azide groups instead of methine bridges found in the naturally occurring porphyrins. Pzs have been investigated as sensitizers for photodynamic therapy [1], metal ion and gas sensors, precursors to optical data recording systems, electrochromic displays, magnetic, electronic, and conductive materials for nanotechnology [2]. Lately, we have published the synthesis, characterization and photochemistry of novel low-symmetry tribenzoporphyrazine with annulated styryldiazepine ring [3]. The present study aims to develop this strategy.
New tribenzoporphyrazine **3** with annulated diazepine rings containing styryl substituents in its 5 and 7 positions was synthesized by mixed macrocyclization reaction of diazepine **1** and 1,2-dicyanobenzene (**2**) using the template effect of magnesium butanolate (Figure). Compound **3** was characterized by UV-vis, MS MALDI, NMR spectroscopy, and subjected to photochemical studies.



The potential photosensitizing activity of the novel tribenzoporphyrazine **3** was evaluated by measuring the ability for singlet oxygen production, which is the result of an interaction between an activated photosensitizer and oxygen. Zinc phthalocyanine (ZnPc) was used as a reference and DPBF (1,3-diphenylisobenzofuran) was used as a chemical quencher which undergoes a cycloaddition reaction with singlet oxygen to produce an endoperoxide. Solution of DPBF and photosensitizer was irradiated with light. Upon interaction with singlet oxygen, DPBF was oxidized and decomposed, which was observed in the UV–Vis spectra as a decrease of the absorbance at 417 nm (Figure, inset). This experiment showed that **3** is a promising, efficient singlet oxygen generator with the $\Phi_{\Delta\ DMF}$ of 0.38, although it is a little lower than that of zinc phthalocyanine ($\Phi_{\Delta\ DMF}$ = 0.56).

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The authors acknowledge financial support for the project from the Polish Ministry of Science and Higher Education (N N401 067238).

P-52

Comparison of Homology Models of 5-HT$_6$R Created with Different Crystal Templates.

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Structures of proteins with transmembrane domains cannot be easily determined, since proper conformation is acquired only in the presence of lipid bilayer, and thus it is almost impossible to construct its 3D structure using common physical methods. This is why homology modeling is extremely helpful in determining structures of such proteins.
5-HT6R (5-hydroxytryptamine receptor 6) is a protein containing 7TM (7 transmembrane helices) domain and is a member of class A GPCR (G-protein coupled receptor) family. It is widely expressed in neural tissue and is considered to be involved in learning and memorizing processes. Blocking the receptor leads to increase in neurotransmission and improves cognition abilities of rodents. The receptor itself is a target for anti-depression drug research.
In the present study a vast number of 5-HT6R homology models was generated on different templates available: adenosine 2 receptor (PDB ID: 3QAK), beta1 (PDB ID: 2Y00) and beta2 (PDB ID: 3P0G) adrenergic receptors, C-X-C chemokine receptor type 4 (PDB ID: 3OE0) and dopamine 3 receptor (PDB ID: 3PBL). Next, a set of representative ligands, from chemically diversified clusters, was used for selecting the best models. They were further used for docking of a complete set of 5-HT6R ligands (over 4000 compounds from ChEMBL database) to determine the best models for further research.

Acknowledgments
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P-53

Zastosowanie Metody HPLC z Detekcją Spektrofotometryczną i Fluorescencyjną do Oznaczania Dwuskładnikowego Preparatu Farmaceutycznego.

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Połączenie amlodypiny i walsartanu jest skuteczną strategią farmakologicznego obniżania ciśnienia krwi u pacjentów z samoistnym nadciśnieniem tętniczym. Działanie tych leków jest komplementarne. Amlodypina jest najdłużej działającym antagonistą kanałów wapniowych, hamuje ona przenikanie wapnia do komórek a przez to powoduje zmniejszenie oporu obwodowego. Natomiast walsartan to swoisty i wybiórczy antagonista receptora AT_1 angiotensyny II, zapobiegający silnemu zwężaniu naczyń krwionośnych.
Celem badań było opracowanie warunków jednoczesnego oznaczania amlodypiny i walsartanu techniką HPLC i zastosowanie tej metody do badania uwalniania substancji czynnych ze złożonego preparatu farmaceutycznego.
Analizę HPLC wykonano stosując kolumnę chromatograficzną LiChrospher® 100 RP–18 (5µm) o wymiarach 125x4 mm. Detekcję spektrofotometryczną prowadzono przy długości fali λ = 254 nm zaś detekcję fluorescencyjną przy długości fali wzbudzenia λ = 255 nm i długości fali emisji λ = 448 nm. Jako fazę ruchomą zastosowano mieszaninę acetonitryl – 0,067 mol/l bufor fosforanowy pH 3,5 – metanol (45:45:10) z szybkością przepływu 1 ml/min. W opisanych warunkach całkowity czas analizy wynosił mniej niż 10 minut; czas retencji amlodypiny wyniósł 5,7 min natomiast czas retencji walsartanu 2,8 min.
Liniowość metody sprawdzono w zakresie stężeń 0,8 – 5,6 µg/ml dla amlodypiny i odpowiednio 12,8 – 89,6 µg/ml dla walsartanu uzyskując wysokie współczynniki korelacji r > 0,998. Metodę zwalidowano także w zakresie precyzji i dokładności. Opracowaną metodę HPLC z detekcją spektrofotometryczną oraz spektrofluorescencyjną wykorzystano do oznaczania amlodypiny i walsartanu w preparacie dwuskładnikowym, w tym do badania i monitorowania procesu uwalniania substancji czynnych z tabletek. Wyniki uzyskane podczas obydwu metod detekcji porównano statystycznie.

Praca powstała z wykorzystaniem sprzętu zakupionego w ramach Projektu: "Wyposażenie innowacyjnych laboratoriów prowadzących badania nad nowymi lekami stosowanymi w terapii chorób cywilizacyjnych i nowotworowych" w ramach Programu Operacyjnego Rozwój Polski Wschodniej 2007-2013, Osi priorytetowej I Nowoczesna Gospodarka, Działania I.3 Wspieranie Innowacji.

P-54

Exploring the Effect of Radioligand Depletion on Affinity Determinations in the Dopamine D2 Binding Assay.

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Dopamine D2 receptors are the main target for antipsychotics and they are investigated in many drug discovery programs. One of the standard method to evaluate the affinity of new agents to target receptor is the radioligand binding assay. Recently, the need for a high throughput rate to screen large number of compounds led to miniaturization of assay formats which opened further possibility of process automatization. However, assay miniaturization increases the risk of radioligand depletion – a phenomenon in which the free ligand concentration is significantly reduced which complicates the interpretation of binding data. This problem is particularly acute for dopamine D2 binding assays with the use of high-affinity radioligands, and is often ignored by investigators leading to substantial errors in the obtained values of affinity measurements.
In our studies, we have explored the effects of volume reduction in D2 binding assay from 0.5 ml to 0.25 ml. As a result, troubleshooting procedure applied to correct inaccuracies arising from ligand depletion is presented.

