IX. Konwersatorium Chemii Medycznej
13-15.09.2018, Lublin

Polskie Towarzystwo Chemii Medycznej

Uniwersytet Medyczny w Lublinie

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SCIENTIFIC PROGRAM

THURSDAY, 13.09.2018

15.00 – 17.00 Registration Hotel Victoria

17.00 – 17.10 Opening Ceremony

17.10 – 18.10 Inaugular Lecture (IL) Hotel Victoria

Arie Gruzman, Bar-Ilan University, Ramat-Gan, Israel

„Development of novel barbituric acid-based total inhibitors of leukocyte transmigration"

18.10 Concert

19.00 Welcome reception

FRIDAY, 14.09.2018 Hotel Victoria

9.00 – 10.30 Lectures L1 & L2 (45')

10.30 – 11.30 Communications C1 – C3 (20')

Session moderators: Jadwiga Turło & Dariusz Matosiuk

L1

Roman Lesyk, Danylo Halytsky Lviv National Medical University, Ukraine

„In the search for new drug-like molecules: focus on thiazolidinone core"

L2

Adam Huczyński, Adam Mickiewicz University, Poznan, Poland

„Anticancer activity of novel tubulin polymerization inhibitors obtained by the chemical modification of colchicine"

C1

Anna Bielenica, Medical University of Warsaw, Poland

„1,3-Disubstituted thiourea derivatives – structural modifications versus bioactivity"

C2

Agnieszka B. Olejniczak, Polish Academy of Sciences, Lodz, Poland

„Synthesis of biologically active compounds modified with carborane pharmacopohore"

C3

Katarzyna Szczepańska, Jagiellonian University Medical College, Cracow, Poland

„Step forward in search for novel histamine H_3 receptor ligands: 4-pyridyl-piperazine derivatives with promising multidirectional pharmacological activity"

11.40 – 12.15 Coffee break

12.15 – 13.35 Communications C4 – C7 (20')

Session moderators: Katarzyna Kieć-Kononowicz & Stanisław Ryng

C4

Marek Stankievič, Marie Curie-Skłodowska University in Lublin, Poland

„Organophosphorus compounds – chirality and reactivity"

C5

Agnieszka Brzyska, Polish Academy of Sciences, Cracow, Poland

„The EGO simulation of the AFM experiments for the selected (bio)oligosaccharides"

C6

Maciej Kubicki, Adam Mickiewicz University, Poznan, Poland

„Experimental charge density determination as a tool for studying intermolecular interactions"

C7

Tomasz Wróbel, [(1)]University of Copenhagen, Denmark, [(2)]Medical University of Lublin, Poland

„Metastable binding site – opportunity for GPCR medicinal chemistry"

13.40 – 15.00 Lunch

15.00 – 15.45 Lecture L3 (45')

15.45 – 16.05 Communication C8 (20')

16.05 – 16.55 Poster oral presentations PP1 – PP5 (10')

Session moderators: Barbara Malawska & Krzysztof Jóźwiak

L3

Manuela Bartolini, Alma Mater Studiorum University of Bologna, Italy

„Fifty shades of tacrine derivatives to hit alzheimer's disease"

C8

Daniele Tedesco, Alma Mater Studiorum University of Bologna, Italy

„Insights into the batch-dependent variability of drug binding to human serum albumin: an induced circular dichroism study"

PP1

Przemysław W Szafrański, Jagiellonian University Medical College, Cracow, Poland

„Fluorescent triazolyl spirooxazolidines: synthesis and NMR stereochemical studies"

PP2

Patryk Kasza, Jagiellonian University Medical College, Cracow, Poland

„Fluorescent labelling of azidothymidine: introduction to personalised antiviral therapy"

PP3

Jakub Grynda, Gdańsk University of Technology, Poland

„Unusual interactions of triazoloacridinone C-1305 with dsDNA"

PP4

Julia Borzyszkowska-Bukowska, Gdańsk University of Technology, Poland

„Candicidin D & Iso-Candicidin D in sterol-containing lipid bilayer environment – a molecular modelling study"

PP5

Greta Klejborowska, Adam Mickiewicz University, Poznan, Poland

„Synthesis and biological evaluation of new colchicine derivatives acting as antimitotic agents"

16.05 – 19.00 Poster session

SATURDAY, 15.09.2018 Hotel Victoria

9.00 – 9.45 Lecture L4 (45')

9.45 – 11.05 Communications C9 – C12 (20')

Session moderators: Dorota Piotrowska & Marek Cegła

L4

Jadwiga Handzlik, Jagiellonian University Medical College, Cracow, Poland

„Aryl-containing compounds with 1,3,5-triazine core as a new grateful family of serotonin 5-HT_6 receptor agents"

C9

Przemysław Kołodziej, Medical University of Lublin, Poland

„Synthesis and antihelmintic activity of new 1,2,4 triazole derivatives"

C10

Beata Morak-Młodawska, Medical University of Silesia in Katowice, Sosnowiec, Poland

„Synthesis and anticancer activities of novel dipyridothiazines with 1,2,3-triazole substituents"

C11

Dawid Panek, Jagiellonian University Medical College, Cracow, Poland

„Synthesis and properties of novel multifunctional ligands, inhibiting cholinesterases and β-secretase as potential treatment of Alzheimer's disease"

C12

Joanna Śniecikowska, Jagiellonian University Medical College, Cracow, Poland

„Novel functionally selective agonists of the serotonin 5-HT_{1A} receptor"

11.10 – 11.45 Coffee break

11.45 – 13.05 Communications C13 – C16 (20')

Session moderators: Anna Bielawska & Krzysztof Bielawski

C13

Marta Ziegler-Borowska, Nicolaus Copernicus University in Torun, Poland

„Magnetic nanomaterials – synthesis and applications"

C14

Małgorzata Łupina, Medical University of Lublin, Poland

„Dipeptidyl peptidase 4 (DPP-4) inhibitor effects on depressive behavior in mice observed in forced swimming test (FST) after morphine discontinuation”

C15

Joanna Warguła, Poznan University of Medical Sciences, Poland

„Selected aspects of the synthesis of new indazole derivatives with anticancer and antibacterial activity”

C16

Beata Żołnowska, Medical University of Gdańsk, Poland

„New 2-alkylthio-4-chlorobenzenesulfonamide derivatives bearing heterocyclic moieties – synthesis, structure and anticancer activity studies”

13.10 – 14.30 Lunch

14.30 – 16.10 Communications C17 – C21 (20’)

Session moderators: Agata Paneth & Jarosław Sławiński

C17

Anna Bogucka-Kocka, Medical University of Lublin, Poland

„The effect of diosmin treatment on the level of oxidative stress biomarkers (isoprostanes) in patients suffering from CVI”

C18

Katarzyna Sowa-Kasprzak, Poznan University of Medical Sciences, Poland

„Synthesis of selected hybrid analoques of curcumin with NSAIDs”

C19

Anna Pawełczyk, Poznan University of Medical Sciences, Poland

„MW-US synergy tool for the rational synthesis of hybrid derivatives”

C20

Małgorzata E. Walczak, Lodz University of Technology, Poland

„Molecular receptors arrays in studies of the binding profile of drugs acting on histamine H1-H4 receptors”

C21

Justyna Frączyk, Lodz University of Technology, Poland

„Functionalization of nanomaterials useful in medicine by simultaneously attachment of targeting molecules and pharmaceutically active compounds”

16.15 – 16.45 Coffee break

16.45 – 18.35 Poster oral presentations PP6 – PP16 (10’)

Session moderators: Monika Wujec & Paweł Zajdel

PP6

Kinga Paruch, Medical University of Lublin, Poland

„Chemical modification of pipemidic acid and its impact on antibacterial activity of synthesized derivatives”

PP7

Damian Kułaga, Cracow University of Technology, Poland

„Synthesis and biological activity of a new 5-cyanoindole derivatives as a dual D_2/5-HT_{1A} receptor ligands”

PP8

Alicja Chrzanowska, Medical University of Warsaw, Poland

„Evaluation of the cytotoxic effect of ciprofloxacin conjugates with fatty acids on cancer cells”

PP9

Jacek Olczak, OncoArendi Therapeutics S.A., Warsaw, Poland

„Optimization of molecular properties of imidazothiazole derivatives as indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors”

PP10

Michał Kryjewski, Poznan University of Medical Sciences, Poland

„Aza-BODIPY bearing amine moieties – synthesis, fluorescence properties and singlet oxygen generation”

PP11

Michał Jóźwiak, Medical University of Warsaw, Poland

„Anticancer effects of alloxanthoxyletin and fatty acids esters”

PP12

Aleksandra Sochacka-Ćwikła, Wroclaw Medical University, Poland

„Synthesis of new 1,3-oxazole derivatives with potential immunomodulatory activity”

PP13

Anna K. Drabczyk, Cracow University of Technology, Poland

„New hexyl o-fluoroarylpiperazines derivatives as 5-HT_{1A} receptor ligands – synthesis and structure-activity relationship”

PP14

Patryk Rybczyński, Nicolaus Copernicus University in Torun, Poland

„Chitosan and phthalocyanine composites as potential PDT materials”

PP15

Damian Bartuzi, Medical University of Lublin, Poland

„In silico investigation of full agonist and partial agonist-induced signal transmission in mu opioid receptor”

PP16

Sylwia Kałużyńska, Lodz University of Technology, Poland

„Benzimidazole derivatives – structure and activity”

16.30 – 19.00 Poster session

20.00 – 24.00 Get-together Party (Hotel Victoria)

Inaugular lecture (IL)

IL

Development of novel barbituric acid-based total inhibitors of leukocyte transmigration

Tamar Getter,[a] Raanan Margalit,[b] Genia Alpert,[c] Sophia Zilber,[d] Shirin Kahremany,[a] Laura Levy,[a] Eliav Blum,[a] Hanoch Senderowitz,[a] Ron Lahav,[c] Paul Bradfield,[e] Beat Imhof,[f] and Arie Gruzman[a]

[a]Division of Medicinal Chemistry, Department of Chemistry, Faculty of Exact Sciences, Bar-Ilan University, Ramat-Gan, Israel, [b]"Science in Action", Ness-Ziona, Israel, [c]"AltA-ZuZ Therapeutics", Ness-Ziona, Israel, [d]Department of Pathology, Shaare Zedek Medical Center, Jerusalem, Israel, [e]"MESENFLOW Technologies", Geneva, Switzerland [f]Department of Pathology and Immunology, University Medical Center, Geneva University, Geneva, Switzerland

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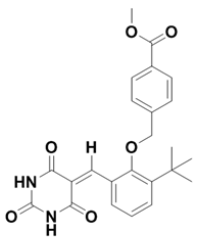
Leukocyte transmigration is one of the most important events in the physiological tissue immune response. However, over-activation of the immune system leads to damage of healthy tissues. Thus, effective leukocyte migration inhibitors are considered as very promising potential therapeutic agents against inflammatory diseases and cancer. Leukocyte adhesion and extravasation across the intestinal endothelium involves a multistep process whereby circulating immune cells are captured, roll, undergo activation, adhere, and finally transmigrate into the damaged tissue. One of the adhesion molecules associated with leukocyte transendothelial migration is PECAM-1 or CD31. PECAM-1 is a member of the Ig-superfamily of cell adhesion molecules expressed on most non-erythroid cells including monocytes, neutrophils, platelets, T cells, and B cell subsets. PECAM-1 is also highly expressed on endothelial cells, where it is a major constituent of the endothelial cell junction. Due to its localization at vascular endothelial cell junctions and expression on extravasating leukocytes, PECAM-1 has the capacity to regulate leukocyte transmigration during inflammation. Further studies have shown that PECAM-1 regulates the endothelial vascular barrier through a variety of intracellular signaling processes in both leukocytes and endothelial cells. Based on a pharmacophore model derived from the activated PECAM-1 dimer structure, twelve new small molecules (potential PECAM-1 inhibitors) were designed in-silico, synthetized and tested in vitro. Human endothelial cells and human monocytes were used for the evaluation of the effect on monocyte transmigration. One of the compounds (GT-73) completely blocked leukocyte transmigration, without damaging monocytes or endothelial cells. (IC_{50}=2.4 μM). So far, even pan-antibody blockers of the beta-1 and 2 integrins were not able to block completely monocyte transmigration. GT-73 (10 mg/kg) was also extremely active in-vivo using Crohn's disease, multiple sclerosis, fat liver and rheumatoid arthritis mouse models. In addition, GT-73 partially blocked B-lymphocytes homing to spleen and liver. Inhibition of the homing of B-lymphocytes to lymphoid organs may be envisioned as a new therapeutic strategy to reduce B-cell lymphoma proliferation and their capacity to reach supportive lymphoid microenvironments. A detailed acute toxicity profile of this lead compound was also studied and the compound was shown no toxic effects in the administrated doses. Such type of molecules might therefore provide a unique starting point for designing a novel class of leukocyte transmigration blocking agents with wide therapeutic applications.



GT-73

Lectures L1 – L4

L1

In the search for new drug-like molecules: focus on thiazolidinone core

Roman Lesyk

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4-Thiazolidinones as privileged heterocycles in medicinal chemistry possess a variety of biological activities (in both screening campaigns and directed experiments). Such compounds are known as leads with antidiabetic, antimicrobial, antiviral and anticancer activities [1]. They are confirmed selective ligands toward various biotargets (PPARγ-receptors, antiapoptotic proteins Bcl-X_L and BH3, TNFα, JSP-1, COX-2, 5-LOX, integrin, Pim-1 & Pim-2 proteinkinases, etc) as well as compounds with unknown mechanism of actions [2]. Currently many thiazolidinones, especially 5-ene-derivatives, have been claimed as PAINS or frequent hitters, mainly due to Michael acceptor functionality. This is discussing and very often applied in non-correct manner; additionally following the new trend, such Michael acceptor functionality can be useful in the creation of new drug-like molecules [3].

Following the previous data the in-house library of new heterocycles have been improved. The new synthetic protocols for transformations of thiazolidinone frame were developed based on combinatorial approach, bioisosteric replacement, molecular hybridization, privileged substructure-based diversity oriented synthesis etc. Screening of biological activity of synthesized compounds led to focuses of main areas: search of anticancer, antiviral, anti-inflammatory, antiparasitic / antimicrobial agents and compounds able to decrease the oxidative stress as a key pathogenetic mechanism in many disorders including above-mentioned. Moreover, following polypharmacological approach and the concept of multi-target drugs design, the compound possessed several pharmacological effects e.g. simultaneous anticancer and antitrypanosomal activities are regarded as an advantage in the development of new hits. Following the activity of the products of thiazolidinone transformations, they can be considered as pro-drugs with efficient characteristics. SAR analysis allowed to outline direction for 4-thiazolidinones optimization: complication of C5 fragment and modification of N3; the isosteric replacement; combination of thiazolidinone core with other pharmacologically attractive fragments; thiazolidinones-based synthesis of other heterocycles (thiopyrano[2,3-*d*]thiazoles, thiazolo[4,5-*b*]pyridines, isothiocoumarines, etc). Additionally Michael functionality of some thiazolidinones should be used in the useful way (Michael acceptors are activators of Nrf2; covalent inhibitors of set of biotargets; modulators ROS-dependent pathways). For active anticancer thiazolidinones PPAR-mediated, ROS-dependent and proapoptotic mechanism of action was proposed that required the further in depth study and search for possible targets. The thiazolidinones as structural mimics of H_2S donors should be studied as potent H_2S releasing agents that opens new oportunities of their usage.

[1] Lesyk R., Zimenkovsky B. *Curr. Org. Chem.* 8 (2004) 1547-1578
[2] Kaminskyy D., Kryshchyshyn A., Lesyk R. *Eur. J. Med. Chem.* 140 (2017) 542-594
[3] Kaminskyy D., Kryshchyshyn A., Lesyk R. *Expert Opin. Drug Discov.* 12 (2017) 1233-1252

L2

Anticancer activity of novel tubulin polymerization inhibitors obtained by the chemical modification of colchicine

Adam Huczyński,[a] *Greta Klejborowska*,[a] *Urszula Majcher*,[a] *Ewa Maj*,[b] *Joanna Wietrzyk*,[b] *Mahshad Moshari*,[c] *Jack A. Tuszynski*[c]

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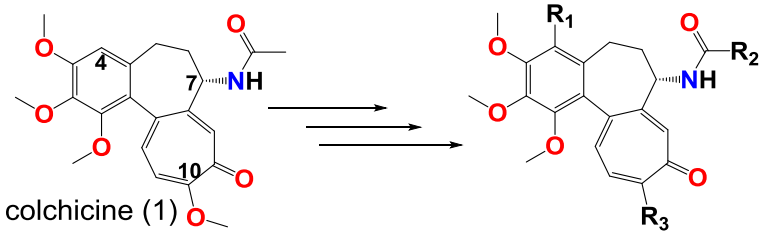
Colchicine **(1)** - a major alkaloid isolated from *Colchicum autumnale* and *Gloriosa superba*, has been in clinical use for a long time for the treatment of acute gout disease and familial Mediterranean fever [1]. In more recent past, a relatively high antiproliferative activity of **(1)** made this compound and its derivatives the focus of numerous studies as a potential anti-cancer drug [2]. The anticancer activity of **(1)** is related to the formation of a colchicine–tubulin complex, which prevents microtubule polymerization due to a conformational inflexibility making tubulin dimers microtubule assembly incompetent. As a consequence, cells exposed to it tend to accumulate in mitotic arrest during the cell cycle, followed by apoptosis [3].



The aim of our work was to develop more selective colchicine derivatives simultaneously maintaining the potent antiproliferative activity of colchicine [4-5]. We synthesized a series of novel triple-modified colchicine derivatives and evaluated their biological activity according to the *in vitro* antiproliferative tests as well as *in silico* studies. The results of our study have clearly showed that the cytotoxicity of almost all colchicine derivatives is higher than the corresponding cytotoxicity of commonly used cytostatic agents – doxorubicin and cisplatin against A549, MCF-7, LoVo and LoVo/DX cancer cell lines. The majority of the derivatives also exhibit a higher cytotoxicity than unmodified colchicine.
In short, these results confirm that the chemical modification of colchicine is a good way to find highly biologically active and less toxic compounds. Some of the obtained compounds are suitable candidates for further tests (*ex vivo*, *in vivo*).

[1] Mandhare A. et. al. *Expert Opin. Ther. Pat.* 29 (2016) 1-18
[2] Kumar A. et. al. *Anticancer Drugs.* 28 (2017) 250-262
[3] Lu Y, *Pharmac. Res.* 29 (2012) 2943-2971
[4] Huczyński A. et. al. *Bioorg. Chem.* 64 (2016) 103-112
[5] Huczyński A. et. al. *Eur. J. Med. Chem.* 90 (2015) 296-301

Acknowledgements: Financial support by grant of the Polish National Science Centre (NCN) – No. 2016/21/B/ST5/00111 is gratefully acknowledged.

L3

Fifty shades of tacrine derivatives to hit alzheimer's disease

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Alzheimer's disease (AD) is an age-related multifactorial neurodegenerative disorder, in which genetic, environmental, and endogenous factors play a role. It is nowadays known that a complex interconnection of molecular events underpins AD, among which extensive loss of cholinergic neurons, abnormal aggregation of amyloid-β-peptide (Aβ), hyperphosphorylation and aggregation of tau protein, oxidative stress, calcium dyshomeostasis, mitochondrial abnormalities, and neuroinflammation.

The inhibition of acetylcholinesterase (AChE) has been so far one of the major available therapeutic strategy for AD patients. However, paralleling the understanding of the molecular mechanisms at the basis of this pathology, the rationale behind the design of new AChE inhibitors has progressively evolved, opening new avenues in AD drug discovery and leading to the design of the so called "multi-target direct ligands" (MTDLs), i.e., single molecules endowed with a multifunctional activity profile. Exploiting this idea, a number of MTDLs has been generated in the last decade by combining fragments endowed with complementary properties, each fragment synergically contributing to the overall activity profile of the molecule.

In particular, the framework of the well known cholinesterase (ChE) inhibitor tacrine (1,2,3,4-tetrahydroacridin-9-amine) has been widely exploited to produce a variety of new MTDLs with a greater therapeutic potential for AD treatment.

On the basis of these premises, this presentation will focus on strategies pursued in the last years by several groups we are collaborating with in the search for new tacrine-based MTDLs to hit the interconnected events underpinning AD.

Definition of SARs and early selection of the best candidate(s) also requires the availability or the development of tailored *in vitro* assays as well as the use of a combination of assays/techniques to get a clear understanding of the mechanism of action and ensure the right selection is made. Thus, the *in vitro* characterization of the mechanism of action of new multi-potent compounds pursued by purposely designed methodologies such as colorimetric, fluorometric methods and circular dichroism, will be also presented. These approaches have allowed the identification of promising new chemical entities, which could be further developed for an effective treatment of AD.

L4

Aryl-containing compounds with 1,3,5-triazine core as a new grateful family of serotonin 5-HT$_6$ receptor agents

Jadwiga Handzlik,[a] Wesam Ali,[a,b] Rafał Kurczab,[c] Dorota Łażewska,[a] Małgorzata Więcek,[a,] Grzegorz Satała,[c] M. Jastrzębska-Więsek,[a] Magdalena Kotańska,[a] Monika Głuch-Lutwin,[a] Barbara Mordyl,[a] Agata Siwek,[a] Muhammad Jawad Nasim,[a,b] Anna Partyka,[a] Anna Wesołowska,[a] Claus Jacob,[b] Katarzyna Kieć-Kononowicz[a]

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The serotonin 5-HT$_6$ receptor (5-HT$_6$R), one of a younger member of serotonin receptors' family, was discovered almost 25 years ago. Due a special location in CNS, the 5-HT$_6$R is able to regulate the balance between excitatory and inhibitory signaling [1]. Results of pre-clinical data indicate a potential usage of 5-HT$_6$R ligands in the treatment of cognitive dysfunctions associated with Alzheimer's disease (AD) and schizophrenia, obesity and feeding behavior impairments and/or mood disorders [1, 2]. Various research teams have been focused on search for both 5-HT$_6$R agonists and antagonists. However, no selective 5-HT$_6$ agent has reached pharmacological market to date. Thus, the search for new 5-HT$_6$R agents is still a challenge for medicinal chemistry. In this context, we have explored a new series of 1,3,5-triazine derivatives that provided three different lead structures (Fig.1) [3].

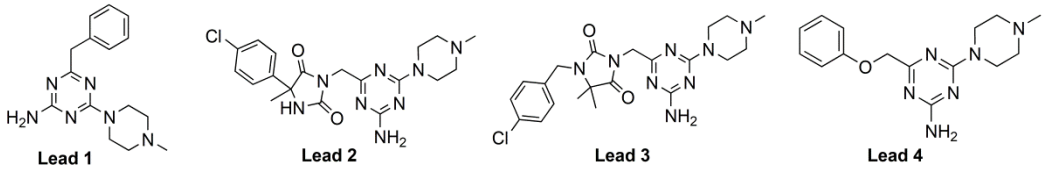

Fig.1

Parallel modifications of the leads provided a series of active 5-HT$_6$R agents, with Ki<5nM for the best ones. The compounds displayed antagonistic action in functional assays, antidepressant, procognitive and anti-obesity properties *in vivo* as well as profitable CNS-drugability. SAR analysis, supported by docking studies, allowed to explain the role of both, aromatic moiety and linker, for the pharmacological action observed.

[1] A. Wesołowska, *et al*,. Int Rev Neurobiol, 2011, 96, 49-71
[2] K. Hirano,. *et al*., Life Sci 2009, 84, 558-62
[3] D. Łażewska,. *et al.* Eur J Med Chem 2017,135, 117-124

Acknowledgements: Studies were partly supported by the Polish National Science Centre (NCN) grant UMO-2015/17/B/NZ/7/02973.

Communications C1 – C21

C1

1,3-Disubstituted thiourea derivatives – structural modifications *versus* bioactivity

Anna Bielenica

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1,3-Disubstituted thiourea system is a structure with a great potential for multiple activities. The reasonably planned modifications of thiourea derivatives structures allow to achieve a good pool of chemicals with high pharmacological properties and low side-effects. The incorporation of an electron-withdrawing group (*e.g*. halogens) into a strategic part of the molecule clearly affects its biological activity, resulting in the increase of lipophilicity, and consequently – the speed of absorption and transport of substances *in vivo*. One of the most serious threats to public health is the problem of drug resistance resulting from the misuse and abuse of classical antibiotics. Particularly dangerous are the methicillin-resistant strains of *Staphylococci,* which are the main etiologic factors of nosocomial infections. The treatment of diseases caused by them lasts longer and usually requires a multi-drug therapy, which increases the risk of severe side-effects and secondary infections. Therefore, the search for new effective chemotherapeutics not only against planktonic microorganisms, but also creating biofilms, is a constant challenge for modern medical chemistry.

The primary goal of investigations was to design and synthesize a series of 1,3-disubstituted thiourea derivatives, mainly halogenated, with multiple modes of biological activity, depending on the chemical nature of their terminal fragments. The most promising compounds among them were then cyclized to 1,3-thiazolidin-4-one and 1*H*-tetrazol-5-yl analogs, as well as complexed with copper (II) salt. Simultaneously the impact of structural modifications of molecules on their *in vivo and in vitro* activities was assessed. The effect of the extended research was also to determine the mechanism of activity of the most potent new derivatives. The collected experiments were to enable the comparison of biological potential of both thiourea forms: linear and cyclic, as well as linear and coordinated with copper (II) ion.

The presented subject is of interdisciplinary nature and combines the competences of many research teams. Evaluation of pharmacological profile of obtained derivatives allowed the selection of those that can compete with standard chemotherapeutics in respect of their bioactivity. New derivatives exerted broad antibacterial, antitubercular and antiretroviral properties. On the other hand, they influenced on the central nervous system of laboratory animals, among others as selective antagonists of 5-HT_{2A} receptor. The most favorable fluorinated derivatives showed higher activity than the respective reference drugs, simultaneously lacking genotoxic properties and did not affect the growth of human normal cells. The relationships between the structure and the activity profile described so far indicate the further promising direction of the search for potential therapeutic substances in the group of thiourea derivatives.

C2

Synthesis of biologically active compounds modified with carborane pharmacopohore

Agnieszka B. Olejniczak,[a] Daria Różycka,[a‡] Sebastian Rykowski,[a‡] Zbigniew. J. Leśnikowski,[a] Eliza Wyszko,[b] Dorota Gurda,[b] Marta Orlicka-Płocka,[b] Agnieszka Kiliszek,[b] Wojciech Rypniewski,[b] Jakub Wojcieszak,[c] Rafał A. Bachorz[a]

[a]Institute of Medical Biology PAS, 106 Lodowa St., 93-232 Lodz, Poland, [b]Institute of Bioorganic Chemistry PAS, 12/14 Z. Noskowskiego St., 61-704 Poznan, Poland, [c]Medical University of Lodz, 1 Muszynskiego St., 90-151 Lodz, Poland

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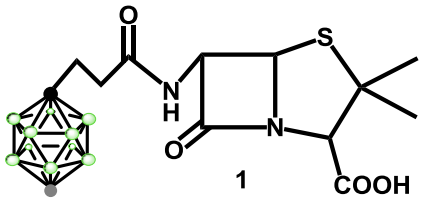
Carboranes are extraordinary robust compounds with desirable properties such as thermal and redox stability, chemical inertness, low nucleophilicity, hydridic hydrogens, high lipophilicity, the neutral or anionic structure making them attractive for several applications such as nanomaterials, molecular electronics, catalysis, and also for the medicinal chemistry - as a potential components of new drugs. Carboranes can act as useful bioisosteres for phenyl ring and adamantane [1, 2].

We have developed methods for the synthesis of several bioactive compounds including:

- penicillin analogues modified with 1,2-dicarba-*closo*-dodecaborane (*ortho*-carborane), 1,7-dicarba-*closo*-dodecaborane (*meta*-carborane), and 1,12-dicarba-*closo*-dodecaborane (*para*-carborane) (**1**) [3]
- naphthalimide-carborane conjugates (**2**, **3**), a class of compounds which bind to DNA by intercalation and have shown anti-cancer activity against a variety of murine and human cancer cell line

Chemistry of these compounds, as well as their biological evaluation will be presented.



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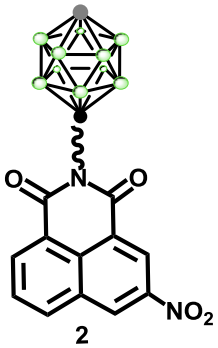

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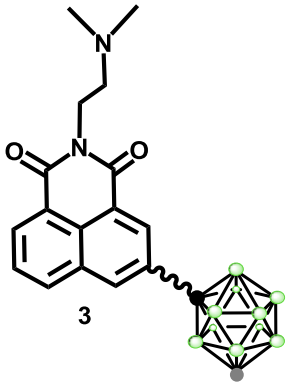

3

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Acknowledgements: This study was supported in part by the National Science Centre, Poland, Grant No. 2014/14/E/ST5/00577, and by an internal grant from IBM PAS.

‡equal contribution

C3

Step forward in search for novel histamine H_3 receptor ligands: 4-pyridyl-piperazine derivatives with promising multidirectional pharmacological activity

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Histamine H_3 receptors (H_3R) are constitutively active G-protein coupled receptors mostly expressed in CNS. Interaction with these receptors results in modulation of histamine levels as well as that of other neurotransmitters. Therefore, blockade of these receptors might provide useful pharmacological target in treatment of many CNS-based diseases such as schizophrenia, Alzheimer and Parkinson's disease, obesity, narcolepsy and attention-deficit hyperactivity disorder (ADHD) [1], also as dual acting ligands [2].

During many years of research on active histamine H_3 receptors ligands in Department of Technology and Biotechnology of Drugs (DTBD), the pharmacophore model for such compounds was developed. Basic core - mostly (homo)(methyl)piperidine moiety - is connected *via* an alkyl chain of variable length with the lipophilic part (an aromatic moiety).

Based on the results of the research so far, it is assumed that the 4-pyridylpiperazine moiety in the basic part of the compound determines their high affinity and selectivity for human H_3R. Moreover, the most promising compounds exhibited anticonvulsant activity in the maximal electroshock-induced seizure (MES) model in mice. Furthermore, the blood-brain barrier penetration, the functional H_3R antagonist potency as well as the pro-cognitive properties in the passive avoidance test were demonstrated for selected compound. On the other hand, pharmacological *in vivo* test results of another ligand clearly indicate that it may affect the amount of calories consumed, thus act as an anorectic compound. Likewise, its protective action against hyperglycemia and the development of overweight has been shown.

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Acknowledgements: We are pleased to acknowledge the generous support of National Science Center, Poland granted on the basis of decision No. 2016/23/N/NZ7/00469, 2016/23/B/NZ7/01063, K/DSC/004310, and K/ZDS/007121.

C4

Organophosphorus compounds – chirality and reactivity

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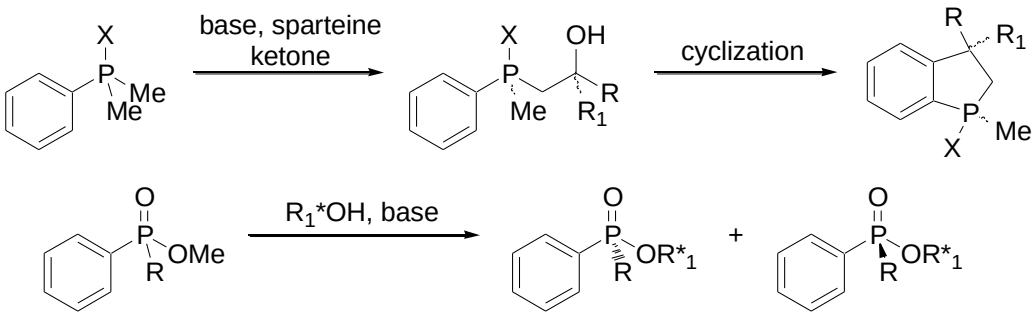
Stereochemistry of transformations of organophosphorus compounds have been a subject of numerous research projects in the past. This is due to quite unique properties of phosphorus atom which can exist in two stable oxidation states possessing different stereochemical properties. In this regard, phosphorus(V) compounds are especially interesting due to the high configurational lability of pentavalent compounds known as Berry or turnstile pseudorotation. On the other hand, the presence of a chirality center at phosphorus in phosphorus(III) and (V) compounds has been used as a chirality source in transition metal-catalyzed transformations although the synthesis of these compounds in an enantiopure from is usually a challenging task.

One of the main research topics in our research group is associated with the synthesis and reactivity of organophosphorus compounds. During the course of the research, two stereochemical problems were recently faced which will be discussed here. The first was associated with the synthesis of enantiopure P-stereogenic bicyclic phosphines and their derivatives where the second was based on the synthesis of non-racemic P-stereogenic organophosphorus compounds using dynamic kinetic resolution methodology.



Acknowledgements: This work was supported by National Science Centre SONATA-BIS Grant no. 2012/07/E/ST5/00544.

C5

The EGO simulation of the AFM experiments for the selected (bio)oligosaccharides

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Polysaccharides may undergo various conformational changes caused by the (stretching) external forces. These changes are examined by Atomic Force Microscopy (AFM). Many recent studies have focused on this field. However, there are still many questions about the potential physiological significance of such forced conformational transitions. The correct interpretation of the AFM experiment can be quite difficult - especially for heteropolysaccharides with the *various* saccharide units connected by the *different* glycosidic bond types. The *different* conformational transitions can occur at the *same* force, which can manifest in *different* ways on the AFM force-extension curve. Molecular insights on the origins of mechanical responses can be inferred from simulations based on theoretical methods. Theoretical simulations of AFM experiments can provide valuable information on the mechanism of the enforced structural changes in the biologically active poly/oligosaccharides [1-3]. In this work we present the results for the different single (bio)oligosaccharide chains obtained within the EGO (Enforced Geometry Optimization) method [4].

[1] A. Brzyska, W.Płaźiński, K. Woliński, *Soft Matter* (2018) DOI:10.1039/C8SM00319
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C6

Experimental charge density determination as a tool for studying intermolecular interactions

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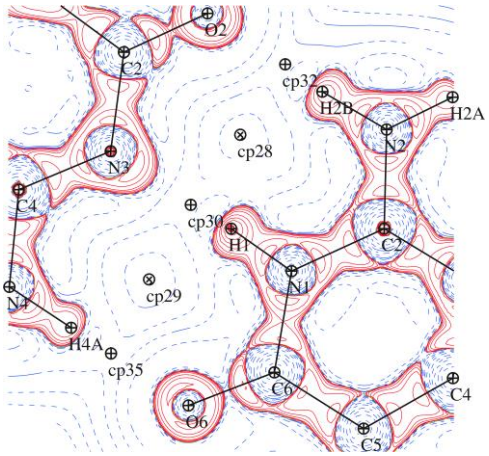
X-ray diffraction provides an insight into the electron density distribution in crystals. Standard methods are based on independent atom model (IAM) approximation, which assume the spherically-averaged, neutral atoms. This model is the basis of unprecedentent success of X-ray crystallography as a tool for "looking at the molecules". However, the details of electron density distribution (bonding density, lone pairs etc.) are outside the possibilities of standard model.

The expansion of IAM into the non-spherical 'pseudoatom' model allows to analyze the fine details of the electron density distribution. This procedure is highly demanding experimentally, but it offers – often together with Atoms-in-Molecules approach – the possibility of deeper understanding of the nature of bonds and other interactions. The results for intermolecular interactions ranging from hydrogen bonds through halogen bonds, $\pi\cdots\pi$ stacking interactions to even more "exotic" ones will be presented.

The "frontier" application of the method is in the field of macromolecules; however, the very subject makes the biggest obstacle: the number of the protein and DNA crystal structures determined at subatomic resolution (<0.8Å) is very small and even for these handful of structures disorder, solvent, ligands etc. make the additional problems. Some preliminary results for proteins [1, 2] and for Z-DNA hexamer [3] will be also shown.



Laplacian map of one of the base pairs in the DNA hexamer.

These results are far from perfect but will probably be a good starting point for the discussion of the limits of the method.

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C7

Metastable binding site – opportunity for GPCR medicinal chemistry

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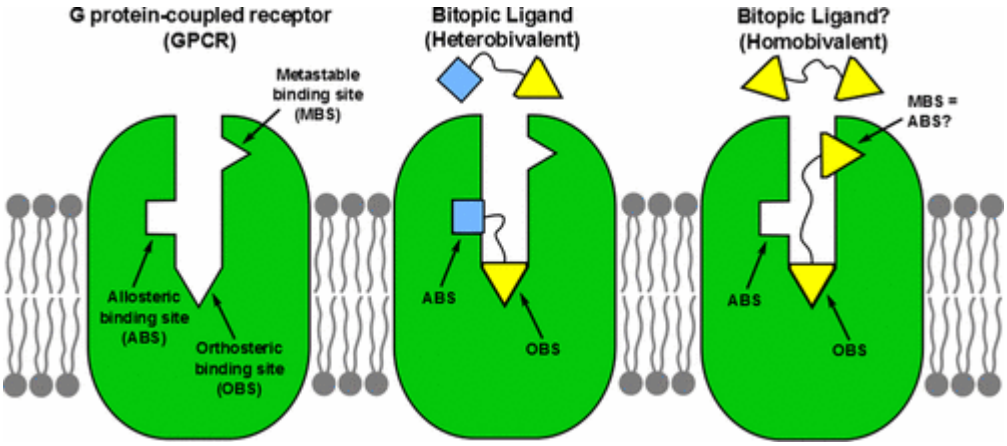

G protein-coupled receptors (GPCRs) belong to a large superfamily of membrane receptors mediating a variety of physiological functions. As such they are attractive targets for drug therapy. However, it remains a challenge to develop subtype selective GPCR ligands. Computational studies on ligand binding to GPCRs have revealed transient, low-affinity binding sites, termed metastable binding sites. Metastable binding sites may provide a new source of allosteric binding sites that could be exploited in the design of bitopic ligands. Herein, the concept of metastable binding sites is outlined, with a focus on the synthesis of bitopic ligands.

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[2] Fronik P. et. al. *J. Med. Chem.* 60 (2017) 4126-4134

C8

Insights into the batch-dependent variability of drug binding to human serum albumin: an induced circular dichroism study

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The ADMET properties of drugs are strongly affected by their binding to human serum albumin (HSA) due to its role as the main carrier protein in plasma. A thorough assessment of the binding affinity of drugs to HSA and the evaluation of binding competition between drugs are therefore important steps for an early characterization of the pharmacokinetic profile of lead compounds in the process of drug discovery and development. The peculiar sensitivity of circular dichroism (CD) spectroscopy towards the stereochemical features of high-affinity binding events can be exploited to assess the binding properties of HSA at its three main drug binding sites: in this study, an analytical protocol based on the use of site-selective induced circular dichroism (ICD) markers was validated and applied to the investigation of commercial HSA samples intended for both R&D-only and clinical applications.

The comparison of binding affinities and capacities for different R&D-only batches of HSA showed that the presence of residual products in the industrial purification of HSA from plasma, such as fatty acids and/or globulins, can lead to a considerable impairment of the binding capacity of HSA at site II and a relatively lower influence on the binding properties at sites I and III; the production process and the resulting purity of HSA batches are therefore crucial factors affecting the reproducibility of *in vitro* binding assays.

The same ICD-based approach can be also applied for the assessment of the binding properties of HSA used as a biopharmaceutical: indeed, the use of octanoate and *N*-acetyltryptophan as stabilizers during the production of pharmaceutical-grade HSA for infusion (*i*-HSA) has a similar modulating effect on the binding capacity of the protein. In this framework, the ICD technique proved to be a suitable technique to investigate the binding properties of *i*-HSA samples, enabling a critical assessment of ultrafiltration and dialysis as methods to remove stabilizers from the formulations.

C9

Synthesis and antihelmintic activity of new 1,2,4 triazole derivatives

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Parasitic diseases and increasing parasitic resistance to available medications pose a very serious medical problem. According to data from WHO, parasitic diseases cause 14 million human deaths every year [1]. Contemporary studies are focused on the search for new synthetic compounds with antihelmintic activity. Among the substances which interest the medical staff are triazole derivatives. The source literature provides study results which confirm their antifungal and antibacterial activity. However, our knowledge of their antihelmintic activity is still not sufficient and requires special attention [2,3].

The aim of this study was to synthesise new 1,2,4-triazole derivatives and assess their antihelmintic activity. The examination covered new 1,2,4-triazole derivatives obtained in the course of a two-stage reaction. The nematode culture and study methods were conducted using 24-well plates for in vitro culture, according to the procedure which was developed by the authors at the Chair and Department of Biology with Genetics, Medical University of Lublin, Poland (patent application number P.421846, Bogucka-Kocka A., Kołodziej P., 2017). As a result of the conducted analysis it was observed that the selected compounds showed antihelmintic activity.

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Acknowledgments: This study was supported by the National Science Centre, Poland, No. 2017/01/X/NZ6/01001.

C10

Synthesis and anticancer activities of novel dipyridothiazines with 1,2,3-triazole substituents

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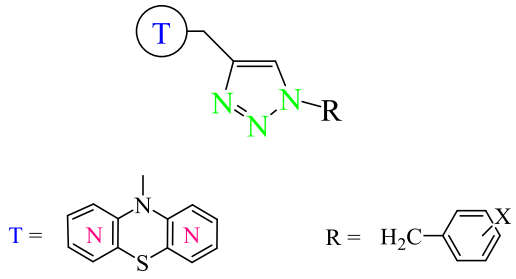
Cancer has now become a global problem and ranked the top leading cause of death worldwide after cardiovascular disease, tuberculosis and malaria combined. Chemotherapy has been still improved in cancer therapy and the survival has been greatly increased but there is need to discover and develop new more potent antitumor agents with better selectivity and reduced side effects [1]. Phenothiazines are important class of heterocyclic compounds with wide spectrum of biological properties. Recent reports showed promising anticancer, antiplasmid, antibacterial, anti-inflammatory and immunosuppressive activities of classical and new phenothiazines [2]. Previously synthesized dipyridothiazine derivatives (1,6-, 1,8-, 2,7- and 3,6-diazaphenothiazines) were shown to possess interesting antiproliferative, anticancer, antioxidant and immunosuppressive activity [3-6]. In continuation of our search we obtained new derivatives of dipyridothiazines with 1,2,3-triazole substituents in the “click chemistry” 1,3-dipolar cycloaddition.



1,6-, 1,8-, 2,7- and 3,6-DIAZAPHENOTHIAZINE

For those compounds, the anticancer action on selected tumor lines (SNB-19, Caco-2, A549, MDA-MB231) was investigated. The compounds exhibited differential inhibitory activities but some compounds were more active (IC_{50} = 0.02 μg/mL) than cisplatin. For the most active compounds the expression of *H3, TP53, CDKN1A, BCL-2* and *BAX* genes are detected by the RT-QPCR method.

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C11

Synthesis and properties of novel multifunctional ligands, inhibiting cholinesterases and β-secretase as potential treatment of Alzheimer's disease

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Alzheimer's disease is a complex, fatal and as-yet incurable neurodegenerative disorder. Its complexity calls for multifunctional compounds which could serve as potential therapeutic agents.

The aim of our research was to search for new, multifunctional ligands targeting two enzymatic systems: cholinesterases and β-secretase, along with two processes: aggregation of neurotoxic β-amyloid and of tau proteins, both related to the underlying mechanisms of Alzheimer's disease. We have designed compounds with a three-part molecular structure, consisting of pharmacophores which mediate activity towards selected biological targets. The first pharmacophore we have chosen was benzylamine, a fragment which appears in many inhibitors of cholinesterase and β-secretase, as well as in various β-amyloid aggregation inhibitors. In the central part, which interacts with the catalytic dyad of β-secretase, we placed two alternative scaffolds: various heterocyclic amines and hydroxyalkylamine. As the terminal fragment we incorporated a phthalimide or a saccharine moiety, as well as various amines selected in virtual screening. All compounds were synthesized and subsequently evaluated for biological activity in an *in vitro* assay [1-3].

Our work resulted in identification of compound **98** as a lead structure, owing to its potency and broad, well-balanced biological activity profile. Compound **98** selectively inhibits butyrylcholinesterase activity (eqBuChE IC_{50} = 2.92 μM, hBuChE IC_{50} = 5.74 μM) in preference to acetylcholinesterase. Its activity profile also involves inhibition of disease-modifying targets and mechanisms: β-secretase (IC_{50} = 41.60 μM), aggregation of β-amyloid (IC_{50} = 3.09 μM) and aggregation of the tau protein (53.8% at 10 μM). Moreover, preliminary in vitro data indicates that compound 98 is capable of crossing the blood-brain barrier.

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[3] D. Panek et. al. *ACS Chem. Neurosci.* 16, (2018), 1074

Acknowledgments: This work was supported by the National Science Center of Poland (Grants UMO-2012/07/B/NZ7/04253, UMO-2016/21/B/NZ7/01744 and UMO-2016/21/N/NZ7/03288).

C12

Novel functionally selective agonists of the serotonin 5-HT$_{1A}$ receptor

Joanna Śniecikowska,[a] Monika Głuch-Lutwin,[a] Adam Bucki,[a] Anna Więckowska,[a] Agata Siwek,[a] Magdalena Jastrzębska-Więsek,[a] Anna Partyka,[a] Karolina Pytka,[a] Krzysztof Pociecha,[a] Agnieszka Cios,[a] Elżbieta Wyska,[a] Anna Wesołowska,[a] Maciej Pawłowski,[a] Mark Varney,[b] Adrian Newman-Tancredi,[b] Marcin Kołaczkowski[a]

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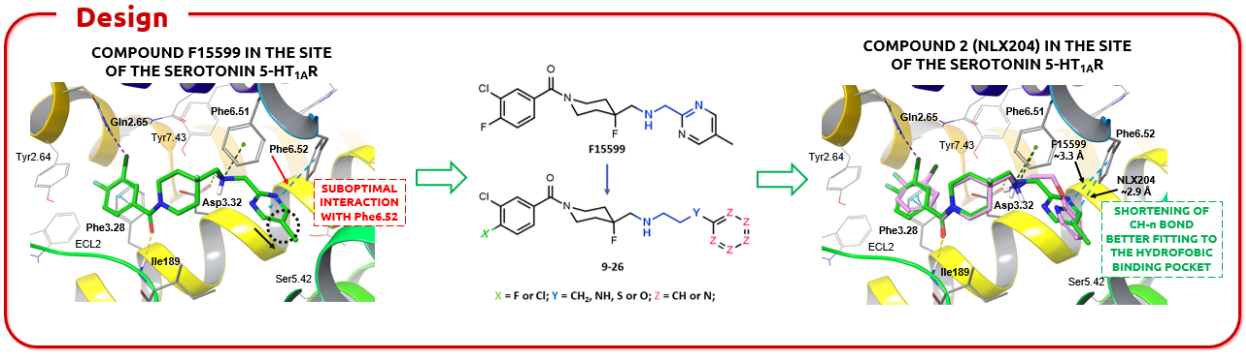
Here we present the discovery of a new generation of functionally selective serotonin 5 HT$_{1A}$R agonists, as potential drug candidates for psychiatric, neurodegenerative and other CNS disorders, in particular depression and Parkinson's disease or rare disorders such as Rett syndrome.