Acknowledgements
The study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism within the Polish-Norwegian Research Fund; http://www.cns-platform.eu/

P-55

The Inhibition of HIV-I Integrase by Ethyl Malonate Amides and Nalidixic Acid Derivatives - Analogue Drug Design and Molecular Modelling.

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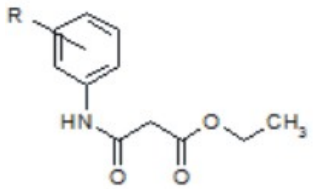
Human immunodeficiency virus that causes AIDS is still one of the most challenging aim of the modern science. Although several drugs are currently available on the market, that disease still remains incurable. HIV enzyme- integrase is one of the potential targets of HIV therapy responsible for integrating the viral DNA into the host genome and is essential to the replication of the virus.
Currently, there is only one integrase aimed drug available on the market. The core of the project is to investigate the possibility for the improvement of the integrase inhibition by the modification of the salicyl subunit defining the intramolecular hydrogen bonding organization. In this context we designed a series of novel compounds, which have been obtained and tested for HIV integrase inhibition in LBPA ENS Cachan in France. Further research have been done to get more information about the mode of action and structure – activity relationships for these compounds.
While searching for IN inhibitors we discovered that some ethyl malonate amides (EMA) are active against this enzyme.



EMA

We observed the similarity between the EMA function included in the investigated compounds and the DKA pharmacophore in several important IN inhibitors. Surprisingly, the EMA pharmacophore very rarely can be found among the investigated compounds or drug candidates. This allowed us to establish and analyze the structure-activity relationship. The similarity to the important classes of HIV integrase inhibitors as well as the synthetic availability of different targets incorporating the EMA fragment makes it an interesting object of further modification. In our investigations we docked the appropriate diketo acid based compounds into the structure of integrase available in the PDB database, using commercially available molecular docking software.Those docked inhibitors were found to interact specifically with aminoacid groups in the catalytic core domain - an active site of integrase that binds magnesium- by intermolecular hydrogen bonding. In this context we designed series of novel compounds, which are obtained and tested for HIV integrase inhibition.

P-56

Does Dehydrocyclization of 4-Benzoylthiosemicarbazides in Acetic Acid Lead to *s*-Triazoles or Thiadiazoles?

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Since recognition of strong pharmaceutical activity of triazoles and thiadiazoles these scaffolds are being subject of vigorous studies. One of the best strategies for synthesis of these azoles is dehydrocyclization of 1,4-disubstituted thiosemicarbazides that leads to *s*-triazoles in alkaline media whereas in strong acidic media 1,3,4-thiadiazoles are formed. However, the literature is troubled with contradictory communications regarding the nature of the product of such reactions under mild acidic conditions. Since these compounds are not amenable to X-ray analysis we have resorted to NMR and theoretical modeling to resolve this discrepancy. We present arguments indicating that dehydrocyclization of 4-benzoyl-thiosemicarbazides in glacial acetic acid leads to thiadiazole derivatives. These structural findings are augmented with studies of bioactivity of a few members of the studied class of compounds which suggest that 4-benzoyltiosemicarbazides and their cyclic derivatives participate in at least two different mechanisms of antibacterial activity; one is connected with inhibition of topoisomerase IV, while the nature of the other cannot be elucidated from the limited data collected thus far.

P-57

Meta-Learning as an Improvement of Machine Learning Methods Performance in Virtual Screening.

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Computational methods are widely used in pharmaceutical industry - both ligand and structure-based approaches are applied to virtual screening tasks, where large libraries of chemical compounds undergo evaluation in order to select drug candidates [1].
Recently, many applications of machine learning methods in this process have been reported. Their major task is to assign objects (in our case: molecules) into classes (here: active or inactive), but they can also carry out numerical classification that might be helpful e.g. in predicting ADME properties [2]. In order to improve the performance of classification algorithms, meta-learning strategy was developed. It gains knowledge from analyzing a number of subtasks, increasing efficiency of base classifier by using additional methods such as bagging and boosting [3].
We took into account four meta-learning algorithms implemented in WEKA package [4] and three different base classifiers. Their performance was examined depending on the type of molecular fingerprints used for representing chemical structures and the number of active compounds present in the training sets. Time required for building predictive models was also measured. For the case study, we used the 5-HT_{1A} antagonists taken from MDDR database (actives), and a set of structures randomly selected from ZINC database [5] (inactives).

Acknowledgements
The study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism within the Polish-Norwegian Research Fund; http://www.cns-platform.eu/

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P-58

The Study on Reactivity of 5-Amino-3-methyl-4-isoxazolecarboxylic Acid Azide with N-Substituted Hydrazines.

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The development of medicine and pharmacology has led to identification of many diseases of the immune system. Therefore, important direction for new drug research is looking for immunomodulatory compounds. Isoxazole derivatives previously synthesized in our laboratory have immunomodulatory effects on cells of the immune system [1-3].
Searching for other isoxazole derivatives with immunomodulatory properties we synthesized new series of substituted hydrazides of 5-amino-3-methyl-4-isoxazolecarboxylic acid. For this purpose, we carried out reactions of 5-amino-3-methyl-4-isoxazolecarboxylic acid azide with N-substituted hydrazines. Depending on the substituent used in the hydrazine we obtained two groups of compounds: N-substituted and N'-substituted hydrazides of 5-amino-3-methyl-4-isoxazolecarboxylic acid. Each of this new structure has potential immunomodulatory activity and opens the possibility of a variety of structural modifications, such as cyclization with orthoesters or nitrous acid. This allow the exploration of new biologically active compounds with immunostimulatory or immunosuppressive activity.

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P-59

Characterization of Thiopurine Derivates Binding Site on Human α_1-Acid Glycoprotein (Orosomucoid) Using Molecular Docking.