A library of 65 novel derivatives of 1-(1-benzoylpiperidin-4-yl)methanamine was designed with the support of molecular modeling and obtained by chemical synthesis, followed by analysis of the relationship between their structure and affinity as well as functional activity at the 5-HT$_{1A}$R. 48 of them showed subnanomolar affinity for the 5-HT$_{1A}$R, high selectivity versus key "anti-targets" adrenergic α_1 and dopaminergic D_2 receptors (K_i ratio over 1000-fold for most compounds), as well as high values of parameters predicting developability of the tested compounds (CNS MPO, Fsp^3 or LELP). Each of these compounds was tested in four signal transduction assays (pERK phosphorylation, cAMP inhibition, Ca^{2+} mobilization and β-arrestin recruitment). These studies enabled identification of 17 novel biased agonists of the 5-HT$_{1A}$ receptor, with diversified functional activity profiles, called “signaling fingerprints”. Among them, the compounds strongly preferring ERK1/2 phosphorylation (**60**) or β-arrestin recruitment (**47**) were identified, having very high bias factors of 2.02 (> 100×) and 3.63 (> 4000×), respectively. The two selected biased agonists with significantly varying in vitro functional pERK1/2 vs. β arrestin selectivity profiles, showed differential in vivo activity in the FST and LLR studies, thus suggesting that different preference for β-arrestin recruitment relative to ERK1/2 phosphorylation (functional selectivity) may be associated with various preferences for activation of particular subpopulations of the 5-HT$_{1A}$ receptors (regional selectivity). The variety of the obtained novel 5-HT$_{1A}$ agonists, displaying diversified functional profiles, may help in future investigation of this physiologically and therapeutically important issue.

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C13

Magnetic nanomaterials – synthesis and applications

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Magnetic nanomaterials are promising and widely used as supports for biomolecules immobilization and adsorption. [1,2] The surface of such nanomaterials is usually specific and highly porous which makes them very good carriers able of binding different molecules with high load of ligands. Because of poor colloidal stability particularly in neutral pH of pure magnetite it needs stabilization and surface modification. The most frequently used for magnetic nanoparticles coatings are polymers. [3] Due to the superparamagnetic core these nanocomposites are easy separable from the reaction mixture and can be reuse in several cycles.

Polysaccharides as chitosan and starch are non-toxic natural polymers widely applied for biomedical applications especially as a polymer shell covering the magnetic nanoparticles. [4-5] In this work several types of magnetite superparamagnetic nanoparticles were synthesized. Magnetic core was coated with pure chitosan aminated chitosan with different content of reactive amino groups on the surface, starch and aminated starch. Moreover, the starch was functionalized on nanoparticles surface via easy and quick solvent free reaction. The structure, size and morphology of nanoparticles were investigated by ATR-FT IR spectroscopy, transmission electron microscopy, X-ray diffraction, dynamic light scattering and low temperature adsorption of nitrogen.

In the next step prepared magnetic nanoparticles were carbonized in several carbonization conditions to carbon magnetic materials as a potential easy separable material able to effective interaction with NSAIDs and their metabolites. The interactions between prepared materials and ketoprofene, ibuprofene, diclophenac and the mixture of all this NSAIDs drugs in different solvents and conditions were investigated by spectroscopic and chromatographic methods. Experimental results were supported with computational methods.

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C14

Dipeptidyl peptidase 4 (DPP-4) inhibitor effects on depressive behavior in mice observed in forced swimming test (FST) after morphine discontinuation

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Morphine, as an effective analgesic, is often used chronically. Unfortunately, in case of chronic use, development of mental and physical dependence is observed. Dependece is characterized by mood-lowering effect after discontinuing the use of addictive substance. Linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is an antihyperglycemic drug used in treatment of type 2 diabetes. Linagliptin inhibits DPP-4 activity by increasing glucagon-like peptide-1 (GLP-1), which enhances insulin secretion [1]. To date, many literature data have been published showing that DPP-4 inhibitors have other pharmacological effects, eg neuroprotective effects, in addition to antidiabetic effects [2]. There are also reports indicating the potential importance of receptors for GLP-1 peptide in inhibiting anxiety and depression [3,4]. Taking all into account, it can be assumed that GLP-1 modulators may influence the depressive behavior occurring after withdrawal of the addictive substances. The aim of the present experiments is to evaluate the effect of DPP-4 inhibitor on depressive behavior in mice after discontinuation of morphine administration, measured in the forced swim test. The results of experiments indicate that the administration of linagliptin together with morphine does not affect the depressive behavior in mice, whereas the administration of linagliptin 20 mg / kg during the withdrawal period of morphine reduces depressive behavior in mice.

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C15

Selected aspects of the synthesis of new indazole derivatives with anticancer and antibacterial activity

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The increasing incidence of cancer and the need to look for new antibiotics, prompted us to design the synthesis of new potentially active compounds. Basing on numerous literature data, as well as, previous experience of scientific team, to obtain compounds the cycle of *VNS* – reduction – cyclization reactions was involved. The planned synthesis, apart from classical methods of the organic synthesis, were led with exploiting assisted techniques: microwave, as well as ultrasonic and ultraviolet energy.
Some final compounds were tested for their ability to inhibit proliferation of the leukemia K562 and colorectal cancer HCT116 cell lines. Two of them, namely the compounds with the 3,5-dimethylpyrazole or carbazole moiety, have been identified as potent proapoptotic agents.
Selected indazole derivatives were tested for antibacterial (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*) and antifungal (*Candida albicans* and *Aspergillus fumigatus*) activity. Two compounds worth of mentioning are pyrazole- and morpholine- derivatives. First compound's antifungal activity was comparable to itraconazole, its antibacterial effect of the compound was lower than amikacin's, but clearly marked. The second one showed antibacterial as well as antifungal activity.

C16

New 2-alkylthio-4-chlorobenzenesulfonamide derivatives bearing heterocyclic moieties – synthesis, structure and anticancer activity studies

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According to statistics, in 2012, there were estimated 1.4 million new colorectal cancer cases and 693,900 deaths. Breast cancer, the leading cause of cancer-related death among females worldwide, gave an estimated 1.7 million cases and 521,900 deaths in 2012. An estimated 527,600 cancer cases and 265,700 deaths in 2012 worldwide were caused by cervical cancer which is the third leading cause of cancer-related death in females [1].

Chemotherapeutics play an important role as anticancer agents, inducing apoptosis or restoring apoptotic functions of proteins. In view of the importance of sulfonamides and nitrogen containing heterocycles as privileged structures for the designing of anticancer agents, we decided to explore the synthesis and anticancer activity of molecular hybrids obtained by the combination of benzenesulfonamide and heterocycles such as imidazole, 1,2,4-triazole, benzimidazole and benzoxazole.

The anticancer activities of compounds were evaluated *in vitro* on MCF-7, HCT-116 and HeLa human tumor cell lines by MTT assay. The most active compounds bearing 3-methyl-2-thioxo-1*H*-imidazol-1-yl moiety exhibited selectivity against HeLa cells with IC_{50} values 6–7 μM. Meanwhile, 2-thioxo-1*H*-benzo[d]imidazole derivatives showed activity against HCT-116 cells in the range of IC_{50}: 17–36 μM. The apoptotic potential of the most active compounds was analyzed through various assays in HeLa cells: phosphatidylserine translocation, cell cycle dystribution and caspase activation. Results indicated that compounds promoted cell cycle arrest at sub-G1 phase in cancer cells, induced caspase activity and increased the population of apoptotic cells.

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C17

The effect of diosmin treatment on the level of oxidative stress biomarkers (isoprostanes) in patients suffering from CVI

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Diosmin is a natural flavonoid applied i.a. in chronic venous insufficiency (CVI). The antioxidant activity of diosmin may have a significant effect in the alleviation of various symptoms in patients with chronic venous insufficiency (CVI). Isoprostanes are compounds, considered as markers of oxidative stress [1,2,3].

The aim of the study was to assess the effect of diosmin treatment on the level of oxidative stress biomarkers (isoprostanes) in patients with chronic venous insufficiency.

The investigations involved patients with chronic venous insufficiency (Department of Vascular Surgery and Angiology, Medical University of Lublin). The qualitative analysis was performed with high-performance liquid chromatography with spectrometry detection (LC-MS 8050 Shimadzu Japan). Statistical analysis of the results was carried out using Statistica 10 software, StatSoft Poland Sp. z o.o..

The analysis of the results of descriptive statistics revealed decrease of isoprostanes content after 3 months of diosmin treatment was observed within the studied group (before treatment mean value was 39.65±42.1 pg/mL and after treatment mean value was 23.97±31.3 pg/mL).

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C18

Synthesis of selected hybrid analoques of curcumin with NSAIDs

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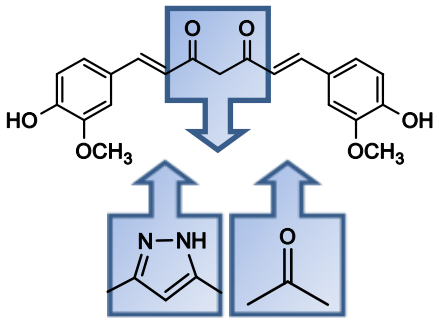
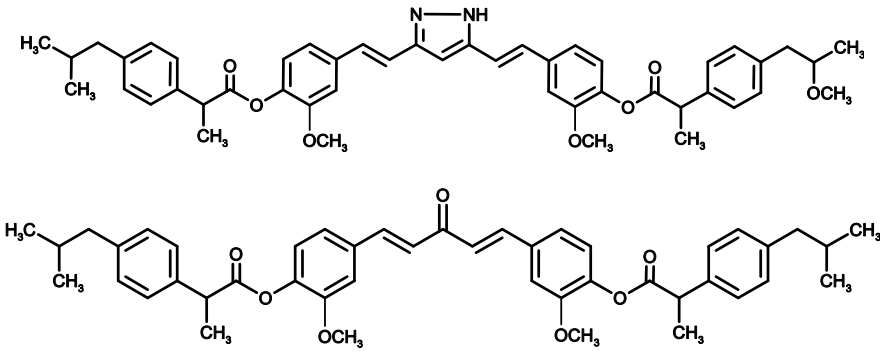
Observing the increase interest in natural substances in the design of pharmacologically active compounds, new combinations were synthesized, using for this purpose popular non-steroidal anti-inflammatory drugs and curcumin and its synthetically obtained analogues. At the same time, the effect of curcumin structure modifications and conditions of the reaction on the NSAID attachment process were examined.

The substrates needed for further research were synthesized – the pyrazole and monocarbonyl analogues of curcumin. The first of the analogues was obtained by blocking the aliphatic chain of curcumin with hydrazine hydrochloride. In turn, removal of one carbonyl group from the dicetone group of curcumin was possible by reacting vanillin with acetone.



Curcumin and its analogues were combined with selected NSAIDs: ibuprofen, naproxen and ketoprofen by the esterification of the phenol group of curcumin and the carboxyl group of NSAID molecule. Reactions were carried out with catalytic agents – DCC and DMAP. The structure of these compounds was confirmed by EI-MS, ESI-MS and ^{1}H-NMR and ^{13}C-NMR data.



Spectral analysis showed that in products synthesized only one phenol group of curcumin was substituted with a drug molecule, whereas in its analogues, one NSAID molecule joined each of the two phenolic groups.

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C19

MW-US synergy tool for the rational synthesis of hybrid derivatives

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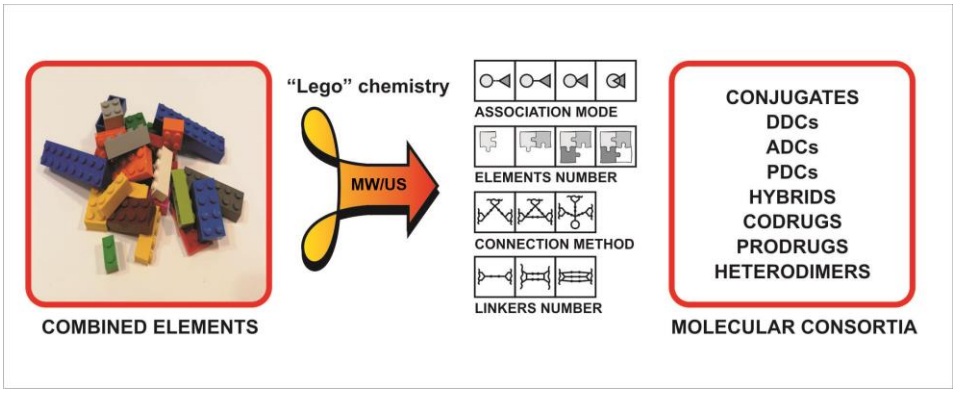
Recently, the environmental impact has become a very important factor in the design of new synthetic methodologies in organic and medicinal chemistry. The use of alternative activation factors, microwaves (MW), ultrasounds (US) and their mutual cross-combination has become very promising and desirable synthetic methodologies in efficient and fast creation of new drug-like structures. Microwave heating and ultrasonic waves are among the most simple, inexpensive, and valuable tools in applied chemistry. Besides saving energy, these green techniques promote faster and more selective transformations [1]. Moreover, the "Lego" chemistry constitutes an interesting approach to the synthesis of drug-like molecules that can accelerate the drug discovery process by utilizing a few practical and reliable reactions by conjugation, hybridization, linker chemistry, pharmaceutical-related polymer chemistry etc. "Lego" chemistry approach complemented with a green chemistry tool can be additionally supported by a natural additional synergy concept that exceeds the sum of the individual effects of the factors considered [2]:

- synergism by combining various active structures - pharmacomodulation of two biologically active molecules by chemical hybridization methods leads to a new combined structure with interesting synergy biological activity,
- synergism by synthesis process intensification by means of combining two non-conventional factors: microwaves and ultrasound. These two effects of process intensification have been used to great effect in drug chemistry field.

Many derivatives, with a particular focus on the triterpenes, have been obtained using the above concepts.



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C20

Molecular receptors arrays in studies of the binding profile of drugs acting on histamine H1-H4 receptors

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The process of new drugs discovery involves many stages, is long and expensive. Despite the use of a whole range of research techniques, the choice of compounds for clinical trials consists a difficult task and gives a small chance of successful completion of this research phase. It is estimated that only 0.1% potential medicines pass this test stage successfully. Thus, the search for new research models that will improve the effectiveness of the search for new drugs, reduce the scope and costs of research conducted on laboratory animals and increase the effectiveness of the selection of compounds for clinical trials are the subject of intensive studies. As part of the research continued at the Institute of Organic Chemistry of Lodz University of Technology it was found that N-lipidated peptides immobilized on cellulose mimic natural receptors and / or enzymes with their actions [1]. The anchored N-lipidated peptides undergo self-organization process forming binding pockets mimicking the molecular receptors, which are able to recognize the shape, size, chirality and polarity of docked ligands and highly selectively interact with them [2]. The basic structural fragment forming receptors are N-lipidated peptides anchored regularly on the cellulose support via a linker containing 1,3,5-triazine and m-phenylenodiamine residues. Attempts to use molecular receptors to study the interactions of the pool of 12 compounds with documented activity against histamine receptors H1-H4 have been made. Peptide fragments of the molecular receptors were built with amino acid residues key for of the native (H1-H4) histamine receptors crucial for interactions with pharmaceutically active compounds [3], expecting that it will allow to obtain systems mimicking molecular environment of the natural histamine receptors. Based on this assumption molecular receptors matrices constituting a permutation or a combination of conservative H1-H4 receptor domains have been obtained was obtained by using SPOT technique. The use of an approach based on experimental determination of differences in the durability of molecular complexes allowed the selection of a set of receptors that selectively and specifically interact with agonists and antagonists of histamine receptors. The result of the studies should allow the construction of new platform for screening of antihistamine compounds, useful as a new research tool in the process of searching for new drugs.

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C21

Functionalization of nanomaterials useful in medicine by simultaneously attachment of targeting molecules and pharmaceutically active compounds

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The progress in nanotechnology contributed to the development of nanomaterials manufacturing methods and on the other hand substantially broadened the fields of their applications. In medicine nanomaterials were applied in nanodiagnostics, nanopharmacology and nanooncology. Among the most popular nanostructures used in medicine there are silver and gold nanoparticles, quantum dots, magnetic nanoparticles, carbon nanomaterials and dendrimers. Among the carbon nanomaterials [1-3], the most extensively used have been carbon nanotubes, nanodiamond, graphene and fullerenes. The unique ability of carbon atoms to participate in covalent bonds linking them with other carbon atoms in diverse hybridization states (sp, sp^2, sp^3) or with nonmetallic elements, enables them to form a wide range of structures, from small molecules up to large molecular complexes. The use of carbon nanomaterials in medicine [4] results from the possibility of their chemical functionalization, which usually involves already present functional groups or susceptibility of defects on their structures towards chemical modification. Often, the initial functionalization consists oxidation of the surface of nanomaterials leading to the introduction of reactive oxygen groups, including carboxyl function, on the surface of the nanomaterial.

One of the areas of research conducted at the Institute of Organic Chemistry of the Lodz University of Technology is research on the functionalization of carbon nanomaterials. Its aim was to is develop the methods of orthogonal functionalization of carbon nanomaterials for the simultaneous and selective attachment of both pharmacologically active compounds, compounds responsible for selectivity of action (targeting) and research probes at the molecular level. To achieve this goal anticancer compounds, non-steroidal anti-inflammatory drugs and/or other medicines were attached to nanocarrier additionally functionalize carbon nanomaterials with folic acid, which should increase the selectivity of the interaction of materials with cancer cells with overexpressed of folic acid receptors. In the studies, 1,3,5-triazine derivatives were used both as a coupling reagent for attachment of biologically active molecules as well as the scaffold enabling incorporation of three different functional groups [5]. As biologically active compounds it is possible to use drugs, homing (targeting) molecules compounds or fluorescent probes.

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Poster oral presentations PP1 – PP16

PP1

Fluorescent triazolyl spirooxazolidines: synthesis and NMR stereochemical studies

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Carbon-heteroatom chemistry is a method of choice for rapid construction of complex molecules. In the recent decade, its various applications flourished thanks to the Click chemistry approach. Herein, we present the synthesis of 1,2,3-triazolyl spirooxazolidines, bearing the fluorenylmethoxycarbonyl (fmoc) substituent, using a combination of C-X formation reactions. Both, the triazolyl spirooxazolidines and their N-fmoc derivatives, synthesized as inseparable diastereoisomeric mixtures, exhibit complex structure with multiple aromatic ring currents causing spectacular diastereotopic effects.

Thanks to the application of 2D-NMR spectroscopic methods and a multilevel computational approach including a medicinal chemistry – inspired conformational search, PM7 semmiempirical and DFT-based geometry optimization, finalized with DFT-GIAO NMR shielding constant calculation, we were able to investigate the conformational space and assign cis/trans configuration in complex NMR spectra. For the obtained fmoc derivatives we recorded UV-VIS absorption and emission spectra. The obtained compounds contain pharmacophoric groups characteristic for endocannabinoid system modulators- CB1 receptor ligands or FAAH inhibitors.

PP2

Fluorescent labelling of azidothymidine: introduction to personalised antiviral therapy

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Azidothymidine (AZT) is an antiretroviral drug, which contains an azide group in its chemical structure. It is used as a stand-alone medication or in complex formulations for HIV infection treatment. However, medication with AZT is associated with many side effects such as myelotoxicity, neutropenia, and hepatotoxicity, which raise concerns about safety of the treatment. In such situation, adjustment of individual dose of the drug is highly beneficial for the patient.[1] It is particularly important if the inter-individual differences in the rate of drug metabolism are considered. Individual profiling of AZT metabolism could be a step towards the treatment of viral infections using the personalized dosage therapy.

Fluorescent labeling allows effective analysis of azidothymidine, significantly increasing the sensitivity of determinations compared with absorption methods. The proposed fluorescent conjugation methodology is based on the copper(I) catalyzed azide-alkyne cycloaddition (CuAAC), which is the main reaction of the *click chemistry* approach. This strategy focuses on the use of efficient and easy to perform reactions and is widely used in pharmaceutical sciences and fluorescent labelling.[2]

Efficient labelling of azidothymidine with a fluorescent marker would allow to easily determine its concentration in samples, first in model solutions and next, in patient blood and urine samples.[3] This would extend the application of personalized medicine to antiviral treatment with azidothymidine. Personalization of the therapy would involve individual adjustment of the azidothymidine dose used in treatment by monitoring azidothymidine concentrations in patients' blood. Such an approach would result in clear and precise determination of the patient's metabolic profile, minimizing side effects and maximizing the therapeutic effect during pharmacotherapy.

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PP3

Unusual interactions of triazoloacridinone C-1305 with dsDNA

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Investigation of activity of novel anticancer derivatives is an important step that may lead to development new clinical anticancer agent. To choose most promising substances researches compare activity, binding constants response on the genome level such as increase or decrease level of expression of enzymes. Yet from time to time some derivatives will be synthesis that mode of action and cell response isn't as typical as from other molecules from same family.

One of such examples is triazoloacridone C-1305 (5-dimethylaminopropylamino-8-hydroxytriazoloacridinone) [1]. Biophysical study shown that this compound present unusual high affinity to guanine triplets in DNA sequence, therefor it was proposed that molecular target for this drug could be G-quadruplexes in telomeres [2]. Other tests shown that triazoloacrodone has lower affinity to topoisomerase type II than amsacrine yet cytotoxicity is similar [3]. To mention just a few examples of untypical properties. Study of aggreagation, DNA complexation and NMR based structural study of the triazoloacridone C-1305 will be presented on the poster.

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PP4

Candicidin D & Iso-Candicidin D in sterol-containing lipid bilayer environment – a molecular modelling study

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Polyene macrolides are leading and most prospective antifungal agents used for the treatment of systemic and topical fungal infections. Depending on the size of macrolactone ring and the number of double bonds constituting the chromophore they are divided into trienes, tetraenes, pentaenes, hexaenes, heptaenes and octaenes. In the class of heptaene macrolides there is a subgroup of aromatic heptaene macrolides (AHM)[1], which displayed tests over one order of magnitude *in vitro* higher antifungal activity, in comparison to Amphotericin B (AmB)[2,3]. Members of the AHM group are characterized by: 1) a presence of an *p*-aminoacetophenone moiety attached to an aliphatic side chain and 2) different, in comparison to non-aromatic heptaenes (AmB), geometry of the chromophore (*cis-trans* for AHM vs. *all-trans* for non-AHM). The most widely known representative of AHM is Candicidin D (CndD).

According to the results of the recent studies on AHM, it has been unambiguously proven that it is possible to obtain a stable isomer of CndD with photochemically transformed polyenic region of macrolactone ring, iso-Candicidin D (iso-CndD). The resulting *all-trans* isomer exhibits geometry of the chromophore identical to the one of AmB[4]. Considering that the iso-CndD is more structurally similar to the AmB, yet still contains an aromatic sidechain which surely contributes into its higher antifungal activity, performing an MD-driven comparison of CndD and iso-CndD interactions with mammalian and fungal sterols within the lipid bilayer environment seemed to be an exciting prospect.

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PP5

Synthesis and biological evaluation of new colchicine derivatives acting as antimitotic agents

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Colchicine, a well-known tropolone alkaloid isolated from *Colchicum autumnale*, is of particular interest due to its antimitotic properties. It has played an important role in studies of mitosis and the therapeutic potential of colchicine binding site has been considered for chemotherapy applications [1,2]. However, colchicine itself as well as many of its derivatives could not be used as anticancer drugs because of their strong side effects. Up to now many structure-activity relationship studies have been done to elucidate the structural features required for the tubulin binding [3-5].

Herein, we report the synthesis, spectroscopic analysis of novel triple-modified colchicine derivatives, as well as evaluation of these derivatives as cytotoxic, tubulin-targeting agents. The antiproliferative effect was tested *in vitro* on five human cancer cell lines, i.e.: human lung adenocarcinoma (A549), human breast adenocarcinoma (MCF-7), human colon adenocarcinoma cell line (LoVo) and doxorubicin resistant subline (LoVo/DX), acute lymphoblastic leukemia (ALL) as well as one normal murine embryonic fibroblast cell line (BALB/3T3). To better understand the interactions between the colchicines derivatives and tubulin, we also investigated potential binding modes of all studied compounds docked into colchicines binding site (CBS) of ßI tubulin using Autodock4 software under flexible ligand and rigid receptor condition.

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PP6

Chemical modification of pipemidic acid and its impact on antibacterial activity of synthesized derivatives

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Microorganisms are an important element of the surrounding world and play a significant role in its functioning, but on the other hand they are undoubtedly a threat to human life and health. Humanity noticed the need to control the destructive plague of bacteria, but they have developed specific defense mechanisms for conventionally used antibiotics [1]. New medicines are therefore needed, what creates broad possibilities for researchers to search for new molecules with potential biological activity. Literature review proves that the priority is to find substances better tolerated by patients, less toxic and at the same time more effective in fighting with microorganisms [2]. An important class of compounds with broad spectrum of biological activity are substances with a 1,2,4-triazole-3-thione system in their structure. They exhibit anti-inflammatory properties [3], as well as antifungal [4], antibacterial [5], anti-cancer [6] and anticonvulsant [7] properties. In our work, we used one more important structure, namely pipemidic acid belonging to the quinolone group. The literature give examples where the combination of these elements allow to obtain a beneficial effect on the antimicrobial activity of the resulting hybrids [8]. Therefore, the presented work discusses the synthesis and antimicrobial activity of a new series of pipemidic acid derivatives.

New compounds were synthesized by a three-step synthesis. In the first step we obtained thiosemicarbazide derivatives by reacting the corresponding hydrazide with isothiocyanates. This process allowed us to obtain 16 compounds, which were then cyclized in a 2% sodium hydroxide solution to 4,5-disubstituted 1,2,4-triazole-3-thione derivatives. Finally a series of Mannich reactions between 1,2,4-triazole-3-thione derivatives, formaldehyde and pipemidic acid were performed what to obtain 16 new pipemidic acid derivatives. The chemical structure of all obtained substances was confirmed by the ^{1}H NMR and ^{13}C NMR spectra analysis.

All synthesized compounds were examined for their antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria and fungi belonging to yeasts *Candida* spp. On the basis of MIC and MBC values we discovered that new pipemidic acid derivatives showed interesting antibacterial activity.

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PP7

Synthesis and biological activity of a new 5-cyanoindole derivatives as a dual D_2/5-HT_{1A} receptor ligands

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The current treatment of central nervous system diseases including depression, schizophrenia or Parkinson's disease is it is not fully effective. Therefore, the need for further research into antidepressants is justified. There are more and more reports in the literature in which the cooperation of two mechanisms of action is described [1,2]. An example for this approach may be Wilazodone well known antidepressant, whose mechanism of action is based on inhibition of serotonin reuptake and it is a 5-HT_{1A} receptor agonist [3]. Another example of a compound used in the treatment of depression is Aripiprazole. Similar to Wilazodone, Aripiprazole also has a dual mechanism of action - it is a partial agonist to D_2 and 5-HT_{1A} receptors [4].

Based on this knowledge, it was decided to synthesize a new group of derivatives of long-chain arylpiperazines (LACPs) with a 5-cyanoindole moiety. These compounds contain a motif from Aripiprazole - chlorophenylpiperazine and from Vilazodone (5-cyanoindolobutyl moiety). Ligands were synthesized in solvent-free reactions supported by microwave irradiation. This method can be regarded as fast, efficient and eco-friendly that fits into the canons of green chemistry. The purified ligands were examined in biological tests to determine the binding to the D_2 and $5HT_{1A}$ receptors. The compounds were also designed for their drug-like properties, calculating for appropriate physicochemical parameters *in-sillico.*

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PP8

Evaluation of the cytotoxic effect of ciprofloxacin conjugates with fatty acids on cancer cells

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Cancer is the leading cause of death and its incidence is still increasing (1). Many potential cancer treatments that could have curative implications show severe side effects because they affect not only cancer cells, but also rapidly proliferating normal cells.

Ciprofloxacin is a widely used second generation quinolone which inhibits bacterial DNA gyrase as well as mitochondrial topoisomerase II in the mammalian cells. This enzyme is essential for DNA replication and thus for cell proliferation. (2,3). Partial impairment of mtDNA synthesis in ciprofloxacin-treated cells may affect mitochondrial energy metabolism and lead to disturbance of mitochondrial respiration and ATP synthesis (4). Besides it, the effect of ciprofloxacin on tumor angiogenesis was expressed by decreased serum level of vascular endothelial growth factor (VEGF) (5).

Ciprofloxacin has a confirmed cytotoxic action on some cancerous cells but in high, not pharmacologically relevant concentrations (6,7,8). Considering features of natural fatty acids such as biocompatibility, biodegradability and increased cellular uptake by cancer cells it seems that combining ciprofloxacin with fatty acids could increase bioavailability and thus specific cytotoxicity of the drug against cancer cells (9).

Therefore the aim of this study was to evaluate the cytotoxic effect of new synthesized conjugates of ciprofloxacin with fatty acids compared to ciprofloxacin alone.

In present study we evaluated the anti-proliferative and apoptosis-inducing effects of ciprofloxacin conjugates with fatty acids on human primary (SW480) and metastatic (SW620) colon cancer, metastatic prostate cancer (PC3) and normal (HaCaT) cell lines. Saturated and unsaturated fatty acids such as docosahexaenoic, linoleic, elaidic, oleic and palmitic were used for the conjugate synthesis.
Cytotoxicity was measured by MTT and LDH assay. Apoptosis induction was evaluated using annexin assay.
All conjugates exhibited higher cytotoxic effects than ciprofloxacin alone in all studied cancerous cell lines but not in normal cells. The most effective were conjugates with DHA, oleic and elaidic acids being from 2 to 13 times more cytotoxic than free ciprofloxacin. Interestingly, conjugate with palmitic acid was less effective than conjugates with unsaturated fatty acids in all studied cancer cell lines. Our studies have shown that PC3 were the most sensitive cells to both conjugated and unconjugated ciprofloxacin. IC50 value for conjugate with oleic acid for PC3 cells was 7.71 µM, i.e. 13 times lower compared to ciprofloxacin alone (IC50 101.38 µM). All conjugates induced late apoptosis in all cancer cell lines but not in normal cells. The most potent inducers were conjugates with DHA in SW480 and PC3 cells and those with elaidic and oleic acids in PC3 cells.
It seems that the conjugation with fatty acids can improve the bioavailability and cytotoxic effect of ciprofloxacin on cancer cells at lower toxicity against normal cells.

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PP9

Optimization of molecular properties of imidazothiazole derivatives as indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors

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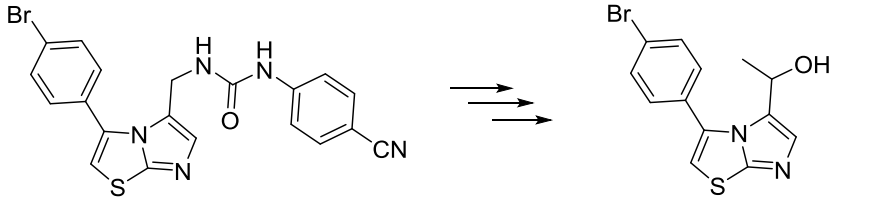
Indoleamine 2,3-dioxygenase 1 (IDO1, EC 1.13.11.52) is a heme enzyme that catalyzes the initial and rate-limiting step of the kynurenine pathway: oxidation of L-Trp to N-formyl kynurenine (NFK) by the incorporation of molecular oxygen and the cleavage of the pyrrole ring of the substrate. It is expressed by tumor cells to escape an immune response and high IDO1 expression is associated with poor prognosis in a variety of cancer types. *In vitro* and *in vivo* studies demonstrate that administration of an IDO1 inhibitor improves the efficacy of therapeutic vaccination, chemotherapy, or radiation therapy. Epacadostat - IDO1 inhibitor developed by Incyte Corporation and indoximod (1-Methyl-D-tryptophan, developed by NewLink Genetics) as a kynurenine pathway inhibitor have entered clinical trials recently. Several other pharma companies with IDO1 inhibitors in their pipeline at present or in the past are Amgen, Bristol-Myers Squibb, Curadev, Dainippon Sumitomo Pharma Corporation, IOmet Pharma, iTeos Therapeutics, and Vertex Pharmaceuticals.

Among thousands of molecules shown to inhibit IDO1, compound **17g** discovered by Toyo and coworkers [1] appeared to us as an attractive starting point for further modification.



compound **17g**, Tojo et al. [1]

hIDO1 IC50 = 77nM (reported value)
506nM (in-house assay)
Molecular Weight: 452,33
clogP = 5.48, PSA = 110.5
HBA number = 7
HBD number = 2

OAT-1615

hIDO1 IC50 = 320nM (racemic)

Molecular Weight: 323,21
clogP = 3.88, PSA = 65.8
HBA number = 4
HBD number = 1

Herein we report optimization of compound **17g** that led us to discovery of compound **OAT-1615** that is characterized by improved molecular parameters (molecular weight, clogP, PSA, number of hydrogen bond donors and acceptors) as compared to the parent compound, while maintaining high inhibitory activity against IDO1. Structure-activity relationship data along the molecular (calculated) and physicochemical (measured) properties of the newly discovered IDO1 inhibitors will be presented.

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PP10

Aza-BODIPY bearing amine moieties – synthesis, fluorescence properties and singlet oxygen generation

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BODIPY and their aza-analogues – aza-BODIPY are small molecules with intriguing optical properties. Apart from their biomedical uses, they are investigated as materials for voltaic cells or optoelectronic devices. These chemicals show fluorescence, and are used as fluorescent probes. Additionally, they generate singlet oxygen upon illumination with light, and are studied as photosensitizers for photodynamic therapy (PDT) [1,2]. In PDT, photosensitizer upon irradiation with light of an appropriate wavelength, generates reactive oxygen species, including singlet oxygen. These have the ability to kill tumor cells or microbes. Antimicrobial PDT is gaining more attention due to its potential application in the treatment of different microbial infections, including those caused by antibiotic-resistant strains which are a growing worldwide health concern.

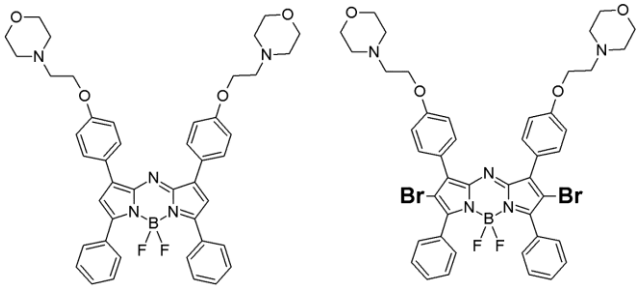

Fig 1.Modified aza-BODIPYs

New aza-BODIPY compounds, bearing morpholinylethoxy substituents were synthesized and characterized using MS and NMR techniques. Additionally, X-ray studies were conducted. Introducing bromine atoms into the molecule led to lower fluorescence quantum yield and higher singlet oxygen generation yield..

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PP11

Anticancer effects of alloxanthoxyletin and fatty acids esters

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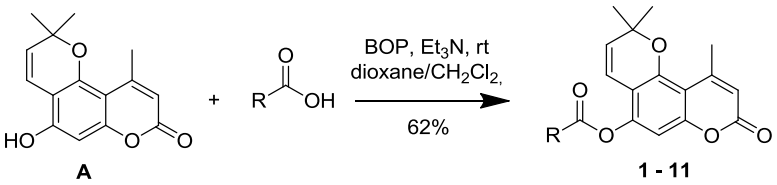
Pyranocoumarins are complex coumarin derivatives displaying cytotoxic activity [1]. These compounds are considered as unsuitable for therapeutic use due to their low solubility and high toxicity [2]. Fatty acids are natural products which display antibacterial, antifungal and antitumor activity, especially unsaturated ones [3,4]. Their chain length distribution affects permeability of the lipid membranes. They can also act as membrane penetration enhancers [5].
Considering the properties of described compounds, conjugates of alloxanthoxyletin (pyranocoumarin) and fatty acids were made, chosen on the basis of the length and unsaturation level of hydrocarbon chain to increase the lipophilicity and cytotoxicity against tumor cells lines.

The starting alloxanthoxyletin (**A**) was obtained in the reaction of 5,7-dihydroxy-4-methylcoumarin with 4,4-dimethoxy-2-methylbutan-2-ol and two-step crystallization. The corresponding ester derivatives **1-11** were obtained by the reaction of the hydroxyl group of alloxanthoxyletin with appropriate fatty acid (Scheme).



Compound	*R*	*Fatty acids*
1	C_2H_5–	propionic
2	C_5H_{11}–	caproic
3	C_7H_{15}–	caprylic
4	$C_{11}H_{23}$–	lauric
5	$C_{13}H_{27}$–	myrystic
6	$C_{15}H_{31}$–	palmitic
7	$C_{17}H_{35}$–	stearic
8	$C_{17}H_{33}$–	oleic
9	$C_{17}H_{29}$–	α-linolenic
10	$C_{17}H_{31}$–	conjugated linoleic (CLA)
11	$C_{21}H_{31}$–	docosahexaenoic (DHA)

The results of this study clearly indicate that human melanoma cells (HTB-140) and human lung cells (A549) were highly sensitive to alloxanthoxyletin derivatives exposure compared to human normal keratinocytes (HaCaT). Compounds **8**, **9**, **10** and **11** (unsaturated fatty acid derivatives) were more cytotoxic than saturated derivatives **1-7**, with compound **11** being the most effective. Both, the cytotoxicity and the migration tests showed a concentration-dependent inhibition of cell growth, although with a different degree of efficacy corresponding to IC_{50} values. Tested compounds induced apoptosis in cancer and normal cells, however, derivatives **8, 9, 10** and **11** were found to be much more potent inducers of early apoptosis in HTB-140 cells than in A549 and HaCaT cells. Further studies are needed to gain more insight into the mechanism of action of tested derivatives.

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PP12

Synthesis of new 1,3-oxazole derivatives with potential immunomodulatory activity

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The functionalization of the 1,3-oxazole ring at the 2-, 4- and 5- positions is convenient approaches to obtain potentially bioactive compounds. The 2-substituted 5-amino-1,3-oxazole-4-carbonitriles induce various biological responses, including anti-cholinesterase activity [1] and inhibition of monoamine oxidase (MAO) [2]. Furthermore, these compounds are used as intermediates in the preparation of new heterocyclic systems, most notably annulated 1,3-oxazoles. Oxazolo[5,4-d]pyrimidines display various biological activities such as inhibition of receptor tyrosine kinases (RTK) and adenosine receptor antagonism [3]. The 5-amino-4-cyano-1,3-oxazole provides also a drug-like template for synthesis of a small-molecule libraries [4].
The new 2-substituted 5-amino-4-cyano-1,3-oxazoles **1** was previously obtained from commercially available aminomalononitrile *p*-toluenesulfonate (AMNT) and corresponding acid chloride in 1-methyl-2-pyrrolidinone (NMP). The present work was aimed to develop an efficient synthesis method of new oxazolo[5,4-d]pyrimidines **2** from compounds **1** (Fig. 1). For newly synthesized derivatives **2**, spectroscopic data has been determined and biological properties are examined.

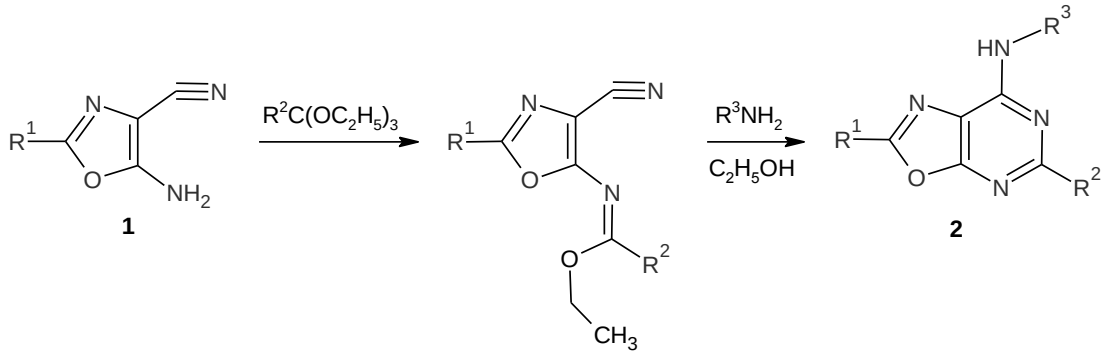

Fig. 1. Scheme of synthesis of new oxazolo[5,4-d]pyrimidines.

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PP13

New hexyl *o*-fluoroarylpiperazines derivatives as 5-HT$_{1A}$ receptor ligands – synthesis and structure-activity relationship

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According to WHO (World Health Organization) reports, after 2015, the number of people suffering from depression exceeded 300 million. Depression thus becomes a significant problem for both physicians and researchers seeking new, better-functioning and safer antidepressants. [1][2] An important point of antidepressant uptake are 5-HT$_{1A}$ receptors, while the more interesting and more frequently studied group of ligands of these receptors are long-chain arylpiperazines (LCAPs). [3]
Inspirations for the presented research were both LCAPs ligands known in the literature and our previous research of the *in vitro* activity of completely new ligands derived from *N*-hexylhaloarylpiperazine. [4][5] We decided to carry out research to explain the effect of fluoride substitution at the *ortho* position in the aromatic ring in the arylpiperazine group.
N-hexyl-(2-fluorophenyl)-piperazines ligands have been synthesized, which in their terminal part contain a phthalimide, a benzamide and a sulfonamide moiety. These ligands were obtained on the basis of a new method of synthesis in the field of microwave radiation, which is part of the "Green Chemistry" trend. All ligands obtained were tested *in vitro* for affinity for 5-HT$_{1A}$ serotonin receptors.

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PP14

Chitosan and phthalocyanine composites as potential PDT materials

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Photodynamic therapy (PDT) is a orm of phototherapy applied in anticancer treatment. It involves light interacting on the photosensitizing substance and generating the reactive forms of oxygen. Porphyrins belon to a group of widely used PDT photosensitizers. The aim of the current project is the designe of new photosensible materials for PDT aplications.

As part of the research photosensitizers were introduced into the biopolymer solution and subjected to irradiation. All analysed systems were characterized by infrared spectroscopy (ATR-IR), atomic force microscopy (AFM), scanning and transmission electron microscopy (SEM, TEM). The thermal stability of the obtained compounds and their polar nature were also determined using the goniometric method. The amount of singlet oxygen produced was determined in the next step, which is crucial for their potential application in photodynamic therapy. The results obtained for synthesized materials were compared with the results obtained for commercially available photosensitizers. The manufactured chitosan-porphyrin films are promising for DPT purpose.

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PP15

In silico investigation of full agonist and partial agonist-induced signal transmission in mu opioid receptor

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G protein-coupled receptors (GPCRs) are a broad and diverse family of receptor proteins. Despite the variety of perceived stimuli, they all share the same scaffold of seven transmembrane helices. Such conservation of the fold, together with a number of very conserved sequence motifs would suggest important role of the complete scaffold in signalling. However, there are known examples of six-transmembrane variants of GPCRs, deprived of the first helix (1TM). Therefore, the role of 1TM becomes ambiguous.

A number of studies on probe dependence and signalling bias phenomena indicate, that very subtle change in structure of the ligand results in dramatic changes in signal processing. Subtle changes in ligand structure can also increase or decrease its efficacy. To get deeper insight in the last problem, we employed molecular dynamics simulations. We investigated behaviour of the human mu opioid receptor in presence of different classes of ligands – full agonist, partial agonists and an antagonist. Structure of the receptor was co-modelled with G protein and immersed in raft-like membrane to ensure native conditions. Subsequently, Gromacs tools were used to analyse relative motions of transmembrane helices. Our results suggest, that behaviour of 1TM is connected to efficacy of the ligand.

PP16

Benzimidazole derivatives – structure and activity

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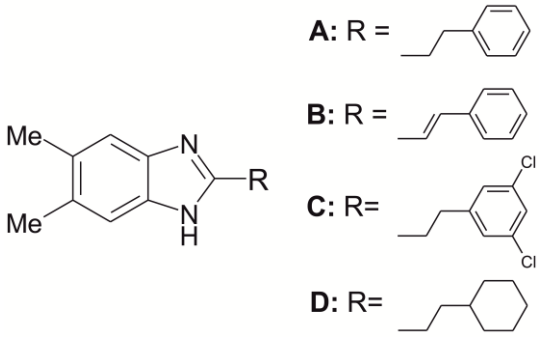
Many benzimidazole derivatives show promising anitbacterial activity. Five crystalline structures of the four derivatives were determined (Figure) by X-ray diffraction of single crystals. Compound **B** was obtained in two forms: as a neutral molecule and a protonated form (with acid oxalate anion as a counterion).



Microbiological studies revealed, that only **B** showed high biological activity against Gram (+) bacteria, and moderate activity against three strains of *Candida*. Flat shape of the molecule **B** (the result of presence of a double bond in the linker) probably affects the activity of this benzimidazole derivative. MIC values of **B** are shown in Table.

	Staphylococcus aureus ATCC25923	*Bacillus subtilis* ATCC 6633	*Staphylococcus aureus* ATCC 6538
MIC [µg/ml]	62.5	15.6	125
	Micrococcus luteus ATCC 10240	*Staphylococcus aureus* ATCC 43300 (muzealny)	*Bacillus cereus* ATCC 10876
MIC [µg/ml]	7.8	125	62.5
	Streptococcus pneumoniae ATCC 49619	*Streptococcus pyogenes* ATCC 19615	*Streptococcus mutans* ATCC 25175
MIC [µg/ml]	31.25	62.5	31.25
	Candida parapsilosis ATCC 22019	*Candida albicans* ATCC 2091	*Candida albicans* ATCC 10231
MIC [µg/ml]	500	500	500

Posters P1 – P142

P1

The search for new broad-spectrum anticonvulsants in a group of hybrid compounds derived from *N*-benzyl-2-(2,5-dioxopyrrolidin-1-yl)-2-phenylacetamide

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In recently years, the molecular hybridization has become the important method in development of new drugs for the treatment of multifactor illnesses, such as e.g. Alzheimer's disease, cancer or epilepsy. Hybrid molecules are defined as chemical entities with two or more structural domains having different biological functions.[1] This strategy allows to get broad activity in preclinical studies and giving hope for a comprehensive and effective therapy for a particular disease. It should be emphasized that in the case of the epilepsy, in nearly 30% of patients pharmacotherapy does not produce expected improvement.[2] Therefore, linking of different molecular mechanisms maybe especially beneficial in the treatment of this disease by providing a broad spectrum of activity in different types of epilepsy and efficacy in drug-resistant epilepsy.

Bearing in mind the assumptions of multi-target strategy and with the aim of obtaining new highly effective and broad-spectrum anticonvulsants, we have developed integrated hybrid molecules derived from the pyrrolidine-2,5-dione ring.[3,4] These compounds were designed by applying the fragment-based approach, thus they overlap on the common structural framework the chemical fragments of three chemically and pharmacologically diversified ADEs such as ethosuximide, levetiracetam and lacosamide. As a result, the hybridization process yielded substances with potent and broad-spectrum anticonvulsant activity that joined pharmacological properties of all AEDs creating hybrid structures.

Continuing the systematic SAR discussion, in the current studies we have obtained the series of new hybrid compounds derived from *N*-benzyl-2-(2,5-dioxopyrrolidin-1-yl)-2-phenylacetamide. These hybrids demonstrated wide spectrum of activity in the preclinical studies as they were effective in the most widely employed animal seizure models, namely, the maximal electroshock (MES) test, the pentylenetetrazole-induced seizure model (*sc*PTZ), and the psychomotor 6 Hz (32 mA) seizure model in mice (*i.p)*.

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Acknowledgments: The studies were supported by the Polish National Science Centre grant 2015/18/E/NZ7/00509.

P2

Selected integrin receptors involved in the migration of human glioblastoma cell lines LN229 and LN18

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Objectives: Glioblastoma multiforme (GBM-WHO grade IV),is the most aggressive primary brain tumor in adults [1]. Gliomas are composed of tumor cells interacting with the components of the tumor microenvironment - extracellular matrix (ECM). Interactions between tumor cells and their microenvironment are critical for cell proliferation and invasion [2]. Migration and motility are important part of the behavioral repertoire of a cancer cells. Recent studies have shown that the integrins play a crucial role in this process. Integrins are the major structural receptors that maintain proper tissue organization through cell-cell and cell-extracellular matrix interaction. Moreover, integrins also participate in the transferring of cellular signals leading to modulation of cell death or survival, proliferation and migration [3]. The understanding of the mechanisms that govern cell migration is therefore critical for finding integrins antagonists with anticancer activity.

Aim of the study: The aim of this study was comparison of the expression of selected integrin subunits in two glioma cells lines with their migration.

Materials and methods: Human glioblastoma cell lines LN18 and LN229 were purchased from ACC (Manassas, VA, USA). Integrins were detected by Immunocytofluorescence and Western Blot with monoclonal antibodies (Santa Cruz Biotechnology). Ability to migration was assayed by „wound healing" test.

Results: The presence of α1, α2 and α5 integrin subunits were revealed in both cell lines, however their expression was higher in LN18 line. In contrast, integrin α9 was expressed only in LN229 cell line. Furthermore, cells of LN229 line in "wound healing" test showed faster migration than cells of LN18 line.

Conclusions: There are significant differences between the expression of α1β1, α2β1, α5β1 and α9β1 integrins in studied glioma cell lines that may be related to the difference in their migration.

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P3

Insights into the structure of γ-aminobutyric acid transporters

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Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the nervous system [1]. It is disposed from the synaptic cleft mainly through the operation of GABA transporters (GAT) which are divided into four types: GAT-1, BGT-1, GAT-2 and GAT-3 [2]. All four proteins belong to one superfamily SLC6 of sodium dependent membrane transporters. Transport of γ-aminobutyric acid is coupled with the transport of Na^+/Cl^- ions, which is a driving force for substrate translocation against chemical gradient. The various types of GAT occur in the different localizations [2]. Dysfunction of GABA-ergic system can lead to many diseases, such as anxiety disorders, epilepsy, insomnia, motion impairment or pain states. Ability to potentiate the GABA effect by inhibiting the reuptake is an attractive therapeutic target. The first drug from this group introduced on the market and so far only one is a selective inhibitor of GAT-1 – tiagabine which is used in the treatment of epilepsy.

The three-dimensional structure of GABA transporters has not been fully known. Only some information was derived from homology modeling studies. Up till now three types of SLC6 membrane transporters *i.e.* leucine, dopamine and serotonin transporters were crystalized and published [3-5]. Therefore, we decided to build new homology models of four types of GAT (GAT-1, BGT-1, GAT-2, GAT-3) based on all templates to fully characterize their structure.

GABA transporters consist of 12 α-helical transmembrane domains. Each domain contains about 20 hydrophobic amino acids. Between domain 3 and 4 there is a large extracellular loop. These transporters have two different binding sites (S1 and S2). The central binding site (S1) is the inner ring, formed by domains TM1, TM3, TM6 and TM8. The surface of S1 pocket is lined by both polar and hydrophobic amino acid residues. It binds substrate and two sodium ions. Close to one sodium ion, Cl^- ion is accommodated. The S1 site is also responsible for binding of competitive inhibitors. The S2 site is located at the bottom of the extracellular vestibule, separated from the S1 site by the extracellular gate. It binds substrate first as well as certain inhibitors also bind in this region. The obtained models enable to understand the reasons of the selectivity of the various ligands and may be applied in the design of novel inhibitors of GABA reuptake.

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P4

Research on the synthesis and properties of thiazole derivatives of dicyclopropyl ketone

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The incidence of fungal infections in hospitalized, immunosuppressed or HIV-infected patients increased significantly in the past two decades [1]. This is to a large extent caused by the widespread use of broad-spectrum antibiotics, immunosuppressive agents, anticancer, and anti-AIDS drugs, which leads to the multi-drug resistant microorganisms [2]. The best known examples of such organisms are methicillin-resistant *Staphylococcus aureus* (MRSA) [3] and vancomycin-resistant enterococci (VRE) [4]. However, majority of these infections is caused by *Candida* spp., with over 50% due to *Candida albicans*, which occurs naturally in the human body [5]. A possible solution to the observed drug-resistance of microorganisms is the responsible use of already existing drugs, and the search for innovative drugs possessing different mechanism of action.

Recently, we have obtained a number of thiazole derivatives containing a cyclopropane fragment. Our results indicated that newly synthesized compounds showed very high antifungal activity towards most reference and clinical strains of *Candida* spp. with MIC = 0.015–7.81 µg/ml [6]. Their antimicrobial effect was similar to and even stronger than nystatin, which is a popular antimycotic drug.

Based on antimicrobial profile of the published compounds it has been assumed that structural modifications through incorporation of two cyclopropyl groups could possibly increase the antifungal activity.

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P5

In silico investigation of full agonist and partial agonist-induced signal transmission in mu opioid receptor

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G protein-coupled receptors (GPCRs) are a broad and diverse family of receptor proteins. Despite the variety of perceived stimuli, they all share the same scaffold of seven transmembrane helices. Such conservation of the fold, together with a number of very conserved sequence motifs would suggest important role of the complete scaffold in signalling. However, there are known examples of six-transmembrane variants of GPCRs, deprived of the first helix (1TM). Therefore, the role of 1TM becomes ambiguous.

A number of studies on probe dependence and signalling bias phenomena indicate, that very subtle change in structure of the ligand results in dramatic changes in signal processing. Subtle changes in ligand structure can also increase or decrease its efficacy. To get deeper insight in the last problem, we employed molecular dynamics simulations. We investigated behaviour of the human mu opioid receptor in presence of different classes of ligands – full agonist, partial agonists and an antagonist. Structure of the receptor was co-modelled with G protein and immersed in raft-like membrane to ensure native conditions. Subsequently, Gromacs tools were used to analyse relative motions of transmembrane helices. Our results suggest, that behaviour of 1TM is connected to efficacy of the ligand.

P6

New thiazolo[4,5-d]pyrimidine derivatives - synthesis and antimicrobial activity

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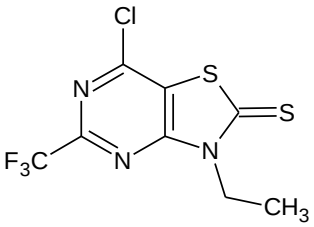
Newly obtained 3-(alkyl/aryl)-5-trifluoromethylthiazolo[4,5-*d*]pyrimidines, with different moieties in pos. 7 of the scaffold, have recently undergone microbiological tests. Activity against three pathogens *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa* was tested. The screened compounds showed bactericidal activity against *Staphylococcus aureus* mostly. It was checked what influence on the antimicrobial effect has a presence of electronegative chlorine atom in position 7. The strongest antibacterial among tested derivatives effect had compounds **1** and **2** (MIC=0,078 and 0,0098 mg/ml, respectively). Treatment of 7-chloro compounds with amines and hydrazine hydrate gave series of the 7-aminosubstituted derivatives. Microbiological tests of the obtained substances showed that the most sensitive to the tested compounds is also *Staphylococcus aureus*. From all of the 7-aminoderivatives inhibited the growth of this pathogen compound 3-(4-chlorophenyl)-7-[N-dibutylamino]-5-trifluoromethyl-thiazolo[4,5-d]pyrimidin-2(3H)-tion **3** inhibited its growth already at concentration 0.078 mg / ml. *Escherichia coli* and *Pseudomonas aeruginosa* are slightly sensitive to the tested 7-aminosubstituted derivatives of 3-(alkyl/aryl)-5-trifluoromethylthiazolo[4,5-d]pyrimidine. The compound with the broadest spectrum of action is the 3-(4-chlorophenyl)-7-hydrazinyl-5-trifluoromethylthiazolo[4,5-d]pyrimidin-2(3H)-tion, which in various extent inhibited the growth of all tested bacteria.



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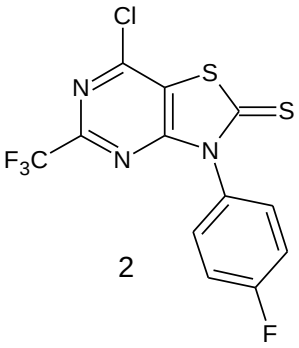

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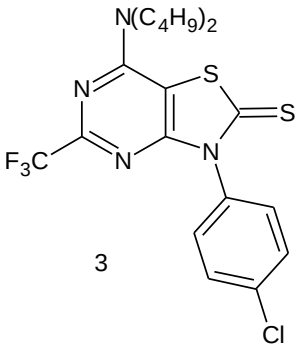

3

P7

The effect of novel diisoquinoline derivative with anti-MUC1 antibody on expression of the selected genes involved in apoptosis and autophagy in AGS cells

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Recently, we synthesized a group of novel octahydropyrazino[2,1-a:5,4-a′]diisoquinoline derivatives. We have evaluated their cytotoxic activity and antiproliferative potency in MCF-7 and MDA-MB-231 breast cancer cell lines. We observed that all compounds induced apoptosis. We demonstrated higher activity of caspases 3, 8, 9 and 10, which confirmed that the induction of apoptosis is associated with external and internal cell death pathway [1].

In the present study, we checked whether apoptosis and autophagy could be involved in the effect of cytotoxicity of novel diisoquinoline derivative (OM-86II) with anti-MUC1 antibody in human gastric cancer cells.
To investigate the mechanism involved in the autophagy-dependent cytotoxicity of tested compounds in AGS cells, we checked the mRNA levels of ATG3 after 48-hour of incubation. The relative expression of mRNA BCL2L11 and TNFRSF10A (DR4) following treatment with the analyzed compounds was also reported.

We found that the relative expression level of ATG3, TNFRSF10A and BCL2L11 genes remarkably increased after 48-hour of incubation with combination of anti-MUC1 antibody with OM-86II.

Our studies confirmed that our tested compounds could affect the expression of apoptotic and autophagy-related genes. We proved that the stimulation of apoptosis and authophagy could be potential strategies for the treatment of gastric cancer.

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Acknowledgements: The study was supported by National Science Centre (Grant DEC-2017/01/X/NZ7/01315).

P8

Effects of treatment with novel series diisoquinoline derivatives on expression of pivotal proteins involved in apoptosis and cell signaling in AGS gastric cancer cells

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Gastric cancer (GC) is a multifactorial disease and still rates as the second most common cause of cancer related deaths in the world. Recently, our research team has synthesized a group of novel octahydropyrazino[2,1-a:5,4-a']diisoquinoline and confirmed their anticancer potential in breast cancer cells. In this study, the most promising agents were selected and their activity in AGS gastric cancer cells was checked. Their anticancer potential was compared with etoposide, which is commonly known chemotherapeutic agent in gastric cancer treatment. The caspases are pivotal players in the best documented mechanism of cancer cell death. Initiator caspases activate executioner caspases that lead to demolishing of key structural proteins and activate other enzymes. The novel diisoquinoline derivatives led to higher expression of caspase-9 in gastric cancer cells. Caspase-3 is one of the executioner caspases and its expression was also increased in analyzed cancer cells after 24 hour of incubation with the tested compounds. The study confirmed that the compound **2** was the most cytotoxic and the strongest activator of caspase-3. P53 plays a key role as a regulator of the programmed cell death. It can modulate pivotal control points in death receptors signaling pathway and mitochondrial apoptotic pathway. It can directly activate the transcription of genes responsible for promotion of apoptosis. The expression of p53 protein was increased in dose dependent manner after treatment with etoposide and the novel diisoquinoline derivatives compared to control. Finally, the effect of different concentrations of the tested compounds and etoposide on expression of AKT and ERK1/2 was analyzed in human gastric cancer cells. A large number of studies has suggested that one of the major functions of AKT/PKB is to promote growth factor-mediated cell survival and to block apoptosis. Cells exposed to various concentrations of the tested compounds decreased the expression of AKT in all cases. The effect was enhanced with the increase of the doses from the lowest to the highest. Our studies also demonstrated that the novel compounds led to accumulation of cells at G2/M phase of the cell cycle and inhibition of topoisomerase II. Their mechanism of action is similar to etoposide, which is a widely used drug for chemotherapy. Our results suggest that novel diisoquinoline derivatives might be promising agents in gastric cancer treatment.

P9

Zinc(II) azadipyrromethene complexes as potential photosensitizers – synthesis and physicochemical properties

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Azadipyrromethenes (ADPMs) are synthetic molecules with strong absorption in the visible light and near-IR region. Usually they are subjected to complexation with boron trifluoride, which results in formation aza-BODIPYs. Aza-BODIPYs are studied as photosensitizers in photodynamic therapy, fluorescent probes or sensors. ADPMs might be utilized as chelating ligands for metal ions [1].

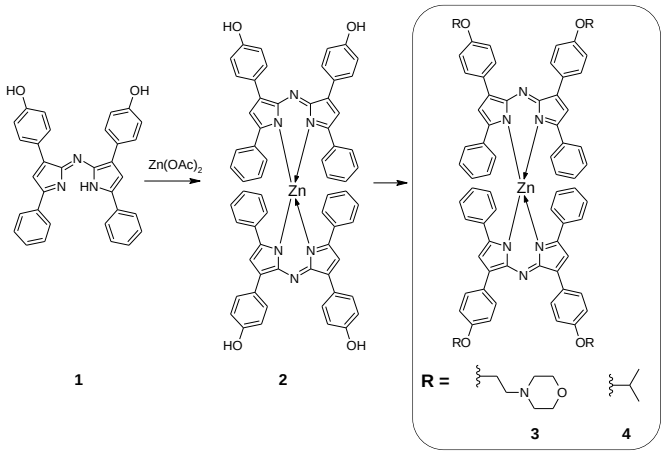

Fig. 1. Zinc(II) ADPM complexes synthesis

Zinc(II) acetate was reacted with ADPM **1** (Fig. 1), and obtained complex (**2**) was alkylated with 4-(2-chloroethyl)morpholine hydrochloride and isopropyl bromide. Resulting compounds **3** and **4** were characterized using NMR and MS Quantum yields of fluorescence and singlet oxygen generation were measured. Additionally, cyclic voltammetry measurements were conducted.

This work was supported by the Polish National Science Centre under grant no. 2015/19/D/NZ7/00401.

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P10

Short cyclopeptides

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In the last few years, short cyclic peptides have attracted an increasing interest due to their unique properties, combining the advantages of proteins with small molecules, or advances in chemistry to produce stable cyclic peptides [1-2]. They have broad-ranging significant biological activities and are components of several biomaterials. Cyclization improves bioavailability, metabolic stability, membrane permeability and reduces the conformational freedom as compared to linear peptides. The latter is often undesirable for biological applications. Cyclic tetrapeptides are sufficiently small to be considered as drugs. Several naturally occurring cyclic peptides like chlamydocin, trapoxin B or HC toxin are useful drugs. Moreover, they can be used as stereoselective hosts in supramolecular applications as well [3-4]. However, the lack of reliable information on supramolecular characteristics and the synthetic difficulties of small cyclic peptides makes their rational "*synthesis by design*" strategy a real challenge.

Medical relevance of short peptides makes them interesting targets for XRD studies [5]. Herein we report synthetic routes and a holistic landscape of supramolecular structure of model compound (Fig. 1), including comparative analysis of the conformation and intermolecular interactions with respect to derivatives as deposited in the Cambridge Structural Database (ver. 5.39, last update May 2018), using either experimental (SC-XRD and NMR, including 2-D NMR techniques) or theoretical studies (DFT, Hirshfeld Surface analysis, Gavezzotti's PIXEL methodology *vs.* CrystalExplorer energy frameworks). This biologically active compound crystallizes in the triclinic system, space group *P1*, with unit cell parameters a = 5.6034(2), b = 9.9007(3), c = 12.5815(4) Å, α = 67.2640(10), β = 87.2840(10), γ = 77.831(2) °, V = 628.839 Å^3, R = 0.0295. Its crystal structure with special emphasis put conformational flexibility and medical properties will be discussed in detail.

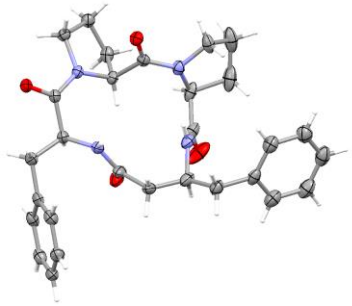

Fig. 1. X-ray structure of cyclo(β^3HoPhe-Phe-Pro-Pro)

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P11

Development of highly active acidic mammalian chitinase (AMCase) inhibitors of zwitterionic character

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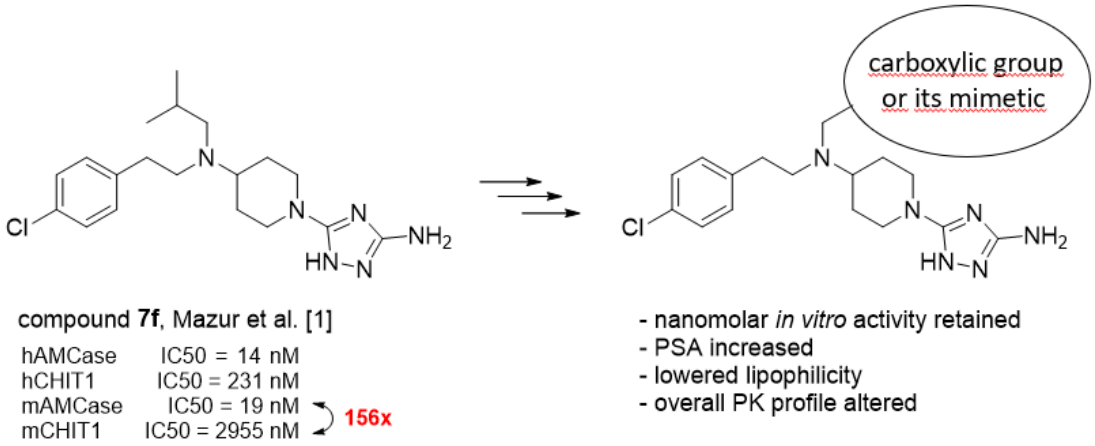
Acidic mammalian chitinase (AMCase) is one of two human secreted enzymes (chitotriosidase 1, CHIT1, is another one) capable of cleaving chitin and chitin-like substrates. AMCase is induced during Th2 inflammation through an IL-13 dependent mechanism. Chitinases are believed to play an important role in the innate immunity against parasites and other infectious agents. Earlier studies suggested that, when produced in dysregulated fashion, chitinases also play an important role in the pathogenesis of allergy and/or asthma.

We recently reported [1] that the potent and selective AMCase inhibitor, compound **7f**, showed significant anti-inflammatory efficacy in mouse model of the acute HDM-induced allergic airway inflammation.
To get further insight into pharmacological properties of AMCase inhibitors we synthesized a series of compounds in which the basicity of the 4-aminopiperidine group has been counter-balanced by introduction of the acidic fragment (carboxylic group and its mimetics of comparable pKa – tetrazole ring and N-acylsulfonamide group). Such modifications impart high polarity in the final molecule, resulting in reduced lipophilicity of the compound, which, in turn, influences its overall pharmacokinetic profile.



The *in vitro* inhibitory activity against both human chitinases along with physicochemical properties and pharmacokinetic profiles of the selected compounds will be presented.

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P12

Candicidin D & Iso-Candicidin D in sterol-containing lipid bilayer environment – a molecular modelling study

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Polyene macrolides are leading and most prospective antifungal agents used for the treatment of systemic and topical fungal infections. Depending on the size of macrolactone ring and the number of double bonds constituting the chromophore they are divided into trienes, tetraenes, pentaenes, hexaenes, heptaenes and octaenes. In the class of heptaene macrolides there is a subgroup of aromatic heptaene macrolides (AHM)[1], which displayed tests over one order of magnitude *in vitro* higher antifungal activity, in comparison to Amphotericin B (AmB)[2,3]. Members of the AHM group are characterized by: 1) a presence of an *p*-aminoacetophenone moiety attached to an aliphatic side chain and 2) different, in comparison to non-aromatic heptaenes (AmB), geometry of the chromophore (*cis-trans* for AHM vs. *all-trans* for non-AHM). The most widely known representative of AHM is Candicidin D (CndD).

According to the results of the recent studies on AHM, it has been unambiguously proven that it is possible to obtain a stable isomer of CndD with photochemically transformed polyenic region of macrolactone ring, iso-Candicidin D (iso-CndD). The resulting *all-trans* isomer exhibits geometry of the chromophore identical to the one of AmB[4]. Considering that the iso-CndD is more structurally similar to the AmB, yet still contains an aromatic sidechain which surely contributes into its higher antifungal activity, performing an MD-driven comparison of CndD and iso-CndD interactions with mammalian and fungal sterols within the lipid bilayer environment seemed to be an exciting prospect.

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P13

Arylsulfone analogs of 3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indoles as designed multiple ligands of improved bioavailability targeting behavioral and psychological symptoms of dementia (BPSD)

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Dementia refers to cognitive issues such as memory loss and thinking inability of variable pathophysiology, the most common being Alzheimer's disease. Regardless of origin, in up to 90% of patients, cognitive decline is complicated by behavioral and psychological symptoms of dementia (BPSD), such as aggression, depression and psychosis. The most bothersome aspects are addressed by antidepressant and antipsychotic drugs, often administered off-label. Yet it's been proven that polypharmacy in elderly patients may promote serious interactions. Furthermore, presently accessible antipsychotics have modest efficacy in the treatment of aggression and psychosis associated with dementia but increase risk of cerebrovascular adverse events and cognitive decline. Consequently, there is still a need for research on well-tolerated and effective therapy of BPSD [1].

In the previous studies, we designed derivatives of 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole, which proved therapeutic-like activity and benign safety profile [2]. Further research, presented herein, focused on improving bioavailability of the molecules, while preserving their pharmacological activity. To this end, we proposed substitution of the metabolically vulnerable arylsulfonamide moiety with a more stable arylsulfone.

The most active compound 5-chloro-3-{1-[3-(4-fluorobenzenesulfonyl)propyl]-1,2,3,6-tetrahydropyridin-4-yl}-1H-indole proved to act as an effective antagonist of the D_2, 5-HT_6 and 5-HT_7 receptors. Moreover, it displayed substantial affinity for the 5-HT_{1A} receptors with partial agonist effect, as well as pronounced blocking activity of serotonin transporter (SERT). Comparing to the original arylsulfonamide, the novel compound was characterized by improved Caco-2 permeability and human liver microsomes stability. The lead molecule reversed hyperactivity induced by amphetamine, showing antipsychotic-like effect, which might be associated with anti-aggressive and antipsychotic activity in dementia patients. It was also active in classic model of antidepressant-like activity (FST). Furthermore, the novel compound didn't induce memory deficits in the step-through passive avoidance test in therapeutically relevant doses, which suggested its usefulness in the treatment of BPSD.

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[2] Bucki, A.; Marcinkowska, M. et al. *J. Med. Chem. 60 (*2017) 7483-7501.

Acknowledgements: The study was financed by the NSC grant No. DEC-2014/15/D/NZ7/01789 and Adamed Pharma S.A.

P14

Synthesis and SAR study of new halogenated analogues of SSRI

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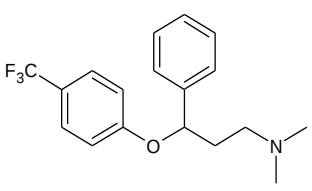
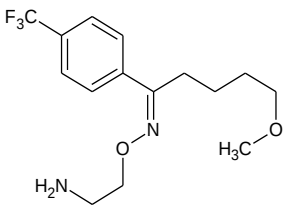
Selective serotonin reuptake inhibitors (SSRI) acting through blockade of serotonin transporter (SERT) are frequently prescribed therapeutic agents in various affective disorders. The SSRIs are therapeutically useful in the treatment of panic disorder, posttraumatic stress disorder, social anxiety disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, and anorexia.[1] Since the first blockbuster SSRI, Fluoxetine (Prozac), arrived on the scene in 1988, SSRIs have dominated the market of antidepressants, because they typically have fewer adverse effects than other types of medicaments with the same effectiveness. To this day, seven drugs in the SSRI class have been approved by FDA (fluoxetine, paroxetine, citalopram, escitalopram, sertraline, fluvoxamine and vilazodone).[2] Although generally well tolerated with numerous advantages over other antidepressants, SSRIs are not devoid of adverse effects, such as anxiety, anticholinergic effects, gastrointestinal and sexual dysfunction. In general, variations in side-effect profiles are attributed to mechanistic differences of SSRI and the difference in patient profiles, ranging from genetic polymorphisms to personality dimensions.[3] Therefore, the discovery of new SSRIs may increase the pool of available drugs and improve the currently available therapies.

As a part of our study on the SERT, novel series of halogenated fluoxetine/fluvoxamine analogues has been designed and synthesized.



Fluoxetine



Fluvoxamine

The SERT affinities for all the synthesized compounds were assessed in radioligand binding experiments. The structure-affinity relationships and the results of molecular modelling experiments are discussed.

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[2] www.fda.gov; [3] Cascade E.et al. (2009). Psychiatry (Edgmont). 6(2):16-18

Acknowledgements: The study was partly supported by the grant SONATA UMO-2016/21/D/NZ7/00620 financed by the Polish National Science Centre.

P15

Novel 5-HT$_7$R antagonists, arylsulfonamide derivatives of (aryloxy)propyl piperidines: add-on effect to the antidepressant activity of SSRI and DRI, and pro-cognitive profile

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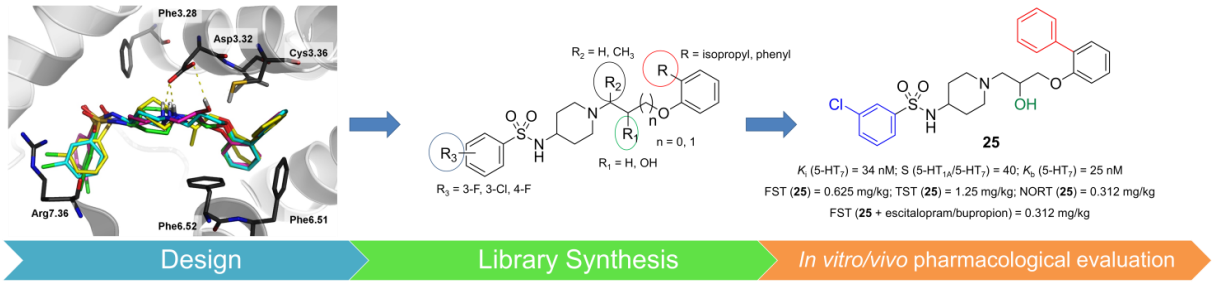
Targeting the 5-HT$_7$R has been proposed as an alternative strategy for the treatment of mood disorders including depression and may have beneficial effects in enhancing the therapeutic effects of clinically used antidepressant drugs.[1] We have recently reported on a series of arylsulfonamide derivatives of (aryloxy)alkyl alicyclic amines as potent and selective 5-HT$_7$R antagonists, with significant *in vivo* behavioral activities in rodent models of depression, anxiety and cognitive impairment.[2,3] In an attempt to extend the SAR studies toward this group of derivatives, we designed, employing machine learning-based algorithm and molecular docking studies, and synthesized a limited series of arylsulfonamide derivatives of (aryloxy)propyl piperidines. Chemical modifications included replacement of an ethyl spacer with a branched or linear propylene linker. Next, in an attempt to increase the stabilization of the ligand-receptor complex *via* the formation of a net of hydrogen bonds, a secondary hydroxyl group was introduced into the propylene spacer.



Among evaluated derivatives, the study allowed the identification of compound **25** (3-chloro-*N*-{1-[3-(1,1-biphenyl-2-yloxy)-2-hydroxypropyl]piperidin-4-yl}benzene sulfonamide, as potent 5-HT$_7$R antagonist (K_i = 34 nM, K_b=25 nM), displaying high selectivity over other serotonin and dopamine receptors, as well as over serotonin, noradrenaline and dopamine transporters. Compound **25** demonstrated significant antidepressant-like activity in the forced swim test (0.625–2.5 mg/kg, *i.p.*) and in the tail suspension test (1.25 mg/kg, *i.p.*), augmented the antidepressant effect of inactive doses of escitalopram (selective serotonin reuptake inhibitor) and bupropion (dopamine reuptake inhibitor) in the forced swim test in mice. Similarly to the reference 5-HT$_7$R antagonist SB-269970, exerted pro-cognitive properties in the novel object recognition task in cognitively unimpaired conditions in rats (0.3 mg/kg, *i.p.*). Such an extended pharmacological profile of the identified 5-HT$_7$R antagonist seems promising regarding the complexity of affective disorders and potentially improved outcomes, including mnemonic performance.

[1] Nikiforuk, A. *CNS Drugs* 29 (2015) 265-275
[2] Zajdel, P. *et al. Med. Chem. Comm.* 6 (2015) 1272-1277
[3] Canale, V. *et al. Eur. J. Med. Chem*. 108 (2016) 334-346

Acknowledgments: Project was supported by the Polish National Science Center Grant DEC-2012/05/B/N27/03076, and by funds for statutory activity of Jagiellonian University Medical College.

P16

Evaluation of the cytotoxic effect of ciprofloxacin conjugates with fatty acids on cancer cells

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Cancer is the leading cause of death and its incidence is still increasing (1). Many potential cancer treatments that could have curative implications show severe side effects because they affect not only cancer cells, but also rapidly proliferating normal cells.

Ciprofloxacin is a widely used second generation quinolone which inhibits bacterial DNA gyrase as well as mitochondrial topoisomerase II in the mammalian cells. This enzyme is essential for DNA replication and thus for cell proliferation. (2,3). Partial impairment of mtDNA synthesis in ciprofloxacin-treated cells may affect mitochondrial energy metabolism and lead to disturbance of mitochondrial respiration and ATP synthesis (4). Besides it, the effect of ciprofloxacin on tumor angiogenesis was expressed by decreased serum level of vascular endothelial growth factor (VEGF) (5).

Ciprofloxacin has a confirmed cytotoxic action on some cancerous cells but in high, not pharmacologically relevant concentrations (6,7,8). Considering features of natural fatty acids such as biocompatibility, biodegradability and increased cellular uptake by cancer cells it seems that combining ciprofloxacin with fatty acids could increase bioavailability and thus specific cytotoxicity of the drug against cancer cells (9).

Therefore the aim of this study was to evaluate the cytotoxic effect of new synthesized conjugates of ciprofloxacin with fatty acids compared to ciprofloxacin alone.

In present study we evaluated the anti-proliferative and apoptosis-inducing effects of ciprofloxacin conjugates with fatty acids on human primary (SW480) and metastatic (SW620) colon cancer, metastatic prostate cancer (PC3) and normal (HaCaT) cell lines. Saturated and unsaturated fatty acids such as docosahexaenoic, linoleic, elaidic, oleic and palmitic were used for the conjugate synthesis.
Cytotoxicity was measured by MTT and LDH assay. Apoptosis induction was evaluated using annexin assay.
All conjugates exhibited higher cytotoxic effects than ciprofloxacin alone in all studied cancerous cell lines but not in normal cells. The most effective were conjugates with DHA, oleic and elaidic acids being from 2 to 13 times more cytotoxic than free ciprofloxacin. Interestingly, conjugate with palmitic acid was less effective than conjugates with unsaturated fatty acids in all studied cancer cell lines. Our studies have shown that PC3 were the most sensitive cells to both conjugated and unconjugated ciprofloxacin. IC50 value for conjugate with oleic acid for PC3 cells was 7.71 µM, i.e. 13 times lower compared to ciprofloxacin alone (IC50 101.38 µM). All conjugates induced late apoptosis in all cancer cell lines but not in normal cells. The most potent inducers were conjugates with DHA in SW480 and PC3 cells and those with elaidic and oleic acids in PC3 cells.
It seems that the conjugation with fatty acids can improve the bioavailability and cytotoxic effect of ciprofloxacin on cancer cells at lower toxicity against normal cells.

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P17

Research on the synthesis and properties of new phenol derivatives as potential antimelanoma drugs

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Tumors are a growing health problem worldwide. They are one of the major causes of death. World Cancer Report is reporting that global cancer rates could increase to 27 million new cases in the year 2030. In the world during the year from cancer die more than 8 million people, where in Poland the number of deaths is more than 90 thousands per year. [1] Also malignant tumors are considered the second cause of death among Poles, and as many as 3600 cases of melanoma have been reported within a year. Melanoma is the most dangerous and malignant form of skin cancer, often resistant to traditional chemotherapy, with high dynamics of progress. in the last 20 years, the number of melanoma cases has almost tripled. [2] The report also reveals that cancer has emerged as a major public health problem in developing countries, matching its effect in industrialized nations. It is therefore still very much attention is paid to the search for the new chemotherapeutic agents and the new cancer therapies. The poor selectivity and very low efficiency of cytostatic drugs currently used in conventional cancer chemotherapy causes that studies are conducted to find new drugs more effective, more selective to cancer cells, and with lower side effects. Among the drugs used against cancer are alkylating agents. This is a group of cytostatics commonly used and best known. Their mechanism of action involves the formation of chemical bonds with the functional groups of molecules such as DNA or protein.

We designed and synthesized such drugs, which contain a phenolic moiety in the *para* position, substrates for tyrosinase, coupled with nitrogen mustard, a DNA alkylating agent. It's known that 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, which can generate reactive quinone metabolites in melanoma cells due to bioactivation by tyrosinase. [3]

Our research concentrated on the synthesis, the selected chemical properties, stability, antitumor activity and toxicity of new compounds, potential drugs for antimelanoma therapy.

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P18

Arylsulphonyl indazole derivatives as potential Check1-kinase inhibitors – computational investigations

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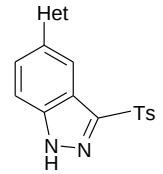
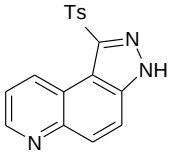
Currently, there is a growing demand for new cytostatic compounds that act selectively. Drugs with anticancer properties exert them through different modes of action. These include inhibition of translation of target proteins, such as kinases that regulate signalling pathways within cells. Kinase inhibitors have attracted significant attention for targeted therapy of many cancers. Heterocycles containing pyrazole are a part of a group of anticancer drugs on which we focused our attention. This type of anticancer compounds includes those which interact with active sites of kinases, e.g. through binding with aminoacids. Continuing our previous research aiming at elucidating the mechanism of indazole anticancer activity [1-3], we carried out *in silico* studies on the interactions of indazole derivative **1**–**6** (**Fig. 1**). In our work, we evaluated binding mode of these previously optimized (*Gabedit 2.4.7*, *Gaussian G16 A.03*) potential ligands **1**–**6** using molecular docking studies (*AutoDock Vina*, pdb entry: 2HOG). As a result we obtained several docking poses from which we chose a model (**Fig. 2**, surrounding residues below 4.0 Å) that conformed best to the following requirements: H-bonding formation, nonpolar contacts, position of the ligand in the binding pocket and finally energy estimated by *AutoDock Vina*. Basing on the obtained results, we concluded that compounds **5** and **6** (**Fig. 2**) seem to have a higher affinity to the receptor, especially due to the number of quality of contacts within the binding pocket. In order to assess the stability of 2HOG–azole complex, we ran molecular dynamics (MD) simulations using *Gromacs 2016.4* package.

Fig. 1

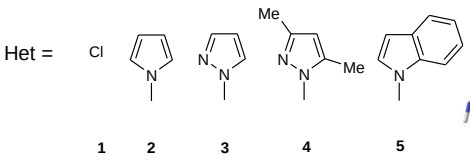


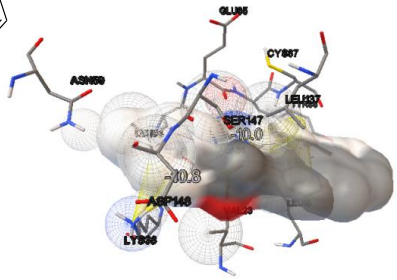
1-**5**



6

Fig. 2





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P19

Induction of apoptosis as a response of fibroblasts and keratinocytes to PAMAM dendrimers

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Polyamidoamine (PAMAM) dendrimers are strongly developed organic compounds that characterize a highly defined, symmetrical structure with unique architecture. Characteristic of these structures is the polyvalence, which is directly related to the presence of many different functional groups on their surface. It allows addition of drugs and other pharmacokinetic modulators to their surface, modifying it according to the intended purpose. These properties make these molecules attractive for medical and pharmaceutical applications.

Due the fact that dendrimers can be used among others as drug carriers for local administration, it is important to determine their toxicity on normal cells. The aim of the study was to investigate the influence of 2nd and 3rd generation PAMAM dendrimers on apoptosis of skin cells: fibroblasts and keratinocytes. To understand the underlying mechanism of apoptosis, changes in the phosphatidylserine allocation, mitochondrial membrane potential decrease, the caspases activation and changes of cell cycle have been examined. All experiments were performed by flow cytometry. The cells were incubated for 24 hours with the dendrimers in concentrations: 0.3 mg/ml, 1.5 mg/ml, 3.0 mg/ml. The changes phosphatidylserine allocation study showed that in the cells treated with the test compounds there was a marked activation of the apoptotic process. Moreover, the study of the change mitochondrial membrane potential has shown that one of the mechanisms of dendrimer activity is directed towards selective accumulation in the mitochondria, which results in an observed fall in this parameter. In addition, the determination of caspases activity has shown that the caspases cascade has been activated. It was also observed that along with the increase in the induction of apoptosis, the cell cycle in the S phase is inhibited. However, in the case of the 3rd generation dendrimer along with the increasing dose, an increase in the number of necrotic cells was observed, which may indicate the high toxicity of this nanoparticle. In all cases, the magnitude and evolution of responses depended on dendrimer generation and dose. Polyamidoamine dendrimer nanoparticles have been demonstrated to elicit a apoptosis/necrosis response in studied cell lines, the response increasing systematically with dendrimer generation and number of surface amino groups.

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P20

Synthesis and biological evaluation of 4-chlorothiocolchicine derivatives as potent tubulin-targeting anticancer agents

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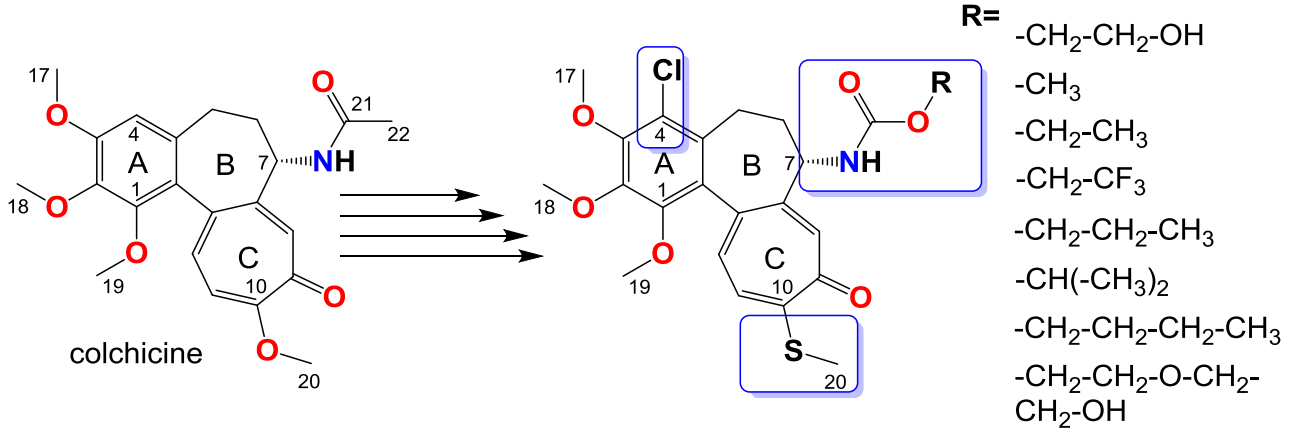
Colchicine is a biologically active tropolone alkaloid of natural origin, that is used clinically to treat acute gout attacks, pericarditis, familial Mediterranean fever and Behçet's disease. Due to its antimitotic properties, colchicine has been considered for chemotherapy applications.[1,2] However, colchicine itself could not be used as anticancer drug because of its high toxicity. Up to now, numerous structure – activity relationship studies have shown that chemical modification of colchicine in appropriate positions can improve its antitumor activity and reduce its cytotoxicity.[3-5]

We report the synthesis and spectroscopic analysis of a series of eight novel triple-modified in C-4, C-7 and C-10 positions colchicine derivatives. The antiproliferative effect of 4-chloro-7-carbamatethiocolchicines was tested *in vitro* on four human cancer cell lines (A549, MCF-7, LoVo, LoVo/DX).



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P21

Searching for the selective 5-HT$_7$ ligands within the imidazolidine-2,4-dione and imidazo[2,1-*f*]purine-2,4-dione derivatives

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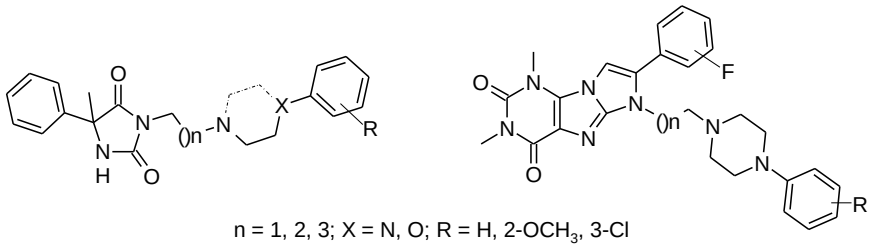
The 5-HT$_7$ receptors are the latest revealed among the other fourteen types of serotonin (5-HT) receptors. They are localized in the central nervous system (CNS) mainly in thalamus, hypothalamus, hippocampus, amygdala and cortex. The CNS distribution of 5-HT$_7$ receptors correlate well with pharmacological effects resulting from the activation or blockade of the receptors. Thus the 5-HT$_7$ antagonists display antidepressant and antipsychotic activity, whereas 5-HT$_7$ agonists are involved in antinociceptive activity. [1] Moreover, several antipsychotic drugs e.g. quetiapine, clozapine, aripiprazole, risperidone or lurasidone and antidepressant drugs e.g. imipramine, desipramine, fluoxetine and vortioxetine exhibit high affinity for 5-HT$_7$ receptors. [2]

As a continuation of our previous search for new potent and selective 5-HT$_7$ receptor ligands, herein, we selected 5-phenyl-5-methylimidazolidine-2,4-dione and 7-phenyl-1,3-dimethyl-imidazo[2,1-*f*]purine-2,4-dione with differently substituted fluorine atom in aromatic ring as core imide fragments. Further modifications comprised the variation in the length of the alkylene linker as well as diversification of the substituent in arylpiperazine ring. Additionally, in case of 5-phenyl-5-methylimidazolidine-2,4-dione derivatives, arylpiperazine fragment was replaced with aryloxyethanamine moiety.



n = 1, 2, 3; X = N, O; R = H, 2-OCH$_3$, 3-Cl

The titled compounds were obtained in two separate routes of synthesis. The imidazolidine-2,4-dione derivatives were prepared from 1-phenylethanone by the Buchere-Berg reaction followed by alkylation with the dihalogenoalkanes and coupling with (un)substituted arylpiperazines or aryloxyethanamine. Whereas imidazo[2,1-*f*]purine-2,4-dione derivatives were obtained in the cyclocondensation reaction of 7-phenacyl-8-bromotheophylline, with appropriate arylpiperazinylalkylamine. Herein, we discuss the influence of the applied structural modifications on the affinity and selectivity for serotonin 5-HT$_7$ receptors.

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Acknowledgements: This study was supported by the UJCM Scientific Research Programs (K/ZDS/006208 and K/ZDS/007207).

P22

Comparative lipophilicity study of selected cephalosporins and NSAIDs

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The lipophilicity plays a significant role in drug and compound discovery and design. Control of this physicochemical properties, within an optimal range, may improve drug quality and the likelihood of therapeutic success. For drug candidates lipophilicity values are measured to promote structure-activity relationships, absorption and tissue distribution prediction, physiologically based pharmacokinetic modeling, preformulation, formulation, and environmental evaluation. Due to the significance of lipophilicity, various methods (experimental and calculated) to assess the value have been developed. Experimental determination of log*P* is simple and accurate, but have some limitations; shake-flask procedure is reliable and accurate but time consuming, HPLC is faster, but pre-knowledge of the structures of the solutes is needed and furthermore, linear regression is required to establish log*P.* Because of existing experimental limitations, searching for a new methods became a valid fulfilment in drug discovery and design.

The presented work compares retention parameters of cephalosporins (cefalexin, cefazolin (I-), cefuroxime, cefaclor (II-), cefotaxime, ceftriaxone, cefpodoxime (III-) oraz cefepime (IV-generation) and selected NSAIDs - coxibs (cimicoxib, firocoxib, celecoxib) and oxicams (isoxicam, tenoxicam, piroxicam, meloxicam). Analysis was performed on RP-18, RP-8 , RP-2, silica gel modified with: -NH_2, -CN and –DIOL stationary phases, and with mobile phase consisted of buffer (pH 1, 2, 7, 8) and organic modifier (methanol or acetone). The pH of the buffers approximately corresponded to the pH occurring on individual sections of the gastrointestinal tract (oral cavity, stomach, duodenum).

Based on the obtained R_F values, R_M data were calculated and using linear regression method RM_0 values were determined for all tested systems. In order to explain the main trends of change, all retention parameters were analyzed by chemometric methods (PCA, HCA, PARAFAC).

The R_F values were arranged as a four-way tensor with the following dimensions: 16 compounds x 6 concentrations x 4 pH values x 12 adsorbent-solvent combinations. In the beginning, HCA was performed on the tensors unfolded along two modes: compounds and adsorbent-solvent combinations. The unscaled PCA of transposed matrix reveals that 77.3% is explained by the first PC and 12.1% by the second (89.4% total). The first PC is explained as the average R_F value: -DIOL and -NH_2 have clearly higher R_F values for all compounds, which confirms also the HCA analysis. The other adsorbents have low PC1 values but clearly differ with PC2 values. Adsorbents with higher value of PC2 (RP-2 and RP-18) are characterized with relatively higher R_F values of the left compound cluster from the dendrogram. RP-8 and -CN are the adsorbents with the opposite behavior. The similarity analysis of compounds shows clear two clusters: one formed by five cephalosporins and isoxicam and the second formed by the other oxicams and three cephalosporins. The analogous similarity analysis of chromatographic systems shows clear separation of -NH_2 and -DIOL systems from the other ones, which are similar and grouped along adsorbents inside this cluster.

P23

New hexyl *o*-fluoroarylpiperazines derivatives as 5-HT$_{1A}$ receptor ligands – synthesis and structure-activity relationship

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According to WHO (World Health Organization) reports, after 2015, the number of people suffering from depression exceeded 300 million. Depression thus becomes a significant problem for both physicians and researchers seeking new, better-functioning and safer antidepressants. [1][2] An important point of antidepressant uptake are 5-HT$_{1A}$ receptors, while the more interesting and more frequently studied group of ligands of these receptors are long-chain arylpiperazines (LCAPs). [3]
Inspirations for the presented research were both LCAPs ligands known in the literature and our previous research of the *in vitro* activity of completely new ligands derived from *N*-hexylhaloarylpiperazine. [4][5] We decided to carry out research to explain the effect of fluoride substitution at the *ortho* position in the aromatic ring in the arylpiperazine group.
N-hexyl-(2-fluorophenyl)-piperazines ligands have been synthesized, which in their terminal part contain a phthalimide, a benzamide and a sulfonamide moiety. These ligands were obtained on the basis of a new method of synthesis in the field of microwave radiation, which is part of the "Green Chemistry" trend. All ligands obtained were tested *in vitro* for affinity for 5-HT$_{1A}$ serotonin receptors.

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Acknowledgments: The study was financially supported by the National Centre for Research and Development, Project LIDER VI (No. LIDER/015/L-6/14/NCBR/2015).