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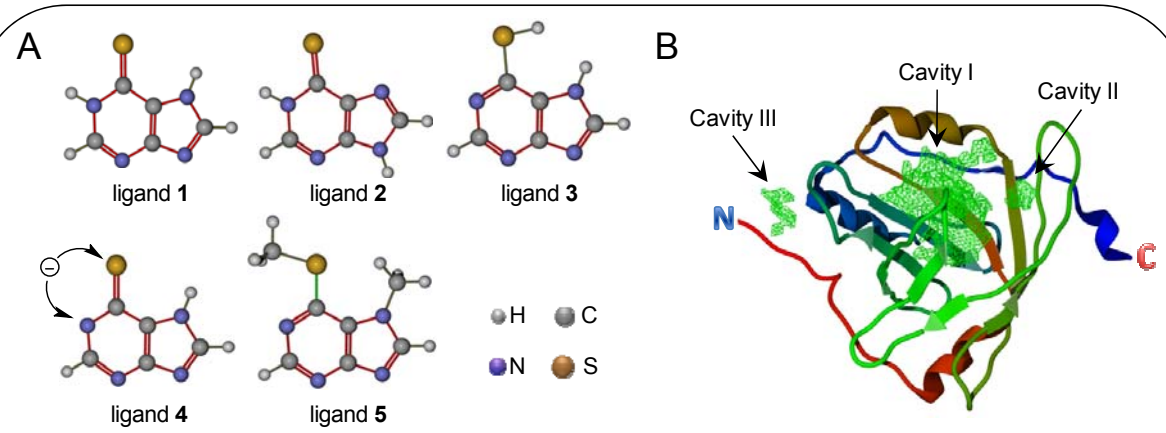
The human blood α-1 acid glycoprotein (AGP), also known as orosomucoid, is a 41-kDa single polypeptide formed of 183 amino acids. It is negatively charged at physiological pH, contains 40 % carbohydrate by weight and has up to 16 sialic acid residues (14% by weight). AGP contains three Trp residues, one residue (Trp160) is at the surface of the protein, and two (Trp25 and Trp122) are located in the protein matrix. Two disulfide bridges are formed between cysteins 5–47 and 72–164 [1]. AGP beside albumin is the main transport protein for most drugs and interacts with a variety ligands. It binds both basic and acidic drugs.
In the present work, we studied the interaction between AGP and thiopurine derivates. Computer simulation of molecular docking was employed to improve the understanding of this interaction. As the docked ligands were selected tautomers of 6-Mercaptopurine (6-MP) (ligands **1**–**3**), anionic form of 6-MP (ligand **4**) and 7-methyl-6-methylthiopurine (ligand **5**).



3D structures of the docking ligands (A) and X-ray structure of α_1-acid glycoprotein (AGP) with the cavities identified by cavity prediction algorithm (B)

Molecular docking experiment was performed with the molecular docking algorithm MolDock using the Molegro Virtual Docker (MVD) Version: 4.2.0 Molegro ApS 2010 [4]. The initial ligand **1**, **2**, **3**, **4** and **5** conformations used in the docking simulation were energy–minimized by means of semi-empirical method (AM1) implemented in CS Chem3D Ultra Molecular Modeling and Analysis Version: 7.0.1 CambridgeSoft 2001 and imported to MVD. The X-ray structure of AGP was obtained from the Protein Data Bank (PDB ID: 3BX6) [5]. Potential ligand binding sites (cavities) were identified automatically using the cavity prediction algorithm. After docking simulation, all poses (ligands orientation in the cavity) have been classified with the use of MolDock scoring function. The top ranked pose for each ligand was selected for further analysis of electrostatic and hydrogen bond interaction.

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P-60

Synthesis of Novel 3β-Acylamine Derivatives of Tropane with Potential Antipsychotic Activity.

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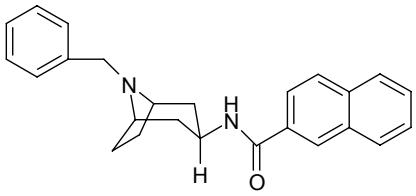
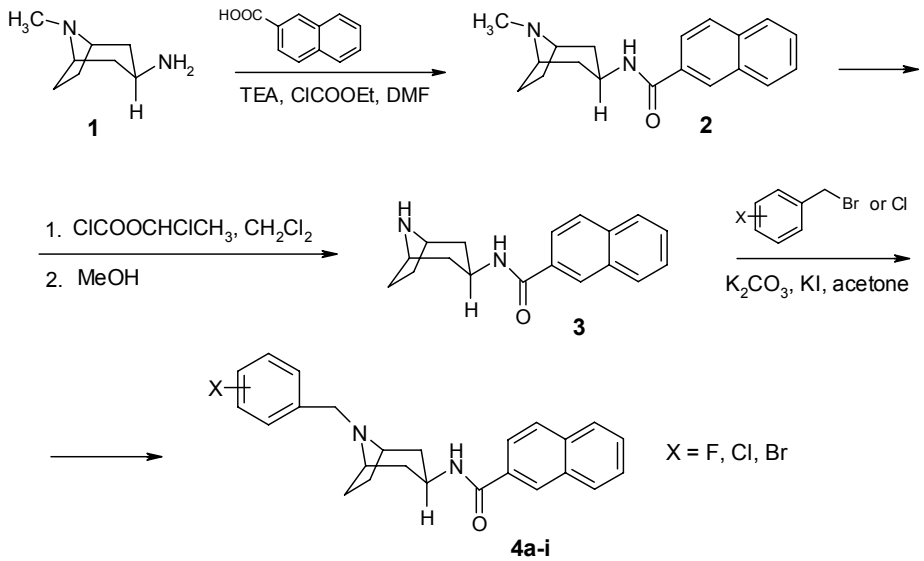
In our paper entitled ”Synthesis and biological investigation of potential atypical antipsychotics with a tropane core. Part 1” we described synthesis and biological activity of compound **A** which displayed very high (in nM) affinity for the monoamine receptors 5-HT_{1A}, 5-$HT_{2A,}$ and D_2.[1] Compound **A** also displayed a favourable Meltzer index (1.21) which is a feature of atypical antipsychotic agents.[2, 3]



A

Synthesis of analogs of active molecule **A** with halogen atom in o-, m- and p- positions of phenyl ring is presented below. The structure of new molecules (equatorial isomers) was confirmed by MS, IR and ^{1}H NMR spectra. For each compound affinity for serotonine and dopamine receptors will be investigated.



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P-61

A Convenient Methods for Conversion of Phenols to Thiophenols and/or Alkylated Thiophenols.

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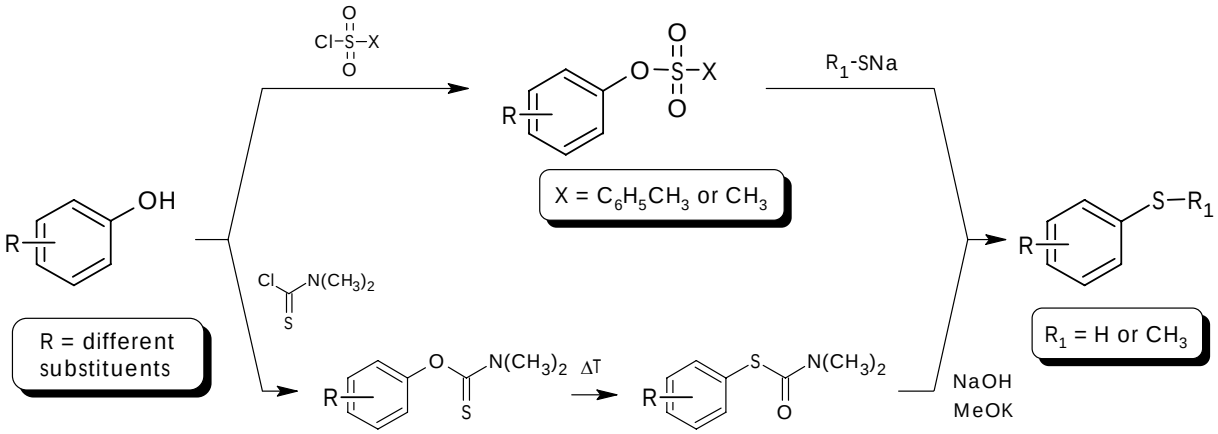
Our research on thioderivatives of natural antioxidants are associated most often with necessary to the replacement of phenolic hydroxyl groups by the corresponding thio or alkylthio groups. These substituents incorporated into a number of natural origin products exhibits biologically active properties [1] therefore methods for the formation of aryl-sulfur bonds are indispensable tools in our workshop.