P24

2-Heteroaryl-1*H*-pyrrole-3-carboxylates, interesting building-blocks for the synthesis of biologically active molecules

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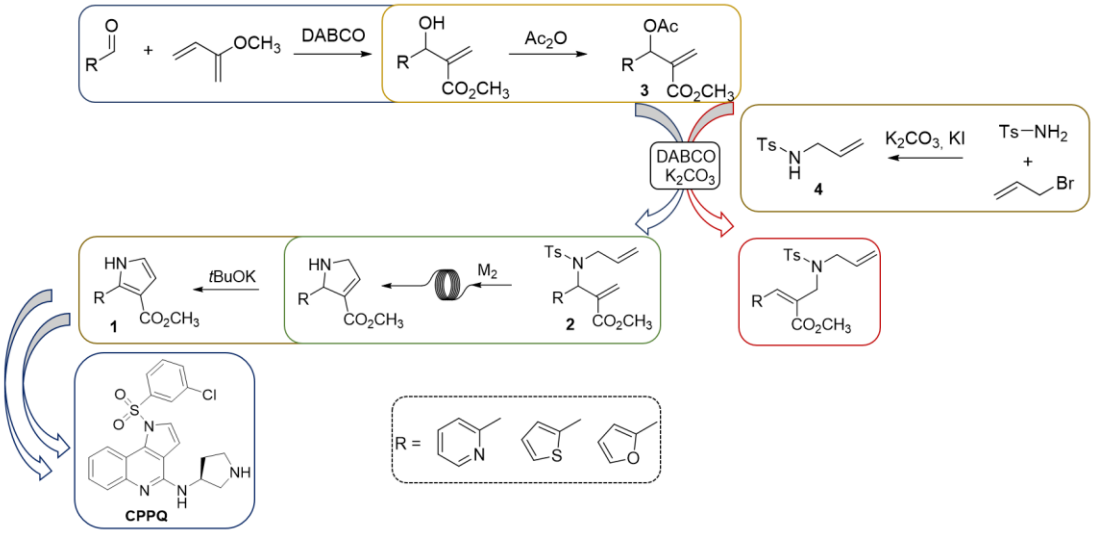
2-Aryl-1*H*-pyrrole-3-carboxylates are important building blocks for the synthesis of biologically active compounds. These scaffolds were applied for the synthesis of pyrroloquinolines, which behaved as 5-HT_6R neutral antagonists. Compounds with such pharmacological activity, i.e. CPPQ, might be used in the treatment of cognitive decline associated with Alzheimer's disease and cognitive disorders caused by genetic abnormalities.[1,2]



Previously developed synthetic route for 2-aryl-1*H*-pyrrole-3-carboxylates, involving generation of methyl 2-[{(N-allyl-4-methylphenyl)sulfonamido}arylmethyl]acrylate (**2**), in the sequence of *aza*-Baylis-Hillman and N-alkylation reactions, was unsuccessful for heteroaryl moieties.[3,4] Herein, we report an alternative synthetic pathway for generation of 2-heteroaryl-1*H*-pyrrole-3-carboxylates (**1**). The synthesis consisted in generation of diene intermediate (**2**), in a multi-step approach *via* Bayllis-Hilman reaction, acetylation and nucleophilic substitution of methyl 2-[acetoxy(heteroaryl)methyl]acrylate (**3**) with N-allyl-tosylamine (**4**), followed with its ring-closing metathesis under continuous flow conditions and deprotection/aromatization to provide final 2-heteroaryl-1*H*-pyrrole-3-carboxylates.

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P25

QSAR models for prediction of CYP1B1 inhibitory activity of *trans*-stilbene derivatives

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Cytochrome p450 family 1 (CYP1) comprises three isoforms: CYP1A1, CYP1A2, and CYP1B1. CYP1s play a pivotal role in procarcinogen activation catalyzing metabolism of 66% of potential carcinogens [1]. CYP1B1 is supposed to be involved in pathogenesis of hormone-induced cancers, being responsible for metabolism of 17-alpha-estradiol (E2) to highly mutagenic and carcinogenic 4-hydroxy-E2 [2]. CYP1A1 and CYP1B1 are targets of anticancer agents because of their overexpression in tumor cells compared to their normal counterparts. Since the 1990s, natural stilbenoids, *trans*-resveratrol (RESV), pterostilbene and piceatannol, as well as synthetic RESV analogues have been extensively studied in relation to chemoprevention [3] and in the context of their interaction with CYP1s.

In the study, relationship between structure of *trans*-stilbene derivatives and their activity as inhibitors of CYP1B1 was investigated. QSAR models were built for *trans*-stilbene derivatives with known IC_{50} values for CYP1B1 inhibition. Bioactive conformations for 3D QSAR were obtained by docking the molecules to the CYP1B1 active site by CDOCKER procedure. The choice of the best 3D QSAR model allowed to generate contour maps of van der Waals and electrostatic interactions, showing the correlations between these interactions and ligand activity. Another method used in the QSAR analysis was Bayesian categorization, which identified structural features that increase or decrease the activity of the compound (encoded in ECFP_6 fingerprints), allowing the ligands to be classified as active or inactive.

The obtained QSAR models of the structure and activity relationship can be used in virtual screening of *trans*-stilbene derivatives to find new potentially active inhibitors of CYP1B1.

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Aknowledgements: This study was supported by the grant from Poznan University of Medical Sciences, Statutory Research no. 502-01-03313427-08870.

P26

Research on the synthesis and properties of thiazole derivatives of dichlorobenzaldehyde

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Food-borne parasites (FBPs) are an increasingly common cause of human health problems [1]. An example of such a parasite is *Toxoplasma gondii* that causes *toxoplasmosis.* Many infected individuals show no symptoms, although in some cases flu symptoms may occur. The pharmacotherapy uses a combination of folic acid antagonists, for example, sulfonamides, trimethoprim or pyrimethamine, also in combination with antibiotics from the group of macrolides and lincosamides [2].

Due to the increasing prevalence of resistance to the above-mentioned drugs, it is necessary to develop new drugs characterized by lower toxicity and other mechanism of action. It is well known that thiazole derivatives exhibit anti-proliferative, anti-parasitic or antibacterial activities [3, 4]. Therefore, we have decided to look for new drugs for toxoplasmosis treatment in this group of compounds.

All new compounds developed within this project were synthesized employing a two-step synthesis. In the first step a series of thiosemicarbazones were obtained with high yield by heating ethanolic solution of dichloro-substituted benzaldehydes and thiosemicarbazide. The second step was the reaction of thiosemicarbazones with the appropriate 2-chloro-*N*-[4-(chloroacetyl)phenyl]acetamide and 3-chloro-*N*-[4-(chloroacetyl)phenyl]propanamide. As a result, twelve new compounds were obtained with high purity and yields. The next step will be to investigate the intensity of *Toxoplasma gondii* BK strain intracellular proliferation in the VERO host cells.

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P27

Synthesis and applications of *Safirinium P* and *Q* derivarives as peptide ionization enhancers

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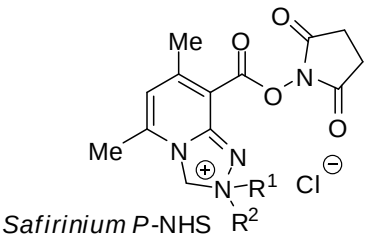
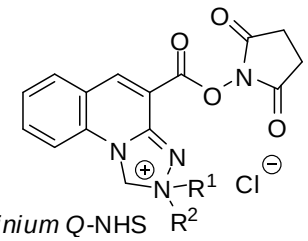
Safirinium P and *Q* are fluorescent triazolinium salts, 2,2-dialkyl derivatives of 8-carboxy-5,7-dimethyl-2,3-dihydro-[1,2,4]triazolo[4,3-*a*]pyridin-2-ium chloride and 4-carboxy-1,2-dihydro-[1,2,4]triazolo[4,3-*a*]quinolin-2-ium chloride, respectively. Due to fluorescent properties, these compounds serve as markers in various applications, e.g. spore imaging, fluorescent labeling of peptides [1,2], amino acids, and antibiotics, as well as imaging the effect of silicones dermal application. They contain also a permanent positive charge due to the presence of a quaternary nitrogen atom, which makes them promising candidates for labelling peptides and proteins in order to lower detection levels in LC-MS analysis.



Safirinium P-NHS



Safirinium Q-NHS

The *Safirinium P* and *Q* dyes in the presence of *N*-hydroxysuccinimide and carbodiimide can be readily converted into active NHS esters reactive towards nucleophilic reagents, which in reactions with primary and secondary amines give stable amide products. The aim of this work was synthesis of amine-reactive *Safirinium P* and *Q N*-hydroxysuccinimide esters substituted with a various alkyl groups within the triazolinium moiety, suitable for labeling of exemplary peptides and enhancing sensitivity of MS peptide analysis. Moreover, isotopicaly labelled analogues of *Safirinium* tags containing ^{13}C atoms in defined positions were prepared to use them in parallel studies (multiplexes). The obtained *Safirinium* derivatives were used for labeling (in solution and solid phase) of synthetic lysine containing peptides, which were further analysed with ESI-MS and ESI-MS/MS methods in scan as well as MRM mode in order to evaluate the applicability of these compounds as signal enhancing tags.

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Acknowledgements: Project supported by Wroclaw Centre of Biotechnology, programme The Leading National Research Centre (KNOW) for years 2014-2018 and Medical University of Gdańsk, research grant for Young Scientist N^{o} 01-0302/08/509.

P29

Interaction of VLO4 disintegrin with LN229, LN18 and LBC3 glioma cell lines

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Objectives: Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor in humans. It exhibits a high rate of recurrence due to the invasive nature of the tumor cells [1]. Despite advancements in the therapy which include surgery, radiotherapy, and chemotherapy, the prognosis for glioblastoma patients is still poor and far from satisfactory; the median survival of patients with GBM is approximately 15 months [2]. Because the invasiveness of glioma cells account for recurrence and tumor progression, the blockage of tumor cell migration and invasion is an interesting approach for the treatment of glioma patients. The key receptors involved in cell migration are the integrins, which are heterodimers of transmembrane α- and β-subunits that connect the extracellular matrix (ECM) to the cell cytoskeleton. Disintegrins as a group of integrin-binding proteins found in snake venoms, are expected to inhibit cell adhesion and migration processes [3]. The aim of the current study was evaluation of interaction of disintegrin VLO4 (*Vipera lebetina obtuse*), which is able to bind to α5β1 integrin, with glioma cells of three lines.

Materials and methods: Human glioblastoma cell lines LN18 and LN229 were purchased from ACC (Manassas, VA, USA). The LBC3 cell line was developed from GBM tissue after surgical resection performed in Temple University Hospital, Department of Neuroscience, Philadelphia, PA, USA [4]. Cell adhesion was evaluated using cells labeled with CellTracker™ Green CMFDA (Invitrogen Inc.) [5].

Results: We checked the direct adhesion of glioma cell lines to immobilized VLO4 first. The number of adhered cells was the highest for the LN229 cell line and the lowest for LBC3 cell line. Next, the inhibitory effect of VLO4 on the adhesion of glioma cell lines to immobilized fibronectin was evaluated. VLO4 at concentration of about 0.001 µg/ml prevented the adhesion of LBC3 cells in 20%, whereas the same percentage of inhibition for other lines (LN229 and LN18) occurred at about a 100-fold higher disintegrin concentration. At 0.01 µg/ml VLO4, there was about 100% inhibition of LBC3 cell adhesion, while the same inhibition of adhesion for other lines required more than 10-fold higher concentration of the disintegrin. VLO4 did not detach the cells adhered to immobilized collagen.

Conclusions: There are differences in glioma cells binding to disintegrin VLO4 and in inhibition of cell adhesion to fibronectin under the influence of VLO4 that are cell-specific and dependent on the disintegrin concentration.

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P30

Synthesis and potential cyclooxygenase inhibition of new pyrrolo[3,4-c]pyrrole derivatives possesing methanesulphonyl pharmacophore

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In our recent paper we reported pyrrolo[3,4-c]pyrrole derivatives possessing strong analgesic activity. The most effective of them were 1,5-5 times more potent than reference drug – ASA [1]. Because of nonsteroidal anti-inflammatory drugs demonstrate a lot of adverse effects, e.g. ulcerogenity, we have decided to continue research on analgesic derivatives of the main scaffold in order to improve safety profile. For this purpose we introduce to the core of pyrrolo[3,4-c]pyrrole pharmacophoric methanesulphone group [2] which occure in nimesulide (preference COX-2 inhibitor) or rofecoxib (selective COX-2 inhibitor). We expect that this modification can lead to obtaining structures acting as preference cyclooxygenase-2 inhibitors.

Here we report the synthesis of novel 4,6-dimethyl-2[(N-methanesulphonylpiperazine)methyl]pyrrolo [3,4-*c*]pyrrole(2*H*,5*H*)-1,3-diones with different substituents on 5 position (Fig.1).

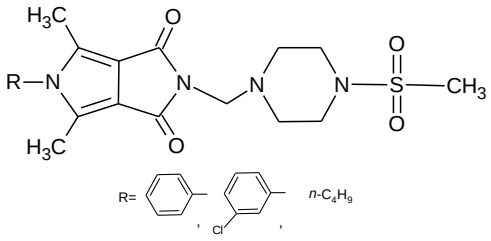

Fig. 1 New derivatives of pyrrolo[3,4-c]pyrrole

The starting materials for the synthesis were corresponding 5-substitued pyrrolodicarboxyimides which were obtained by the general procedure developed in Department of Chemistry of Drugs in Wroclaw Medical University [3]. Imides were condensed with 37% formaldehyde and 4-(methanesulphonyl)piperazine creating Mannich bases. Structures of new compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and element analysis techniques.

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P31

Novel 4-phenylpiperazin-picolinonitrile derivatives: synthesis, characterization and tuberculostatic activity

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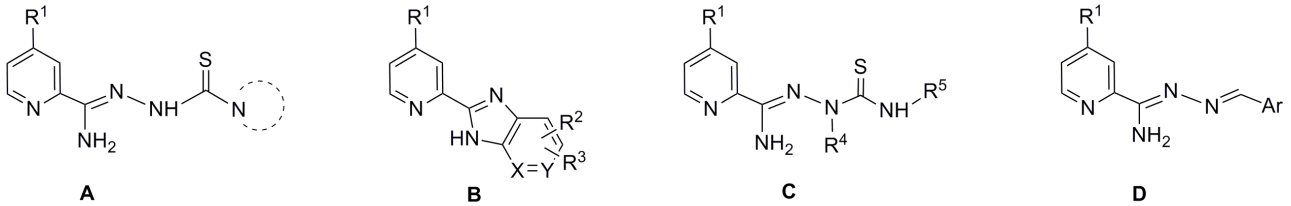
Previously we reported a tuberculostatic activity of some hydrazinecarbodithioic acid esters and amides derived from azinamidrazones or azinocarbohydrazides [1,2]. Then we described the synthesis of novel 4-phenylpicolinonitrile derivatives [3]. Here we disclose the results of our research on the synthesis of new picolinonitrile derivatives substituted with phenylpiperazine moiety at the 4 position. The starting 4-chloropicolinonitrile with phenylpiperazine gave 4-phenylpiperazinpicolinonitrile which transformed into methyl 4-(4-phenylpiperazin-1-yl)picolinimidate while treated with DBU in methanol. Methyl imidate was used in the reaction with few cycloalkylamino-1-carbothiohydrazides to thiosemicarbazides (**A**). Methyl imidate also underwent the reaction with ammonium polysulfide giving corresponding thioamide which was subjected to reaction with various 1,2-diamines to benzimidazoles (**B**).



A **B** **C** **D**

R^1: –N⟨⟩N–Ph ; ⟨⟩N: N⟨⟩O, N⟨⟩, N⟨⟩, –N⟨⟩N–Ph ; R^2: H, Me, F, Cl; R^3: H, Me; X, Y: CH, N;

R^4: H, Me ; R^5: Et, CH_2=CH-CH_2, Ph, CH_2Ph ; Ar: Ph, 4-NO_2-Ph, ⟨O⟩NO_2, ⟨S⟩NO_2

Then methyl imidate was converted into amidrazone and methylamidrazone under the reaction with hydrazine hydrate or methylhydrazine. Both products underwent the reaction with various isothiocyanates giving thiosemicarbazides (**C**). Moreover, amidrazone was condensed with various aldehydes to corresponding imines (**D**). All the newly synthesized compounds were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra. They have been also tested for tuberculostatic activity *in vitro* against *M. tuberculosis* strains: H_{37}Rv standard strain and Spec. 210 resistant strain.

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Acknowledgements: This project was funded by the National Science Centre (Cracow, Poland) on the basis of decision number DEC-2017/25/B/NZ7/00124.

P32

Development of new method for prediction of blood-brain barrier permeability using capillary electrophoresis

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The new drug development process requires both evaluation of the pharmacological activity of the newly synthesized molecule and the optimization of its pharmacokinetic profile, determined by physicochemical properties. An important element in optimizing the physicochemical properties of bioactive compound is the study of its permeability through biological membranes, also in terms of penetration across the blood-brain barrier. The brain penetration is essential for drugs acting within the central nervous system, and is also important to peripherally active compounds due to their possible brain-related adverse effects. The scientific objective of this project was to develop and optimize the *in vitro* method for studying permeability of compounds across the blood-brain barrier (BBB), based on capillary electrophoresis technique[1] and using liposomes as structural analogues of natural biological membranes.

The developed method is based on a capillary electrochromatography technique (variant of capillary electrophoresis), where the electrophoretic separation of the tested compounds is carried out in a capillary covered with a semi-permanent phospholipid layer, composed of large unilamellar liposomes.

This innovative method for estimation of the permeability of compounds across the blood-brain barrier has the potential to be a good, faster and cheaper alternative to the PAMPA-BBB assay[2] (Parallel Artificial Membrane Permeability Assay for Blood-Brain Barrier) currently used. The method will be immediately applicable to scientific research in medicinal chemistry field that is focused on obtaining of new bioactive compounds with optimal drug-like properties.

In the first stage of the analysis, after coating the capillary with a liposomal layer, separation parameters were optimized. Then, the migration times for the set of 26 selected reference drugs were examined. On this basis, a logarithm of the retention factor (log k) and the electrophoretic mobility was determined for each reference drug. The log k values were then compared with experimentally obtained blood-brain barrier permeability parameters such as log BB (logarithm of brain and blood drug concentration ratio measured in a steady state) or log P_e (penetration rate) determined using appropriate reference methods. Correlation coefficients were calculated. Correlation of log k and log BB parameters, as well as log k and log P_e values was rather weak, therefore, the method needs further optimization in order to create appropriate calibration curves for further validation and analytical purposes.

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Acknowledgments: This work was supported by the National Science Centre, Poland (grant UMO-2016/21/B/NZ7/01744).

P33

The influence of etoposide with anti-MUC1 antibody on expression of the selected genes involved in apoptosis and authophagy in human gastric cancer cells

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Mucin 1 (MUC1) belongs to the mucin family and it was identified in normal and malignant gastric epithelial cells. In normal epithelial cells it is located in the apical surface and it plays a role in protecting the gastrointestinal tract from bacterial infection. The anti-apoptotic function of MUC1 in cancer cells is associated with resistance to anticancer drugs.

The aim of the study was to check the influence of etoposide with anti-MUC1 antibody on expression of selected apoptosis and autophagy related genes such as: TNFRSF 10A (DR4), BCL2L11, ATG3, Beclin 1 in AGS human gastric cell line. Cancer cells were exposed to anti-MUC1 antibody, etoposide and anti-MUC1 with etoposide for 48 hours. mRNA expression levels of the analyzed genes were evaluated in human gastric cancer cells using quantitative polymerase chain reaction (qPCR).

The investigations revealed that anti-MUC1 antibody with etoposide increased the relative expression level of TNFRSF 10A (DR4), BCL2L11, ATG3, Beclin 1 genes.

Our studies proved that etoposide together with anti-MUC1 antibody could initiate apoptosis through the activation of extrinsic pathway associated with the increased TNFRSF 10A (DR4) expression. Furthermore, such a combination also induced autophagy by increasing the expression of mRNA ATG3 and Beclin 1 levels.

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P34

Tribenzoporphyrazines – synthesis and antimicrobial photodynamic activity evaluation

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Microbial infections constitute a severe problem for human health. Treatment of infectious diseases is often hindered by a scarce number of new drugs introduced to clinical practice as well as the increased occurrence of drug-resistant strains. Those are also the reasons for scientists to look for new methods of treating such diseases. One of such treatment approaches is photodynamic antimicrobial chemotherapy (PACT) [1]. PACT is based on a combination of three factors: photosensitizer, light, and oxygen. Energy absorbed by the photosensitizer in the form of light is transferred to triplet oxygen molecule ($^3O_2$) and subsequently transformed into singlet oxygen ($^1O_2$). Singlet oxygen is known to be a highly reactive oxygen agent, which is capable to oxidize biomolecules, cell components, and tissues. Finally, it can lead to microbial cell death. Photosensitizers currently researched for PACT are porphyrinoids, derivatives of phenothiazine, squaraines, dipyrromethene dyes, fullerenes, naturally derived products like hypericin and photoactive inorganic nanoparticles [2].

Sulfanyl porphyrazines (Pzs) functionalized with bis(benzyloxy)benzyl substituents have been already found to improve the electrochemical, as well as photochemical properties of parent Pzs [3]. Based on our studies, unsymmetrical A3B-type derivatives of Pzs, tribenzoporphyrazines, substituted in three parts with phenyl rings exhibit higher biological activity when compared to their A4-type symmetrical analogues [4]. Based on these premises new sulfanyl tribenzoPz was synthesized and characterized using mass spectrometry, NMR, and UV-Vis spectroscopy. Particular emphasis was put on singlet oxygen generation quantum yield. After that, their ability to inactivate pathogenic microbes was tested and compared to some of our previously published tribenzoporphyrazines.

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[2] Abrahamse H, Hamblin MR. *Biochem J* 2016;473:347-64
[3] Figueira F *et al. Curr Org Synth* 2014;11:110-26
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Acknownledgements: This study was supported by the National Science Centre, Poland under grant 2016/21/B/NZ9/00783.

P35

Synthesis and anticonvulsant activity of new amides derived from 3-(2-chlorophenyl)-2,5- dioxo-pyrrolidin-1-yl acetic acid

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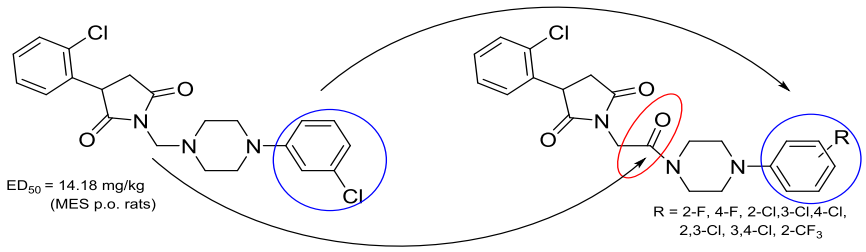
The previous studies from our laboratory have demonstrated the various anticonvulsant activity among the 3-phenylpyrrolidine-2,5-dione derivatives with electron-withdrawing substituents in the phenyl ring. In these series, the most active were N-Mannich bases with 2-chlorophenyl at position-3 of pyrrolidine-2,5-dione moiety.[4] It is well documented that important structural features crucial for anticonvulsant activity are defined by nitrogen heterocyclic system, containing at least one carbonyl group and phenyl ring or alkyl substituent attached to the heterocycle.[1-3]

Taking into consideration above mentioned facts and as a part of our efforts to design new anticonvulsant agents, in this study a new series of amides, in which 2-chlorophenyl group was introduced at position-3 of pyrrolidine-2,5-dione ring was synthesized (Figure). These compounds was designed as analogues of previously obtained N-Mannich bases with an additional amide bond between methylene group and 4-arylpiperazine fragment. The proposed modifications allow to assess the role of supplementary amide function on anticonvulsant properties in this group of compounds. In order to ensure a reliable SAR discussion variously substituted 4-arylpiperazine groups have been introduced as amine function.



The target compounds were synthesized in three-step procedure. The starting 2-(2-chloro-phenyl)succinic acid was prepared according to the method described elsewhere.[5] In the next step the cyclocondensation of above mentioned acid with an 2-amineacetic acid yielded in an intermediate compound: 3-(2-chlorophenyl)-2,5-dioxo-pyrrolidin-1-yl-acetic acid. The final compounds were obtained in the coupling reaction of 3-(2-chlorophenyl)-2,5-dioxo-pyrrolidin-1-yl-acetic acid with equimolar amounts of appropriate 4-arylpiperazines in the presence of carbonyldiimidazole reagent.
All obtained compounds have been evaluated for their anticonvulsant activity in the maximal electroshock (MES), subcutaneous pentylenetetrazole (*sc*PTZ) and 6-Hz seizure tests.

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Acknowledgements: This study was supported by the UJCM Scientific Research Programme (K/ZDS/007864).

P36

Novel 1*H*-pyrrolo[3,2-*c*]quinoline derivatives as dual 5-HT$_6$/D$_3$ receptors antagonists with procognitive properties

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Cognitive impairment, which involves memory and attention disturbances, constitutes a common feature of various central nervous system disorders such as schizophrenia and Alzheimer's disease.[1] Although various procognitive drug candidates have been investigated in clinical trials for cognitive dysfunction, most of them failed to display clinically relevant effects. Recent results of advanced preclinical and clinical studies indicate the role of serotonin 5-HT$_6$ and dopamine D$_3$ receptor antagonists, in the control of cognitive functions.

We have recently described compound CPPQ ((*S*)-1-[(3-chlorophenyl)sulfonyl]-4-(pyrrolidine-3-yl-amino)-1*H*-pyrrolo[3,2-*c*]quinoline), a neutral 5-HT$_6$R antagonist (K_i = 3 nM, K_b = 0.41 nM). In the presented study CPPQ was used as a chemical template for the development of dual 5-HT$_6$/D$_3$ receptors antagonists.

Herein, we report chemical synthesis of novel *N*-alkylated analogs of CPPQ, their biological evaluation, followed by determination of neuroprotective properties and evaluation of procognitive properties in novel object recognition test (NOR) in rats. The study allowed for the identification of compound **16**, classified as dual 5-HT$_6$/D$_3$ receptors antagonist, which displayed neuroprotective properties against astrocyte damage with doxorubicin. Additionally, compound **16** reversed phencyclidine (PCP) induced memory deficits in NOR test in rats.

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P37

Unusual interactions of triazoloacridinone C-1305 with dsDNA

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Investigation of activity of novel anticancer derivatives is an important step that may lead to development new clinical anticancer agent. To choose most promising substances researches compare activity, binding constants response on the genome level such as increase or decrease level of expression of enzymes. Yet from time to time some derivatives will be synthesis that mode of action and cell response isn't as typical as from other molecules from same family.

One of such examples is triazoloacridone C-1305 (5-dimethylaminopropylamino-8-hydroxytriazoloacridinone) [1]. Biophysical study shown that this compound present unusual high affinity to guanine triplets in DNA sequence, therefor it was proposed that molecular target for this drug could be G-quadruplexes in telomeres [2]. Other tests shown that triazoloacrodone has lower affinity to topoisomerase type II than amsacrine yet cytotoxicity is similar [3]. To mention just a few examples of untypical properties. Study of aggreagation, DNA complexation and NMR based structural study of the triazoloacridone C-1305 will be presented on the poster.

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P38

Simple and efficient synthesis of amide derivatives of tetrahydro-beta-carboline – potential cannabinoids receptor ligands

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The hydrogenated carboline structures like tetrahydrocarboline (THC) for years have attached the attention of neurochemists. The carboline skeleton is present in drugs and drugs candidates with the therapeutic potential as analgesic, antitumor, anti-inflammatory agents. More recently γ-carboline scaffold has been successfully used in designing of novel class cannabinoid agonists (EC_{50} = 5 nM, hCB1R).[1] The endogenous cannabinoid system (ECB) is neuromodulatory system consisting of two G-protein-coupled receptor subtypes (CB1R and CB2R), cannabinoid type 1 receptor (CB1R) is the most abundant and is mainly expressed in the central nervous system (CNS) where it modulates function such as memory, cognition, emotion and pain control, cannabinoid type 2 receptor (CB2R) is mainly localized in the immune system (macrophages).[2] Obtaining new ligands is advisable especially for various type of pain and neurologic disorders that are difficult to treat with available medications.

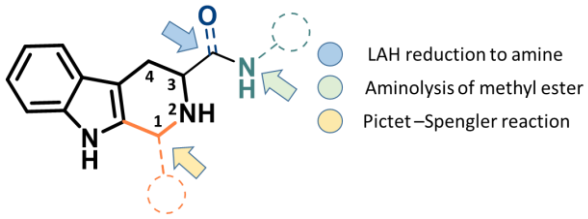

Figure 1. Overall strategies of modifying the tetrahydro-beta-carboline core.

Series of THβC analogs with aromatic and aliphatic side chains in 1 and 3 position of β-carbolines (βC) structural unit have been designed as a potential ligands for CB1R and CB2R (see Figure 1.). Based on the Pictet – Spengler reaction of four different aldehydes and methyl tryptophanate we obtained family of 1-substitued THβC-3-carboxylic acid esters. Simple aminolysis lead to desired first set of compounds with high yields. Further derivation was obtained by amide reduction displayed increased basicity. Synthesized compounds will be evaluated as CB1R and CB2R ligands using *in vitro* affinity test and computational studies.

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P39

Synthesis, X-ray crystal structures, and biological activities of novel 2-(1*H*-indol-2-yl)acrylonitrile derivatives

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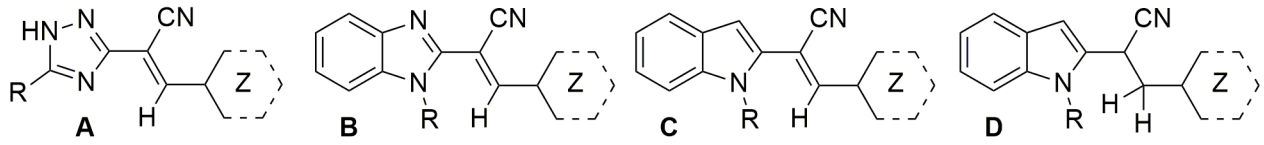
2,3-Disubstituted acrylonitriles represent an interesting class of biologically active compounds. Of special interest are the anticancer properties of acrylonitrile derivatives. Reports from our laboratories disclosed structures of heteroarylacrylonitriles of types **A** and **B** as potential caspase-9 activators possessing cytotoxic activity on human cancer cell lines. Additionally, some of them were found to be active against *Staphylococcus epidermidis* and *Staphylococcus aureus* [1,2].



R = H, alkyl, acyl; **Z** = aryl, heteroaryl

In order to explore further the structure-activity relationships for this class of compounds, we synthesized a new series of heteroarylacrylonitriles of type **C** containing an indole ring at position 2 of the acrylonitrile moiety. To investigate the importance of the acrylonitrile double bond on the cytotoxic activity, analogues of type **D** lacking this bond were also prepared.

The structures of novel compounds were confirmed by IR, NMR and MS spectroscopic data as well as single crystal X-ray analysis.

The *in vitro* antitumour properties of the compounds depicted as **C** and **D** were tested at the National Cancer Institute (USA) on a panel of 60 cell lines derived from 9 types of human cancers. The selected compound with remarkable anticancer activity (GI_{50} = 0.26-6.60 μM, TGI = 0.64-9.49 μM) was (*Z*)-3-[4-(dimethylamino)phenyl]-2-(1*H*-indol-2-yl)acrylonitrile of type **C** (**R** = H, **Z** = 4-$(CH_3)_2N$-C_6H_4).

The newly obtained compounds were also evaluated for their potential antimicrobial activities against Gram-negative and Gram-positive bacteria as well as *Candida albicans*.

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P40

Identification of hypothetical allosteric site at SIRT7

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The family of sirtuins includes 7 members (SIRT1-SIRT7) and all of them are NAD+-dependent histone deacetylases. The activity of SIRT7 is associated with cardiovascular diseases, diabetes and different types of cancer. SIRT7 is currently considered as a promising therapeutic target.

All of the family members have crystal structure apart from SIRT4 and SIRT7. Moreover, crystal structures of sirtuins include mainly the protein core, while N- and C- termini are cut. However, these termini could have an important role in sirtuins activity.

The aim of this study was to create *in-silico* model of SIRT7 with its N-terminus, which is known to affect the enzyme's catalytic activity, and to find pockets that could be targeted by structure-based virtual screening.
Methods: Three-dimensional model of SIRT7 structure was prepared using X-ray structures of SIRT1, SIRT2, SIRT3, SIRT5, SIRT6 and a resolved fragment of the N-terminus of SIRT7 as templates. All of them are available in Protein Data Bank database (PDB ID's: 4ZZH, 1J8F, 3GLS, 3RIG, 3K35 and 5IQZ, respectively). Sequence alignment was prepared with MAFFT. Spatial orientation of NAD+ and acetyllysine-containing peptide inside the SIRT7 were established by molecular docking using Surflex and FlexPepDock, respectively. The results were validated by comparison with ligand positions in X-ray structures of other sirtuins. The solvated model was then subjected to molecular dynamics (MD) simulations in GROMACS program with AMBER 03 force field, to reveal possible hidden pockets. RESP charges for the cofactor and the non-standard residue were obtained with RED Server Development, and topologies were created with ACPYPE.
Results*:* Our investigation has proven resemblance of catalytic core of SIRT7 to the rest of family members. Moreover, our investigation showed that N-terminus of SIRT7 remains in spatial proximity of the catalytic core, and therefore, it may affect its catalytic activity. We managed to find the preferred orientations of NAD+ and acetyl-lysine inside SIRT7, with all components forming a stable complex. Pocket search provided hypothetical pockets that will be targeted with virtual screening.
Conclusion*:* Our study allowed to model reliable SIRT7 *in silico* structure. It will be a useful tool in searching for its inhibitors, which can be potential drugs in cancer treatment.

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P41

Erythropoietin intensifies proapoptotic activity of LFM-13 in colon cancer cells

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Bruton's tyrosine kinase (BTK) inhibitor (LFM-A13) now widely explored as antileukemic agent, but recently applications in solid cancer have been found. The compound promotes apoptosis, has an antiproliferative effect, and increases cancer cell sensitivity to chemotherapy drugs. Colorectal cancer is one of the most frequent human malignant neoplasms. This kind of cancer often accompanied by anemia which is treated with erythropoietin supplement.

We decided to assess the impact of simultaneous use of Epo and LFM-A13 for signal transduction on colon DLD-1 and HT-29 cells. The induction of apoptosis by Epo and LFM-A-13 in cells was confirmed by phosphatidylserine externalization, loss of mitochondrial membrane potential and expression of BAX and BCL-2 in colon adenocarcinoma cells.

Simultaneous use of Epo and LFM-A13 severely inhibits cell growth and activates apoptosis. The addition of Epo to LFM-A13 intensified the antiproliferative effect of LFM-A13 alone, confirmed by loss of mitochondrial membrane potential and accumulation of apoptotic colon cancer cells with externalized PS.

These preclinical results suggest that the combination of Epo and LFM-A13, due to high proapoptotic activity, should be tested in the clinic for treatment of solid tumors, such as colon cancer.

P42

Indole-imidazole conjugates as potential nootropics and antinociceptives for the treatment of neuropathic pain

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Fluorine substitution, which had been merely perceived as a means of increasing the lipophilicity while not adding bulk, later gained a reputation of a complex personality, with effects such as increased metabolic stability due to strength of C-F bond, polar hydrophobicity, changes in acidity/basicity, changing conformation via hyperconjungation or dipole-dipole interaction, being constantly exploited. Ever since more and more subtle fluorine effects have been discussed such as the enhancement of halogen bonding via sigma hole enlargement.

A study of fluorinated 3-(1-alkyl-1*H*-imidazol-5-yl)-1*H*-indoles[1] which were designed to optimize the halogen bond formation between ligand and the receptor backbone revealed potent and highly drug-like 5-HT_7R agonists: 3-(1-alkyl-1*H*-imidazol-5-yl)-5-iodo-4-fluoro-1*H*-indoles. Compounds exhibited high selectivity over related CNS targets, high metabolic stability and low toxicity in HEK-293 and HepG2 cell cultures. A rapid absorption to the blood, high blood-brain barrier permeation and a very high peak concentration in the brain were found for compounds AGH-192 and AGH-194 after *i.p., p.o.* and *i.v.* (2.5 mg/kg) administration in mice. AGH-194 was shown to produce procogonitive effects at very low doses in NOR and ASST tests. Both 5-HT_7R agonists were shown to produce potent anti-nociceptive effect in mice model of neuropathic pain.

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P43

2-Aminoimidazole-based antagonists of a serotonin receptor, a new concept in aminergic GPCR ligand design

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Until now, the chemical space of ligands of aminergic G protein-coupled receptors (GPCR) has been expanding mainly by the employment of novel bioisosteric building blocks, resulting in a large diversity of core scaffolds, aromatic systems, linkers, hydrogen bond donors and acceptors. This is in sharp contrast to the very narrow pool of amine-like groups that have been used to replace the aminoalkyl chains of endogenous neurotransmitters and classical ligands. Interestingly, hardly any attempts have been made to employ aromatic basic groups in the design of aminergic GPCR ligands. 2-Aminoimidazole (2-AI) remains an unexplored highly basic scaffold, and it has been found to be a common molecular framework of numerous marine alkaloids[1] and synthetic antibacterial (antibiofilm) agents.[2]

Highly selective 5-HT_6 receptor antagonists of various basicities were designed by employing 2-AI and 2-aminothiazole moieties as the amine-like fragment of the ligand. Considering the multiple functionalization sites of the embedded guanidine fragment, a diverse library was constructed, and the relationships between the structure and activity, metabolic stability, and solubility were established.
The lead compound in the series 4-methyl-5-[1-(naphthalene-1-sulfonyl)-1*H*-indol-3-yl]-1*H*-imidazol-2-amine (AHN-208) was shown to reverse the cognitive impairment caused by the administration of scopolamine in rats indicating procognitive potential.

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Molecular hybridization in the development of new broad-spectrum anticonvulsants

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Hybrid molecules are compounds that contain several pharmacophores merged on one chemical scaffold. The combination of several structural domains in one chemical molecule gives the possibility of interaction with many molecular targets through the use of one substance. Therefore, hybrid molecules seem to be especially beneficial in treatment of multifactorial diseases such as Parkinson's disease, Alzheimer's disease and epilepsy but also diseases with high risk of drug resistance. The main advantages of multifunctional compounds are less risk of drug interactions, limited side effects and better compliance of the patient with the planned therapy [1, 2].

One of the newest and the most interesting hybrid anticonvulsants is padsevonil. This compound combines on common framework fragments of levetiracetam and zolpidem. Thus, padsevonil has a dualistic and innovative mechanism of action, as it binds to the SV2A protein (levetiracetam) and also acts as agonist of the $GABA_A$ receptor (zolpidem). As a result padsevonil revealed broad spectrum of activity in the animal models of epilepsy - the maximal electroshock (MES), the subcutaneous pentylenetetrazole (PTZ) and the six-Hertz (6 Hz) tests [3]. Notably, the aforementioned compound is currently in the third phase of clinical trials.

Bearing in mind the molecular hybridization strategy for the development of new antiepileptic drugs, in our recent studies we have proposed the structure of novel hybrid anticonvulsants based on the pyrrolidine-2,5-dione fragment as a core structure [4-7]. These compounds merge on one structural template the fragments of three chemically and pharmacologically diversified drugs such as the ethosuximide (pyrrolidine-2,5-dione derivative, effective in PTZ seizure model), levetiracetam (pyrrolidin-2-one derivative with butanamide moiety, effective in 6 Hz model), and lacosamide (classified as functionalized amino acid, effective in both MES and 6 Hz seizure models). *In vivo* data of hybrid pyrrolidine-2,5-diones proved to possess broad spectrum of activity across the preclinical seizure models, such as the MES, PTZ, and 6 Hz.Thus, the compounds tested could be effective in various human epilepsies including tonic-clonic seizures, absence seizures, and pharmacoresistant seizures.

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P45

Anticancer effects of alloxanthoxyletin and fatty acids esters

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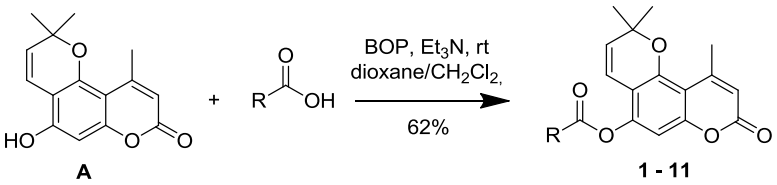
Pyranocoumarins are complex coumarin derivatives displaying cytotoxic activity [1]. These compounds are considered as unsuitable for therapeutic use due to their low solubility and high toxicity [2]. Fatty acids are natural products which display antibacterial, antifungal and antitumor activity, especially unsaturated ones [3,4]. Their chain length distribution affects permeability of the lipid membranes. They can also act as membrane penetration enhancers [5].
Considering the properties of described compounds, conjugates of alloxanthoxyletin (pyranocoumarin) and fatty acids were made, chosen on the basis of the length and unsaturation level of hydrocarbon chain to increase the lipophilicity and cytotoxicity against tumor cells lines.

The starting alloxanthoxyletin (**A**) was obtained in the reaction of 5,7-dihydroxy-4-methylcoumarin with 4,4-dimethoxy-2-methylbutan-2-ol and two-step crystallization. The corresponding ester derivatives **1-11** were obtained by the reaction of the hydroxyl group of alloxanthoxyletin with appropriate fatty acid (Scheme).



Compound	*R*	*Fatty acids*
1	C_2H_5–	propionic
2	C_5H_{11}–	caproic
3	C_7H_{15}–	caprylic
4	$C_{11}H_{23}$–	lauric
5	$C_{13}H_{27}$–	myrystic
6	$C_{15}H_{31}$–	palmitic
7	$C_{17}H_{35}$–	stearic
8	$C_{17}H_{33}$–	oleic
9	$C_{17}H_{29}$–	α-linolenic
10	$C_{17}H_{31}$–	conjugated linoleic (CLA)
11	$C_{21}H_{31}$–	docosahexaenoic (DHA)

The results of this study clearly indicate that human melanoma cells (HTB-140) and human lung cells (A549) were highly sensitive to alloxanthoxyletin derivatives exposure compared to human normal keratinocytes (HaCaT). Compounds **8**, **9**, **10** and **11** (unsaturated fatty acid derivatives) were more cytotoxic than saturated derivatives **1-7**, with compound **11** being the most effective. Both, the cytotoxicity and the migration tests showed a concentration-dependent inhibition of cell growth, although with a different degree of efficacy corresponding to IC_{50} values. Tested compounds induced apoptosis in cancer and normal cells, however, derivatives **8, 9, 10** and **11** were found to be much more potent inducers of early apoptosis in HTB-140 cells than in A549 and HaCaT cells. Further studies are needed to gain more insight into the mechanism of action of tested derivatives.

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P46

D2AAK4 as a potential multi-target antipsychotic

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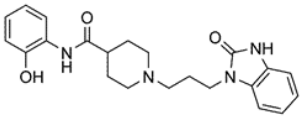
The modern approach to drug design and discovery for the treatment of complex diseases, like neurodegenerative diseases, cancer and many psychiatric disorders, involves searching for medicinal substances which fulfil criteria of several pharmacophores, instead of acting on a single molecular target. Indeed, in complex psychiatric illnesses, including schizophrenia, selective single-target drugs have been to a great extent a failure. The pharmacological profile of clozapine reflects the molecular pathogenesis of schizophrenia, which involves cross-talk of many neurotransmitter systems (especially dopaminergic, serotonergic, adrenergic and glutamatergic). The new paradigm in drug design and discovery is to search for compounds which modulate the activity of several molecular targets simultaneously. To achieve this, it is necessary to identify structural features that link important classes of drug targets, which will enable the design of drugs with the desired selectivity profiles.

We identified a novel multi-target ligand of aminergic GPCRs, D2AAK4, using structure-based virtual screening [1]. D2AAK4 possesses nanomolar or low micromolar affinity to D_1, D_2, D_3, 5-HT_{2A} and 5-HT_7 receptors, making it an ideal candidate for a multi-target drug. Here we present homology modeling, molecular docking and molecular dynamics of D2AAK4 and its molecular targets and animal studies of D2AAK4 as a potential antipsychotic. The main contact of D2AAK4 and all the receptors studied is the electrostatic interaction between the protonatable nitrogen atom of the ligand and the conserved Asp(3.32) as typical for orthosteric ligands of aminergic GPCRs. We demonstrated antipsychotic and, importantly, procognitive properties of D2AAK4 in mouse models.



D2AAK4

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P47

Benzimidazole derivatives – structure and activity

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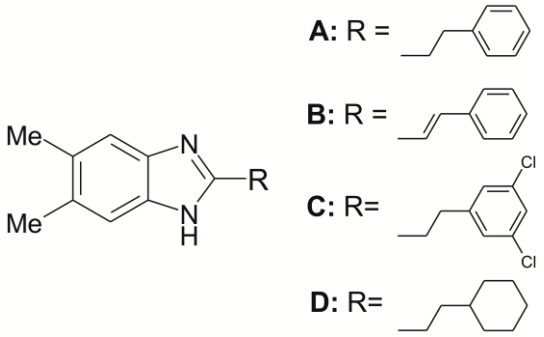
Many benzimidazole derivatives show promising anitbacterial activity. Five crystalline structures of the four derivatives were determined (Figure) by X-ray diffraction of single crystals. Compound **B** was obtained in two forms: as a neutral molecule and a protonated form (with acid oxalate anion as a counterion).



Microbiological studies revealed, that only **B** showed high biological activity against Gram (+) bacteria, and moderate activity against three strains of *Candida*. Flat shape of the molecule **B** (the result of presence of a double bond in the linker) probably affects the activity of this benzimidazole derivative. MIC values of **B** are shown in Table.

	Staphylococcus aureus ATCC25923	*Bacillus subtilis* ATCC 6633	*Staphylococcus aureus* ATCC 6538
MIC [µg/ml]	62.5	15.6	125
	Micrococcus luteus ATCC 10240	*Staphylococcus aureus* ATCC 43300 (muzealny)	*Bacillus cereus* ATCC 10876
MIC [µg/ml]	7.8	125	62.5
	Streptococcus pneumoniae ATCC 49619	*Streptococcus pyogenes* ATCC 19615	*Streptococcus mutans* ATCC 25175
MIC [µg/ml]	31.25	62.5	31.25
	Candida parapsilosis ATCC 22019	*Candida albicans* ATCC 2091	*Candida albicans* ATCC 10231
MIC [µg/ml]	500	500	500

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Novel approaches to the development of compounds with antioxidant effects

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Search for new antioxidants is a phase of new drug-like molecules creation, due to the role of oxidative stress and ROS-mediated processes. The ability to reduce the amount of ROS *in vitro* (evaluation of free radicals scavenging and estimation of LPO products level) still remains to be an important and usually the only one stage in the evaluation of the antioxidant potency of compounds. It very often is considered as beneficial additional effect to main action of compound. Such approach needs to be ammended because: *i*) many known antioxidants do not show direct antiradical activity *in vivo* and *vice versa*; *ii*) proved antioxidants exhibit dualistic role acting as antiradical and pro-oxidant agents simultaneously; *iii*) effects of the known antioxidants are related rather to their indirect action; *iv*) compounds with pro-oxidant action are out of interest. There are increasing evidences that therapeutic effects of some drugs (e.g. anticancer) are linked rather to their pro-oxidant action.

4-Thiazolidinones are known class of heterocycles with a broad spectrum of biological activities and sources for new drug candidates. Search for anticancer, anti-inflammatory, antidiabetic, and antimicrobial agents is of special interest. Moreover, creation of compounds with several types of action is considered as benefit within poly-pharmacological approach and the conception of the multi-target drugs inferring different activities of a single compound including the antioxidant one. Various 4-thiazolidinones have been screened for their antiradical actions and hit-compounds were identified, but mainly compounds possess moderate activity. Despite, the therapeutic effects of 4-thiazolidinones (anticancer, anti-fibrotic activities etc.) are linked to the ROS-depended mode of action and pro-oxidant effect. In this spirit, 5-ene-4-thiazolidinones are one of the most prominent subtype. But very often 5-ene-thiazolidinones are claiming as PAINS those are useless in medicinal chemistry, due to their Michael acceptor functionality (conjugation of 5-ene fragment to the C4 carbonyl group). This statement should not be regarded as a general knockout criterion that excludes compounds from further development. While Michael acceptor functionality should be analyzed in-deeps and explored in the useful way. Michael acceptors are: *i*) effective activators of Nrf2 through the Keap1 modification (This correspond to the thesis that antioxidant activity requires "…that the antioxidant be, or be converted to, an electrophile… and α,β-unsaturated carbonyl compounds are an active form of the antioxidant." [1]); *ii*) inductors of phase 2 enzymes and inducible phase 2 proteins; *iii*) covalent inhibitors of validated biotargets; *iv*) agents for multidrug resistance cancer treatment; *v*) modulators of H2S-related processes (possible H2S releasing agents); *vi*) Red/Ox modulators. This opens new perspectives in the treatment of oxidative stress depended diseases, and together with SAR-data should be involved into development of new directions of thiazolidinone based drug-like molecule design and optimization.

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P49

The search for pharmacologically active compounds in biomass produced by microalge *Chlorrella*

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Microalgae farms offer easy access to valuable bioactive compounds such as pigments, polysaccharides, polyunsaturated fatty acids, vitamins, alginates, proteins, peptides, amino acids and others [1]. Bioactive compounds from microalgae can be isolated directly as being primary metabolisms (proteins, fatty acids, vitamins, and pigments), or secondary metabolites. Many of them demonstrate antifungal, antiviral, anti-algal, anti-enzymatic, or antibiotic activity [2]. Moreover, many of abundant components of algae biomass have antimicrobial, antioxidant, and anti-inflammatory properties, and they can be used for the reduction and prevention of diseases [3-6].

The studies undertaken at the Institute of Organic Chemistry of the Lodz University of Technology are focused on the isolation of valuable components of Chlorella sp biomass (especially peptides, proteins and amino acid derivatives) for pharmaceutical and cosmetic industry. Due to the technological aspect of this work, it is assumed that the crucial preliminary stage is the optimization of separation methods, which ensure the high efficiency and homogeneity of isolated components, preserving their biological activity. In the first step of the study, two standard protein precipitate methods were compared. Further efforts were focused on isolation and identification of lipidic biomass components by LCMS.

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P50

Fluorescent labelling of azidothymidine: introduction to personalised antiviral therapy

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Azidothymidine (AZT) is an antiretroviral drug, which contains an azide group in its chemical structure. It is used as a stand-alone medication or in complex formulations for HIV infection treatment. However, medication with AZT is associated with many side effects such as myelotoxicity, neutropenia, and hepatotoxicity, which raise concerns about safety of the treatment. In such situation, adjustment of individual dose of the drug is highly beneficial for the patient.[1] It is particularly important if the inter-individual differences in the rate of drug metabolism are considered. Individual profiling of AZT metabolism could be a step towards the treatment of viral infections using the personalized dosage therapy.

Fluorescent labeling allows effective analysis of azidothymidine, significantly increasing the sensitivity of determinations compared with absorption methods. The proposed fluorescent conjugation methodology is based on the copper(I) catalyzed azide-alkyne cycloaddition (CuAAC), which is the main reaction of the *click chemistry* approach. This strategy focuses on the use of efficient and easy to perform reactions and is widely used in pharmaceutical sciences and fluorescent labelling.[2]

Efficient labelling of azidothymidine with a fluorescent marker would allow to easily determine its concentration in samples, first in model solutions and next, in patient blood and urine samples.[3] This would extend the application of personalized medicine to antiviral treatment with azidothymidine. Personalization of the therapy would involve individual adjustment of the azidothymidine dose used in treatment by monitoring azidothymidine concentrations in patients' blood. Such an approach would result in clear and precise determination of the patient's metabolic profile, minimizing side effects and maximizing the therapeutic effect during pharmacotherapy.

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P51

Does antiproliferative action of NSAID is cyclooxygenase dependent only? Role of NSAIDS in proline oxidase activation

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Strategies for cancer therapy and prevention involve many different groups of drugs. Recent studies show important role of nonsteroidal anti-inflammatory drugs (NSAIDs) in this process. Numerous reports proved that in patients who regularly used NSAIDs the risk of cancer is reduced even up to 67% depending on type of cancer and used NSAIDs. Postulated mechanism of antiproliferative and proapoptotic action for NSAID is explained on the basis of their inhibitory effect on cyclooxygenase (COX) which is frequently overexpressed in different cancer. From the other side it was also demonstrated that NSAIDs are able to evoke similar antiproliferatory effect in cancer cells which do not express COX enzyme or in model of cancer cells with knocked-down COX.

Regarding the numerous publications, NSAIDs may be responsible for antineoplastic activity through PPARγ receptor. PPAR receptors belongs to the nuclear receptor family and are known from their transcriptional activity. They play important role involved in gene expression, regulation of energetic metabolism, inflammation processes and apoptosis. It is well known that NSAIDs are ligands for PPARγ receptor which induces PRODH/POX expression and it leads to activation of apoptosis pathway. PRODH/POX is a mitochondrial enzyme catalyzing the conversion of proline to pyrrolidine-5-carboxylic acid (P5C). During the conversion of proline to P5C, electrons are transported to the respiratory chain, producing ATP or reactive oxygen species (ROS). In the first case, activation of PRODH/POX leads to the production of ATP for survival, in the second one, ROS induces apoptosis.

Presented study was performed to investigate the influence of selected NSAIDs on the breast cancer cells viability and its molecular mechanism of anticancer action regarding antiproliferative properties by activation of proline oxidase as an alternative death pathway.

MCF-7 breast cancer cells were treated with selected NSAIDs for 24 hours in atmosphere of 5% CO2, 37^{o}C and full humidity. After incubation MTT test was used to measure cells viability. DNA biosynthesis was determined by [methyl-3H]thymidine incorporation into DNA by radiometric assays. Selected proteins involved in apoptosis pathway were determined by immunocytochemistry by using confocal microscopy.

Our experiments, proved dose-dependent inhibitory effect of investigated drugs on cell viability in MCF-7. This effect was related to decreased DNA biosynthesis level and increased expression and translocation of proapoptotic proteins as: p53, caspase 9 and PRODH/POX.

P52

The anti-proliferative and proapoptotic action of amide derivatives of JNJ7777120 - non-imidazole H4R antagonist - on human T-cell lymphoma (HuT102)

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Histamine is a biologically-active molecule which, by activation of four subtypes of histamine receptors, modulates both physiological and pathological processes [1]. Histamine receptors all belong to the seven transmembrane signaling proteins also known as G protein-coupled receptors (GPCRs). Numerous studies associates GPCRs and their downstream signaling as a promising therapeutic target in cancer treatment, as it plays a crucial role in the promotion of malignant transformation [2]. More recently, scientific and medical reports confirmed the presence of functional receptors of histamine H4 (H4R) in several types of tumors and that it was involved in the proliferation of tumor cells [3]. Therefore, it is suggested that compounds with anti-H_4R activity can be potential therapeutic agents in cancer treatment.

Recently, we received and examined a group of amide analogues of JNJ7777120 – first selective, non-imidazole H_4R antagonist [4, 5]. In this group of compounds L50, L58, L60, L63 were selected and tested according to 1) evaluate preliminary anticancer activity (MTS assay), 2) distinguish non-specific cell toxicity from the desired activity, 3) assess apoptotic activity (caspase 3/7 assay) that is very attractive as a potential drugs in cancer treatment. In addition the selected compounds have been already tested for mutagenic activity in the AMES test, and in all cases a negative results were obtained. The present study was performed using human cancer cell line HuT102 (T-cell lymphoma) in which we confirmed the H_4R expression. We have also evaluated the cytotoxicity of selected compounds on normal human fibroblast.

Our results showed that all tested compounds affected the metabolic activity in a concentration-dependent manner when they were added in the concentration range of $6.6x10^{-9}$ – $5x10^{-5}$ M for up to 48 h to the cells. The compounds L60 and L63 showed the highest effect on HuT102 cells viability with IC50 values of 2.213 μM and 1.892 μM, respectively. Furthermore, no viability inhibition was observed in normal human fibroblast except for L50 and L60 in the concentration range of 25-50 and 50 [μM], respectively. All tested compounds caused a significant membrane damage after 24h at the highest concentration of 50 μM. However, L60 caused a significant cytotoxic effect also at lower concentrations range of 4-25 [μM]. We also demonstrated that treatment HuT102 cells with L50, L58 and L60 induced apoptosis by caspase-3,-7 activation.

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P53

Synthesis and biological evaluation of new colchicine derivatives acting as antimitotic agents

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Colchicine, a well-known tropolone alkaloid isolated from *Colchicum autumnale*, is of particular interest due to its antimitotic properties. It has played an important role in studies of mitosis and the therapeutic potential of colchicine binding site has been considered for chemotherapy applications [1,2]. However, colchicine itself as well as many of its derivatives could not be used as anticancer drugs because of their strong side effects. Up to now many structure-activity relationship studies have been done to elucidate the structural features required for the tubulin binding [3-5].

Herein, we report the synthesis, spectroscopic analysis of novel triple-modified colchicine derivatives, as well as evaluation of these derivatives as cytotoxic, tubulin-targeting agents. The antiproliferative effect was tested *in vitro* on five human cancer cell lines, i.e.: human lung adenocarcinoma (A549), human breast adenocarcinoma (MCF-7), human colon adenocarcinoma cell line (LoVo) and doxorubicin resistant subline (LoVo/DX), acute lymphoblastic leukemia (ALL) as well as one normal murine embryonic fibroblast cell line (BALB/3T3). To better understand the interactions between the colchicines derivatives and tubulin, we also investigated potential binding modes of all studied compounds docked into colchicines binding site (CBS) of ßI tubulin using Autodock4 software under flexible ligand and rigid receptor condition.

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P54

Protective effect of cinnamic acid derivatives on doxorubicin-induced cardiotoxicity a correlation with the inhibition of carbonyl reductase mediated metabolism

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Doxorubicin (DOX) is frequently used in cancers therapy. Despite a great efficacy against broad spectrum of neoplasms, its application is limited by several adverse effects – cardiotoxicity, which affect patients treated with approved doses and cancer cell resistance which decreases response to treatment. One of the hypothesis that explains the emergence of side effects, indicated the role of cytosolic enzyme - carbonyl reductase (CBR). Human carbonyl reductase 1 (CBR1), a member of the short-chain dehydrogenase/reductase superfamily, reduces DOX to their less potent anticancer C-13 hydroxy metabolite –doxorubicinol (DOXol), what is linked with pathogenesis of cardiotoxicity. Due to the undesirable activity of DOXol, there is a clear need for searching a new carbonyl reductase enzyme inhibitors that will improve the effectiveness of therapy. To take up such a challenge our group designed and synthesized a new potential inhibitors of CBR1 in a group of cinnamic acid derivatives (CA).

Firstly, our study examined the biotransformation process of DOX in the presence of CA in human cytosol fraction. Molecular modeling analysis was conducted to predict potential interaction of CA with active site of CBR1 enzyme. Cytotoxic and cytostatic activity of DOX+CA were investigated on human lung cancer cell line (A549). Cytoprotective effect CA was determined using rat cardiomicytes model (H9c2). Preliminary studies have shown that synthetic cinnamic acid analogues 1-8 exhibit differentiated synergistic effects with doxorubicin. All analyzed compounds exert cytoprotective effect against DOX-induced cardiotoxicity in H9c2 cells. Taking into account these results, it can be concluded that CA, a new potential inhibitors for CBR1, are thought to be promising agents for adjuvant therapy with a double beneficial effect in improving the therapeutic response to DOX while reducing the cardiotoxic side effects in patients undergoing chemotherapy.

Acknowledgements: This work was supported by funds granted for the Faculty of Pharmacy of Jagiellonian University Medical College by the Polish National Science Centre no. 2016/21/D/NZ7/01546.

P55

Novel aryloxyethyl derivatives of 1-(1-benzoylpiperidin-4-yl)methanamine as the ERK1/2 phosphorylation-preferring serotonin 5-HT$_{1A}$ receptor biased agonists with robust antidepressant-like activity

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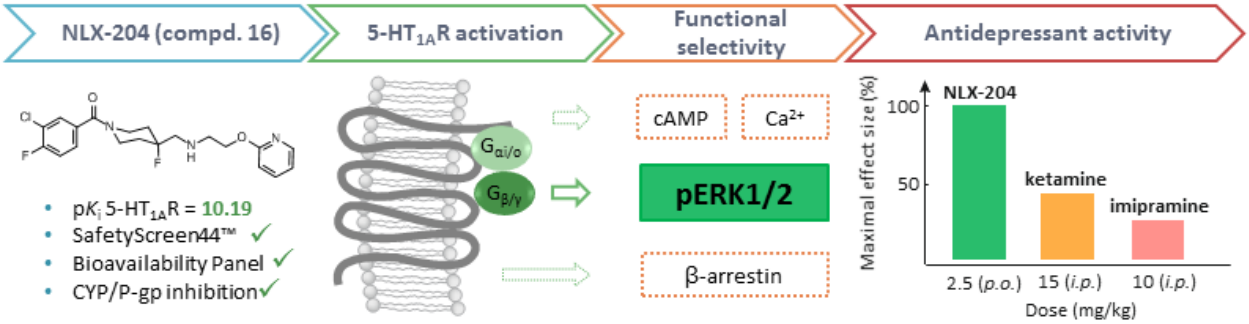

A series of novel 1-(1-benzoylpiperidin-4-yl)methanamine derivatives was designed and synthesized as potential biased agonists of the 5-HT$_{1A}$ receptor. Each compound was tested in four signal transduction assays (pERK phosphorylation, cAMP inhibition, Ca^{2+} mobilization and β-arrestin recruitment), which permitted identification of the desired ERK1/2 phosphorylation-preferring ligands among the aryloxyethyl derivatives. The novel series showed very high 5-HT$_{1A}$ receptor affinity, selectivity versus α_1R and D_2R (>1000-fold), and favorable drug-likeness parameters (CNS-MPO, Fsp^3, LELP). The lead structure, (3-chloro-4-fluorophenyl)(4-fluoro-4-(((2-(pyridin-2-yloxy)ethyl)amino)methyl)piperidin-1-yl)methanone (**16,** NLX-204), displayed high selectivity in the multi-target SafetyScreen44™ panel (including the hERG channel), high solubility, metabolic stability and Caco-2 penetration, and was free from blockade of CYP3A4, CYP2D6 isoenzymes and P-glycoprotein. Its beneficial ADME properties were confirmed in preliminary in vivo pharmacokinetic studies. Finally, the lead structure showed unprecedentedly efficacious and dose-dependent antidepressant-like activity, at very low doses after oral administration (MED = 0.16 mg/kg), achieving an exceptionally large effect size (total elimination of immobility in the rat Porsolt test).

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P56

D2AAK1_3 as a new dopamine D2 receptor antagonist

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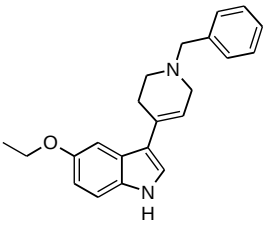
Compound D2AAK1_3 (see below) was designed as a modification of the lead structure D2AAK1 (an *in vivo* active multi-target compound with nanomolar affinity to a number of aminergic GPCRs) [1,2] and synthesized in the reaction of 5-ethoxyindole and 1-benzyl-4-piperidone in methanol/KOH. This compound has affinity to human dopamine D_2 receptor with K_i of 151 nM.



The aim of studies was structural and thermal characterization of the compound D2AAK1_3. In particular, X-ray studies, molecular docking and molecular dynamics as well as thermal analysis were performed [3].

The studied compound crystallizes in orthorhombic system, in chiral space group $P2_12_12_1$. The compound has a non-planar conformation. The dihedral angle between planes of benzyl group and indole moiety is 85.6(1) Å. The structure of compound is stabilized by a week N1-H1a·N2 hydrogen ($d_{D\cdot A}$ = 3.223(3) Å) bonds which leads to formation of one-dimensional chains running parallel to the [001] direction.

The studied compound was docked to the novel X-ray structure of the human dopamine D_2 receptor in the inactive state (PDB ID: 6CM4) and established the main contact between its protonatable nitrogen atom and Asp(3.32) of the receptor as expected for orthosteric ligand of aminergic GPCRs. The obtained binding pose was stable in molecular dynamics simulations.

Thermal stability of the compound was investigated using TG-DSC technique in air atmosphere. The studied compound is characterized by good thermally stability. During heating under oxidizing conditions, the first change has been recorded on the DSC curve as the endothermic peak (T_{peak} = 154 °C) and is associated with melting process. The enthalpy of fusion calculated from DSC is 26.42 kJ mol^{-1}. The combustion and thermal degradation of compound start over 200 °C and proceeds in three stages. The first step (204-389 °C) is characterized by a thermal decomposition of the greater part of the compound (54.41%) and probably is mainly associated with the defragmentation, release of volatile products and their combustion processes. The formed unstable products undergo further decomposition process which is not clearly marked on TG curve but it has been recorded on DTG curve. The last stage is observed in the temperature range 458-650 °C and corresponds to the complete destruction and combustion of the remaining parts of the compound. In order to better understand the mechanism of thermal decomposition of compounds the TG-FTIR analyses in air and nitrogen atmosphere were also performed.

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P57

Novel multi-target agents to treat schizophrenia

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Schizophrenia is a severe, chronic and disabling mental disorder that affects how the person feels, thinks, and behaves. It is characterized by deficits in thought processes, perceptions, emotional responsiveness and likewise distortions in language, sense of self and behaviour. It often includes psychotic experiences, such as hearing voices and delusions. Schizophrenia begins typically in late adolescence or early adulthood (first symptoms are usually observed between the ages of 16 and 30) and is estimated to affect 1% of population. The causes and pathomechanism of schizophrenia are still poorly understood, hence the treatment focuses on reducing symptoms of the disorder. Currently available antipsychotic drugs are usually effective in reducing positive symptoms (e.g. hallucinations, delusions, thought and movement disorders) but their effectiveness is lesser on negative symptoms, which include i. a. social withdrawal, apathy and problems with motivation. In complex diseases, whose pathomechanism involve several neurotransmitters (such as schizophrenia), selective drugs turn out to be ineffective. Therefore new compounds affecting several different receptors are searched. Those multi-target agents with affinity to different aminergic GPCRs may contribute to reducing positive, as well as negative and cognitive symptoms, and cause fewer side effects, comparing to currently used drugs.

P58

Synthesis and structure of novel *(Z)*-1-[1-(4,5-dihydro-1*H*-imidazol-2-yl)-2-phenylvinyl]-1*H*-indole derivatives with potential biological activity

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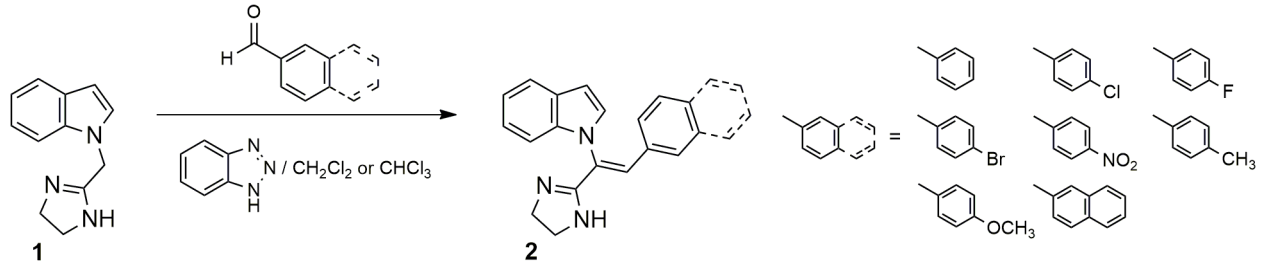
N-vinylindoles represent structural motifs in both natural and synthetic compounds of biological interest including antifungal and antiproliferative agents [1]. On the other hand, the pharmacological importance of 2-imidazoline-contaning compounds is evident from their widespread applications as antihypertensives, vasoconstrictor, rhinological therapeutics, skeletal muscle relaxants, appetite depressants as well as antimicrobial and antineoplastic agents [2].

The above mentioned information suggested that it would be of interest to investigate biological potential of the compounds incorporating both the *N*-vinylindole and 2-imidazoline pharmacophoric groups. Therefore, we wish to report a new class of *N*-vinylindole derivatives of type **2** synthesized by the Knoevenagel condensation reaction of the 1-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]indole (**1**) with the corresponding aromatic aldehydes in the presence of 1,2,3-benzotriazole.



Structures of the compounds obtained were confirmed by IR, NMR and MS spectroscopic data as well as X-ray crystallographic study. The newly prepared compounds were tested for their antimicrobial activities against representative strains of Gram-positive and Gram-negative bacteria, and yeast. In antibacterial assay some compounds of type **2** displayed activity (MIC = 13.75 – 30 μg/mL; MBC = 27.5 – 55 μg/mL) against *S. epidermidis* ATCC, methicillin-resistant *S. epidermidis* (MRSE) and methicillin-resistant *S. aureus* (MRSA). Further studies of the potential anticancer properties of the compounds obtained will be performed at the NCI (USA) on a panel of 60 human tumor-derived cell lines.

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P59

Study on the effect of statins on the catalytic activity of adenylate kinases

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Adenylate kinases (AK) affect many biological processes by controlling the cellular energy charge or regulating the activity of membrane nucleotide receptors. Despite the significant role of these enzymes, so far no attention has been paid to the mechanisms of their regulation [1, 2]. The only AK inhibitors known so far are the dinucleotide polyphosphates (e.g. P1,P5-diadenozyno-5'pentaphosphate, Ap5A). The literature data and our studies suggest that depending on the phylogenetic classification, tissue distribution and AK structure, Ap5A inhibits adenylate kinases with different efficiency [3, 4]. It was shown that the change in the LID domain position is one of the important steps of the reaction catalyzed by AK, and closure of LID enables the phosphate transfer. It was also shown that opening of the LID domain is a step determining the catalytic reaction rate [5].

Adenylate kinase participates in the control of HDL cholesterol endocytosis by liver cells [6]. In cardiology, the drugs used for lowering the blood cholesterol level are statins. Our research indicated for the first time that statins efficiently inhibit human adenylate kinase (isoenzyme 1, hAK1, short type) while do not change significantly the activity of adenylate kinase from the Gram positive thermophilic bacteria *Geobacillus stearothermophilus* (AKst, long type). Statins structure differs from the AK substrates, but their common β-hydroxy acid moiety might mimic the binding interactions of the AK substrate phosphates. Therefore, it is interesting to determine if the additional protective effect of statins used in the therapy of the circulatory system might be related to the regulation of activity and function of adenylate kinases.

For experiments we have selected four statins: simvastatin (SVS), rosuvastatin (RVS), fluvastatin (FVS), and pravastatin (PVS). The hAK1 was inhibited by all tested compounds, and the largest effect was found for SVS. The hAK1 activity was determined in a presence of SVS at the concentration range 0.25-10 μM what enabled the determination of IC_{50}. For the ADP and ATP syntheses, SVS IC_{50} is 3.0 μM and 3.5 μM, respectively. At the above concentration range, we have not detected any significant effect of SVS on the AKst activity in both directions. Also, for the other statins (RVS, FVS, and PVS), no inhibition of AKst was observed.

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P60

New 2,4-disubstituted thiosemicarbazide derivatives of pyridine with antitubercular activity

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Tuberculosis is one of the leading cause of death among the communicable diseases. According the World Health Organization in 2016 10.4 mln new cases of tuberculosis were reported and 1.8 mln people died due to tuberculosis. The dramatic growth of bacterial resistance to used antibiotics results in the need for development of new antitubercular drugs[1].

Previously we obtained derivatives of 4-methylpicolinonitrile and 4-phenylpicolinonitrile. Obtained compounds showed variety tuberculostatic activity. Compounds with the most potent tuberculostatic activity exhibited also low cytotoxic effect against neonatal human dermal fibroblasts [2]. The aim of our study was design, synthesis and evaluation of biological activity of novel derivatives of 2,4-disubstituted pyridine. Thiosemicarbazides of various structure were obtained. All compounds were characterized by IR, ^{1}H NMR spectra and elemental analysis. They have been tested for tuberculostatic activity in vitro against M. tuberculosis strains: H_{37}Rv, Spec. 210, Spec. 192. For the most active compounds cytotoxic activity was also evaluated. The cytotoxic activity was determined by MTT method on mouse melanoma cell line B16-F10 and human dermal fibroblasts HDF.

The cycloalkylaminothiosemicarbazide derivatives exhibited the highest tuberculostatic activity among obtained compounds. Furthermore compounds with the highest antitubercular activity demonstrated also low cytotoxicity towards human dermal fibroblasts HDF. Crystallographic studies performed for cycloalkylaminothiosemicarbazide derivatives determined the zwitterionic structure of these compounds. The findings indicate that the supplied derivatives are good leading structure for discovery of new tuberculostatic agents.

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P61

The effect of novel diisoquinoline derivative with anti-MUC1 antibody on induction of apoptosis in MDA-MB-231 breast cancer cells

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Breast cancer is the most common cancer disease in women's population worldwide. MUC1 overexpression is often observed in breast cancer cells and it is also connected with poor prognosis. Targeted therapy based on anti-MUC1 monoclonal antibody represents an interesting approach for improving the therapeutic effects of breast cancer conventional treatment [1, 2].

The goal of the study was to analyze the influence of anti-MUC1 monoclonal antibody with novel diisoquinoline derivative (OM-90) on viability, mitochondrial membrane potential and induction of apoptosis in MDA-MB-231 breast cancer cells.

The human breast cancer cells were treated for 24 hours with various concentrations of compounds used alone (OM-90, etoposide) and in combination with anti-MUC1 antibody. The cells' viability was analyzed using Carmichael's method. Flow cytometer was used to analyze changes in mitochondrial membrane potential and to detect the induction of apoptosis in MDA-MB-231 breast cancer cells.

The combination of OM-90 with anti-MUC1 antibody was the most cytotoxic and had the strongest proapoptotic potential in MDA-MB-231 breast cancer cells compared to monotherapy and combined therapy with etoposide and anti-MUC1 antibody. OM-90 together with anti-MUC1 antibody significantly reduced the mitochondrial membrane potential compared to other compounds in MDA-MB-231 breast cancer cells.

The results of our studies confirmed that combination of anti-MUC1 antibody with OM-90 might be a promising strategy in breast cancer therapy and can be an alternative way of treatment to chemotherapy.

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P62

Aza-BODIPY bearing amine moieties – synthesis, fluorescence properties and singlet oxygen generation

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BODIPY and their aza-analogues – aza-BODIPY are small molecules with intriguing optical properties. Apart from their biomedical uses, they are investigated as materials for voltaic cells or optoelectronic devices. These chemicals show fluorescence, and are used as fluorescent probes. Additionally, they generate singlet oxygen upon illumination with light, and are studied as photosensitizers for photodynamic therapy (PDT) [1,2]. In PDT, photosensitizer upon irradiation with light of an appropriate wavelength, generates reactive oxygen species, including singlet oxygen. These have the ability to kill tumor cells or microbes. Antimicrobial PDT is gaining more attention due to its potential application in the treatment of different microbial infections, including those caused by antibiotic-resistant strains which are a growing worldwide health concern.

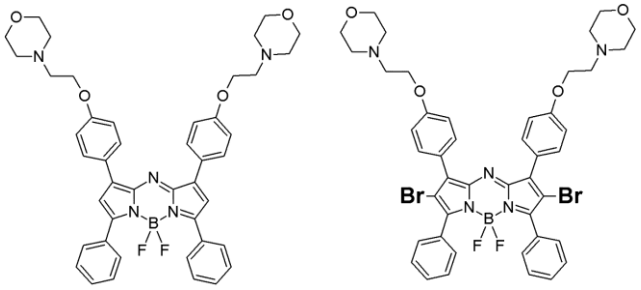

Fig 1.Modified aza-BODIPYs

New aza-BODIPY compounds, bearing morpholinylethoxy substituents were synthesized and characterized using MS and NMR techniques. Additionally, X-ray studies were conducted. Introducing bromine atoms into the molecule led to lower fluorescence quantum yield and higher singlet oxygen generation yield..

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Acknowledgments: This work was supported by the Polish National Science Centre under grant no. 2015/19/D/NZ7/00401.

P63

Search for drug-like molecules among thiopyranothiazoles

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The results obtained in the earlier study of 4-thiazolidinones as potential small drug-like molecules and the established fact of saving their pharmacological activity in fused analogs prompt the ongoing research of thiopyranothiazoles biological activity. Among others this class of compounds has been characterized by anticancer, antiviral as well as antiparasitic activity [1]. One more argument in favour of thiopyranothiazoles choice is that the latter can not be treated as PAINS (pan assay interference compounds) and do not possess Michael acceptor functionality.

For realization of synthetic schemes the various types of reactions were used, such as «domino» Knoevenagel-*hetero*-Diels-Alder reaction, Michael reaction, reactions of N-alkylation. Series of different thiopyrano[2,3-*d*]thiazoles were obtained in the Knoevenagel-*hetero*-Diels-Alder reactions of iso- and thiorhodanine with such dienophiles as 3,7-dimethyloct-6-enal (citronellal), 2-allyloxybenzaldehydes, etc. NH-Acidic centers at position N3 of basic heterocycles made possible the synthesis of various N-substituted derivatives. The latter were obtained in the alkylation reactions of thiopyranothiazoles by bromoacetophenones, different acetamides, ethylchloroacetate or 1-(2-chloroacetyl)-1H-indole-2,3-diones, cinnamaldehyde, 1-(2-chlorobuta-1,3-dienyl)-4-nitrobenzene through the stage of hydrazide formation.

Anticancer activity evaluation of synthesized compounds was carried out at 60 cell lines derived from nine neoplastic subpanels in accordance with the protocol of the Drug Evaluation Branch, National Cancer Institute, (USA, Bethesda). Drug assays of bloodstream forms of Trypanosoma brucei brucei (Tbb) were based on the conversion of a redox-sensitive dye (resazurin) to a fluorescent product by viable cells. Primary antiviral assay was performed on a respiratory viruses panel (Flu A (H1N1), Flu A (H3N2), Flu A (H5N1), Flu B, SARS CoV).

Anticancer activity was the most promising one showed by thiopyranothiazole derivatives in different bio-assays. Among studied thiopyranothiazoles, compounds that inhibited growth of different cancer cell lines at micro- and submicromolar concentrations were identified. Moreover, some isothiochromeno[4a,4-*d*]thiazoles as well as chromeno[4',3':4,5]thiopyrano[2,3-*d*]thiazol-2-ones were highly active towards influenza virus type A (H1N1) virus strain California/07/2009 with the SI from 68 to 150-180.

Established thiopyranothiazoles anticancer activity has become an argument for repurposing strategy application, when anticancer drugs (e.g. bortezomib, aclarubicin, doxorubicin, mitoxantrone) were studied against *Trypanosoma brucei* and showed trypanocidal activity comparable with commercial antitrypanosomals. In the case of thiopyranothiazoles study repurposing approach turned out to be rather useful method as there were identified isothiochromeno[4a,4-*d*]thiazoles and chromeno[4',3':4,5]thiopyrano[2,3-*d*]thiazol-2-ones inhibiting growth of *Trypanosoma brucei brucei* with micromolar IC_{50} values. For the most active compounds, acute toxicity (mice) was studied. The detected LD_{50} values were within the range of 270-480 mg/kg that describe these substances as perspective for further investigations.

Taking into account methods of synthesis, stereochemical characteristics and chemical properties as well as low levels of acute toxicity of thiopyranothiazoles, the latter have significant potential for medicinal chemistry. The established pharmacological prophile of thiopyranothiazoles along with the given arguments indicate that these heterosystems can be the basis for design of potential "drug like molecules" and further implementation in medical practice as innovative medicines.

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P64

Significance of absolute configuration in the search for serotonin 5-HT$_7$ receptor antagonists among hydantoin derivatives

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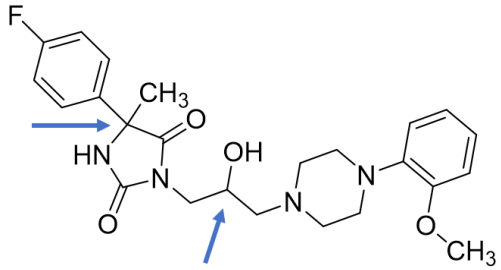
According to literature 5-HT$_7$R antagonists may have particular activity in depression treatment and coexisting cognitive impairment and anxiety [1]. Our previous studies led to synthesis and pharmacological evaluation of ~50 hydantoin derivatives, of which more than 20 bind to 5-HT$_7$R with K_i<20 nM. Among the most active ones, 6 compounds turned up to cause antidepressant effect in Porsolt's test [2-4]. Worth noting that all the above-mentioned hydantoin derivatives were synthesized as racemic mixture. It is proved that stereoisomers may differ from each other in terms of both biological activity and pharmacokinetic properties [5]. Hence, isolation, biological characterization and finally selection of the stereoisomer with the most desired properties seems to be necessary task within preclinical studies.

The aim of this work was to synthesis, separation and evaluation in radioligand binding assay of 4 stereoisomers of lead structure (compound MF-8) as a representative of the whole series. The resulted data enabled to analyze the influence of particular absolute configuration on 5-HT$_7$R affinity and selectivity over 5-HT$_{1A}$R.



The representative compound (MF-8) with indicated stereogenic centers.

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P65

Synthesis and biological activity of a new 5-cyanoindole derivatives as a dual D_2/5-HT_{1A} receptor ligands

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The current treatment of central nervous system diseases including depression, schizophrenia or Parkinson's disease is it is not fully effective. Therefore, the need for further research into antidepressants is justified. There are more and more reports in the literature in which the cooperation of two mechanisms of action is described [1,2]. An example for this approach may be Wilazodone well known antidepressant, whose mechanism of action is based on inhibition of serotonin reuptake and it is a 5-HT_{1A} receptor agonist [3]. Another example of a compound used in the treatment of depression is Aripiprazole. Similar to Wilazodone, Aripiprazole also has a dual mechanism of action - it is a partial agonist to D_2 and 5-HT_{1A} receptors [4].

Based on this knowledge, it was decided to synthesize a new group of derivatives of long-chain arylpiperazines (LACPs) with a 5-cyanoindole moiety. These compounds contain a motif from Aripiprazole - chlorophenylpiperazine and from Vilazodone (5-cyanoindolobutyl moiety). Ligands were synthesized in solvent-free reactions supported by microwave irradiation. This method can be regarded as fast, efficient and eco-friendly that fits into the canons of green chemistry. The purified ligands were examined in biological tests to determine the binding to the D_2 and $5HT_{1A}$ receptors. The compounds were also designed for their drug-like properties, calculating for appropriate physicochemical parameters *in-sillico.*

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Acknowledgments: The research was supported by the National Centre for Research and Development, LIDER VI project (LIDER/015/L-6/14/NCBR/2015).

P66

The significance of halogen bonding in ligand-receptor interactions - the lesson learned from Molecular Dynamic simulations of D4 receptor

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Halogen bond (XB) is a non-covalent interaction defined as a directional bond between a covalently bound halogen atom (acting as a donor) and a Lewis base as an acceptor [1–3]. The XB strength is comparable to weak or moderate hydrogen bonds and increases in the order of Cl < Br < I. XB has been indicated to play an essential role in supramolecular systems, liquid crystal engineering, nanomaterials, nanowire formation, catalysis, and also recently, in drug design and lead optimization processes [4,5].

Recently, a computational approach combining a structure-activity relationship library containing pairs of halogenated and the corresponding unsubstituted ligands (called XSAR) with QM-based molecular docking and binding free energy calculations was developed and used to search for amino acids frequently targeted by halogen bonding (hot spots) [6]. However, the analysis of ligand–receptor complexes with halogen bonds obtained by molecular docking provides only a limited ability to study the role and significance of halogen bonding in biological systems. Thus, we performed a set of molecular dynamic simulations (MD) using OPLS3 force field, which have a well-documented parametrization for XB. The dopamine 4 receptor, recently crystalized with antipsychotic drug nemonapride (5WIU) and XSAR library (containing 52 sets), were used to define staring geometries. A 100 ns MD simulations were performed using Schrödinger Desmond software. Each ligand–receptor complex was immersed into a POPC (300 K) membrane bilayer, and system was solvated by water molecules described by the TIP4P potential. All calculations were performed on GPU (CUDA) processors.
The results of MD simulations supported by the experimental data showed that steric restrictions, and the topology of molecular core have a key impact on the stabilization of the ligand-receptor complex by halogen bonding. The amount of enhancement in the activity of the halogen derivative compared to its unsubstituted analog depends on the stability of the halogen bond.

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P67

Erythrosine-phthalocyanine coniugates – microwave synthesis and characteristic

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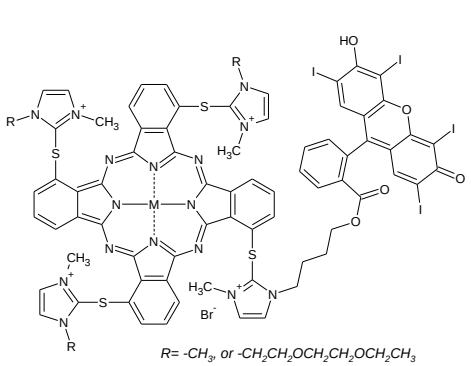
Both phthalocyanines and erythrosine are dyes with possible uses in photodynamic therapy, using photosensitizing compound which generates singlet oxygen after irradiation with visible light. Singlet oxygen as reactive form of oxygen is capable of killing cancer cells as well as microorganisms. Adhering to the principles of “green chemistry” microwave synthesis allows conducting reactions faster, with better yields, less solvents or even without them.

In our work we set out to develop new compound combining properties of these two groups as well as increasing solubility. First we synthesized fluorescein using microwave reactor without the use of solvent in very good yield (80%) from simple substrates (phthalic anhydride and resorcinol). Then using it we obtained erythrosine in reaction with iodine in water with high yield (75%) and purity (95% +). Subsequently we connected it with short chain linker containing halogen through esterification. After that we prepared phthalocyanines bearing methylimidazole substituents through microwave reaction in 30 % yield and subsequently their cationic salts with quantitative yield **(2)** for comparison with planned compounds **(1)**. Obtained phthalocyanine and erythrosine compounds were characterized by mass spectrometry and NMR spectroscopy (1D and 2D). Compound **(2)** was also subject to biological activity studies against LNCaP and MCF7 cancer cell lines exhibiting IC_{50} values in micro molar range. (LNCaP IC_{50}=0,53μM; MCF7 IC_{50}=0,44μM).



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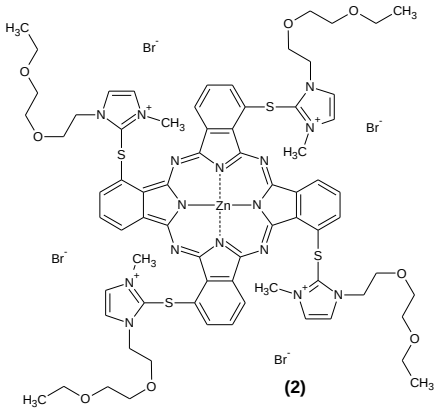

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P68

Thiazoles with cyclopropyl fragment as antimicrobial agents. Synthesis, toxicity evaluation, and molecular docking study

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Due to the widespread and irresponsible use of broad-spectrum antibiotics, anticancer, immunosuppressive, and anti-HIV drugs a significant increase of number of multi-drug resistant microorganisms have been observed [1]. One of the most common groups of such pathogens, causing invasive fungal infections leading to hospitalizations and death, are *Candida* spp. [2]. Therefore novel, effective antimicrobial drugs are required.

For many years, our research has focused on the search for thiazole derivatives that show high activity against *Candida* spp. [3, 4], and recently also against the *Toxoplasma gondii* parasite [5]. In continuation of our search we have modified the thiazole system by adding cyclopropane ring. Compounds were tested on their antifungal activity against a panel of reference strains of nineteen microorganisms, and we also investigated intensity of *Toxoplasma gondii* RH virulent strain intracellular proliferation in the VERO host cells.

The newly synthesized compounds showed very high antifungal activity towards most reference and clinical strains of *Candida* spp. ATCC with MIC = 0.015–7.81 μg/ml [6]. Their antimicrobial effect was similar and even stronger than nystatin, which is a popular antimycotic drug. Some thiazoles also showed significant anti-*Toxoplasma gondii* activity, with IC_{50} values 31 to 52 times lower than those observed for sulfadiazine. The results of the cytotoxicity evaluation showed that microorganisms growth was inhibited at non-cytotoxic concentrations for the mouse L929 fibroblast and the African green monkey kidney (VERO) cells. Molecular docking studies indicated secreted aspartic proteinase (SAP) as possible antifungal target.

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P69

Biosynthetically produced selenized polysaccharides with antioxidant activity

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Selenium is a trace element of fundamental importance to human health as a cofactor of Se-dependent enzymes involved in cellular protection from severe oxidation by free radicals. Therefore, it has received considerable attention mainly due to antioxidant function, enhancement of body's immune, as well as inhibition of cancer and chromosome damage [1]. There is also increasing number of evidences that many mushroom-derived polysaccharides show similar pharmacological effect, including protective effect against oxidative damage caused by reactive oxygen species (ROS). We assumed that the insertion of selenium into a glycosidic bond or pyranosic ring of polysaccharide molecule may lead to a synergistic effect [2], which would be manifested by the enhanced antioxidant activity.

The crude Se-E fraction was isolated from mycelial cultures of *Lentinula edodes* mushroom, which had been cultivated in the liquid medium containing 30 μg/mL of selenium supplemented as its inorganic Na_2SeO_3 compound. The hot-water extraction of the parent polysaccharide and subsequent fractionation was applied according to the method of Chihara et al. [3], giving Se-EC-11, Se-EC-12, and Se-EC-13. The corresponding polysaccharide fractions without selenium were obtained in the same manner, and were used as control.

The protein content in the crude polysaccharide fraction, measured according to the colorimetric protein assay [4], was 4.7%, whereas the separated compounds were almost free of amino acid residues. As it was deduced from RP-HPLC determination of monosaccharide composition, the main subunits of the polymer chains were glucose, mannose and galactose, with a distinct majority of glucose moieties. However, the inverse ratio of monosaccharides with a predominance of galactose over glucose was found for EC-12 and the corresponding selenized Se-EC-12 fraction. In the anomeric region of FTIR spectra (between 950 and 750 cm^{-1}) a series of overlapping bands mostly resulting from C-O stretching vibrations near 940–900 cm^{-1}, including the C-O-H, C-C-H and O-C-H bending of α-anomeric configuration have appeared [5]. The only fraction with the additional signals characteristic for β-glucans (894 cm^{-1}) was non-selenized EC-11. High performance gel permeation chromatography (HPGPC) indicated that the molar masses of all polysaccharides are as large as several million daltons (Da). The content of selenium assayed by the method described by Turło et al. [6] reached a value of 85-135 μg/g. The results of the determination of antioxidant activity [7] indicated that at the highest concentration tested (2 mg/mL) all separated fractions show similar, dose-independent reducing power, 3-5 times weaker than that of the reference antioxidants (ascorbic acid, α-Tocopherol, BHA, and BHT). Chelating ability on ferrous ions was remarkably smaller compared to EDTA, but close to the value of citric acid at the given concentrations: the maximal value of about 8% was observed in the case of EC-12 and Se-EC-12 fractions. Considering a very high activity of the crude polysaccharides together with no differences between selenized and non-selenized fractions, as well as monosaccharide composition of EC-12 and Se-EC-12, one can be concluded that factors affecting the antioxidant activity are most likely the presence of protein component and the type and proportion of monomers.

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P70

New 1,2-benzothiazine 1,1-dioxide derivatives: synthesis and their interaction with model phospholipid membranes

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Oxicams, e.g. piroxicam, meloxicam, are a class of non-steroidal anti-inflammatory drugs (NSAIDs) with a distinguishing structure of 1,2-benzotiazine scaffold. They are used clinically to treat both acute and chronic inflammation, and to relieve pain of various etiologies. Unfortunately, like most classic NSAIDs, they cause side effects, mainly to the gastrointestinal tract [1].

Our reason for looking into new, safer oxicams derivatives was the discovery that they might selectively inhibit the microsomal prostaglandin E_2 synthase-1 (mPGES-1). This enzyme, like cyclooxygenase (COX), participates in the arachidonic acid transformation pathway, but it works at a further stage. Moreover, it is activated in response to an inflammatory stimulus. For this reason, selective mPGES-1 inhibitors are expected to inhibit PGE_2-induced inflammation biosynthesis, while not affecting the production of constitutive PGE_2 and remaining prostanoids (prostacyclin, thromboxane), which would result in reduced side effects of the drug [2].

In order to achieve the main cellular target of NSAIDs – proteins associated with the endoplasmic reticulum membrane (either COX or mPGES-1), these compounds have to pass through the biological membranes first. Changes induced in lipid phase, such as an alteration of membrane curvature and phase behavior may in consequence indirectly modify a conformation of membrane proteins. For that reason the investigation of drug-membrane interactions is essential for understanding of drugs' pharmacokinetics and molecular mechanisms of their action. This knowledge is crucial in designing new drug structures [3–5].

Taking oxicams as a lead structure, the present study focused on the synthesis of a new class of analgesic agents with an arylpiperazine moiety linked to the 1,2-benzothiazine scaffold with two types of linker – a propylene or 2-oxoethylene linker. In the present work we have used differential scanning calorimetry to study the interactions of five new 1,2-benzothiazine 1,1-dioxide derivatives with lipid bilayers in comparison to meloxicam. We have shown that these interactions indicate dependence on the chemical structure of individual compounds.

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P71

Effect of methylparaben on expression of hialuronic acid synthases in human skin fibroblasts

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Objectives: Cosmetic preparations are used frequently by a great number of people without distinction of age, sex or race and, generally, during a long period of time. Skin care products are composed of various chemicals: active substances, surfactants, solubilizers, perfumes, penetration enhancers, colouring agents, preservatives, etc. These constituents come in contact with human skin and they could have a local potential penetration, skin layers accumulation and, in specific conditions, an eventual passage to the general circulation [1]. One of the most common preservative is methylparaben (MP), which is a methyl ester of p-hydroxybenzoic acid. In our previous study, the inhibitory effect of MP on collagen type I, the main component of the extracellular matrix (ECM), was revealed [2]. The aim of the current study was to estimate the impact of MP on hyaluronic acid (HA) synthesis in skin fibroblasts.

HA is an unbranched polymeric carbohydrate, belonging to the glycosaminoglycans (GAGs), which consists of alternating disaccharide units. It is a barrier that protects tissues from bacterial infections as well as a natural antioxidant that protects our skin from harmful UV rays. Half of all hyaluronic acid contained in the human body is in the skin. Over 50% of our body is water, HA allows us to maintain a large part of this water (water of hydration) in the body and is therefore a very important element in maintaining beautiful, healthy and smooth skin [3]. Hyaluronan 1, 2 and 3 synthases (HAS1, HAS2, and HAS3) are the isoforms of enzymes responsible for the synthesis of HA. In the skin fibroblast the main form is HAS2 [3, 4].

Methods: Primary dermal fibroblasts purchased from the American Type Culture Collection (line CRL 1747) were treated with (MP), in concentration: 0,001%, 0,01%, 0,03% and 0,05% and incubated for 24 h. Hialuronic acid synthases (HAS1, HAS2, HAS3) expression was studied by real time PCR.

Results: Expression of HAS1 in fibroblasts treated with all MP concentrations increased more than 3 times (0.001% MP), twice (0.01% MP), about 8 times (0.03% MP) and about 12 times (0.05% MP) in compared to controls. Expression of HAS2 decreased by 55%, 47%, 90% and 96%, respectively. In the case of HAS3, MP in concentrations of 0.001%, 0.01% and 0.03% did not cause significant changes. However, the highest concentration caused an increase in the expression of the HAS3 gene more than twice.

Conclusions: Because HAS2 appeared to be the predominant isoform in skin fibroblasts, we can assume that its inhibition at mRNA level under influence of MP may be associated with inhibition of HA synthesis.