Generally, we've focused on two methods:

1) Reaction of substituted hydroxyaryls with mesyl or tosyl chloride and replacement of esters by thio or alkylthio moiety [3]. Introduction as well as replacement of alkyl- or arylsulfonyloxy groups by thio or methylthio groups proceed in mild conditions. This method has been used especially in the conversion of phenolic hydroxyl groups in naturally occurring compounds.

2) Newman-Kwart Rearrangement (NKR), where O-aryl thiocarbamates obtained from substituted hydroxyaryls and N,N-dimethylthiocarbamoyl chloride have been then converted to S-aryl thiocarbamates [2]. Subsequent hydrolysis of S-aryl thiocarbamates allowed to obtain corresponding thioaryls which after akylation can be converted to according alkylated derivatives. NKR need much higher temperatures than reactions with sulfonyl chlorides.



We performed synthesis of few methylthiobenzaldehydes using above methods yet. These intermediates will be used in the synthesis of different biologically active compounds like stilbenes, chalcones or flavonoids. Current work focused on direct replacement of phenolic hydroxyl groups by thio or alkylthio moiety in the final compounds.

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P-62

Synthesis, Structure Analyze and Microbilogical Evaluation of the Novel Tryptamine Thiourea Derivatives.

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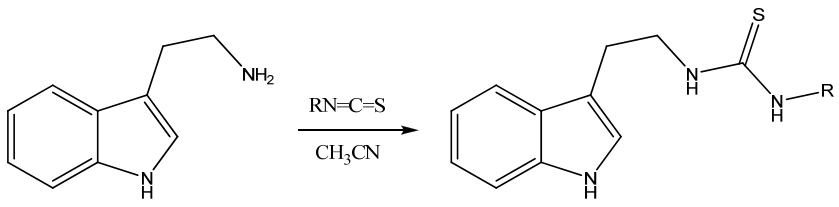
Tryptamines are a family of compounds structurally derived from tryptamine, which consists of a double ring structure and side chain. The family includes neurotransmitter serotonin (5-hydroxytryptamine) and hallucinogenic/psychedelic drugs such as LSD, Psilocybin - both widely-used, and other, less common, synthetic drugs such as dimethyl-tryptamine (DMT). There are several other implications of tryptamines as potential medicines. For example, N,N-dimethyltryptamine N12-oxide, a natural alkaloid from liver-protective medicinal plant *Evodia fargesii Dode (Rutaceae),* had potent inhibitory effect on HBV DNA replication (IC_{50} = 17.6 μM, SI >5.7) in the HepG2.2.15 cell line. Tryptamine analogues such might be the ligands of 5-HT (5-hydroxytryptamine, a neurotransmitter) receptor, which possibly involve in obesity and certain neuropsychiatric disorders.
We decided to synthesize novel tryptamine (Scheme 1) analogues with biological activity. Our idea was to combine thiourea side chain with active tryptamine structure. It is widely known that thiourea derivatives possess microbiological activity, they also play important role in anticancer agents because of their good inhibitory activity against Receptor tyrosine kinases (RTKs), protein tyrosine kinases (PTKs), and NADH oxidase, which play critical roles in many aspects of tumorigenesis.
Scheme 1.



We have synthesized 21 thiourea derivatives of tryptamine. For all compounds microbiological evaluation was done. In the result of this investigation we have obtained MIC values from 6.25 to 200 μm/mL. Chosen derivatives will be investigated for other possible pharmaceutical use. MS and ^{1}H NMR spectra confirmed the identity of the products. The molecular structures of selected thiourea derivatives were determined by an X-ray crystal structure analysis.

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P-63

Synthesis of New Cyclic Arylsulfonylurea Derivatives with Potential Pharmacological Activity.

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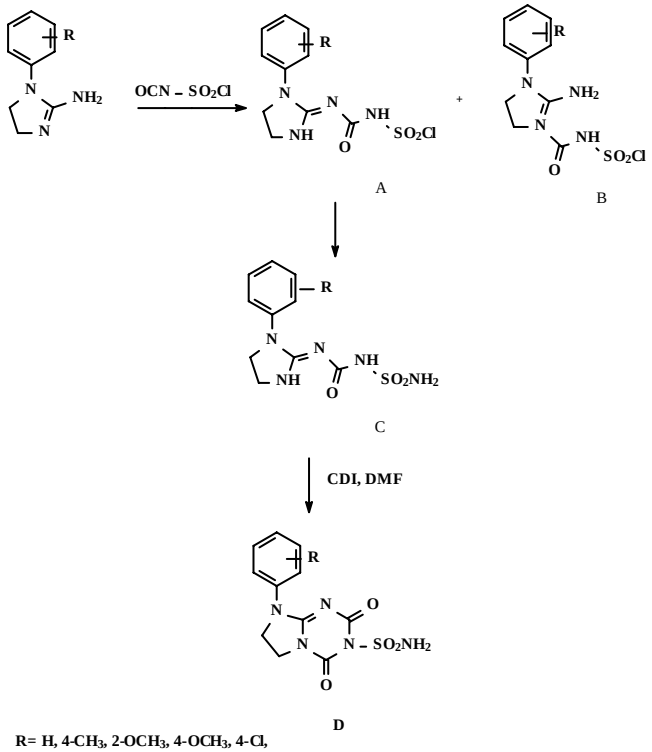
1-Aryl-2-aminoimidazoline were used to synthesize many chain and fused imidazoline derivatives exhibiting pharmacological activity. Compounds bearing the 1-aryl substituted were found to process significant central activity, especially antinociceptive and serotonergic [1-3].
When reserching new compounds with potential pharmacological activity 1-aryl-6-(aminesulfonyl)-5,7(1H0-2,3-dihydroimidazo[1,2-a][1,3,5]trizines were received. This heterocyclic system was obtained in two-step reaction.
Novel cyclic derivatives of dihydroimidazo[1,2-a][1,3,5]trizines (D) were receicved by condensation of 1-(1-arylimidazolidyn-2-ylideno)-3-aminosulfonylureas (C) with CDI.

Scheme:



R= H, 4-CH_3, 2-OCH_3, 4-OCH_3, 4-Cl,

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

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P-64

Planarity of Derivatives of Dithiocarbonate Esters Showing Tuberculostatic Activity.