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P72

Synthesis and biological evaluation of new 1*H*-benzimidazole derivatives as AChE and BuChE inhibitors

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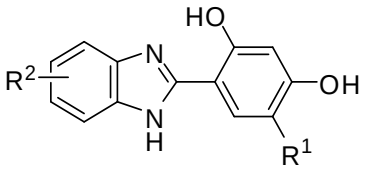
Acetylcholine (ACh) is one of the CNS neurotransmitter, which is rapidly degraded by enzymes - acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). AChE inhibitors are used in medicine as active substances in drugs of various neurodegenerative diseases, e.g. Alzheimer's (AD). A lot of research present benzimidazole derivatives as good inhibitors of these enzymes [1, 2]. Our previous studies in this area have shown that compounds with resorcinol moiety have high activity against acetylcholinesterase at the nM level, with some of them having high AChE selectivity against BuChE [3]. Continuing research in this field we decided to design and obtain new 1*H*-benzimidazoles functionalized by 2,4-dihydroxyphenyl moiety.

14 derivatives of 4-(1*H*-benzimidazol-2-yl)benzene-1,3-diol were prepared by the reaction of sulfinylbis[(2,4-dihydroxyphenyl)methanethione] or its methyl-, ethyl- and chloro- analogues with the corresponding benzene-1,2-diamine. Their chemical structures were elucidated by IR, ^{1}H NMR, ^{13}C NMR and EI-MS spectral data.



R^1: Me, Et, -Cl
R^2: Me, -F, -Cl, -COOEt, -CN, $-CF_3$

Using modified Ellman's method the compounds were tested *in vitro* to determine their ability to inhibit AChE and BuChE activity [4]. IC_{50} values were determined. The activity of the compounds was compared with the activity of standard - neostigmine - the directional inhibitor of these enzyme systems. For the most active derivatives, IC_{50} values were at the level of several nM. The selectivity of the test substances was also determined with respect to both cholinesterases. Molecular modeling studies were performed to find the crucial interaction of the most active compounds with AChE.

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P73

Synthesis and immunosuppressive properties of a new isoxazole derivative

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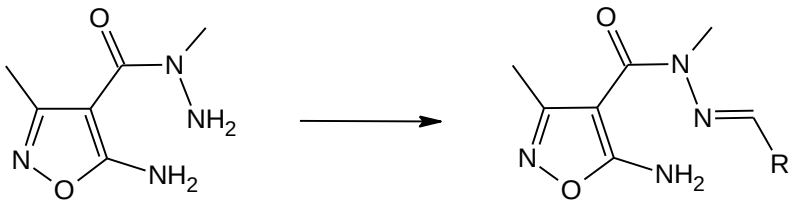
A new series of N'-substituted derivatives of 5-amino-N,3-dimethyl-1,2-oxazole-4-carbohydrazide (MM1-10) were synthesized in reaction of nucleophilic addition of primary amine group (terminal group of 5-amino-N,3-dimethyl-1,2-oxazole-4-carbohydrazide) with appropriate aromatic. As a product received imine derivatives, which were tested in several *in vitro* models using human cells. The compounds inhibited phytohemagglutinin A (PHA) – induced proliferation of peripheral blood mononuclear cells (PBMC) to a various degree. Toxicity of the compounds with regard to a reference A549 cell line was also differential.

Among the synthesized group of isoxazole derivatives, MM3 compound was selected for further investigations because of lack of toxicity and strongest antiproliferative activity and suggested its molecular mechanism of action. The compound was shown to inhibit lipopolysaccharide (LPS) induced tumor necrosis factor (TNF α) production in human whole blood cell cultures. In the model of Jurkat cells MM3 elicited strong increases in expression of caspases, Fas and NF-κB1, indicating that a proapoptotic action may account for its immunosuppressive action in the studied models.

The compound is a good candidate for further studies in *in vivo* models to evaluate its potential therapeutic utility.



P74

The effect of 2,3',4'-trimethoxy-trans-stilbene on tubulin polymerization *in vitro* and EROD activity in A549 and MDA-MB-231 cell lines

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Beneficial properties of natural *trans*-stilbene derivatives are well recognized. *Trans*-Resveratrol (3,4',5-trihdroxy-*trans*-stilbene) is a bioactive polyphenol occurring in grapes, berries and herbs. Recently, it has been widely introduced to dietary supplements. However, its low bioavailability has contributed to the search for synthetic compounds with better pharmacokinetic parameters. The tested 2,3',4'-trimethoxy-*trans*-stilbene (2,3',4'-TMS) has been reported to exhibit strong inhibitory action on cytochrome P450 family 1 activities, particularly CYP1B1, which is responsible for drug resistance in cancer chemotherapy [1].

The aim of the present study was to assess cytotoxicity of 2,3',4'-TMS and combretastatin A-4 (CA-4) used as a positive control, against human lung adenocarcinoma A549 and human breast adenocarcinoma MDA-MB-231 cell lines. To explain the mechanism of cytotoxic activity of 2,3',4'-TMS and CA-4, their effect on tubulin polymerization was examined. Moreover, the influence of the *trans*-stilbene derivative on the catalytic activity of cytochromes P450 family 1 in A549 cells was determined with the use of 7-ethoxyresorufin O-deethylase (EROD) assay.

The studies showed the cytotoxic effect of 2,3',4'-TMS in A549 cells with IC_{50} in the range from 10 to 100 μM for both 24 h and 48 h treatment. In the studied cells 2,3',4'-TMS significantly inhibited EROD activity. The effect of 2,3'4'-TMS on tubulin polymerization was stronger than that observed for CA-4. The IC_{50} value for the studied compound was estimated to be below 0,1 μM. Molecular docking confirmed the interaction of the *trans*-stilbene derivative with the colchicine binding site on tubulin. Lower cytotoxic effect of 2,3',4'-TMS as compared to CA-4 observed in A549 cells might be due to metabolism of 2,3',4'-TMS catalyzed by cytochromes P450 family 1, in particular CYP1B1. Our mechanistic studies of the synthetic trans-resveratrol analogue provide hope for a novel active compound with a multitargeted action.

[1] Mikstacka R. et al. *Med. Chem. Commun.* 5 (2014) 496-501

Acknowledgments: This study was supported by the grant from Nicolaus Copernicus University in Toruń, Collegium Medicum fund No. DS-UPB-WF-411.

P75

Synthesis and evaluation of antitumor activity of tricyclic derivatives of pyrazolo[4,3-*e*][1,2,4]triazine

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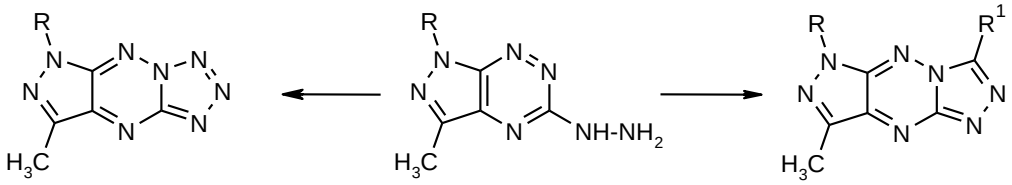
Presented results are an extension of research topic concerning tricyclic heterocyclic systems i.*e.* derivatives of pyrazolo[4,3-*e*][1,2,4]triazine fused with triazole or tetrazole ring.[1,2] The study was designed to examine the effects of obtained compounds on the proliferation and apoptosis of the RPMI-8226 (human myeloma cell line) and Jurkat (human acute T cell leukemia) to investigate the possible mechanism. Cell proliferation was analyzed using the thiazolyl blue tetrazolium bromide method. The synthesis pathway leading to the title compounds is depicted in scheme.



2a : R = 4-CH_3-Ph
2b : R = 4-CH_3O-Ph
2c : R = 4-Cl-Ph
2d : R = 3-Cl-Ph
2e : R = Ph
2f : R = CH_3

1a-f

3a : R = 4-CH_3-Ph; R^1 = H
3b : R = 4-CH_3O-Ph; R^1 = H
3c : R = 4-Cl-Ph; R^1 = H
3d : R = 3-Cl-Ph; R^1 = H
3e : R = 4-CH_3-Ph, R^1 = CH_3
3f : R = 4-CH_3O-Ph; R^1 = CH_3
3g : R = 4-Cl-Ph; R^1 = CH_3
3h : R = CH_3; R^1 = H
3i : R = CH_3; R^1 = CH_3
3j : R = CH_3, R^1 = CH_2Cl
3k : R = Ph, R^1 = H
3l : R = Ph, R^1 = CH_3

The preliminary anticancer studies revealed that tested compounds exhibited antiproliferative activity *in vitro.*

1. M. Mojzych, *J. Chem. Soc. Pak*., 2011, *33*, 123
2. M. Mojzych, P. Tarasiuk, Z. Karczmarzyk, M. Juszczak, W. Rzeski, A. Fruziński, A. Woźny, *Medicinal Chemistry*, 2018, *14*, 53

P76

Research on the synthesis and properties of the pyrazoline-thiazole derivatives

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In recent years, there has been a significant increase in systemic fungal infections, especially in immunodeficient patients and those hospitalized with tumours, and organ transplantation [1]. The main causes of fungal infections are *Candida* spp. commonly found in the human body. The widespread and irresponsible use of antibiotics, immunosuppressive agents and anticancer drugs, leads to the multi-drug resistant microorganisms [2]. A possible solution to the observed drug-resistance of microorganisms is a search for new drugs possessing a different mechanism of action. Thiazole is one of the most important scaffolds in drug design and discovery [3, 4]. The aim of the study was to design and synthesize 2,4-disubstituted-1,3-thiazoles containing a pyrazoline ring. New compounds were obtained with high purity and with 64 to 92% yields. The next stage of our research will be examination of the derivatives' activity against *Candida* spp. and bacteria, both gram-positive and gram-negative.

[1] Grossi P. et. al. *Transplantation* 70 (2000) 112-116
[2] Nucci M. et. al. *Clin. Infect. Dis.* 41 (2005) 521-526
[3] Łączkowski K.Z. et. al. *J. Enzyme Inhib. Med. Chem.* 31 (2016) 24-39
[4] Łączkowski K.Z. et. al. *J. Enzyme Inhib. Med. Chem.* 31 (2016) 1576-1582

P77

Unnatural amino-acids and amino-alcohols derived from tyrosine and phenylalanine

TriMen Chemicals

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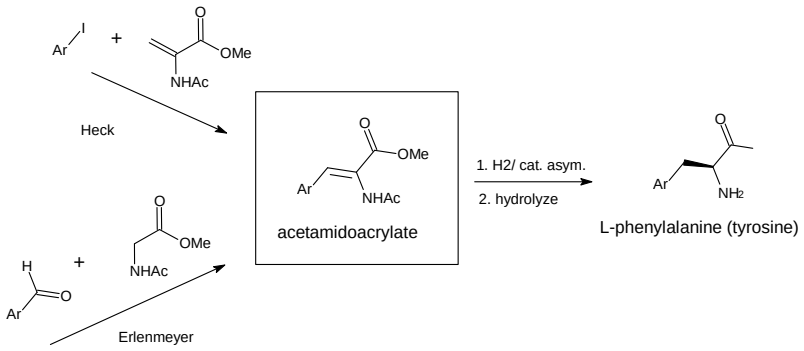
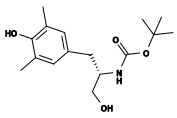
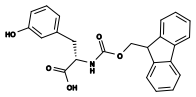
The importance of unnatural amino-acids in the research area of medicinal chemistry is well known. The number of natural amino-acids creates an abundance of possibilities for modifications of the existing structures and creation of new ones. Among them phenylalanine and tyrosine constitute a special group due to the presence of the aromatic ring inclined for new substituents. As a custom synthesis company we have already made fluorinated- and methylated-phenylalanines[1,2] or dimethyltyrosines[3] for our customers and partners. Recently we have prepared several acetamidoacrylates by Heck[4] and Erlenmeyer[5] reactions. The acrylates were later subjected to asymmetric hydrogenation to give substituted phenylalanines and tyrosines, later converted to protected and unprotected amino-acids and their corresponding amino-alcohols.



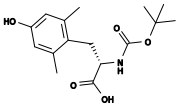
Some examples of obtained derivatives



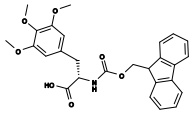
Boc-3,5-dimethyl-L-tyrosinol



Fmoc-L-meta-tyrosine



Boc-2,6-dimethyl-L-tyrosine



Fmoc-3,4,5-trimethoxy-L-Phe

[1] R. Perlikowska et al. *Peptides* 2014; 55: 145-150; [2] J. Piekielna et. al. *ACS Med hem Lett*. 2015; 6: 579-583; [3] K. Gach-Janczak et al. *Peptides*. 2017; 95: 116-123; [4] C. F. B. Praquin *Org. Process Res. Dev.*, 2011, 15 (5), 1124-1129; [5] C.E. Humphrey Org. Process Res. Dev. 2007, 11, 1069-1075

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P78

Immobilization of human serum albumin on magnetite nanoparticles coated with modified chitosan

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One of the most interesting field in magnetic nanoparticles applications is binding of biomolecules such as proteins on nanoparticles surface. To be able for such interaction magnetic nanoparticles needs surface modification. Usually magnetite nanoparticles are composed of iron oxide core coated with inorganic or organic molecules which are responsible for the oxidative stabilization and functionalization of these materials. One of the most interesting polymer for magnetic nanoparticles coating is chitosan. Its biocompatibility and presence of amino and hydroxyl groups allow to use this material in biomedical and synthetic applications.

The systems resulting from the modification of magnetic nanoparticles coated with chitosan, which lead to an increase in the number of free amino groups have a great potential of application in biomedical science. To obtain one long amine substituent in chain, the chitosan was reacted with glutaraldehyde and ethylenediamine. Materials containing two and three amine substituents were prepared in the reaction of chitosan with epichlorohydrin in alkali solution to form carbonyl groups which were treated with glutaraldehyde and finally with ethylenediamine.

Human serum albumin immobilized onto the surface of the new magnetic supports with use of N-(3-dimetyhlaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC)/N-hydroxy sulfo-succinimide sodium salt (sulfo-NHS). The amount of immobilized protein on the magnetic nanoparticles was determined by measuring the initial concentration of protein and its final concentration in supernatant after immobilization using the Bradford method. Finally, the influence of the method of drying magnetic materials on the amount of immobilized protein was investigated..

[1] M. Ziegler-Borowska , D. Chelminiak-Dudkiewicz , et al., Catalysts, (2017), 7, 14
[2] M. Ziegler-Borowska, D. Chełminiak, H. Kaczmarek, A. Kaczmarek-Kędziera, JTAC, 124 (2016) 1267-1280
[3] Marta Ziegler-Borowska, Tomasz Siódmiak, Dorota Chełminiak, Aleksandra Cyganiuk, Michał P Marszałł, Appl. Surf. 288 (2014) 641-648

Acknowledgments: This work was supported by the National Science Centregrant 2014/15/D/N27/01805.

P79

Synthesis and photodynamic properties of magnesium(II) phthalocyanines possessing menthol substituents

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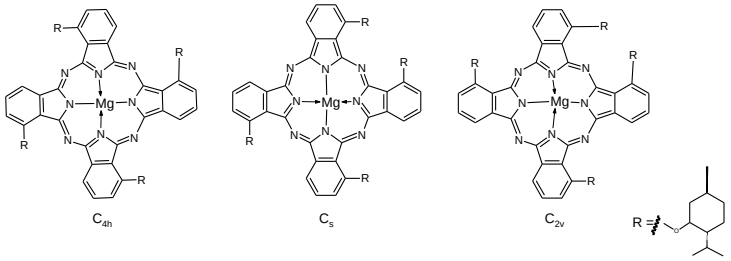
There is a number of synthetic tetrapyrrole macrocycles of which the best known are phthalocyanines. They differ from the naturally occurring porphyrins by the presence of *aza* bridges and the presence of four annulated benzene rings in the periphery. Replacement of methine bridges with *aza* groups provides a stronger binding of metal ion to the core. Moreover, introduction of substituents to the ring at position α or β and the introduction of different metal ions at the center is a practical method of modifying the properties of the macrocyclic compounds [1, 2].
Porphyrinoids have the ability to generate reactive oxygen species (ROS) under the influence of light. Among ROS, singlet oxygen is seen as one of the most important and frequently studied. Thanks to these properties, they are used as photosensitizers in photodynamic therapy (PDT) and photodynamic diagnosis (PDD), which aim to treat and diagnose cancer. The use of photosensitizers as an alternative to the treatment of bacterial infections (PACT) is also contemplated [3].

Materials and methods:



A magnesium(II) phthalocyanine with menthol substituents in the periphery was synthesized according to Linstead reaction, which resulted in formation of a mixture of regioisomers. The structures of obtained phthalocyanine regioisomers were characterized by MALDI MS spectrometry, UV-Vis and NMR spectroscopy (^{1}H NMR, ^{13}C NMR, ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC i ^{1}H–^{13}C HMBC). The ability to generate singlet oxygen was tested in two solvents: N,N-dimethylformamide (DMF) and dimethylsulfoxide (DMSO).

Conclusions: Spectroscopic and spectrometric studies shows that three regioisomers of magnesium(II) phthalocyanine with menthol substituents were synthesized. Obtained compounds exhibit the ability to generate singlet oxygen in two different solvents. This tests confirmed that resulting compound has potential to be used as a photosensitizer in photodynamic therapy or photodynamic diagnosis.

[1] Michael S. L. J. et. al. *Prog. Inorg. Chem.* 50 (2001) 473-590
[2] Rodriguez-Morgade M.S. et. al. *J. Porph. Phthalocyanines* 8 (2004) 1129-1165
[3] Allison R.R. et. al. *Photodiag. Photodyn. Ther.* 7 (2010) 61-75
Acknowledgments: The study was supported by the National Science Center under grant No. 2016/21/N/NZ7/02695.

P80

Synthesis and antimicrobial activity of 2-(3-nitrobenzylidene)amino-1H-benzimidazole derivatives

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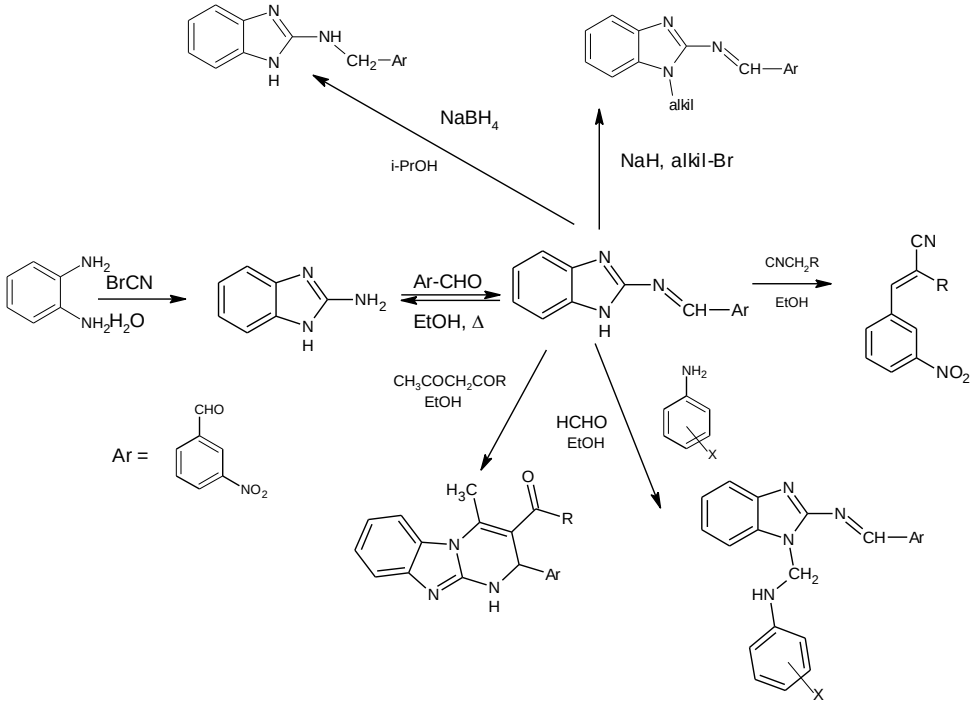
The review of scientific publication shows that the 2-amino-1H-benzimidazole structure is present in many compounds with potential biological activity. Schiff bases are very important in medicinal and pharmaceutical fields because of their diverse spectrum of biological activities such as antibacterial, antifungal as well as anticancer activity.

The aim of work was to synthesize new 2-(3-nitrobenzylidene)amino-1H-benzimidazole derivatives by various chemical ways, for example: reduction of azamethine bond, N-alkylation, Mannich reaction with primary and secondary amines and reactions with compounds containing active methylene group: selected nitriles and 1,3-diketones. The substrate for the chemical modification was Schiff base, received in reaction between 2-amino-1H-benzimidazole and 3-nitrobenzaldehyde with catalytic amount of Triflate.

Obtained new compounds were analyzed and their chemical structure was confirmed by ^{1}H NMR spectra, IR and elemental analysis. All new compounds were screened for their antibacterial activities against selected Gram positive (*Staphylococcus aureus, Enterococcus faecium*, *Enterococcus faecalis*) and Gram negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacterial strains.



P81

Chemical modyfications and antimicrobial activity of new methylbenzylidene derivatives of 2-amino-1H-benzimidazole

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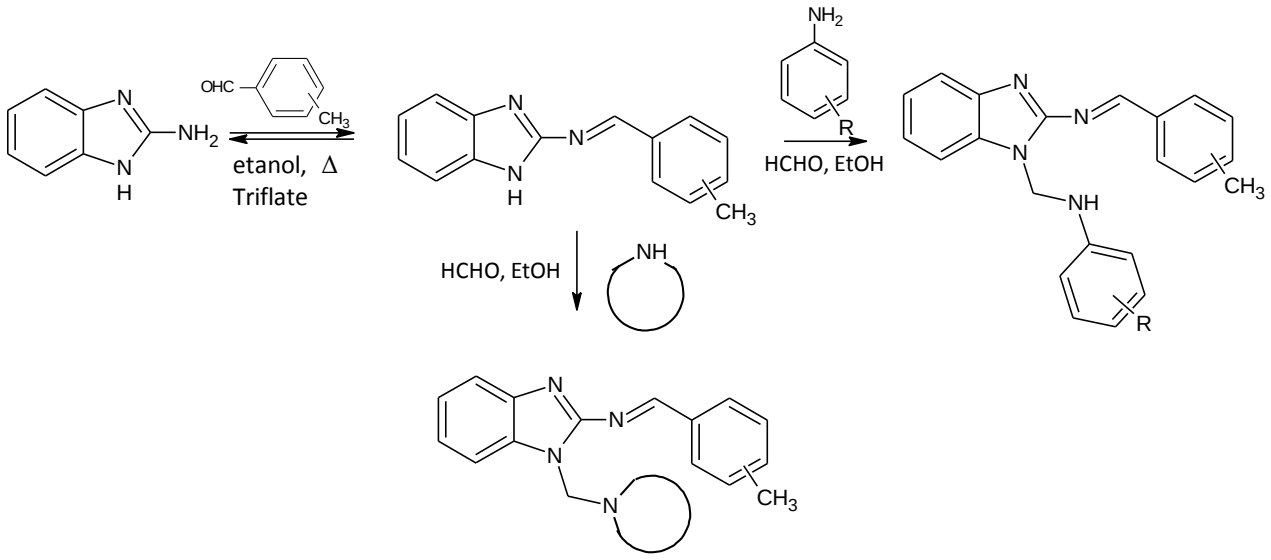
The literature review shows that, compounds containing in their structure 2-amino-1H-benzimidazole exhibit a variety of biological and pharmacological activities. Schiff bases exhibit various biological activity such as anticancer, antioxidant and analgesic as well as the inhibition of lipid peroxidation. Imines are active against a wide range of bacteria, fungi or protozoan. Mannich bases, containing various heterocyclic systems, were found to possess potent activities such as anticancer, anticonvulsant, antibacterial, antiviral, antimalarial and CNS depressant. Chemical modification of various heterocyclic compounds containing azomethine bond and aminomethyl group provides biological activity.

A series of new 2-amino-1H-benzimidazole derivatives were synthesized. In reaction of o-phenylenediamine and cyanogen bromide, the 2-amino-1H-benzimidazole was obtained. It was used as a substrate for Schiff base synthesis with methylbenzaldehyde. In the next step, obtained imine was subjected to Mannich condensation with selected primary and secondary amines in presence of formaldehyde in ethanol medium.

Structures of all obtained compounds were confirmed by the results of elemental analysis, IR and ^{1}H NMR spectra. The newly synthesized Schiff and Mannich bases were screened for their antibacterial activity against *Staphylococcus aureus*, *Enterococcus faecium*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* bacterial strains by microdilution method.



P82

Synthesis, physicochemical and pharmacological properties of new N-morpholin-alkyl derivatives of 3 substituted pyrrolidine-2,5-dione with potential anticonvulsant activity

Jolanta Obniska,[a] Anna Rapacz,[b] Anna Czopek,[a] Małgorzata Góra,[a] Krzysztof Kamiński[a]

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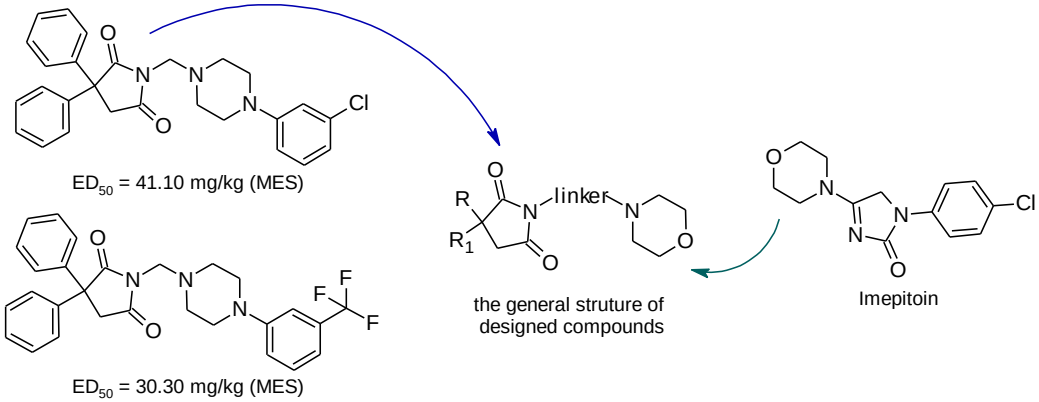
Previous researches from our laboratory have identified many compounds with potential anticonvulsant activity derived from differently substituted five-membered pyrrolidine-2,5-diones. Many of these molecules were effective in the maximal electroshock (MES) and/or subcutaneous pentylenetetrazole (scPTZ) tests.[1,2] Among them, the most promising were N-Mannich bases, representing 3-methyl-3-phenyl- or 3,3-diphenyl-pyrrolidine-2,5-diones derivatives with differently substituted 4-aryl-piperazines moiety.[1,2]

The imidazolone derivatives – imepitoin is one of the recently discovered anticonvulsant drug with broad spectrum of activity in diverse seizure and epilepsy models, which acts as week partial agonist of $GABA_A$ receptor and blocks voltage-gated calcium channels.[3] Based on key structural features of imepition and with the aim of continuing systematic SAR studies within five-membered heterocyclic compounds, in the present work we synthesized a library of 3-substituted-pyrrolidin-2,5-diones with alkylmorpholine moiety. In order to assess the role of the linker between imide ring and morpholine fragment for anticonvulsant properties we elongated it from one to three methylene units.



The compounds with ethylene and propylene linker were obtained in the cyclization of 3-substituted succinic acids with aminoalkyl-morpholine moiety, whereas the derivatives with methylene linker were prepared following Mannich reactions.

All synthesized derivatives have been evaluated for their anticovulsant activity in the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) seizure tests. The results revealed that majority of them exhibited anticonvulsant activity in the MES or/and scPTZ tests.

This study was supported by the UJCM Scientific Research Programme (K/ZDS/007864)

[1] Obniska, J. et.al. Arch. Pharm. 346, (2013) 71-82
[2] Kamiński K. et.al. Eur. J. Med. Chem. 66, (2013) 12-21
[3] Rundfeldt, C.; Löscher, W. CNS Drugs 28 (1), (2014) 29-43

P83

Optimization of molecular properties of imidazothiazole derivatives as indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors

Jacek Olczak, Julita Nowicka, Krzysztof Matyszewski, Karol Jędrzejczak, Roman Błaszczyk, Paulina Stanczak, Anna Siwinska, Agnieszka Zagozdzon, Barbara Dymek, Karolina Dzwonek, Jakub Golab, Adam Golebiowski

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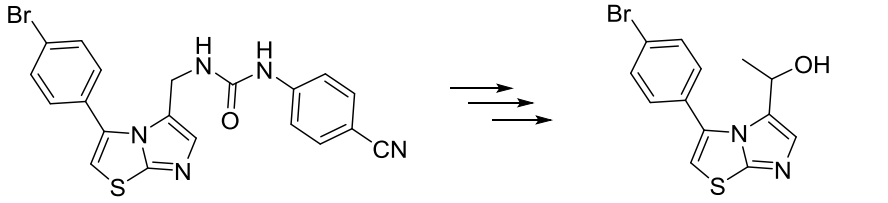
Indoleamine 2,3-dioxygenase 1 (IDO1, EC 1.13.11.52) is a heme enzyme that catalyzes the initial and rate-limiting step of the kynurenine pathway: oxidation of L-Trp to N-formyl kynurenine (NFK) by the incorporation of molecular oxygen and the cleavage of the pyrrole ring of the substrate. It is expressed by tumor cells to escape an immune response and high IDO1 expression is associated with poor prognosis in a variety of cancer types. *In vitro* and *in vivo* studies demonstrate that administration of an IDO1 inhibitor improves the efficacy of therapeutic vaccination, chemotherapy, or radiation therapy. Epacadostat - IDO1 inhibitor developed by Incyte Corporation and indoximod (1-Methyl-D-tryptophan, developed by NewLink Genetics) as a kynurenine pathway inhibitor have entered clinical trials recently. Several other pharma companies with IDO1 inhibitors in their pipeline at present or in the past are Amgen, Bristol-Myers Squibb, Curadev, Dainippon Sumitomo Pharma Corporation, IOmet Pharma, iTeos Therapeutics, and Vertex Pharmaceuticals.

Among thousands of molecules shown to inhibit IDO1, compound **17g** discovered by Toyo and coworkers [1] appeared to us as an attractive starting point for further modification.



compound **17g**, Tojo et al. [1]

hIDO1 IC50 = 77nM (reported value)
506nM (in-house assay)
Molecular Weight: 452,33
clogP = 5.48, PSA = 110.5
HBA number = 7
HBD number = 2

OAT-1615

hIDO1 IC50 = 320nM (racemic)

Molecular Weight: 323,21
clogP = 3.88, PSA = 65.8
HBA number = 4
HBD number = 1

Herein we report optimization of compound **17g** that led us to discovery of compound **OAT-1615** that is characterized by improved molecular parameters (molecular weight, clogP, PSA, number of hydrogen bond donors and acceptors) as compared to the parent compound, while maintaining high inhibitory activity against IDO1. Structure-activity relationship data along the molecular (calculated) and physicochemical (measured) properties of the newly discovered IDO1 inhibitors will be presented.

[1] Tojo S. et. al. *ACS Med. Chem. Lett.* 5 (2014) 1119-1123

P84

Searching for anticancer properties - preliminary evaluation of anticancer activity of imidazothiazinones

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Cancer is still the second most common cause of death in Europe in last few years. Since year 2002 incidence and mortality on account of all types of cancer in the World increased rapidly. [1,2]
The National Cancer Institute (NCI) is the part of the United States National Institute of Health. The Institute was established in 1937 and from that time is addressed for research and training needs for cause, diagnosis, and treatment of cancer. Developmental Therapeutics Program (DTP) is the drug discovery and development arm of the NCI. One of DTP lead programs is anti-cancer compound screening program for identifying novel chemical leads and biological mechanisms of drugs actions. [3]

Imidazothiazinones are interesting scaffolds. They were reported to be antagonists of GPR18 orphan receptor, that made them the potential drug target for inflammatory diseases and cancer immunotheraphy. [4, 5] Therefore we decided to test the series of imidazothiazinones for they anticancer properties.

As the result of our cooperation with NCI, a series of imidazothiazinones, were accepted for a primary pharmacological screening in DTP program. Compounds were tested in one concentration (10 μM) at 60 different human cancer cell lines: prostate, breast, ovarian, colon, renal, central nervous system, non-small cell lung cancer, melanoma and leukaemia. Evaluated structures exhibit low, moderate or high effect on cancer cells growth.

[1] http://epp.eurostat.ec.europa.eu/statistics_explained/index.php/Causes_of_death_statistics
[2] http://globocan.iarc.fr/Default.aspx
[3] http://dctd.cancer.gov/ProgramPages/dtp/
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Acknowledgments: Partly supported by the Polish National Science Centre project Opus, granted on the basis of decision nr DEC-2013/11/B/NZ7/04865.

P85

Antioxidant activity of some thiosemicarbazide and dicarboximide derivatives

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Reactive oxygen species (ROS) are a natural by-products of enzymatic reactions occurring in the organism. They are produced during endogenous processes (cell respiration, phagocytosis, biosynthesis, catalysis, and biotransformation) and can be also introduced from external source such as radiation, sunlight, heavy metals, bacteria, fungi, protozoa and viruses [1]. In the normal metabolism of oxygen, ROS could regulate cell signals and homeostasis. In pathological conditions, ROS cause destruction of cells and tissue, and they are also very important factors in the aging processes, oxidative stress (OS) and in the pathogenesis of various diseases such as cancer, rheumatoid arthritis, various neurodegenerative and pulmonary diseases, atherosclerosis and DNA damage [2]. Probably, OS is the result of imbalance between production of free radicals and the speed of their neutralization in the body. Antioxidants are natural or synthetic compounds which play the shielding role against OS by reacting with free radicals, chelating catalytic metals and also by acting as oxygen scavengers [3].

The aim of this study was to evaluate antioxidant activity of some thiosemicarbazide and dicarboximide derivatives. Preliminary assessment of the antioxidant activity of synthesized compounds was screened using DPPH-TLC assay. The antiradical activity was assayed using an improved $ABTS^{\bullet+}$ decolorization assay. To determine EC_{50} of samples, the technique using 96-well microplates was used. Trolox - very strong antioxidant was used as reference standard. Among examined compounds all presented significant or quite good activity with EC_{50}=8.21-17.49 µg/ml. One compound displayed antioxidant activity better than trolox.

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P86

Pharmacologic approach to proline oxidase-mediated apoptosis/autophagy as a novel, experimental anti-cancer strategy

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Extracellular matrix (ECM) plays important role in modulation of receptor-dependent signaling pathways that regulate cell growth, differentiation, gene expression, metabolism of proteins, carbohydrates and lipids. The mechanism of this process undergoes through interaction of ECM constituents (e.g. collagen) with integrin class of adhesion receptors. In cancer cells, this mechanism is disturbed. Increased activity of metalloproteinases (MMPs), that usually accompany cancer cell growth and invasion, contribute to extracellular collagen degradation and attenuation of collagen-integrin interaction. However, as well as important in deregulation of cellular metabolism is proline released intracellularly from collagen degradation products. Recent reports on the role of proline metabolism in apoptosis/autophagy gives new perspectives for cancer treatment.

The last step of collagen degradation is catalyzed by cytoplasmic enzyme, prolidase. Released proline, bearing reducing potential is considered as a stress sensor. For removal of reducing potential proline must be converted into pyrroline-5-carboxylate (P5C) by mitochondrial proline oxidase (POX) or utilized for collagen biosynthesis. POX-dependent conversion of proline into P5C generate ATP for survival (autophagy) or reactive oxygen species (ROS) that induce apoptosis. In breast cancer cells with silenced POX expression (by shRNA POX), inhibition of collagen biosynthesis by 2-methoxy-estradiol (MOE) increased intracellular proline concentration and induced autophagy, while in wild type of breast cancer cells, such conditions induced apoptosis. In this report we present novel experimental strategy to induce apoptosis in cancer cells.

The molecular mechanism of POX-dependent apoptosis involves up-regulation of collagen degradation leading to increase in prolidase activity and concentration of proline in the cytoplasm, inhibition of collagen biosynthesis and finally utilization of proline in mitochondria by POX, generating ROS-dependent cascade of processes inducing apoptosis. These studies suggest that availability of proline and high expression of POX facilitate apoptosis while low POX expression may promote pro-survival pathways in breast cancer cells. Therefore, POX-activating factors (e.g. AMPK, metformin) could be considered as a potential anti-cancer agent.

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P87

The synthesis and antibacterial activity of a new amidrazone-derived gold(III) complex

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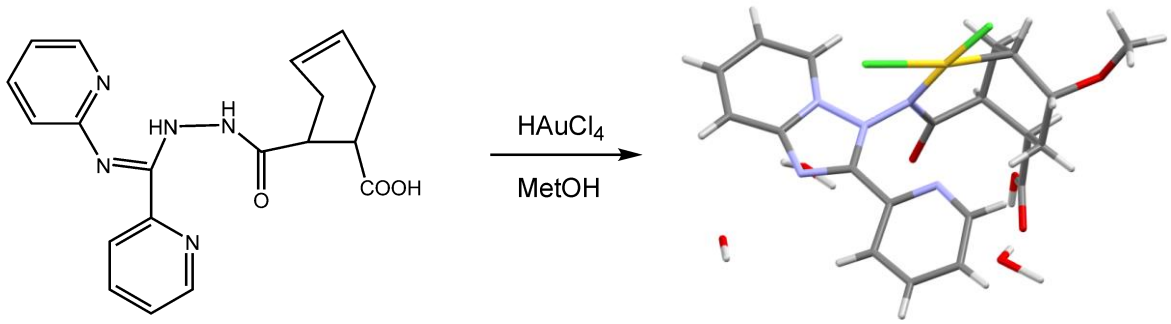
Antibiotic resistance is currently recognized as one of the biggest threats to global health. Searching for new potential antimicrobial drugs is necessity to win this race. Amidrazone constitute an interesting class of organic ligands, known to react with many transition metals. On the other hand, gold complexes have shown promising antimicrobial and antitumoral properties.

A new Au(III) complex was synthesized from a previously described amidrazone derivative [1] and tetrachloroauric acid in the presence of methanol. The cyclization process converted the amidrazone moiety into the 1,2,4-triazolo[1,5*a*]pyridine ring system, which was immediately followed by Au(III) chelation. The crystal and molecular structure of the final compound was studied by single crystal X-ray diffraction as well as by ^{1}H-^{13}C and ^{1}H-^{15}N HMQC- and HMBC-NMR spectroscopy.

Obtained complex exhibited good antibacterial activity against *Staphylococcus aureus* (MIC = 4 μg/mL) and was proved to be more potent than amoxicillin against *Bacillus subtilis* and the drug resistant strain of *Klebsiella pneumonia.*



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P88

Chemical modification of pipemidic acid and its impact on antibacterial activity of synthesized derivatives

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Microorganisms are an important element of the surrounding world and play a significant role in its functioning, but on the other hand they are undoubtedly a threat to human life and health. Humanity noticed the need to control the destructive plague of bacteria, but they have developed specific defense mechanisms for conventionally used antibiotics [1]. New medicines are therefore needed, what creates broad possibilities for researchers to search for new molecules with potential biological activity. Literature review proves that the priority is to find substances better tolerated by patients, less toxic and at the same time more effective in fighting with microorganisms [2]. An important class of compounds with broad spectrum of biological activity are substances with a 1,2,4-triazole-3-thione system in their structure. They exhibit anti-inflammatory properties [3], as well as antifungal [4], antibacterial [5], anti-cancer [6] and anticonvulsant [7] properties. In our work, we used one more important structure, namely pipemidic acid belonging to the quinolone group. The literature give examples where the combination of these elements allow to obtain a beneficial effect on the antimicrobial activity of the resulting hybrids [8]. Therefore, the presented work discusses the synthesis and antimicrobial activity of a new series of pipemidic acid derivatives.

New compounds were synthesized by a three-step synthesis. In the first step we obtained thiosemicarbazide derivatives by reacting the corresponding hydrazide with isothiocyanates. This process allowed us to obtain 16 compounds, which were then cyclized in a 2% sodium hydroxide solution to 4,5-disubstituted 1,2,4-triazole-3-thione derivatives. Finally a series of Mannich reactions between 1,2,4-triazole-3-thione derivatives, formaldehyde and pipemidic acid were performed what to obtain 16 new pipemidic acid derivatives. The chemical structure of all obtained substances was confirmed by the ^{1}H NMR and ^{13}C NMR spectra analysis.

All synthesized compounds were examined for their antimicrobial activity against Gram-positive bacteria, Gram-negative bacteria and fungi belonging to yeasts *Candida* spp. On the basis of MIC and MBC values we discovered that new pipemidic acid derivatives showed interesting antibacterial activity.

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P89

Cytotoxic and antiproliferative activity of novel octahydropyrazino[2,1-a:5,4-a']diisoquinoline derivatives in AGS gastric cancer cells

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Gastric cancer represents a major health problem worldwide. Despite a decrease in incidence in past decades, stomach cancer remains the fifth most common type of cancer and the third leading cause of cancer-related mortality worldwide. Regardless advances in the early diagnosis and treatment of gastric cancer, the side effects of chemical drugs and recuperation are still problematic. Therefore, the development of chemotherapeutic agents for gastric cancer is crucial for reducing the mortality rate of patients.

The aim of the current study was to examine cytotoxic and antiproliferative activity of the novel diisoquinoline derivatives in human gastric cancer cells (AGS). The cellular response of AGS cells to the new compounds was studied with the use of etoposide as a reference agent.

Evaluation of the cytotoxic effect of diisoquinoline derivatives was performed using MTT assay. The DNA biosynthesis was checked by inhibition of [^{3}H]-thymidine incorporation into DNA in AGS gastric cancer cells. Flow cytometry was used to investigate the distribution of AGS cell cycle. Electrophoresis was carried out to prove that the tested compounds are topoisomerase II inhibitors. Annexin V binding assay and dual acridine orange/ethidium bromide staining were applied to confirm induction of apoptosis in AGS cells.

All compounds decreased the number of viable cells in a dose-dependent manner after 24- and 48-hour incubation, although a compound 2 was a more cytotoxic agent, with IC_{50} values of 21 μM and 6 μM, compared to 80 μM and 45 μM for etoposide. Compound 2 had also the strongest time-dependent antiproliferative effect in the tested cells with IC_{50} values of 16 μM and 6 μM after 24- and 48-hour incubation, respectively. The cytotoxic and antiproliferative properties of novel compounds were associated with the induction of apoptotic cell death. The highest percentage of early and late apoptotic cells was observed after 48-hour incubation with the compound 2 (89.9%). The value was higher compared to a compound 1 (20.4%) and etoposide (24.1%). The acridine orange (AO) and ethidium bromide (EB) double staining confirmed that compound 2 possessed the strongest proapoptotic properties in comparison with untreated cells as well as with cells incubated with compound 1 and etoposide. The changes in cell morphology characteristic of apoptosis, such as chromatin condensation and membrane blebbing, were observed. The mechanism of the novel octahydropyrazino[2,1-a:5,4-a']diisoquinoline derivatives was connected with inhibition of topoisomerase II and accumulation of cells in the G_2/M phase of cell cycle.

These data strongly support (8aS, 16aS)-2,10-dimethoxy-8a,16a-diphenyl-5,6,8,8a,13,14,16,16a octahydropyrazino[2,1-a:5,4-a']diisoquinoline-3,11-diol (compound 2) as a promising agent for the treatment of gastric cancer.

P90

Solvatochromic fluorescence and antioxidant characteristics of resveratrol and its hydroxylated analogs

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Resveratrol (trans-3,4',5-trihydroxystilbene, R), commonly found in grapes and wine, is a small polyphenol that has been intensively studied in many therapeutic areas. Basic and clinical studies confirm its protective role in cardiovascular, metabolic, and age-related disorders, including neurodegeneration and some types of cancer. Moreover, numerous clinical trials are focused on the use of resveratrol as a drug or dietary supplement. Interestingly, resveratrol itself may serve as a lead structure for the development of new biologically active compounds.

It is well known that a drug molecule changes its environment many times during the way to the target receptor (from polar protic – physiologic fluid to a relatively non-polar receptor area). On the ground that physicochemical properties of a solute molecule greatly depend on microenvironment, it is reasonable to identify interactions of a potent drug molecule with its chemical environment.

The principal goal of the present study was to evaluate spectroscopic properties of resveratrol and its hydroxylated analogs A-C (Fig. 1). Two of them are known to inhibit cyclooxygenase-2 (COX-2) selectively (in contrast to non-selective cyclooxygenase inhibition activity presented by resveratrol) [1]. The 3D absorption and emission spectra of all tested compounds in the different type of solvents (protic, polar aprotic and non-polar aprotic) were made and subsequently analyzed. We aimed to find relations between the type of solvent and obtained spectroscopic data.

The presence of hydroxyl substituents in resveratrol and the other tested compounds prompted us to estimate their antioxidant activity, using DPPH (diphenylpicrylhydrazyl) assay. We have found that half effective concentration (EC50) strongly depends on the number of hydroxyl groups.

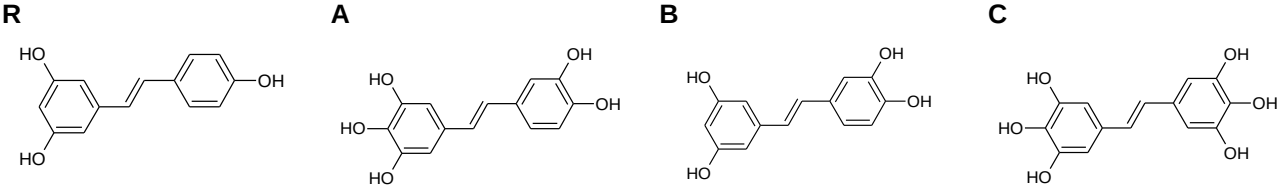

Figure 1. Chemical structure of resveratrol (R) and hydroxylated analogs (A-C).

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P91

PDB and CSD databases survey in searching of fluorine containing interactions

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The fluorine atom in organic compounds acting as an acceptor of hydrogen bond (H-bond) is considered controversial and remains the subject of many disputes. There is a lot of evidence for the existence of C-H· · · F-C hydrogen bonds, but for more electronegative donors, i.e. OH or NH, the H-bonds with fluorine is much less frequent and at the same time weaker than in the case when the acceptors are nitrogen, oxygen or other halogens.[1–3] No doubts that fluorine has become one of the most common elements used in the design and development of new drugs. Indeed, since the 1950s, over 150 fluorine-containing drugs have been released to the market which now make up approx. 20% of all pharmaceuticals.[4] It is important to determine the role of fluorine in the formation of hydrogen bonds in ligand-protein complexes to fully use its unique properties to improve the biological activity of compounds.

Herein, we report a statistical analysis of structural data and a detailed inspection of the geometric parameters of intermolecular hydrogen bonds of fluorine from the aromatic ring in structures deposited in the Cambridge Structural Database (CSD) and Protein Data Bank (PDB).

The results showed that indeed hydrogen bonds of fluorine with -CH donors are much more frequent than with the stronger electronegative donors (-OH, -NH). Interestingly, in the protein environment where fluorine is present in hydrophobic areas of the binding pocket it forms C-H···F-C H-bonds with leucine twice more frequently (21%) than with valine (12%), phenylalanine and isoleucine (10%).

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P92

Synthesis and pharmacological screening for novel phenoxyalkyl derivatives of 1,3,5-triazine as ligands of 5-HT6 serotonin receptor

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5-HT6 serotonin receptor is the most recently identified and cloned member of serotonin receptor superfamily. Since then, numerous studies proved 5-HT6R involvement in depression, anxiety, obesity and memory, making it a new, promising therapeutic target in treatment CNS disorders [1,2]. In a recent study it has been proved that 1,3,5-triazine derivatives feature high affinity towards 5-HT6 receptor [3]. The purpose of this research was to assess the effect on both affinity and selectivity by introducing modifications within aryl moiety as well as alkyl linker of the lead structure. Furthermore, in silico screening has been performed to predict P-glycoprotein inhibition and blood-brain barrier permeability of synthesized compounds. Among obtained compounds, two showed highest affinity ($K_i < 5$ nM) and selectivity towards 5-HT6 receptor.

Syntheses were performed within Student Medicinal Chemistry Club (Studenckie Koło Chemii Medycznej UJ CM). Partly supported by the Polish National Science Centre (NCN) grant UMO-2015/17/B/NZ/7/02973.

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P93

Biologically active nucleobase-derived nitrones

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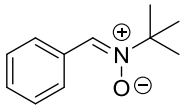
Nitrones have shown interesting biological activity in many experimental animal models [1]. They were found to be able to trap free radicals in chemical as well an in biochemical systems. Since abnormal levels of free radicals and oxidative stress have been noticed in many diseases, including stroke, cancer development, Parkinson and Alzheimer diseases. For example, the neuroprotective properties of α-phenyl-β-*tert*-butylnitrone **1** have been proved. Recent research has shown that PBN-related nitrones, derivatives of **1**, exhibit also anticancer activity toward several cancers. Various nitrones derived from (hetero)aromatic aldehydes as well as more complex moieties such as quinoline- or steroid-hybrids were studied as free radical scavengers [2]. Capability of phosphorylated nitrones and *N*-oxides containing the pyrrolidine ring (**2** and **3**) to trap various radicals has been well recognized [3,4]. Moreover, new 2-(diethoxyphosphoryl)-*N*-(benzylidene)propan-2-amine oxide derivatives **4** have been recently synthesized by Pietri et al. [5] and their antioxidant potency have been proven. Thus, a search for new therapeutics among compounds containing nitrone functionality is justified.

We designed new series of nucleobase-derived nitrones of general formula **5** and their biological activity was screened.



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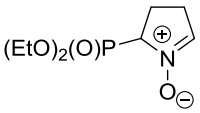

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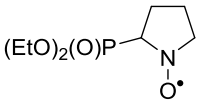

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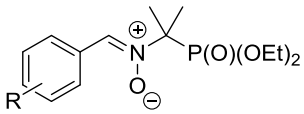
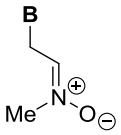


4

R = OH, OMe, NO_2, AcNH, COOH, COOEt, CF_3, Me, Cl



5

B = nucleobase (Ura, Thy, Ade *etc.*)

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P94

Anthracyclines as substrates of metabolizing enzyme carbonyl reductase 1 – consequences for cytotoxicity

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Drug metabolism is a crucial process affecting drugs activity. In case of anthracyclines, metabolic two electron reduction of side chain carbonyl moiety to hydroxyl one, catalyzed by cytosolic enzymes - particularly carbonyl reductase 1 (CBR1), leads to formation of alcohol metabolites exhibiting decreased cytotoxic properties and increased cardiotoxicity [1]. Taking into consideration the significance of this process in anthracyclines efficacy, in this study metabolism and metabolism-dependent modulation of activity of clinically relevant and experimental anthracyclines – doxorubicin, daunorubicin, epirubicin, idarubicin, amrubicin and aclarubicin, were evaluated. The purpose of the study was to determine and compare the anthracyclines metabolic stability, the influence of CBR1 on anthracyclines cytotoxicity, and their binding modes in CBR1 active site.

Metabolic stability was examined by incubation of anthracyclines with human liver cytosol and monitoring of biotransformation by LC-MS. Intrinsic clearance was determined for each drug. Investigations of CBR1-dependent cytotoxicity were conducted on non-small lung cancer A549 and A549 CBR1-transfected cell lines. Differences between IC_{50} for each drug on both cell lines were determined using MTT assay. Binding modes of studied anthracyclines were obtained by molecular docking to the protein target represented by optimized CBR1 crystal structure (PDB code 1WMA).

Studied anthracyclines indicated different values of intrinsic clearances in liver cytosol. Also, differences in anthracyclines cytotoxicity between untransfected and CBR1-transfected cell lines were found, as well as, anthracyclines binding modes with enzyme catalytic site were varied. Results increase the knowledge in field of anthracyclines metabolism and significance of biotransformation in their efficacy. Further studies in this direction may be useful for designing CBR1-avoiding anthracyclines, thus exhibiting increased cytotoxic and decreased cardiotoxic properties.

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P95

The antioxidant properties of thiosemicarbazide derivatives

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In the 21st century, an increase in the impact of civilization diseases on human life is observed. We live in constant stress, which causes overload, fatigue and disorder of the body's natural defenses. Antioxidant stress is the result of disrupting of the balance of the body between free radicals and antioxidants. Uncontrolled and excessive production of free radicals by cells can lead to tumorigenesis. Scientific knowledge about antioxidant activity is still insufficient.

Researchers searched for the source of antioxidant compounds in various types of plant materials. It has been suggested that flavonoids and other phenols may play a preventive role in civilization diseases. There are increasing number of publications on coumarins and flavonoids, which demonstrate the importance of understanding the chemistry behind the antioxidant activities of both natural and synthesized compounds, considering the pharmacological use [1]. Polyphenols possess ideal structural chemistry for free radical-scavenging activities, and have been shown to be more effective antioxidants in vitro than vitamins E and C [2].

It was found that some coumarin derivatives show better antioxidant properties than ascorbic acid.
Additionally, in the literature, pyrazole, 1,2,4-triazole and pyrrole derivatives have been described as antioxidant agents [3]. In addition, some semicarbazides exhibited antioxidant capacity comparable to that of Trolox.

In our work, we decided to investigate the antioxidative potential of thiosemicarbazide derivatives. Although these compounds exhibit a wide range of pharmacological activities, their ability to scavenge free radicals requires additional research. The antioxidant activity of the newly prepared 1-(2,4-dichlorophenoxyacetyl)-4-substituted thiosemicarbazide derivatives was determined by spectrophotometric analysis. The antioxidant concentration needed to lower the initial 2,2-diphenyl-1- picrylhydrazyl (DPPH) radical content by half (EC_{50}) was determined. The obtained data was compared with the results obtained for the standard antioxidant-Trolox solution (a synthetic derivative of vitamin E). The obtained results confirm the high biological potential of newly obtained derivatives.

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P96

Research on the synthesis and properties of new phenol derivatives as potential prodrugs for MDEPT

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According to data from the Polish National Cancer Registry malignant tumors are considered the second cause of death among Polish society. Only in 2015 in Poland there were 3600 new cases of melanoma, the most dangerous and malignant form of skin cancer. This disease is characterized by high dynamics of progress. At the turn of two decades the number of melanoma incidence increased almost threefold [1]. These statistics are alarmed and show how important is work on improving the diagnostic and therapeutic process. The key to effective therapy is early diagnosis combined with surgical intervention. Unfortunately, the rapid development and progression of cancer is the reason why in most of cases it is diagnosed in a too advanced, metastatic stage which is associated with unpleasant prognosis for patients [2]. In addition, melanoma is often resistant to traditional chemotherapy. Combination of this facts shows that melanoma remains a challenge for modern medicine. It also creates the need for further exploration and development of new therapeutic options to reduce mortality and improve control over the development of the disease [3].

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P97

New derivatives of *N'*-(2-alkylthio-4-chloro-5-methylbenzenesulfonyl)-1-(2,5-dihydro-1*H*-pyrazol-1-yl)amidine – synthesis and cytotoxic activity

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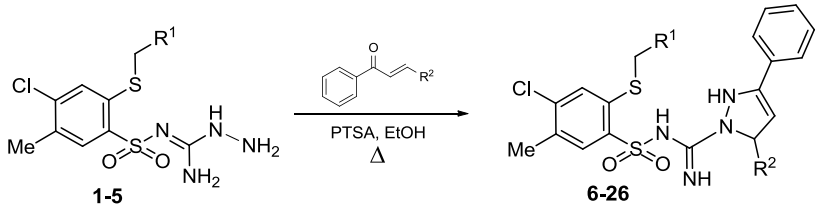
Benzenesulfonamide dreivatives containing pyrazole ring display significant cytotoxic activity against human cancer cells [1-2]. As a continuation of our studies [1-2], new derivatives of *N'*-(2-alkylthio-4-chloro-5-methylbenzenesulfonyl)-1-(2,5-dihydro-1*H*-pyrazol-1-yl)amidine **6−26** were designed. The final compounds **6−26** were synthesized by refluxing the appropriate 1-amino-2-(benzenesulfonyl)guanidines **1−5** with chalcone derivatives and 4-toluenesulfonyl acid in ethanol. The structures of compounds **6−26** were confirmed by IR, ^{1}H NMR and elemental analyses.



1-5 → **6-26**

7 R^1 = Ph; R^2 = 2-OH-C_6H_4
8 R^1 = Ph; R^2 = 4-OH-C_6H_4
12 R^1 = 4-Me-C_6H_4; R^2 = 4-OH-C_6H_4
15 R^1 = 4-Cl-C_6H_4; R^2 = Ph
16 R^1 = 4-Cl-C_6H_4; R^2 = 4-OH-C_6H_4
20 R^1 = 1-naphthyl; R^2 = 4-OH-C_6H_4
24 R^1 =  ; R^2 = 4-OH-C_6H_4

The synthesized derivatives **6**-**26** were evaluated *in vitro* by MTT assays for their activity against three human cancer cell lines: colon cancer HCT-116, breast cancer MCF-7 and cervical cancer HeLa. The most sensitive cell line was HCT-116, however, good results were also observed for HeLa cells. MCF-7 cell line was slightly less susceptible. The obtained data suggest a relation between compounds' structure and activity, mainly with regard to R^2 group. The preferred R^2 substituent is hydroxyphenyl scaffold. Compounds with nitrophenyl, chlorophenyl, or methoxyphenyl groups did not exhibit antiproliferative effect. The most prominent activity was observed for compounds **7**, **8** and **12**. The IC_{50} values against 3 tested cell lines were in the range of 13−25 μM, 12−21 μM, and 12−18 μM for **7**, **8** and **12**, respectively. Compounds **16** and **20** inhibited the growth of HCT-116 while **24** was active against HCT-116 and HeLa cell lines with IC_{50} ~ 12 μM for the three derivatives. Compound **15** displayed cytotoxic effect on HeLa cells (IC_{50} = 17 μM).

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P98

Nitrofurazone analogues: synthesis and antimicrobial properties

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The development of safe antimicrobial agents with better effectiveness is required to overcome the increasing number of cases of multidrug-resistant infections difficult to diagnose and treat [1]. One of several routes to find new chemotherapeutic agents is to modify the chemical structure of existing medicines [2]. Due to these facts we decided to synthesized nitrofurazone analogues, because nitrofurazone is an important antibacterial agent [3] and in its structure we found the hydrazide-hydrazone moiety which is known to possess interesting biological activity [4-7].

In this research we synthesized nitrofurazone analogues on the basis of the condensation reaction of various (hetero)carboxyclic acid hydrazides with 5-nitro-2-furaldehyde [8]. Synthesized compounds were identified with the use of ^{1}H NMR and ^{13}C NMR spectroscopy. The *in vitro* screening of antimicrobial properties of synthesized compounds revealed a wide spectrum of antimicrobial activity. Most of obtained compounds showed very high bactericidal effect towards *Staphylococcus* spp. ATCC and *Bacillus* spp. ATCC (MIC = 0.002 – 7.81 mg/ml and MBC = 0.002 – 31.25 mg/ml) in many cases the level of activity was far better than the activity of commonly used chemotherapeutic agents [8].

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P99

Photoprotective activity of some 5-arylidenehydantoin derivatives

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Sunscreens are top products used for protection of skin against acute and chronic consequences of ultraviolet radiation. The main active ingredients of sunscreens are organic or inorganic compounds called UV-filters. The modern UV filter molecules are expected to be not only broad-spectrum UV-absorbers but also that they will be photostable, safety and easy to formulate. Hence the search for new UV filters is compared to the search for new drugs [1]. Unfortunately, many of the currently used compounds have some limitations related to systemic absorption, endocrine disruption, contact and photocontact allergy induction and low photostability. In 2015, the popular UV filter – 3-benzylidene camphor has been banned for use in cosmetics [2], which encouraged our research group to searching for an alternative to unsafety compounds.
The aim of study was to design, synthesize and test ten compounds in group on 5-arylidenehydantoin derivatives with potential photoprotective activity. The chromophore system of 5-benzylidenehydantoin or 5-cinnamylidenehydantoin with various substituents shows the absorption in the desired wavelength range but it is difficult to be incorporated to the cosmetic formulation. Thus the chromophore system was modified by incorporating one or two ester groups by means of N-alkylation or N,N-dialkylation. The obtained compounds were incorporated to the neutral cosmetic formulations (2% w/w) and their *in vitro* photoprotective activity ($SPF_{in\ vitro}$, UVA PF, λc) and photostability were evaluated with SPF-290S Analyser (Solar Light Company, USA) and solar light simulator Suntest CPS+ (Atlas, Germany). Results indicate that they are potential UVB ($SPF_{in\ vitro}$ 1,8 to 3,1) or UVA filters (UVA PF 2,3 to 8,4) with photostability comparable to commercial UV filter 4-MBC. The safety profile of compounds was evaluated in three cell lines of human origin.Additionally the estrogenic activity of compounds was excluded by assessing effect on the proliferation of the estrogen-dependent breast cancer cell line MCF-7 in a medium that was not supplemented with hormones.

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Acknowledgements: This work was supported by funds granted to the Faculty of Pharmacy of Jagiellonian University Medical College by the Polish National Science Centre (Grant 2016/21/B/NZ7/01756) and by Funds for Statutory Activity of Jagiellonian University Medical College (K/ZDS/007826).

P100

Novel boron-dipyrromethene derivatives as potential photosensitizers for the photodynamic therapy

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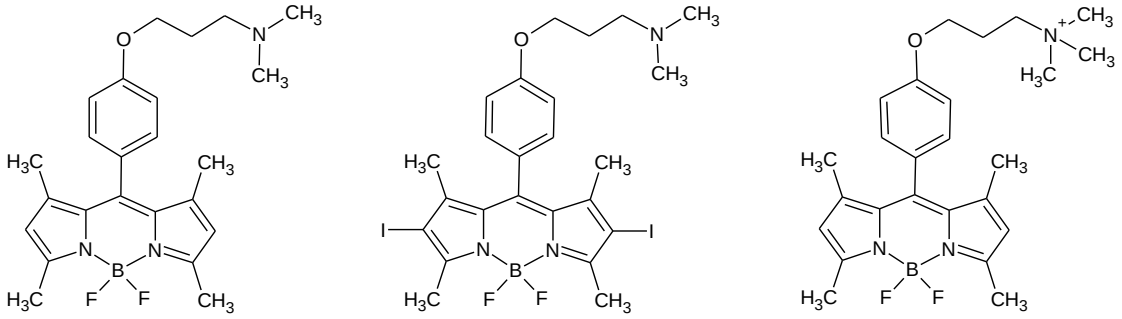
Photodynamic therapy (PDT) is a medical treatment used to cure localized cancer and noncancer diseases and also perspective modality to treat microbial induced pathologies. Antimicrobial PDT is gaining more attention due to its potential application in the treatment of different microbial infections, including those caused by antibiotic-resistant strains which are a growing worldwide health concern [1].

Boron dipyrromethene (BODIPY) derivatives are a class of dyes possessing distinctive photophysical properties and high synthetic versatility making them ideal candidates as photosensitizers for the PDT [2]. Important features of PDT agents to combat microbial cells are high quantum yield of the generation of singlet oxygen and high affinity of photosensitizer for pathogen cells. Cationic derivatives are active against both Gram(+) and Gram(-) bacteria [3].

Herein, we present synthesis, characterization and photophysical studies of novel BODIPY derivative possessing N,N-dimethylpropylamine substituent and its methylated cationic analog. Maish and coworkers demonstrated that porphyrin containing cationic N,N,N-trimethylpropylaminium substituents exhibited selective activity against Gram-positive bacteria at low, nanomolar concentrations [4].



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P101

Chitosan and phthalocyanine composites as potential PDT materials

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Photodynamic therapy (PDT) is a orm of phototherapy applied in anticancer treatment. It involves light interacting on the photosensitizing substance and generating the reactive forms of oxygen. Porphyrins belon to a group of widely used PDT photosensitizers. The aim of the current project is the designe of new photosensible materials for PDT aplications.

As part of the research photosensitizers were introduced into the biopolymer solution and subjected to irradiation. All analysed systems were characterized by infrared spectroscopy (ATR-IR), atomic force microscopy (AFM), scanning and transmission electron microscopy (SEM, TEM). The thermal stability of the obtained compounds and their polar nature were also determined using the goniometric method. The amount of singlet oxygen produced was determined in the next step, which is crucial for their potential application in photodynamic therapy. The results obtained for synthesized materials were compared with the results obtained for commercially available photosensitizers. The manufactured chitosan-porphyrin films are promising for DPT purpose.

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P102

Comparison of the activity against adenosine receptors between meta- and para- aminophenol xanthine derivative isomers

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Adenosine is the endogenous ligand of G protein-coupled adenosine receptors, of which four subtypes exist: A_1, A_{2A}, A_{2B}, A_3. They exhibit distinct distribution profiles in tissues, and different pharmacological and biochemical properties. Modulation of adenosine receptor activity may be useful in the treatment of disorders of the cardiovascular, respiratory, immune and central nervous system [1]. For a number of years, research has aimed at developing new selective adenosine receptor ligands [1,2]. On the basis of earlier studies, two series of amide derivatives of tricyclic xanthines with m- and p-aminophenol substituents at N9 position of the xanthine core were investigated.

The designed compounds were synthesized according to previously described procedures [3,4]. The xanthine core was obtained and subsequently the heterocyclic ring system was extended and connected with an appropriate phenol derivative. Then the corresponding ester was obtained and an alkylamine was introduced yielding the final products. Affinities of the synthesized tricyclic xanthine derivatives for the adenosine receptor subtypes were determined in radioligand binding studies. Affinity to A_1R was tested on rat brain cortical membranes, to A_{2A}A, A_{2B} and A_3R on human adenosine receptors expressed in Chinese hamster ovary (CHO) cell membranes.

Drug-like properties (logP, logS, toxicity, drug score) of the obtained compounds were evaluated by using the OSIRIS program [5].

The analysis of the structure-activity relationships revealed that the compounds with p-aminophenol moiety and aliphatic diamines have higher affinity for A_1, A_{2A} and A_{2B}R. On the other hand m-aminophenol and cyclic diamine derivatives in most cases have shown better affinity to all adenosine receptors. Compounds from both groups with aliphatic amines were weakly active or inactive toward all AR.

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P103

Synthesis of new 4-arylmethylthio-pyridine-3-sulfonamide derivatives with potential biological activity

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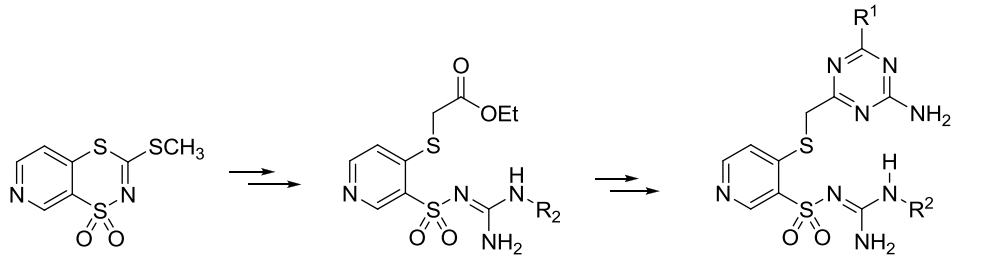
Pyridine-3-sulfonamide constitute an important class of biologically active compounds. As a continuation of our studies [1-3], new series of 2-{4-[(4-amino-1,3,5-triazin-2-yl)methylthio]-3-pyridinesulfonyl}guanidine derivatives **6-21** were designed. The final compounds were synthesized by refluxing the appropriate ethyl 2-{3-[*N*-(diaminomethylene)sulfamoyl]piridin-4-ylthio}acetates **2-5** with corresponding biguanide hydrochlorides in sodium methanolate. The structures of compounds **2-21** were confirmed by IR, ^{1}H NMR and elemental analyses.



1 **2-5** **6-18** (R^2 = H) **19-21** (R^2 = -N=CH-alkyl/aryl)

The compounds **6-21** were evaluated *in vitro* by MTT assays for their activity against three human cancer cell lines: colon cancer HCT-116, breast cancer MCF-7 and cervical cancer HeLa. The most sensitive cell line was breast cancer (MCF-7), however, good results were also observed for HCT-116 cell lines. The most prominent activity was observed for compounds **8**, **17** and **20**. The IC_{50} values against 3 tested cell lines were in the range of 61−74 μM, bearing R^1 = 4-ClPhNH-, 1-indoline or 4-morpholine moieties, respectively.

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P104

Synthesis of new 1,3-oxazole derivatives with potential immunomodulatory activity

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The functionalization of the 1,3-oxazole ring at the 2-, 4- and 5- positions is convenient approaches to obtain potentially bioactive compounds. The 2-substituted 5-amino-1,3-oxazole-4-carbonitriles induce various biological responses, including anti-cholinesterase activity [1] and inhibition of monoamine oxidase (MAO) [2]. Furthermore, these compounds are used as intermediates in the preparation of new heterocyclic systems, most notably annulated 1,3-oxazoles. Oxazolo[5,4-d]pyrimidines display various biological activities such as inhibition of receptor tyrosine kinases (RTK) and adenosine receptor antagonism [3]. The 5-amino-4-cyano-1,3-oxazole provides also a drug-like template for synthesis of a small-molecule libraries [4].
The new 2-substituted 5-amino-4-cyano-1,3-oxazoles **1** was previously obtained from commercially available aminomalononitrile *p*-toluenesulfonate (AMNT) and corresponding acid chloride in 1-methyl-2-pyrrolidinone (NMP). The present work was aimed to develop an efficient synthesis method of new oxazolo[5,4-d]pyrimidines **2** from compounds **1** (Fig. 1). For newly synthesized derivatives **2**, spectroscopic data has been determined and biological properties are examined.

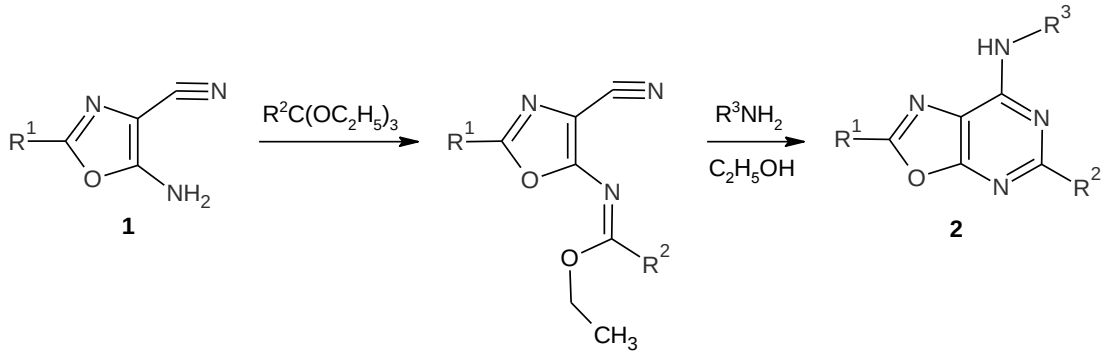

Fig. 1. Scheme of synthesis of new oxazolo[5,4-d]pyrimidines.

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P105

Chemometric analysis of retention parameters of chosen NSAIDs

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The potential biological activity of a molecule largely depends on its lipophilicity. It is a physicochemical property of principal importance in drug discovery and development. It affects three phases of drug activity: pharmaceutical, pharmacokinetic and pharmacodynamics action. Lipophilicity is defined as the affinity of a drug for a lipid environment. It has become a critical parameter in the pharmaceutical industry, which indicates the relationship of a drug with their biological, pharmacokinetic and metabolic properties. Understanding the relationship between the activity, structure and the physicochemical properties of the examined compound provides the opportunity to identify its potential bioactivity. The selection of structural parameters that are important for the behavior of molecules in a biological medium is facilitated by applying the chemometric analysis.

The aim of this study was to determine the lipophilicity of chosen NSAIDs (coxibs and oxicams) using thin-layer chromatography (TLC). The chromatographic measurements were carried out on TLC plates with different absorbents (RP-2, RP-8, RP-18, silica gel modified by -NH_2, -CN i -DIOL groups). Series of drug's solutions were analyzed in the presence of two organic modifiers in various concentrations (methanol, acetone). The average value of R_F was calculated and converted into R_M values. Based on linear dependence of R_M on the concentration of organic modifier in the mobile phase for the tested compounds, by extrapolation to the zero concentration of the methanol or acetone, R_{M0} values (equivalent to logP) were determined.

In order to examine and visualize similarities and differences between lipophilicity, properties of organic solvents and adsorbents, and grouping of the compounds based on chemical properties, chemometric analysis were performed. Correlations were made using Hierarchical Cluster Analysis (HCA), Principal Component Analysis (PCA) and PARAFAC. The R_F values were arranged as a four-way tensor with the following dimensions: 8 compounds x 11 concentrations x 6 stationary phases x 2 solvents. Then, the tensor was analyzed with HCA based on Euclidean Distance in two modes: unfolded along compounds and unfolded along 12 combinations of stationary phase and solvent.

Next, the transposed matrix (chromatographic systems x compounds) were subjected to PCA. The comparison of compounds shows visibly and clearly that the two groups form two distinct groups. The comparison of chromatographic systems clearly separates -DIOL and -NH_2 plates. On the contrary, -CN plates behave similarly to all RP plates and the differences between them are not connected with any solvent or stationary phases trend.

A three-way PARAFAC with orthogonality constraint along the first mode was performed on the original tensor. It can be seen, that the compound groups are clearly separated in the space of the second PARAFAC vector. Oxicams have large values of PARAFAC2, whereas coxibs have this value much smaller. The factor associated with concentrations exposes the nonlinearity of the chromatographic response. -NH_2 and DIOL are a distinct cluster, which is similar to HCA analysis results.

P106

Halogen bonding in serotonin transporter ligand-receptor complexes

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Halogen bonds (XB) are specialized non-covalent interactions known to chemists since XIX century, but only recently they were recognized as important in biological molecules. According to the IUPAC definition, halogen bond is “a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity”.[1] Docking of a recently obtained polypharmacological compounds[2] to a crystal structure of SERT, revealed their possible affinity towards this target. Because five out of six FDA approved SSRIs possess halogens in their structure, which suggests important role of halogen bonds in interaction between ligand and SERT, a halogen-enriched combinatorial library was prepared which was further analysed using the docking protocol. Obtained database contained a ranking list of structures with increasing potential affinity towards SERT. Subsequently, a group of compounds was selected and synthesized, and their affinity towards SERT was measured. The poster presents obtained results.

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P107

Design, synthesis and biological evaluation of novel chalcone derivatives as potential microtubule targeting agents

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The microtubular system with its dynamic nature characterized by the polymerization and depolymerization of α,β-tubulin heterodimers, is essential in a variety of cellular processes, including maintenance of cell shape, regulation of motility and cell division [1]. Because of the latter function microtubules are one of the significant and more successful molecular target for designing of new active molecules possessing anticancer activity. Among this group of compounds chalcones (1,3-diphenylprop-2-en-1-on derivatives) represent a promising class of compounds with a simple structure, taking the possibility of extensive structural modifications that improve their natural anticancer properties.

Their mechanism of action including the inhibition of tubulin assembly by binding to the colchicine binding domain resulting from their structural similarity to other active ligands that have the same molecular target (e.g. combretastatin A-4, CA-4). Our successful investigation on novel potent inhibitors of tubulin polymerization from group of CA-4 thioderivatives [2] prompted us to extend our research on chalcone scaffold.

Herein we present synthesis, molecular modelling studies, X-ray structural characteristics and biological evaluation of novel chalcone thioderivatives. Their antiproliferative activity was determined using panel of human cancer and normal cell lines, tubulin inhibition, and cell cycle analyses.

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Acknowledgements: The project was supported by research grant OPUS (UMO-2015/17/B/ST4/03701) financed by Polish National Science Center.

P108

One-pot synthesis and antiproliferative activity of novel double-modified derivatives of the polyether ionophore monensin A

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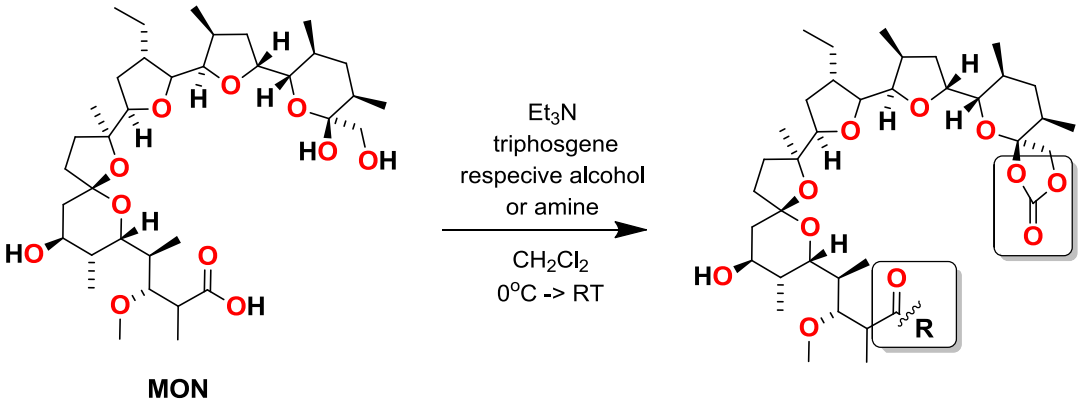
Monensin A (MON) is an ionophore antibiotic of natural origin and it is isolated from the bacterial strain *Streptomyces cinnamonensis*. MON exhibits a wide spectrum of biological and pharmacological properties, such as antibacterial, antifungal, antiviral and antiproliferative activity. The high MON activity is related to the possibility of complexation of metal cations and transport them through natural lipid membranes that change the Na^+/K^+ concentration gradient. As a result, intracellular pH is disturbed and ultimately apoptosis occurs [1, 2].



MON

New MON derivatives such as double-modified ester-carbonates and double-modified amide-carbonates were obtained by a new and efficient one-pot synthesis with triphosgene as the activating reagent and the respective alcohol or amine. All new derivatives were tested *in vitro* for their antiproliferative activity against two drug-sensitive (MES-SA,LoVo) and two drug-resistant (MES-SA/DX5, LoVo/DX) cancer cell lines, and were also studied for their antimicrobial activity against different *Staphylococcus aureus* and *Staphylococcus epidermidis* bacterial strains [3].

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[2] Antoszczak M. et. al. in: Brahmarchi G. *Bioactive natural products* (2015) *Wiley-VCH*, Weinheim, Germany
[3] Klejborowska G. et. al. *Chem Biol Drug Des* (2018) doi: 10.1111/cbdd.13320

P109

Synthesis and biological evaluation of imidazo[1,2-a]imidazole derivatives

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Numerous derivatives of 1-aryl-5,6(1H)dioxo-2,3-dihydroimidazo[1,2-a]imidazoles have effect on the central nervous system (CNS). They present analgesic, neuroleptic and anxiolytic activity. Matosiuk and co-authors[1] had synthesized series of 1-aryl-5,6(1H)dioxo-2,3-dihydroimidazo[1,2-a]imidazoles with high affinity to μ-opioid receptor. Their antinociceptive properties were evaluated on behavioral tests. What is crucial, these compounds showed no depressive effect on the respiratory system, and their pharmacological action was only partially reversible when an antagonist (naloxone) was used.

The aim of our work was to obtain a number of new derivatives of the imidazo[1,2-a]imidazole and to determine their biological activity. Structure of the final products was confirmed with ^{1}H NMR spectroscopy and TLC chromatography (Fig. 1).

All obtained 1-aryl-5,6(1H)dioxo-2,3-dihydroimidazo[1,2-a]imidazoles were referred to biological evaluation as the potential novel CNS-active agents. *In vitro* studies with usage of radioligand binding assay revealed no affinity of the title compounds to the orthosteric centre of μ-opioid receptor on nanomolar levels. While, the intrinsic activity tests at the antagonist mode using cAMP assay applying DAMGO as reference agonist showed that 1-(4-methylphenyl)-2,3-dihydro-1H-imidazo[1,2-a]imidazole-5,6-dione demonstrated a weak antagonistic effect (EC50 = 21nM, Emax = 71%). Lack of orthosteric affinity and inhibition efficacy of DAMGO may suggest that this compound is a negative allosteric modulator of μ-receptor (NAM).

The obtained results suggest a different mechanism of activation than this characteristic for classical opiates and thus require further investigation to determinate their effect on opioid receptors.

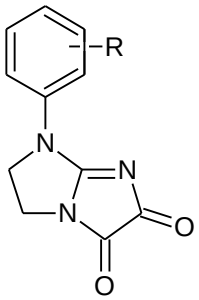

Fig. 1

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P110

Synthesis of N-(4-metoxyphenyl)-1*H*-tetrazol-5-amine based compounds possessing antimicrobial activity

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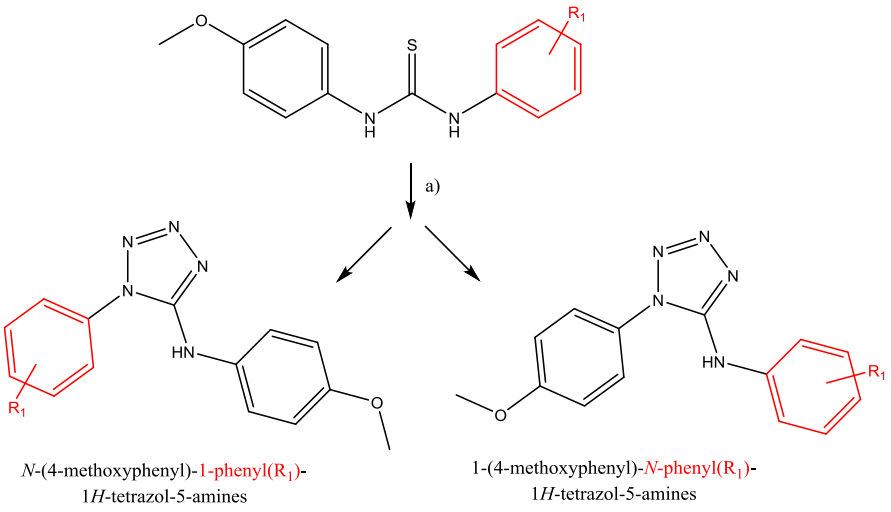
Tetrazol-5-amine incorporating structures are of high importance pharmacologically due to the to their wide spectrum of applications. Tetrazole moiety has poly-nitrogen electron-rich planar structural features, which allows their derivatives to easily bind with various enzymes or receptors through weak interactions, including hydrogen bounds, hydrophobic effect, coordination bonds or van der Waals force. Moreover, biological and physicochemical properties of tetrazole derivatives can be modified by the attachment of several structurally distinct substituents to the heterocycle ring. This feature makes them desirable main scaffolds in many studies aimed at the development of new bioactive compounds. Furthermore, the tetrazole ring can be used as an attractive linker to combine or stabilize different pharmacophore fragments to generate special functionalized molecules. Tetrazole-based derivatives have been successfully developed and commonly used as clinical drugs such as antihypertensives Lorsartan and Valsartan, antibiotics Flomoxef and Cefonicid, and antinociceptive Alfentanil to treat various diseases.



Scheme 1. a) Reaction conditions: NaN_3, $HgCl_2$, DMF, Et_3N, 6h, 20°C.

Predefined thioureas were synthesized for transformation to tetrazoles. In all derivatives 1-(4-methoxyphenyl)thiourea was constant scaffold. Tetrazoles can be obtained using four main methods. In our specific synthesis 1,5-disubstituted tetrazoles were generated via oxidative desulfurization of 1,3-disubstituted thioureas using sodium azide as external nucleophile. Mercury (II) chloride was used as desulfurization agent. The reaction was carried out at room temperature in DMF and in the presence of triethylamine (Scheme 1). Assumptions based on preliminary experiments results have been confirmed, for designed reaction two products occur simultaneously in similar yields.

This research has been dedicated to identify new class of antibacterial drugs. Interesting candidate was found possessing antibacterial activity against standard and hospital Gram positive and Gram negative bacterial strains.

P111

Influence of double-modification on the anticancer activity of salinomycin derivatives

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Salinomycin (**SAL**) has been used in veterinary medicine because of its activity against Gram-positive bacteria. In 2009 there was a breakthrough in the perception of **SAL** as a novel chemotherapeutic drug candidate. The tests conducted on ~16.000 chemical compounds proved that **SAL** shows amazing ability to kill breast cancer stem cells (CSCs), which are the subpopulation of extremely difficult to control auto-renew cells responsible for disease recurrence and metastasis. **SAL** activity could not match any cytostatic drug tested, and the best of them was nearly 100 times weaker [1]. Just after three years **SAL** was approved for testing on humans [2], and in recent years, many scientific papers describing the remarkable anticancer properties of **SAL** have been published [3]. In the light of these reports, a very interesting direction of research is rational, chemical modification of **SAL** molecule, which should significantly improve the biological activity of resulted derivatives compared with the parent compound.

Previous studies have shown that either acylation of the C20 position or esterification/amidation of the C1 carboxylate moiety is beneficial in terms of **SAL** biological properties. Here, we present the first analogs combining such modifications. Evaluation of the antiproliferative activity against a series of cancer cell lines showed that the activity of several of the doubly modified analogs surpasses that of commonly used cytostatic drugs in the LoVo/DX multi-drug resistant cell line. All analogs were tested against primary acute lymphoblastic leukemia cells; three were more potent than **SAL**. Further studies revealed that selected analogs induced characteristics of apoptotic cell death and increased expression of p53. Importantly, using an *ex vivo* model of breast tumor, tumor cell viability significantly decreased after treatment with **SAL** or its selected double-modified derivative in a time-dependent manner. The present findings indicate that double-modified **SAL** derivatives constitute promising lead compounds for targeting various types of cancer [4].

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Acknowledgements: MA wishes to acknowledge the Polish Science Centre (NCN) for financial support through the grant SONATA (2016/23/D/ST5/00242) and the Foundation for Polish Science (FNP) for a scholarship START.

P112

Overexpression of PGC-1α alters sphingomyelin metabolism in skeletal muscle cells

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Sphingomyelin is a lipid-derived compound located mostly in the outer layer of the plasma membrane as well as in the membranes of organelles [1]. This sphingolipid breakdown is responsible for the generation of bioactive compounds, such as ceramides, through the increased activity of specific sphingomyelinases (acidic, alkaline and/or neutral) [2]. Recently, PGC-1α has been revealed as a crucial regulator of cellular lipid homeostasis through the coactivation of various transcription factors [3]. In our study for pharmacological activation of PGC-1α we used pyrroquinoline quinone (PQQ). Because PQQ modulates oxidative cellular capacity via activation of PGC-1α, a number of pathways associated with fatty acid metabolism remains under PQQ control. In accordance with this notion, sphingolipid metabolic routes may be targets for PQQ. Therefore, the aim of our study was to determine changes in sphingomyelin metabolism of L6 muscle cells exposed to several concentrations of PQQ (0.5, 1 and 3 μM) in two incubation times (2 and 24 h). First, we evaluated the efficiency of PGC-1α activation at mRNA and protein levels with the use of real-time PCR and Western Blot methods. The cellular content and composition of sphingomyelin was determined by gas liquid chromatography. The protein expression of alkaline and neutral sphingomyelinases was analyzed by Western Blot. We revealed that PQQ significantly elevated PGC-1α level with the highest efficiency for 0.5 μM (mRNA: 2 h: +108%; 24 h: +179%; protein: 2 h: +24%, 24 h: +22%; $p<0.05$) and 1 μM (mRNA: 2 h: +123%; 24 h: +208%; $p<0.05$). The protein amount of neutral and alkaline sphingomyelinases was not significantly changed in cells treated with PQQ. However, prolonged (24 h) exposure to all doses of PQQ substantially diminished sphingomyelin content (0.5, 1 and 3 μM vs. ctrl: -15%, -24%, -15%, respectively, $p<0.05$), whereas short-time (2 h) incubation declined its level after 1 and 3 μM (-13%, -27%, respectively, $p<0.05$). As regards to fatty acid composition of sphingomyelin, we observed a decrease in saturated fatty acids content after prolonged (0.5, 1 and 3 μM vs. ctrl: -15%, -26%, -16%, respectively, $p<0.05$) and short-term treatment with PQQ (1 and 3 μM vs. ctrl: -16%, -28%, respectively, $p<0.05$). The level of unsaturated fatty acids declined after 2 h incubation with 3 μM (-19%, $p<0.05$) and under long-term (24 h) exposure to 0.5 and 1 μM of PQQ (-16%, -17%, respectively, $p<0.05$). In summary, PGC-1α stimulates sphingomyelin hydrolysis, what may contribute to the initiation of many cellular signaling pathways.

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[2] Straczkowski M. and Kowalska I. *Rev. Diabet. Stud.* 5 (2008) 13-24
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Acknowledgements: The study was funded by National Centre of Science grant no. N/NCN/MI/17/001/1118 and by Medical University of Bialystok grants no. N/ST/ZB/16/013/1118 and N/ST/ZB/17/011/1118. Agnieszka Mikłosz is supported by the Foundation for Polish Science (FNP).

P113

Rosmarinic acid changes the expression of Tn and T antigens in CRL-1739 gastric cancer cells

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Introduction: Glycosylation is the most common posttranslational modification of proteins that can be classified into two major types: N- and O-glycosylation. O-glycosylation is initiated by the polypeptide α-N-acetylgalactosaminyltransferase (ppGalNAcT), which catalyzes the addition of GalNAc to Ser/Thr to form Tn antigen. Core 1 (T antigen) is formed by the addition of a Gal unit to Tn antigen by a β-glycosidic bond [1, 2]. Tn and T antigen overexpression occurs in many types of cancer cells including gastric, colon, breast, lung, esophageal, prostate, and endometrial cancer [3].
Rosmarinic acid (RA) is an ester of caffeic acid and 3,4-dihydroxyphenyllactic acid, often occurring in many plants, e.g. in the family Lamiaceae or Boraginace. It is known that RA exhibits several beneficial, biological activities, such as anti-inflammatory, anti-cancer, anti-bacterial, anti-viral and others. A general mechanism of its action is not fully understood [4].
Because studies of the effects of RA action in gastric cancer cells are limited we decided to evaluate the influence of RA on the expression of Tn and T antigens in gastric cancer cells.

Aim: The aim of our study was to determine changes in Tn and T antigens expression in gastric cancer cells line CRL-1739 after RA treatment as well as gene expression of glycosyltransferases involved in the biosynthesis of examined sugar structures.

Materials and methods: The research was performed on CRL-1739 gastric cancer cells cocultured for 24 h with 100 and 200 μM RA. To assess the level of glycosylated structures, ELISA-like tests and Western blotting analyses with biotinylated VVA and PNA lectins were performed. ppGalNAcT and C1GalT1 glycosyltransferases gene expression was evaluated using real-time PCR.

Results: ELISA test revealed inhibitory effect of RA on both antigens expression in cell lysates and culture medium. In Western blotting, stimulatory effect of higher dose of RA on Tn antigen in cell lysates was revealed. T antigen expression increased with 100 μM RA and decreased with 200 μM RA. *ppGalNAcT* and *C1GalT1* increased upon 100 μM RA action.

Conclusions: The data suggest potential usefulness of RA as a complementary agent supporting chemotherapy in cancer treatment.

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P114

Prolidase-dependent apoptosis in MCF-7 cells

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Proline metabolism is implicated in apoptosis/autophagy in cancer cells. Conversion of proline into pyrroline-5 carboxylate (P5C) catalyzed by proline dehydrogenase/proline oxidase (PRODH/POX), generate ATP for protective autophagy or reactive oxygen species (ROS) that may induce apoptosis. We considered that proline availability to this pathway may represent switching mechanism of apoptosis and autophagy. Cytoplasmic concentration of proline is dependent on activity of prolidase (proline releasing imidodipeptidase). We made expression constructs of prolidase and obtained stable transfection in MCF-7 breast cancer cells (MCF-7^{PL}). Increased proline level in the cells was achieved by providing substrate for prolidase, glycyl-proline (Gly-Pro). In order to targeting proline for PRODH/POX –dependent pathway we blocked proline utilization in collagen biosynthesis, using 2-metoxyestradiol (MOE). Prolidase overexpression in MCF-7^{PL} contributed to 3 fold increase in the enzyme activity, while it significantly decreased cell viability, DNA biosynthesis compared to wild type MCF-7 cells. Although, no significant effect of studied compounds (MOE and GlyPro) on the mean percentage of living cells was found in MCF-7 cultures, in MCF-7^{PL} cells MOE decreased cell survival to about 35% and Gly-Pro to about 20% of control. MOE inhibited also DNA biosynthesis in both cell lines and GlyPro evoked inhibitory effect on the process only in MCF-7^{PL} cells. However, an addition of MOE+Gly-Pro contributed to inhibition of DNA biosynthesis in both cell lines. The inhibitory effect of studied compounds on cell viability, DNA in MCF-7^{PL} was accompanied by increase in the expression of AMPKs, mTOR, HIF-1α, Atg5, Atg7 and Beclin-1 without any effect on the expression of active caspase-3 and caspase-9. These findings suggest that up-regulation of prolidase activity contribute to pro-survival phenotype of MCF-7 cells.

Acknowledgements: This work was supported by the National Science Center (number of project: N/ST/ZB/17/004/2214).

P115

Synthesis and pharmacological evaluation of some 1-[1-alkyl(aryl)-4,5-dihydro-1*H*-imidazo]-3-substituted urea derivatives

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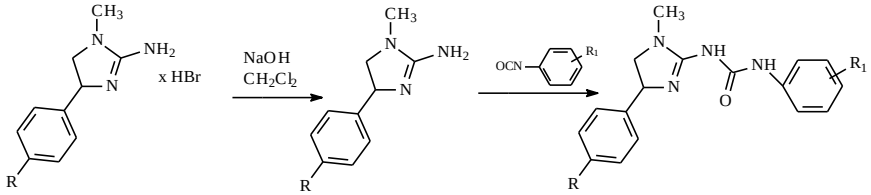
One of the most important tasks of modern psychopharmacology is the search for new, more effective forms of therapy. Despite the undeniable, rapid development of medical science, pharmacotherapy of some diseases still remains ineffective and does not bring the expected results, and in addition, it often involves the occurrence of a large number of nuisance side effects. Therefore, there is a need for continuous search for new molecules that will be characterized by high efficiency, rapid achievement of the optimal therapeutic effect and a limited amount of adverse reactions. Careful pharmacological screening of potential candidates such as this study is a part of these efforts.

The tested compounds are a group of 1-[1-alkyl(aryl)-4-aryl-4,5-dihydro-1*H*-imidazo)-3-substituted urea derivatives with expected potential activity in the central nervous system (CNS). Modification of the chemical structure makes it possible to obtain new compounds with pharmacological activity, higher selectivity and fewer adverse effects. Compounds from this group were evaluated in behavioral tests. They exhibited strong impact on the central nervous system (CNS) of laboratory animals and suggest potential antinociceptive, antidepressant and antipsychotic activity.

All tested compounds significantly reduced the number of writhing episodes in mice after injection with 0.6% acetic acid, 1-(1-methyl-4-phenyl-4,5-dihydro-1*H*-imidazo)-3-(4-metylphenyl)urea and 1-(1-methyl-4-phenyl-4,5-dihydro-1*H*-imidazo)-3-(2,6-dichlorophenyl)urea inhibited the number of head twitches, and 1-(1-methyl-4-phenyl-4,5-dihydro-1*H*-imidazo)-3-(4-metylphenyl)urea additionally decreased body temperature of mice, indicating the involvement of serotonin system in its mechanism of action. Moreover, the same compound and also compound 1-[1-methyl-4-(4-methylphenyl)-4,5-dihydro-1*H*-imidazo]-3-phenyl urea significantly arrested hyperactivity induced by amphetamine. This effect is often connected with antipsychotic activity of the substances, suggesting their usefulness in the treatment of schizophrenia symptoms. Furthermore, it is very important to underline that none of the new compounds neither reduced the motility of mice nor impaired their coordination, which could influence the animals' behavior in other tests.
Novel compounds were synthesized from appropriate 1-alkyl(ary)-4,5-dihydro-1*H*-imidazo-2-amines and appropriate isocyanate in dichloromethane (Scheme 1).