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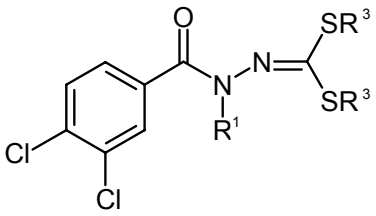
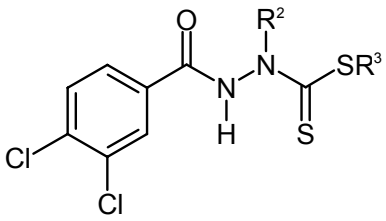
Increasing resistance of *Mycobacterium tuberculosis* against existing agents and resulting spread of the pathogen also in developed countries made a search for new tuberculostatics an important issue. One of the promising chemical classes showing action against tuberculosis were pyridincarbon-imidoyldithiocarbazonic acid esters and N1-thioamido substituted pyrazincarboxy-amidrazones, of which over hundred compounds have been synthesized and tested against *M. tuberculosis* strains. Compounds 1-5 (Scheme) have been crystallized from methanol and their structures determined by X-ray diffraction method.



Nr	R^1	R^3
1	H	Me
2	H	Bz
3	Me	Me



Nr	R^2	R^3
4	Me	Me
5	Me	Bu

The molecule of 1 is flat and it has the greatest activity. The compound 2 isn't active tuberculostatic, because the large end groups are not coplanar with the rest of the molecule. The larger group in position R1 (compound 3) causes rotation around the C-N bond. Molecules of 4 and 5 are not flat due to the presence of CH3 group at the nitrogen atom and exhibit only low activity.

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P-65

Synthesis and Physicalchemical Properties of Porphyrazines Possessing Bulky Peripheral Substituents.

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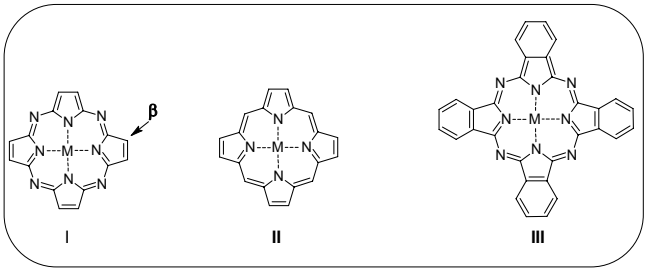
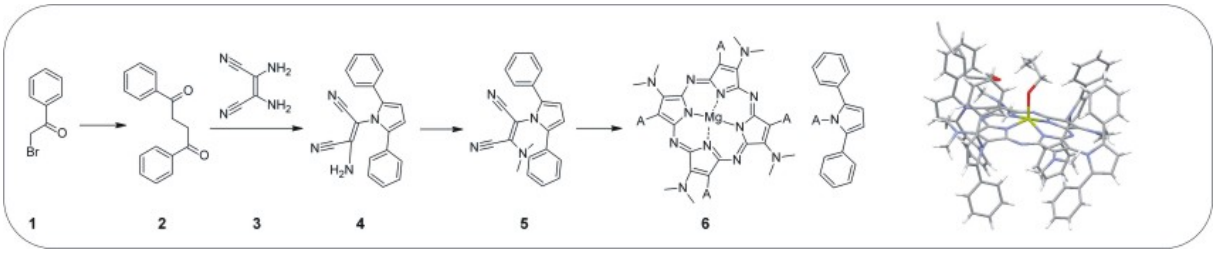
Peripherally functionalized porphyrazines **I** form a distinct class of novel macrocycles, along with the functionalized porphyrins **II** and phthalocyanines **III** (Figure). The porphyrazine (pz) macrocycle is isoelectronic with porphyrine, but in comparison it has substantially different electronic properties. The first possibility to modify pz is to substitute the core with metal entities (M), while the second one is connected with peripheral modifications. Pzs substituted in the periphery possess many potential applications as photosensitizers in photodynamic therapy, sensors, molecular semiconductors and non-linear optical materials [1].





2-Bromoacetophenone **1** was used in the Würtz-like type reaction leading to diketon **2** (Scheme) [2]. The Paal-Knorr reaction of diaminomaleonitrile **3** with diketon **2** gave 2-amino-3-(2,5-diphenyl-1*H*-pyrrol-1-yl)-(2*Z*)-butene-1,4-dinitrile **4** [3]. Product **4** was subjected to methylation reaction to novel dinitrile **5**, which was successfully utilized in the Linstead macrocyclization towards magnesium symmetrical porphyrazine **6** [4]. The purity of pz **6**, which was isolated as the major product, was confirmed by HPLC and NMR studies.
Moreover, the structures of dinitrile **5** and porphyrazine-Mg complex **6** (Scheme) were determined by X-ray crystallography. The single crystal analysis shows that **6** is a symmetrically substituted porphyrazine derivative with 2,5-diphenylopyrrolyl and dimethylamino groups located alternately in the *β*-positions of the macrocycle. The pyrrole substituents are nearly perpendicularly oriented to the porphyrazine core, whereas the dimethylamino groups are situated in the plane of the macrocycle.

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The authors acknowledge financial support for the project from the Polish Ministry of Science and Higher Education (N N404 069440).

P-66

Preliminary Evaluation of anti-*Helicobacter pylori* Activity of Some New Xanthone Aminoalkanol Derivatives.

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Searching for the new biologically active structures in the group of xanthone derivatives belongs to main scientific topics at the Department of Bioorganic Chemistry in the collaboration with the Department of Pharmaceutical Microbiology, Faculty of Pharmacy UJ CM. Bibliography confirms wide range of biological activity of both naturally occurring and synthetic xanthone derivatives (e.g. antimalarial [1], antituberculotic [2], antibacterial [3] and antifungal [4]).
Scientific works conducted at the University La Sapienza in Roma proved anti-*Helicobacter pylori* efficacy of some N-substituted 2-oxo-2*H*-1-benzopiran derivatives, revealing structural similarity to xanthone skeleton [5]. More over, our synthetic and microbiological research in the group of xanthone derivatives enabled selection of a few compounds with microbiological activity especially against *Mycobacterium tuberculosis* [6] and pathogenic dermatophytes [7]. Results of those investigations constituted subject of our former publications and conference presentations. Those facts, prompted us to undertake searching for new xanthone derivatives with hindering effectiveness against growth of *Helicobacter pylori* strains.
Our interest in this field is also due to worldwide increase of the primary and the secondary resistance of *Helicobacter pylori* strains to the using therapies. Nowadays, the treatment of choice is simultaneous application of proton's pomp blockers or bismuth salts and two from the antibiotics: metronidazole, clarithromycin, amoxycyllin and tetracycline. Nevertheless, such a therapy is effective in about 70 % of patients. In the case of failure of *Helicobacter pylori* eradication, the second-line quadruple therapy is used and after all last chance therapy with increased doses. In this light, searching for the new, more effective and less toxic agents seems to be well grounded [8, 9].
Herein we report on preliminary investigation of anti-*Helicobacter pylori* activity of some aminoalkanol xanthone derivatives including efficacy against resistant strains collected from hospitalized patients. Microbiological analysis was conducted using agar disc-diffusion method and zones of growth inhibition were measured. For the most active compounds, these zones ranged tens mm (1 % mixtures of the tested compound in DMSO). Currently, quantitative assays are performed to estimate MIC values of the most active compounds. These investigations are conducted in the cooperation with the Department of Pharmaceutical Microbiology with the financial support from promoter's grant no NN 405 619.

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P-67

Studies on Phenylalanine-Based AMPA/KA Receptor Ligands.

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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 GluA-4, while kainate receptors are tetrameric assemblies of GluK1-5 subunits.
Most of AMPA agonists and antagonists activate also kainate receptors, showing low or none selectivity. In the group of competitive amino acidic antagonists with the structure based on glutamic acid, the affinity to AMPA/KA receptors residues almost exclusively in (S)-enantiomers.
The present project is a continuation of earlier studies on potent and selective competitive AMPA and/or KA receptors ligands among phenylalanine derivatives [1]. A series of new compounds was synthesized and pharmacologically characterized on both native (NMDA, AMPA, KA) and cloned (GluA1-3, GluK1-3) receptors. Within the group of obtained amino acids several AMPA-preferring as well as GluK1-preferring ligands were indentified. For the most active phenylalanines, substituted with 3-hydroxy- or 3-carboxyphenyl fragment, the affinity of individual enantiomers obtained by synthesis or HPLC resolution was determined as well. In contrast to earlier literature reports we found that, in some cases, (R)-amino acids were eutomers showing AMPA affinity, while their (S)-counterparts turned out to be distomers. Activity of (R)-enantiomers for tested phenylalanines is supposed to be connected with the ligand binding mode different from those described in the literature so far for amino acidic antagonists of AMPA/Ka receptors. In attempt to explain the pharmacological data, two complexes of the most active phenylalanine analogs bound to GluA2 binding core were co-crystallized and will be discussed in the near future.
On the base of obtained pharmacological results the new group of phenylalanine derivatives was designed and their synthesis is described in the present work. The whole series of compounds will be pharmacologically characterized on both native and cloned ionotropic glutamate receptors.

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P-68

Structure Activity Relationship Analysis of Ibogaine Analogs with the Use of Molecular Descriptors and Docking Simulations.

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Structure Activity Relationship (SAR) analysis applies predictive models derived from application of statistical tools to correlate biological activity of chemicals with descriptors representative of molecular structure or other properties. SAR analysis provides an understanding of the effect of structure on activity and can be used to help elucidate interactions between functional groups in the potentially active molecules and the binding sites of the receptor. Docking simulations give better insight into molecular mechanisms of ligand – receptor mode of binding. Computational modeling studies combined with SAR help explaining the experimental results.

In our research we developed a panel of interdisciplinary methods to determine the molecular descriptors and characterize interactions of analogs of ibogaine with different subtypes of the nicotinic receptor (AChR). The alkaloid ibogaine and its natural and synthetic analogs behave pharmacologically as noncompetitive antagonists (NCAs) of several AChRs. It has been hypothesized that this inhibitory activity is related to their anti-addictive properties. Firstly, we performed a set of molecular modeling simulations for the models of ion channel domain. In the project the molecular model of transmembrane domain of the AChR obtained using cryoelectron microscopy of *Torpedo marmorata* (PDB id: 2BG9) was used. It was further modified to represent model of the human muscular subtype. Docking procedures of a flexible ligand into the rigid model of the ion channel were performed and allowed classification of ligands in respect to their binding energies. The binding energy estimated in simulations could be related to experimental values for ibogaine analogs. Secondly we calculated the molecular descriptors of ibogaine analogs. In the case of studied compounds the most important correlation was found for ligand molecular volume (MOLPROP_Volume, MOLPROP_Area – surface is computed as a solvent accessible surface, essentially a van der Waals surface) with experimental data and docking simulation studies. We also estimated the CoMFA model for ibogaine analogs. A better understanding of the interaction of ibogaine analogs with AChRs is the crucial information to develop a new safer drug with anti-addictive properties.

P-69

Synthesis of New 1-Pyridin-6*H*-pyrido[4,3-*b*]carbazole Derivatives and their Cytostatic Activity.

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Both alkaloids Ellipticine and Olivacine are natural 6*H*-pyrido[4,3-*b*]carbazole derivatives, known for their cytostatic properties. Olivacine was firstly isolated from the bark and stem of *Aspidosperma olivaceum* Müll. Arg. Until now a huge number of olivacine analogues were obtained synthetically, from which several compounds exhibited stronger antiproliferative properties accompanied with diminished toxicity than the mother alkaloid [1-3]. Our recent work was focused on chemical modifications of olivacine molecule with substituted 2-pyridil moiety at 1 position.
Thirteen of the newly obtained by us compounds were subjected to preliminary *in vitro* cytostatic activity screening against murine leukemia (L1210), human lung cancer (A549), human colon cancer (HT29) and human kidney cancer (A498) cell lines and compared with activity of reference compound Ellipticine.
Cytostatic properties tests of all newly obtained compounds were performed in Institute of Immunology and Experimental Therapy (POLAND).

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P-70

Molecular Modeling Study of Interaction Between the AMPA Receptor and Selected Positive Modulators.

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Modern science has a comprehensive collection of methods, which can be applied to search for new therapeutic agents. In addition to traditional experiments, wider and wider are used modern computational methods, especially for modeling and predicting molecular interactions of proteins with potential drug molecules. One of the targets in current research is the AMPA receptor.
AMPA receptor (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor) is a protein complex of four types of subunits (GluR1, GluR2, GluR3, and GluR4). Most AMPAs are heterotetramers, consisting of symmetric 'dimer of dimers' of GluR2 and either GluR1, GluR3 or GluR4 [1]. Because AMPAs are ionotropic transmembrane receptors for glutamate and can mediate fast synaptic transmission in the central nervous system (CNS), new drugs which positively modulate this receptor can improve the life quality of people suffering Parkinson's or Alzheimer's disease.
The aim of the current research is to apply molecular modeling methods to determine basis of ligand interactions (e.g. IDRA-21 and others) with AMPA receptor and find derivatives with better activity and selectivity. In the first step, information about crystal structures and activity of compounds were collected from Protein Data Bank (PDB). In the next step receptors were aligned and receptor dependent orientation of the ligands was collected. Receptor derived alignment was used for Comparative Molecular Field Analysis and pharmacophore elucidation for studied molecules as well as to design *in silico* a number of new derivatives with improved affinity towards the binding site.

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P-71

Preclinical Evaluation of Antiepileptic Drugs for Analgesic Properties.

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Neuropathic pain is related with functional abnormality of neurons and is still considered an unmet need. Nowadays, there are few drugs registered for this condition, such as pregabalin [1], gabapentin [2], duloxetine [3], carbamazepine [4], and lidocaine [5]. Among them, pregabalin, gabapentin and carbamazepine are well known antiepileptic drugs.
Anticonvulsant mechanism of action is on the first place among primary indications for drugs revealing potential analgesic activity. Therefore, many drug candidates for epilepsy, still in preclinical stage, are being evaluated for activity in neuropathic pain.
Within our interest there are antiepileptic drugs, which are evaluated for their analgesic activity in major tests related with pain, especially neuropathic one. Relation between structure, mechanism of action and result in tests such as the Chung model (spinal nerve ligation SNL), the Bennett model (chronic constriction injury of sciatic nerve CCI) and other tests are considered.

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P-72

Search for Histamine H_4 Receptor Ligands in the Group of 1,3,5-Triazine Derivatives.

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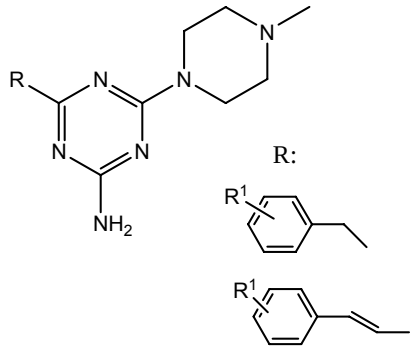
The biogenic amine histamine mediates its effects through binding to four, so far known histamine receptor subtypes, designed H1 to H4 (H1R-H4R). All of them belong to the family of G-protein coupled receptors, and differ in their tissue expression and functions. Our interest is concentrated on the search for histamine H4R ligands. The expression of these receptors in various cells of the immune system (eosinophils, T-lymphocytes, dendritic cells, mast cells, basophils) indicate the H4R to play an important role in different inflammatory, autoimmune and allergic disorders. Positive effects of H4R antagonists were observed in *in vivo* models of some diseases e.g. asthma, allergic rhinitis, pruritus, pain or inflammatory bowel disease [1, 2].
In 2003 Jablonowski *et al* described JNJ 7777120 the first orally active, potent and selective H4R antagonist [3]. This compound has become a reference agent and most of the pharmacological studies to understand of pharmacology and function of H4R both *in vitro* and *in vivo* was done with JNJ 7777120. From this time other potent and selective H4R antagonists were described, in the primary and patent literature [4, 5], also in the group of methylpiperazinyl-substituted azines [6].



Our investigation deals with the search for H4R ligands in the group of 1,3,5-triazine derivatives. Thus the series of 6 (un)-substituted benzyl and 6 (un)substituted styryl derivatives of 2-amine-4-(4-methylpiperazin-1-yl)-1,3,5-triazine were synthesized (Fig 1) and tested for their affinities at human H4R in the radioligand binding assay. Additionally their physicochemical and drug-likeness properties were evaluated *in silico*.

Fig 1.

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P-73

Application of Interaction Patterns to Discriminate Ligand Preference to Target/Antitarget Protein.

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SIFts (Structural Interaction Fingerprints) are precise and rapid tool for binding site description. In this research, SIFt describing physical ligand-protein interactions consists of 9-bit fragments providing information with residues and type of interaction (hydrophobic, aromatic, charge, polar, sidechain, backbone). A collection of such fingerprints is then merged into an averaged string showing frequencies of occurrence of each interaction.
In this project, interaction patterns are generated for active (Ki < 10 nM) and inactive (Ki > 1000 nM) ligands docked into our target (5-HT6R) and antitarget (H1R) receptor structure.
Having those interaction profiles, we compare them with SIFt fingerprints produced for our test set. Basing on complementarity between those two we can select compounds with high affinity to our target and low affinity to antitarget.

Acknowledgments
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P-74

Pitfalls of Flash Purification Using Built-in Detector.

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Flash chromatography is widely used in practical organic chemistry. This method provides fast purification of chemical compounds that couldn't be easily purified otherwise. Modern instrumentation helps to automate it. There are however many pitfalls which one should be aware of. A case of an acceptable separation is presented which initially looked like a failed one. The sample being purified contained impurity with high molar absorption which caused chromatogram to be partly illegible. This would not be a satisfactory result when analytical goal was considered, however our objective was to obtain pure compound which we accomplished and confirmed by TLC.

P-75

Using Microwave to Speed up Synthesis of Novel N-alkyl Derivatives of Dextrometorphan.

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Microwave synthesis is now a well established area in organic synthesis which greatly accelarates reactions. Growing numbers of publications on microwave synthesis since mid eighties prompted us to develop a new method for synthesis of novel derivatives of dextrometorphan which exhibit activity towards nicotinic acetylcholine receptor.
Nicotinic acetylcholine receptors (nAChRs) are pentameric neurotransmitter receptors and members of the super-family of Cys-loop ligand-gated ion channels. The nAChRs consist of an extracellular ligand binding domain, a cation selective membrane spanning pore and an intarcelullar domain.

P-76

Synthesis and X-ray Crystallographic Studies of 1,2,4-Triazolin-5-thione Derivatives.

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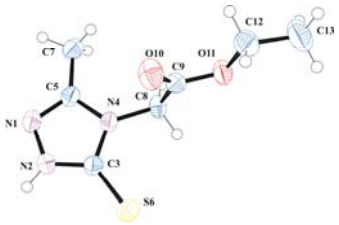
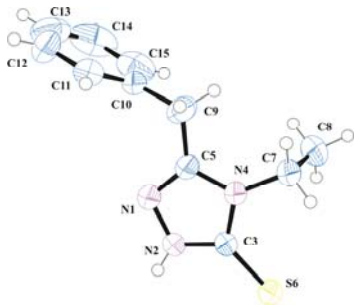
Several five membered aromatic systems having three hetero atoms at symmetrical position have been studied because of their interesting physiological properties. It is also well established that various derivatives of 1,2,4-triazole exhibit broad spectrum of pharmacological properties such as antibacterial and antifungal activities. The available therapeutically important medicines are itraconazole, fluconazole and ribavirin *etc*. are some of the examples which contain one of these heterocyclic nucleus.

In this paper we presented crystallographic structures of some 1,2,4-triazolin-5-thione derivatives which were synthesized as substances with potential biological activity. Compound **1** was obtained in the reaction of amidrazone hydrochlorides with ethoxycarbomethyl isothiocyanate whereas cyclization reaction of appropriate thiosemicarbazide in alkaline medium give compound **2**. Compound **3** was synthesized in the substitution reaction of 4-phenyl-3-(pyridin-2yl)-1,2,4-triazolin-5-thione with formaldehyde solution.



1



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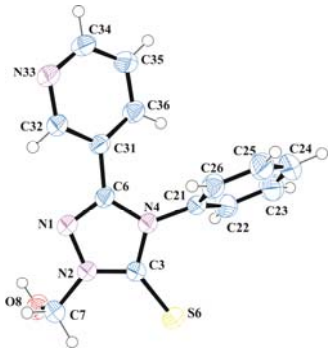

3

*Crystal data of **1**:* $C_7H_{11}N_3O_2S$, M_r = 201.26, monoclinic, $P2_1/c$, a = 6.4438(19), b = 15.2328(15), c = 9.9672(8) Å, β = 98.416(19) °, V = 967.8(3) Å^3, Z = 4, D_x = 1.381 gcm^{-3}, T = 296 K, MoKα, λ = 0.71073 Å, μ = 0.307 mm^{-1}, R = 0.0602 for 1571 reflections.

*Crystal data of **2**:* $C_{11}H_{13}N_3S$, M_r = 219.31, monoclinic, $P2_1/c$, a = 7.3731(5), b = 8.9408(19), c = 16.9936(8) Å, β = 91.892(4) °, V = 1119.6(3) Å^3, Z = 4, D_x = 1.301 gcm^{-3}, T = 296 K, MoKα, λ = 0.71073 Å, μ = 0.259 mm^{-1}, R = 0.0568 for 1385 reflections.

*Crystal data of **3**:* $C_{14}H_{12}N_4OS$, M_r = 284.35, triclinic, P-1, a = 5.834(3), b = 8.0966(16), c = 15.2027(17) Å, α = 96.448(13), β = 96.30(3), γ = 104.69(3) °, V = 683.1(4) Å^3, Z = 2, D_x = 1.382 gcm^{-3}, T = 296 K, MoKα, λ = 0.71073 Å, μ = 0.238 mm^{-1}, R = 0.0449 for 2004 reflections.

P-77

The Synthesis and Pharmacological *in vitro* Screening of New Imidazo- and Pyrimido[2,1-f]theophylline Derivatives.

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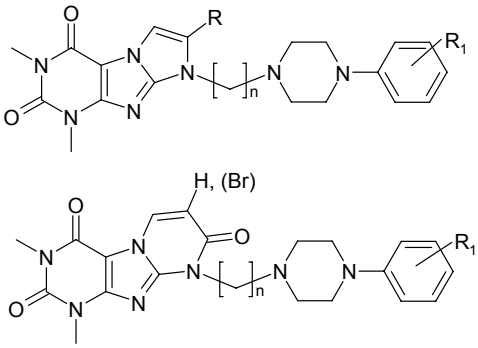
The multidirectional profile of pharmacological activity of methylxanthines and their biochemical mechanism of action is the reason for the development of the research in this group. Tricyclic theophylline derivatives, annelated six or seven membered heterocyclic ring at 7,8-position of theophylline generally demonstrated a different profile of its central nervous system activity, in comparison to the reference compound (theophylline). The pharmacological evaluation of a series of tricyclic theophylline derivatives with a pyrimido- or diazepino-moiety demonstrated sedative, hypothermizing and neuroleptic-like effects on the CNS [1]. Derivatives of imidazo- and pyrimido[2,1-f]theophylline with various LCAPs moiety showed high or very high 5-HT_{1A} receptor affinity and diversified pharmacological profile [2, 3].
From chemical point of view one of the most explored class of 5-HT receptor ligands are 1-arylpiperazines. The structural modifications of this pharmacophore led to 4-substituted derivatives with different length, flexible, aliphatic chain, called long chain arylpiperazines (LCAPs). Many original papers and reviews were showed that structural modification within LCAPs at the terminal part (amide or imide moiety) or substituent at phenyl ring, led to ligands with good selectivity and activity for selected 5-HT receptors [4].
In the course of exploring structure-activity relationships in the group of tricyclic theophylline derivatives, the aim of this work was to obtain new derivatives of imidazo- and pirymido [2,1-f]theophylline with 2,3-dimetoxy- or 3,4-dichloroarylpiperazine moiety. Newly synthesized compounds were *in vitro* screening towards monoaminoergic receptors (α_1, 5-HT_{1A}, 5-HT_{2A}, 5-HT_6, 5-HT_7, D_2, D_3) and serotonin transporter (SERT).



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P-78

Synthesis and Pharmacological Evaluation of Quinolone- and Isoquinoline-Sulfonamides of Long-Chain Arylpiperazines as 5-HT$_7$ Antagonists.

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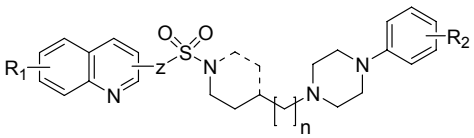
The most recently discovered member of the serotonin receptor family, the 5-HT$_7$ receptor, has received great interest over the past decade [1]. The prominent position of 5-HT$_7$ receptor in the thalamus, limbic and cortical regions of the brain, as well as high affinity for several antipsychotic and antidepressant agents suggest its involvement in depression and control of circadian rhythm. This was further supported by the results of several preclinical studies, in which 5-HT$_7$ receptor antagonism unveiled as a promising mechanism for the treatment of anxiolytic and antidepressant-like properties.
Although the structures of compounds active at 5-HT$_7$R are diversified, a relatively large group of ligands contain several common fragments, for example, an amine moiety (mostly 4-N-arylpiperazine, tetrahydroisoquinoline or 4-substituted tetrahydropyridine), which is connected by a different length alkyl chain (2–5 carbon atoms) to a terminal aromatic fragment.



z = 3, 4, 6, 8
R_1 = H, Cl
R_2 = 3-Cl, 4-Cl
n = 1, 2

Continuing search for new 5-HT$_7$ receptor antagonists in a group of sulfonamide derivatives, we designed a series of quinolone- and isoquinoline-sulfonamides of 3- and 4-chloro-phenylpiperazines containing different length flexible and rigid alkylen spacer [2]. The quinolinesulfonyl chlorides used were synthesized according to the previously reported method [3].
Herein we report synthesis, biological evaluation for 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_6$, and 5-HT$_7$ receptors and determination of therapeutic potential of the newly synthesized sulfonamides in animal model of depression and anxiety.

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P-79

The Study of Processes Initiated by Gamma Radiation Effect on Pyrimidine Nucleosides.

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Ionizing radiation effect on DNA and nucleosides as its main constituents causes adverse biological effects such as mutagenesis and carcinogenesis and at the end result in cell and the whole organism aging. Kinetic study of processes occurring during the action of radiation be possible determination of such reaction mechanisms. This knowledge is very important for radiation stability evaluation of some anticancer drugs and more effective development of diagnostic and radiotherapeutic methods. So the influence of radiation on the nucleic acids components has been intensively investigated [1-3]. In our studies processes initiated by gamma radiation occurring in aqueous solutions of pyrimidine nucleosides were examined by means of UV spectrometry, HPLC, HPLC-MS and GC methods. Kinetic study of nucleosides disappearance and formation of radiolysis products were investigated. It was found that irradiation of aqueous solutions of pyrimidine nucleosides leads to theirs complete disappearance at dose above the level of 1,5 kGy. Chromatographic analysis showed that several main products detectable by UV are formed during irradiation in the dose range of 0,2 – 1,5 kGy. It was proved that pyrimidine nucleosides disappearance follows the pseudo-first-order rate kinetics.

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P-80

Use of Humic Substances in the Medicine.

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Humic substances are complex and heterogeneous mixtures of polydispersed materials formed in humification process. In recent years is recorded increasing interest in these substances, which is associated with a number of specific properties of these compounds and they are increasingly used in various fields in medicine. Humic substances are most relevant in the treatment of human skin. They speed up healing of burns and have a positive effect on the skin to breathe, so they can be used as a natural poultice diseased tissue. They are also used to reduce inflammation, increase circulation and control bleeding, to regulate the immune system and hormone systems and as an anti-cancer and anti-tumor therapy. Humic and fulvic acids can be used internally for the treatment of stomach hyperacidity and other gastric disturbances, gastric ulcers and gastroenteritis in humans. The aim of this study is to present a review of references on the use of humic substances in medicine.

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