Obtained results of pharmacological studies indicate, that compound 1-(1-methyl-4-phenyl-4,5-dihydro-1*H*-imidazo)-3-(metylphenyl)urea seems to be the most promising substance from the group, in the context of treatment of mental disorders. However, further studies are needed to confirm this assertion.

P116

Synthesis and biological evaluation of new secondary and tertiary pyridine-3-sulfonamide derivatives

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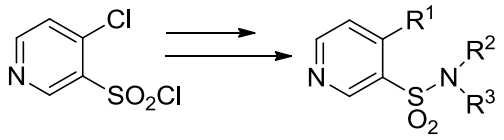
Since the discovery of antibacterial activity of sulfanilamide, the aryl- and heteroarylsulfonamides have become a well-established group of compounds known for having a broad spectrum of biological activity. Secondary and tertiary sulfonamides are defined by the single or double *N*-alkyl or *N*-aryl substitution of the primary sulfonamide SO_2NH_2 moiety. This type of modification results in their wide range of biological activity and application in the treatment of: CNS diseases (like alzheimer and cognitive diseases, anxiety and insomnia or migraine),cardiac disorders, inflammation diseases, glaucoma or as anti-virals or anti-cancer agents [1]. Considering the research field of sulfonamides with anti-cancer activity, the structural similarity of secondary *N*-arylsulfonamides to colchicine and related to this targeting of tubulin polymerization, seems to be particularly promising research direction [2].



R^1 : piperazine , hetaryl
R^2, R^3: H, alkyl, aryl

Thus, basing on our previous research on multidirectional activity of 4-substituted pyridine-3-sulfonamide derivatives [3, 4], we have undertaken the synthesis of new secondary and tertiary pyridine-3-sulfonamide derivatives. A series of new compounds have been obtain in multistep reactions from 4-chloropyridine-3-sulfonyl chloride and submitted for biological screening.

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P117

Fluorescent triazolyl spirooxazolidines: synthesis and NMR stereochemical studies

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Carbon-heteroatom chemistry is a method of choice for rapid construction of complex molecules. In the recent decade, its various applications flourished thanks to the Click chemistry approach. Herein, we present the synthesis of 1,2,3-triazolyl spirooxazolidines, bearing the fluorenylmethoxycarbonyl (fmoc) substituent, using a combination of C-X formation reactions. Both, the triazolyl spirooxazolidines and their N-fmoc derivatives, synthesized as inseparable diastereoisomeric mixtures, exhibit complex structure with multiple aromatic ring currents causing spectacular diastereotopic effects.

Thanks to the application of 2D-NMR spectroscopic methods and a multilevel computational approach including a medicinal chemistry – inspired conformational search, PM7 semmiempirical and DFT-based geometry optimization, finalized with DFT-GIAO NMR shielding constant calculation, we were able to investigate the conformational space and assign cis/trans configuration in complex NMR spectra. For the obtained fmoc derivatives we recorded UV-VIS absorption and emission spectra. The obtained compounds contain pharmacophoric groups characteristic for endocannabinoid system modulators- CB1 receptor ligands or FAAH inhibitors.

P118

Synthesis, structure and activity of arylpiperazines

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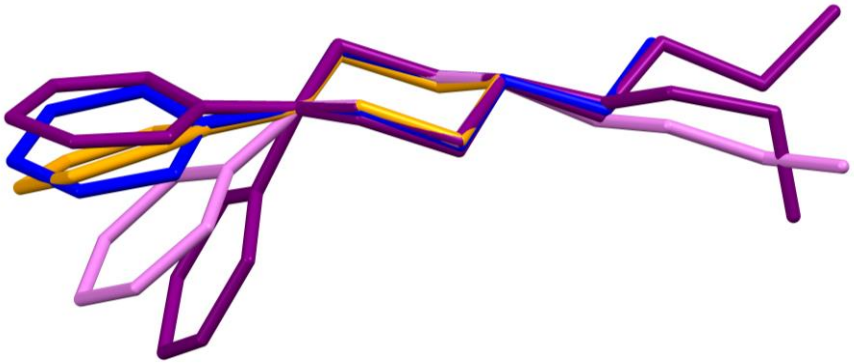
Aryl-Piperazines are a well-known class of serotonin receptor ligands and their molecular structures, conformations and activities were subjects of numerous studies [1,2].
In this study, we present four new structure (Figure).



The interesting finding of the study was statistics on substituents found in *ortho* position in axially oriented aryl ring at N1. Most often the aryl was 2-pyrimidine, 2-pyridine or 2-fluorophenyl, i.e. the ortho substituents of the aryl ring are preferentially either lone pair or fluorine, which both are small and bear partial negative charge.

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P119

Design and synthesis of new Mannich base derivatives of pyrrolo[3,4-*d*]pyridazinone as potential antinociceptive and anti-inflammatory agents

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Effective and safe treatment of different types of pain is a challenge in the field of medicine and pharmacy. Some derivatives of pyridazin-3(2*H*)-one are known as potent analgesic and anti-inflammatory agents with significantly reduced ulcerogenic effect [1]. Similarly, derivatives of pyrrolo[3,4-*d*]pyridazinone present a wide range of biological activity e.g. antibacterial, anticancer or analgesic. When considering analgesic activity, some derivatives of pyrrolo[3,4-*d*]pyridazinone were even stronger than morphine [2,3]. This fact was a powerful prompt to design and synthesis of new analgesic and anti-inflammatory compounds, bearing pyrrolo[3,4-*d*]pyridazinone scaffold, which would be deprived of adverse effects characteristic for NSAIDs, especially gastrotoxicity.

We report herein the synthesis of some novel Mannich base derivatives of pyrrolo[3,4-*d*]pyridazinone as potential analgesic agents. In order to reduce ulcerogenicity we turned carboxyl group into hydrazide and, in the next step, obtained the ring of 1,3,4-oxadiazole-2-thione. Such modification allows to receive derivatives possessing promising analgesic and anti-inflammatory activity, but devoid of gastrointestinal toxicity [4, 5]. In the last step of synthesis derivatives of pyrrolo[3,4-*d*]pyridazinone were condensed with formaldehyde and different secondary amines e.g. piperazines or piperidines with different substituents on 4 position, in order to receive Mannich bases. Structures of new compounds were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and element analysis techniques.

According to literature and our own previous investigations, presence, in the structure of Mannich base derivatives of pyrrolo[3,4-*d*]pyridazinone, both the ring of 1,3,4-oxadiazole-2-thione and 4-substituted piperazine/piperidine moiety could by essential for pharmacological activity and low toxicity of new compounds as well.

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P120

Induction of proline oxidase-dependent apoptosis by acetylenic derivative of betulin in endometrial cancer cells

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It was suggested that proline availability may represent an important factor inducing apoptosis in cancer cells [1]. We provided hypothesis that compounds of dual action: inhibiting collagen biosynthesis (the most effective proline utilizing process) and inducing prolidase activity (the enzyme releasing proline from imidodipeptides e.g. Gly-Pro) may result in increase in intracellular proline level. Mitochondrial enzyme proline oxidase (POX) converts proline into Δ1-pyrroline-5-carboxylate. During this process electrons are transported to electron transport chain producing ATP for survival or they directly reduce oxygen, producing reactive oxygen species that may induce apoptosis [2]. We studied several betulin derivatives [3] among which we found its acetylenic derivative 28-O-propynoylbetulin (proBet) exhibiting prolidase-inducing and collagen-inhibiting activity.

Our data show that proBet is almost twice stronger inhibitor of collagen biosynthesis than betulin in endometrial cancer (EA) cells expressing high POX level. The mechanism of collagen downregulation was found at the level of NF-κB p65. This transcription factor inhibits expression of α1 and α2 chains of type I collagen. The decrease in collagen biosynthesis in proBet treated cells was correlated with increase in prolidase activity and expression as well as elevated intracellular proline concentration. Betulin and proBet evoked comparable cytotoxicity against EA cells. However proBet induced apoptosis more efficiently than Bet. This was a result of activation of caspase-9 and caspase-3 in proBet treated EA cells. Therefore higher effectiveness of proline utilization in mitochondria by POX may explain the more pronounced pro-apoptotic potency of proBet versus betulin.

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P121

Polyamine conjugates with bicyclic systems as potential anticancer agents

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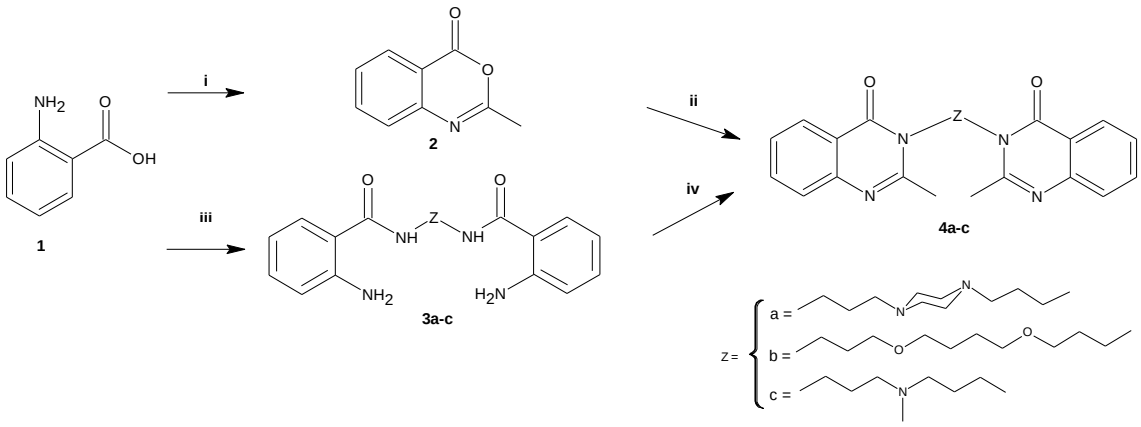
Our quest for new anticancer drugs is focused on symmetrical polyamine conjugates with bicyclic systems designed in agreement with bisintercalators' structural requirements. As a part of our research we obtained polyamine derivatives with 2-methylquinazolin-4(3*H*)-one 4a–c: via conversion of internal amidine salts formed in the reaction of 2-methyl-4(*H*)-benzoxazin-4-one with 0.5 equiv. of an appropriate polyamine a–c according to the mechanism described by Errede et al. and Stanczak et al. [1-3] or direct formation from bisanthranilamides in an excess of acetic anhydride (Scheme 1). Structures of obtained compounds were confirmed by ^{1}HNMR, ^{13}CNMR, elemental analysis and X-ray structure analysis. Antiproliferative activity of compounds 4a-c against the PC–3 prostate adenocarcinoma cell line, the DU–145 prostate carcinoma cell line and the MCF–7 mammary gland adenocarcinoma cell line was evaluated [4].



Scheme 1. Synthesis of polyamine derivatives with terminal quinazoline moieties. Reagents and conditions: (i) $(CH_3CO)_2O$, reflux, 3 h; (ii) H_2NZNH_2, CH_3CN, reflux, 1 h, NaOHaq, rt, 24 h; (iii) CDI, DMF or CH_3CN, rt, 3 h; (iv) $(CH_3CO)_2O$, reflux, 3 h

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P122

The proapoptopic effect of novel tricyclic 1,2,4-triazine derivatives in HT-29 colon adenocarcinoma

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Apoptosis is the programmed cell death with characteristic morphologic and biochemical changes such as shrinkage of the cell, fragmentation into membrane-bound apoptotic bodies etc. This type of cell death is triggered by cascade activation of caspase family. We can distinguish two apoptotic pathways: intrinsic and extrinsic. Defects in apoptosis represents an important role in progression of cancers. One of the hallmarks of cancer is avoiding apoptosis by cancer cells. Targeting cellular death pathways may be a potential target for therapeutic treatment in all cancers [1].

We have designed a novel series of tricyclic 1,2,4-triazine derivatives that might have a potential anticancer effect. Recently we have proved that novel synthesized compounds significantly decreased cell viability, biosynthesis of DNA and induced apoptosis in AGS gastric adenocarcinoma cells. The aim of our study was to evaluate the cytotoxic and proapoptopic effect of tested compounds against HT-29 - colon adenocarcinoma cell line. The induction of apoptosis was determined using annexin V and propidium iodide, and the cells were stained with acridine orange and ethidium bromide.

The novel tricyclic 1,2,4-triazine derivatives had a significant cytotoxic effect in HT-29 colon adenocarcinoma comparable to roscovitine. We showed that the tested compounds led to apoptosis in the analyzed cell line. Further study will be required to see the detailed molecular mechanism of action of novel series of tricyclic 1,2,4-triazine derivatives.

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P123

The molecular mechanism of apoptosis by novel diisoquinoline derivative OM-86II with anti-MUC1 in AGS gastric cancer cells

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Mucins are a family of major glycoproteins present in the mucus of the apical surface of most ductal epithelium. The first identified membrane mucin was MUC1 and it was also the first that was characterized structurally. For the past 30 years mucin 1 has been considered as a possible therapeutic target due to its up-regulation, lost polarization and aberrant glycosylation in many adenocarcinomas. A new strategy aimed at increasing the anticancer therapy effectiveness is to combine monoclonal antibodies with anticancer agents. Monoclonal antibodies against MUC1 block its functions which may increase the response of tumor cells to chemotherapeutic agents and increase their therapeutic effect [1].

We have proved in our previous study that novel diisoquinoline derivative (OM-86II) combined with monoclonal antibody against MUC1 significantly decreased the viability and strongly induced apoptosis in AGS gastric cancer cells. The aim of the presented study was to investigate the effect of anti-MUC1 antibody with new diisoquinoline derivative (OM-86II) on the concentration of $ERK_{1/2}$, NF-κB and p53 engaged in apoptosis in AGS gastric cancer cells using confocal microscopy bioimaging.

The results of the study demonstrated that combined treatment of OM-86II and anti-MUC1 antibody decreased the expression of $ERK_{1/2}$ and NF-κB, and increased the expression of p53. Our study proved that the apoptosis occurred dependently with p53.

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Acknowledgements: The study was supported by National Science Centre (Grant DEC-2017/01/X/NZ7/01315).

P124

Application of FMO-EDA calculation to study of ligand-receptor interaction

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Quantum mechanical calculations for biological systems are usually too computationally expensive; however, one relatively new method fragment molecular orbital (FMO), allows the calculation of energies of large systems in a reasonable time. Additionally, the FMO might reveal key ligand–protein interactions that would be difficult to detect using, for example, simple molecular mechanical methods. Next, a pair interaction energy decomposition analysis (PIEDA) can be performed to calculate the ligand–amino acid residue interactions in terms of the electrostatic, exchange-repulsion, charge transfer energies, and correlation (dispersion) contributions [1,2]. The FMO methodology was successfully applied to various large biological systems [3-6].

In this study the structure of long-chain arylpiperazines complexed with serotonin receptors has been investigated by means of quantum mechanical methods. At the beginning, the test compound was docked to receptors and next optimized with ONIOM method. For thus obtained structures FMO-EDA calculations were performed.

Results shed some lights on the interpretation of the experimental results concerning the affinity to receptors, as well as they provided the reasonable binding energies and binding patterns of ligand-protein interactions.

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P125

New class of TRPA1 antagonists based on purine-2,6-dione and benzimidazole scaffolds with potential analgesic and anti-inflammatory activity

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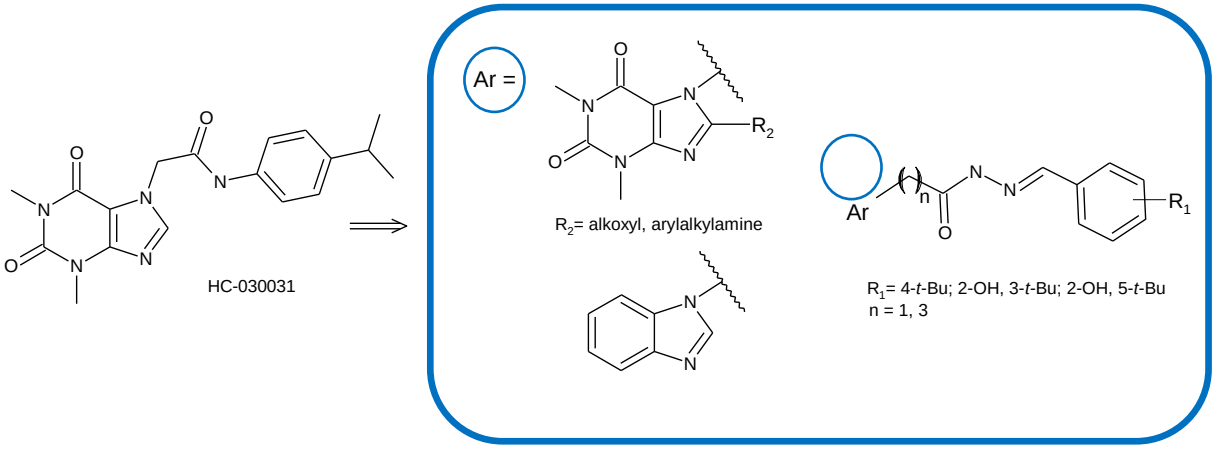
Chronic pain e.g. neuropathic pain has high prevalence around the world. It significantly decreases quality of patients' life, occupational functioning, and general mood. Despite recent progress in understanding the pathophysiological mechanism, diagnosis and treatment of neuropathic pain, many patients remain refractory to, or intolerant to the existing pharmacological treatment.
TRPA1 channel antagonists are considered as one of the most relevant strategies in the search for novel analgesics for the treatment of inflammatory and neuropathic pain syndromes [1].
Based on our encouraging finding of purine-2,6-dione derivatives as analgesic and anti-inflammatory agents [2,3] and inspired by the structure of HC-030031, a selective TRPA1 blocker we designed and synthesized a new series of 1,3-dimethyl-2,6-dione and 1*H*-1,3-benzodiazole derivatives with hydrazide moiety as a new class of TRPA1 antagonists.



For the new compounds, biological evaluation for TRPA1 antagonistic properties was performed using the kinetic fluorescent determination of calcium influx in human TRPA1 transfected HEK-293 cells.
Some of the evaluated compounds showed a percentage of channel inhibition at evaluated concentrations higher or similar than that of reference HC-030031. The potential binding mode analysis in the TRPA1 site was performed for the most potent antagonists from the evaluated series. The potential analgesic and anti-inflammatory activity was observed *in vivo* in formalin test in mice, in which pain is mediated *via* the TRPA1 channels.

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P126

Erythropoietin significantly enhances the antitumor activity of LFM-A13 in murine colon cancer model

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Background: Bruton's tyrosine kinase (BTK) is non-receptor tyrosine kinases involved in the activation of signaling pathways responsible for the maturation and viability of the cells. BTK has previously been described to be overexpressed in colon cancers. This kind of cancer often accompanied by anemia, which is treated with erythropoietin supplement.
Purpose: The goal of the present work was to evaluate the effects of combination therapy with erythropoietin beta (Epo) and LFM-A13 (BTK inhibitor) in murine models of colorectal cancer.
Experimental Design: Nude mice were inoculated with adenocarcinoma cells and treated with Epo and LFM-A13. All processes were done in accordance with the guidelines for animal experiments and the protocol approved by the Local Ethics Committee (31/2013). After a single-week acclimation period, the animals were randomized into two groups. The mice in the first group have injected subcutaneously on the dorsal side with 50 μl suspension containing $1x10^8$ DLD-1 cells in PBS; while the second group of mice with 50 μl suspension containing $1x10^8$ HT-29 cells in PBS.
Results: The combined administration of Epo (600 IU/ml) and LFM-A13 (10 mg/kg) significantly reduces the rate of growth of tumor cells while it showed high-profile safety with no induce nephrotoxicity, hepatotoxicity, or changes in the hematological profile.
Conclusions: Our findings demonstrate that Epo significantly enhances the antitumor activity of LFM-A13. The results of our study indicate the potential use of a combination of Epo and LFM-A13 as an effective therapeutic approach for patients with colorectal cancer.

P127

Synthesis of 3-carboxyalkyl-5-(pyridinylmethylidene)-2-thioxo-1,3-thiazolidin-4-ones as potential antimicrobial compounds

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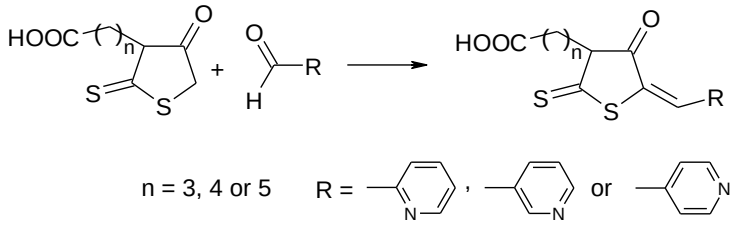
The search for new compounds with antimicrobial and antifungal activities is a significant challenge for modern medical chemistry. One of the currently tested groups of compounds are 2-thiothiazolidine-4-one derivatives commonly named as rhodanines [1]. Previous studies have shown that the presence of nitrogen atom in an arylidene substituent at C-5 position is essential for the increase of the antibacterial activity of rhodanine derivatives [2].

In order to study the influence of the nitrogen atom position in an arylidene substituent on antibacterial activities, we have synthesized a series of 3-carboxyalkylrhodanine derivatives containing pyridinolidene substituents at C-5 atom. The condensation procedure of 3-carboxyalkylrhodanine acids with pyridine aldehydes was carried out applying a previously reported procedure [3] in accordance with the Knoevenagel condensation mechanism.



The obtained compounds were tested against antibacterial and antifungal activities. All derivatives showed moderate activities against selected gram-positive bacteria, while they were not active against tested gram-negative bacteria and yeast.

For one of the presented compound (n=3) the crystal and molecular structure with the use of X-ray diffraction method was determined. Two molecules of the investigated compound are connected into a dimer by strong hydrogen bonds O-H···N formed by the carboxyl group and nitrogen atom in R substituent. This type of dimer was not previously observed in known crystal structures of 3-carboxyrhodanine derivatives.

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P128

Search for potential anti-Alzheimer's disease therapy within a group of molecules with anti-oxidant properties targeting cholinesterases and serotoninergic system

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Alzheimer's disease (AD) is one of the global public health priorities, as it is the leading cause of dementia in aging population of western countries [1]. Although extensive research to elucidate exact causes of AD and to find new treatments has been carried out for many years, the disease remains incurable and leads inevitably to death of AD patients.

Pathophysiological features of AD include impairment of cholinergic neurotransmission and oxidative stress within cholinergic neurons in brain areas responsible for cognitive and behavioural functions [2]. According to the well-established cholinergic theory of AD, increasing of acetylcholine levels in central nervous system alleviates symptoms of AD. Such effect can be achieved by inhibiting cholinesterases (e.g. butyrylcholinesterase, BuChE) or blocking 5-HT_6 receptors (5-HT_6Rs). The use of 5-HT_6R antagonists seems to be very promising strategy in the treatment of AD, as they possess also anxiolytic and antidepressant activity, which could be very beneficial for AD patients [3].

Complex nature of AD prompts scientists to the search of multifunctional molecules, which could interact with more than one important biological target, thus offering potentially more effective treatment of AD.

Herein we present a series of novel multifunctional ligands combining BuChE inhibitory activity with 5-HT_6R antagonism and potent anti-oxidant properties. Screening of 5-HT_6R antagonists based on N_1-4-piperazinindole moiety against BuChE revealed their ability to moderate inhibition of the enzyme. In order to increase the relative activity towards BuChE we synthesized series of N_1-phthalimide derivatives of 4-piperazinoindole. Among the synthesized molecules, compound KS-24 revealed multifunctional profile of activity (K_i 5-HT_6R = 150 nM, IC_{50} eqBuChE = 3,4 μM) and turned out to possess very strong anti-oxidant activity, much higher than that of vitamin C itself (169% in FRAP assay). Such unique profile of activity with strong anti-oxidant properties allows to classify compound KS-24 as an interesting starting point for further search of novel, effective anti-AD therapies.

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P129

Search for new inhibitors of AcrAB-TolC efflux pump of *Enterobacter aerogenes* among piperazine arylideneimidazolone derivatives

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Efflux pumps are considered as key contributors to multidrug resistant phenotype of bacteria. They are membrane transporter proteins that actively extrude out of the bacterial cells variety of antimicrobial agents, thereby reducing their intracellular concentrations to levels that are insufficient for induction of antibacterial effect [1]. The tripartite efflux complexes AcrAB-TolC play an essential role in the acquisition of multidrug resistance in numerous species of Gram-negative bacteria. Due to strong involvement of AcrAB-TolC efflux pumps in therapeutic failure, intensive research efforts have been made to discover new molecules able to block this kind of membrane transporter that would restore lethal effects of anti-infective agents against clinically relevant pathogens [2]. To date, several EPI compounds that act against the AcrAB-TolC efflux pump have been described in the literature, nevertheless, none of them has been successfully introduced into the market [3].

Our previously conducted studies have shown that piperazine arylideneimidazolone derivatives exhibit great ability to inhibit AcrAB-TolC efflux system presented in *Enterobacter aerogenes and Escherichia coli* bacteria [3,4]. In this approach, the modulatory effect of a new series of piperazine arylideneimidazolone derivatives was evaluated on AcrAB-TolC exporter in *E. aerogenes*. The mechanism of action of all molecules under investigation and their membranotropic effect was assessed by employing real-time efflux assay (RTE), fleroxacin accumulation assay, nitrocefin hydrolysis assay, as well as by monitoring the influx or efflux of molecules tested on the real-time basis. The results of the study have indicated that none of compound tested exert antibacterial effect against *E. aerogenes* strains enrolled in the experiments. Moreover, molecules under investigation do not enhance the activity of selected for the study antibiotics, including chloramphenicol, erythromycin, norfloxacin, and doxycycline. Although compounds are devoid of antibiotic adjuvant properties, they are able to promote the accumulation of the fluorescent dye 1,2'-dinaphthylamine (1,2'-DNA) through the inhibition of its efflux outside bacterial cells overexpressing AcrAB-TolC. Accumulation assay performed with the use of naturally fluorescent quinolone antibiotic fleroxacin confirmed EPIs properties of compounds tested. Since good EPI candidate cannot permeabilize the outer membrane of bacteria, the influence of compounds on the cell envelope was assessed by nitrocefin hydrolysis method. The outcomes of the assay pointed out that none of compound tested at the dose of 100 µM affected membrane permeability of bacteria. In conclusions, the study allowed to identify several potent hydantoin based modulators of the clinically relevant AcrAB-TolC system in *E. aerogenes* bacteria. In a therapeutic context, this could open new perspectives for rational design and synthesis of new agents that are capable to restore the activity of various antibiotic families affected by membrane-associated resistance processes.

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P130

Synthesis of new derivatives of quinazolin-2-one with potential biological activity

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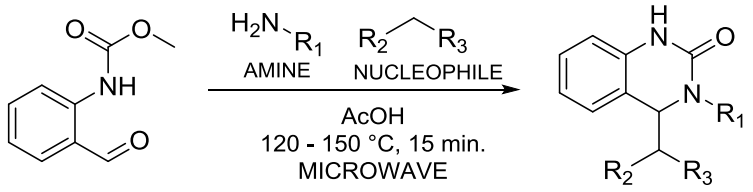
Quinazoline- and quinazolinone-derivatives constitute an important group of pharmacologicaly-active compounds. As inhibitors of enzymes and receptor ligands they have been investigated for decades and found application in treatment of various prevalent diseases (e.g. doxazosin, methaqualone, erlotinib) [1].
The work described herein is a continuation of chemical and pharmacological studies in the group of derivatives of 3,4-dihydroquinazolin-2(1H) –one with potential biological activity. [2-4] The aim of the project was to obtain a series of new 3,4-dihydroquinazolin-2(1H)-one (1,2,3,4-tetrahydroquinazolin-2-one) derivatives for the purpose of chemical and biological studies. As the main method of synthesis, facile, fast and environmentally-friendly microwave-assistedthree-component cyclisation was applied. [2-4] Considering the simplicity of the method and the functional group compatibility (e.g. EWG, carbonyl) this transformation has proven useful in medicinal chemistry projects - as a source of easily-accessible building blocks or final structures.



Using different amines and nucleophiles a series of various 3- and 4-substituted 3,4-dihydro-1H-quinazolin-2-ones was obtained in good yields. The use of “new” types of nucleophiles allowed us to obtain a new types of substitution in position 4 (including e.g. nitrille, phthalimide or barbituric acid). Several of the obtained compounds were used as intermediates for further modifications (e.g. Huisgen 1,3-dipolar cycloaddition). The obtained derivatives are being used in chemical and biological studies carried out in our team.

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P131

Regulation of activity of bacterial adenylate kinases

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Molecular architecture of adenylate kinases (AK) is described with three domains: CORE responsible for the enzyme stability, and LID and NMP related to the catalytic activity. AKs catalyze the opposite reactions of phosphate transfer between ATP and AMP or between two ADP molecules. By affecting the levels of adenine nucleotides, AKs control the cellular energy levels and regulate the homeostasis and are involved in inter-cellular signalization. Also they regulate many endo-energetic intra- and extracellular processes such as the hormone secretion, transport in cell nucleus, or synthesis and repair of DNA [1]. Adenylate nucleotides are involved in different processes, including blood platelet aggregation, tissue repair, but also myocardial infarction, Alzheimer disease, epilepsia or inflammation. Therefore, development of regulators of AK activity might be an important element of treatment of different diseases. So far, only di-adenosine pentaphosphate Ap5A or similar compounds were reported to inhibit the AK activity [2], but no activators are known.

Adenylate kinases from the thermophilic bacteria *Bacillus stearothermophilus* (Bs, gram-positive) *and Aquifex aeolicus* (Aa, gram-negative) were selected for the research on their regulation. The LID domain in the Aa kinase is shorter by 7 amino acids from the corresponding domain in Bs (long form). Based on the similarity of heteroatom distribution to the natural substrates, the Schiff bases derived from camphor were selected and tested as possible regulators of the AK activity at 50/100 μM concentration. The network of AK – Schiff base interactions was expected to mimic to certain extend the AK – substrate interactions. The Schiff bases of interest differ in the chirality of the camphor C2 and C3 atoms with OH and imine substituents, as well as substituents in the aromatic moiety. Crystal structure of Schiff bases revealed the presence of intramolecular resonance assisted H-bonds (RAHB) involving the OH and imine NH groups. As a consequence, the only polar group available for AK activity regulation is the camphor OH. Only weak regulation of adenylate kinase from Aa by selected Schiff bases was found, and it depends on the presence of hydrophobic substituents in the phenyl moiety and chirality of C2. Contrary, activity of AK from Bs was increased 2-2.5 times for the ATP/AMP synthesis and reduced by 15-70% for the ADP synthesis. Results suggest that efficiency of the investigated Schiff bases can be related to their binding near the LID domain of AK, between two substrate binding sites, and possibly to their assist in the phosphate transfer between two ADP substrates. The observed differences in the regulator action might be related to the LID architecture.

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P132

Adenylate kinase as a new potential target for modulating cellular hypoxic responses in pulmonary hypertension

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Pulmonary hypertension (PH) is a progressive disease characterized by increased pulmonary arterial pressure and inward vascular remodeling, leading to right ventricular failure and death. Despite many scientific efforts, there is currently no cure for PH. The recently emerged metabolic theory places mitochondria at the center stage for our understanding of PH pathogenesis and for the development of novel therapeutic options. The metabolic dysfunction in PH is manifested by glycolytic shift where mitochondrial glucose oxidation is suppressed contributing to the antiapoptotic and proproliferative phenotype of the pulmonary cells. For these reasons, proteins involved in cellular metabolism and mitochondrial activity are more frequently considered as potential therapeutic targets for PH.

Such a candidate is adenylate kinase 4 (AK4), a mitochondrial enzyme which is essential for energy and metabolic homeostasis. However, the role of AK4 in the pathogenesis of PH remains unknown. In the present study, we investigated a role of AK4 in hypoxia driven cellular responses of murine and human pulmonary cells. AK4 expression was shown to be increased in chronic hypoxia mouse model representing group III of the PH classification (PH due to lung disease and/or hypoxemia) and in both pulmonary artery smooth muscle cells (PASMC) and endothelial cells (PAEC) exposed to hypoxia. In addition, we found increased level of AK1 isoenzyme in patients with idiopathic pulmonary arterial hypertension suggesting a potential diagnostic relevance of AK. AK4 expression is also upregulated in PASMC following the stimulation with transforming growth factor β (TGF-β) which is known to increase the stability of the hypoxia-inducible factor-1α (HIF-1α), and excessive TGF-β–mediated signaling is implicated in the pathogenesis of PH. Our study demonstrates that AK4 regulates the activation status of adenosine-monophosphate-activated protein kinase (AMPK) in PAEC. AMPK is an important metabolic player, critical for the regulation of cell proliferation, migration and apoptosis under hypoxia, and has recently emerged as a potent therapeutic target for the treatment of PH. By performing fluorescence- and luminescence-based functional assays, we found that siRNA-mediated downregulation of AK4 results in antiapoptotic and proproliferative phenotype of PAEC and PASMC under hypoxia, respectively. Finally, we identified new downstream targets of AK4, such as metabolic enzyme hexokinase II, protein kinase ERK1/2, proliferation marker cyclin D1, and proapoptotic players, including BAX and caspase 3.

The results suggest that AK4 might contribute to beneficial effects on the pulmonary vasculature under hypoxia and the development of AK4 activators could be a new therapeutic option for pulmonary hypertension.

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P133

Synthesis and antimicrobial activity of new 5-methyl-7-phenyl-pyrido[3,4-d]pyridazine-1,4-dione derivatives

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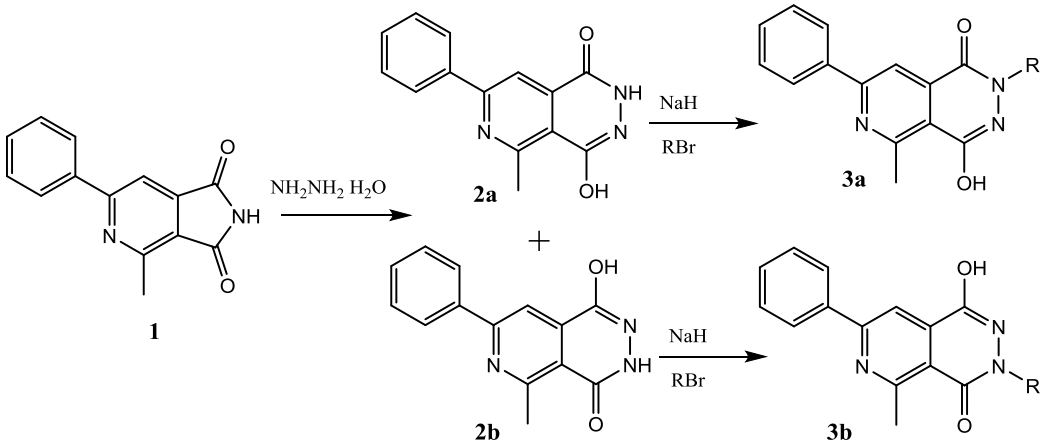
There are the six structural isomers of the bicyclic ring system containing pyridine moiety condensed with a pyridazine ring. Pyridopyridazine derivatives have been the subject of research on their biological activity. The most active pyridopyridazines are the [3,4-*d*], [2,3-*c*] and [2,3-*d*] isomers. Most of them show anticancer, analgesic, diuretic, antimicrobial activity and also effects on the nervous and immune system [1]. The broad spectrum of biological activity of pyrido[3,4-*d*]pyridazine derivatives is the main of reason for the preparation of new compounds containing this scaffold.

The aim of this study was the synthesis of new 5-methyl-7-phenyl-pyrido[3,4-*d*]pyridazine derivatives with potential antibacterial activity. Treatment of obtained before [2] 4-methyl-6-phenyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3-dione **(1)** with hydrazine monohydrate resulted in the rearrangement to the 5-methyl-7-phenyl-pyrido[3,4-d]pyridazine derivatives in two tautomeric forms **2a-b**. The obtained compounds **2a-b** was alkylated to the corresponding *N*-alkil derivatives **3a-b**. Their structures were confirmed by IR, NMR, MS spectra. All newly synthesized compounds were screened for antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli* by microdilution method. Some of new synthesized derivatives showed the moderate activity against the tested bacterial strains.



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P134

Synthesis of 2-pyrimidynyl-piperazinyl-alkyl derivatives of 1H-imidazo[2,1-*f*]purino-2,4(3H,8H)-dione with antidepressant- and anxiolytic-like properties

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Recently, 11th revision of the International Classification of Diseases (ICD-11) is considered of *anxious depression* (6A73) in new classification as important form of mixed depressive and anxiety disorder in general medical practice [1]. Clinically observed common core symptoms of major depressive disorder (MDDM and generalized anxiety disorder are reflected overlap in etiology, regarded the idea that reduced serotonin (5-HT) signalling in central nervous system (CNS) is a risk factor. Buspirone (8-(4-(4-(2-pyrimidinyl)-1-piperizinyl)butyl)-8-azaspiro(4,5)decane-7,9-dione) is an anxiolytic agent, which is used for the management of anxiety disorders or the short-term relief of the symptoms of anxiety, and also as an augmentation of SSRI-treatment against depression. The general structure of buspirone-like compounds is as follows: 1-(2-pyrimidinyl)-piperazine moiety is coupled via an alkyl chain to an amide function. It is known that the structure of amide function has a stabilizing effect on forming the ligand-receptor complex and receptor agonism-antagonism effect [26, 27] especially on 5-HT_{1A} receptor. Replacement of 1-(2-pyrimidinyl)-piperazine group of buspirone by 1-(2-metoxyphenyl)-piperazine moiety yielded BMY 8227. Switching azaspirodecanedione moiety of BMY 8227 to N-phtalimido group gave NAN-190, very active 5-HT_{1A} antagonists however not selective towards adrenergic α_2 receptors.

Continuing our study on a group of tricyclic purine derivatives with psychotropic activity [2,3], we designed a series of 2-pyrimidynyl-piperazinyl-alkyl derivatives of 1*H*-imidazo[2,1-*f*]purine-2,4(3*H*,8*H*)-dione. We were particularly interested to determine whether the presence of 2-pyrimidynyl-piperazinyl moiety instead of arylpiperazine moiety is decisive for receptor affinity and pharmacological profile of activity in comparison with those described for earlier compounds. 2-Pyrimidynyl-piperazinyl-butyl chain could be regarded as a fragment of the structure of buspirone, a selective 5-HT_{1A} agonist.

The most of tested compounds possessed high affinity at 5-HT_{1A}Rs with K_i from 2.2 to 20 nM and were inactive towards 5-HT_7 receptors. Compounds **4b** with the highest activity towards 5-HT_{1A}R, selected for functional profile characterization showed antagonist properties. The potential antidepressant-like and anxiolytic-like activity of **4b** was evaluated in the mouse forced swim test (FST) and four plate test (FPT) and its activity was compared with that of imipramine and diazepam, respectively. The effect of the tested compounds on the spontaneous locomotor activity of mice was also investigated.

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Acknowledgements: The studies were supported by JU MC grants K/ZDS/007206 and K/ZDS/007135.

P135

The effect of estradiol on proline dehydrogenase/proline oxidase-mediated apoptosis in breast cancer MCF-7 cells

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Estrogens are important regulators of cell proliferation, survival and differentiation in various tissues. An important function of estrogens is regulation of connective tissue metabolism. Estradiol stimulates collagen turnover by enhancing the biosynthesis and degradation of this protein. The rate of collagen turnover is reflected by prolidase activity (the enzyme releasing proline from imidodipeptides for collagen re-synthesis). One of the metabolites of estradiol is 2-methoxyestradiol (MOE), which inhibits collagen biosynthesis and cell proliferation in various cancer cells.

Proline dehydrogenase/proline oxidase (PRODH/POX) is a mitochondrial enzyme catalyzing conversion of proline to pyrrolidine-5-carboxylic acid (P5C). During the conversion, electrons are transported to the respiratory chain, producing ATP or reactive oxygen species (ROS). In the first case, activation of PRODH/POX leads to the production of ATP for survival, in the second one, ROS induces apoptosis. The mechanism of switching the PRODH/POX function from inhibitory to stimulatory for cancer cell growth is not known. We hypothesize that the availability of proline for this process may play an important role in the mechanism of regulation of apoptosis/autophagy.

The aim of the study was to evaluate the role of estradiol on PRODH/POX-dependent apoptosis in MCF-7 breast cancer cells. We generated knocked-down PRODH/POX MCF-7 breast cancer cells (MCF-7shPRODH/POX). We found that the deficiency of estradiol contributed to decrease in cell viability and MOE augmented this process. However, the DNA biosynthesis was strongly induced in the cells with silenced expression of PRODH/POX. Estradiol deficiency decreased collagen biosynthesis and MOE augmented this process in both cell lines, although in both conditions the prolidase activity was elevated. MOE upregulated also expression of pro-apoptotic proteins, however only in MCF-7 cells.

The data suggest that estradiol deficiency augments PRODH/POX-dependent apoptosis in MCF-7 cells and MOE supports this process. The impairment of estrogen receptor function through MOE should therefore contribute to the induction of the pro-apoptotic phenotype in MCF-7 cells.

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P136

Cholinesterases inhibition of novel histamine H_3 receptor ligands as multifunctional compounds on Alzheimer's disease

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Alzheimer's disease (AD) is a progressive and degenerative brain disorder characterized by the gradual loss of neurons in the central nervous system (CNS) and it is responsible for most cases of dementia [1,2]. In reference to the well-established cholinergic theory of AD, we decided to design and synthesize novel compounds which could improve cholinergic neurotransmission by elevating acetylcholine (Ach) level in the CNS. To achieve this, we obtained a series of multi-target-directed ligands (MTDLs) combining potency against histamine H_3 receptors (H_3Rs) with inhibitory activity at cholinesterases (acetylcholinesterase, AChE, and butyrylcholinesterase, BuChE). The obtained series of histamine H_3R ligands such as 4'-[1,1'-biphenyl]-4-carbonitrile derivatives of homopiperidine, 3- and 4-methylpiperidine with different alkyl linker lengths (Fig.1), were investigated regarding both their cholinesterase inhibitory activity (IC_{50}) which was determined using the method established by Ellman et al. [3]. *In vitro* affinity (K_i) for human H_3R stably expressed in HEK293 cells was evaluated as described previously [4], and compounds showed affinities in nanomolar range (K_i < 300 nM). The kinetic studies of AChE and BuChE inhibition were performed with compound E307 as one of the most potent cholinesterase inhibitor presented herein (Fig.1).

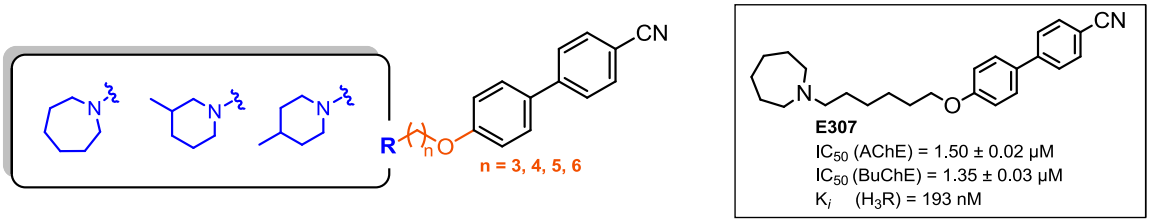

Figure 1: Obtained compounds as MTDLs

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P137

New methoxy and ethoxy arylpiperazines from hexyl-1,2,4-triazolo[4,3-a]pyridin-3(2H)-ones as dual 5-HT1A / D2 ligands

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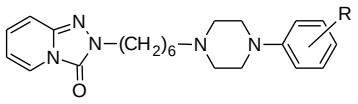
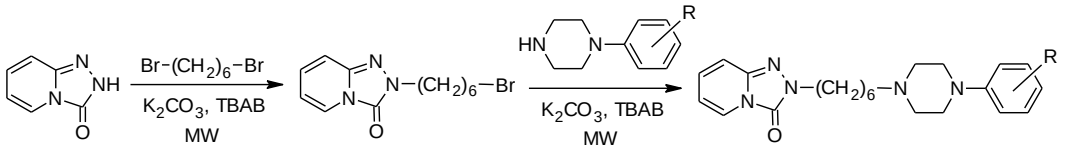


1

R = OCH_3, OC_2H_5

Figure 1. General structure of ligands

It is now known that many neurotransmitter systems are responsible for diseases of the central nervous system. Very important role in the pathogenesis and treatment of depression and anxiety is played by 5-HT_{1A} receptors [1,2] and D_2 dopamine receptors [3]. The high efficacy of dual 5-HT_{1A} / D_2 ligands has been proven in the fight against depression, therefore it seems reasonable to look for new compounds with this profile of action [4].



2 3 4 1

R = OCH_3, OC_2H_5

Figure 2. Synthesis plan

The aim of the conducted research was to search for ligands for dual 5-HT_{1A} / D_2 receptors. The activity of four compounds belonging to the 2-[6-(4-arylpiperazin-1-yl)hexyl]-1,2,4-triazolo[4,3-a]pyridin-3(2H)-one group with the methoxy and ethoxy substituent at arylpiperazine ring were tested. Compounds were synthesized by a two-step synthesis involving *N*-alkylation of 1,2,4-triazolo[4,3-a]pyridin-3(2H)-one (**2**) by 1,6-dibromohexane (**3**) followed by condensation with selected arylpiperazine (**4**). Reactions were carried out in the presents of microwave radiation. The synthesized compounds were tested in *in-vitro* studies. Among the tested combinations, compounds showing high affinity for the tested receptors were found.

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P138

The universal QSAR model for dopamine D_2 receptor antagonists

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Dopamine D_2 receptor belonging to aminergic G protein-coupled receptors (GPCRs) is the main molecular target for all currently marketed antipsychotics. The first and the second generation antipsychotics are competitive antagonists of the dopamine D_2 receptor while the third generation antipsychotics are partial or biased agonists of this receptor.

In order to search for novel antipsychotics it is necessary to know the structure-activity relationships for dopamine D_2 receptor antagonists. In this context we constructed the universal 3D QSAR model for competitive antagonists of dopamine D_2 receptor.

222 compounds (characterized with IC_{50}) from chemically different groups were taken from the CHEMBL database, prepared with LigPrep and docked with Glide to the novel X-ray structure of the human dopamine D_2 receptor in the inactive state (PDB ID: 6CM4). Selected poses (among those where a protonatable nitrogen atom of the ligand interacted with the conserved Asp(3.32) were used for CoMFA alignment. CoMFA model was constructed using Sybyl-X. The compounds were divided into the training set (200 molecules) and the test set (22 molecules).

The CoMFA model gave a cross-validated coefficient Q^2 of 0.74 and R^2 of 0.96. The field contributions of parameters were 58% and 42% for the steric field and the electrostatic field descriptor, respectively. These statistical parameters indicate that the CoMFA model is statistically significant. As the first step in validation, the IC_{50} of the 22 compounds from the test set was predicted with R^2 of 0.91. Furthermore, a progressive scrambling test was performed as an additional validation. The CoMFA fields were mapped onto the dopamine receptor binding site which enabled to discuss the structure activity relationship based on ligand-receptor interactions. The CoMFA model can be used to predict potential activity of novel dopamine D_2 receptor antagonists.

P139

Synthesis and *in vitro* antiproliferative activity of new tetracyclic pyridine azafenothiazine derivatives

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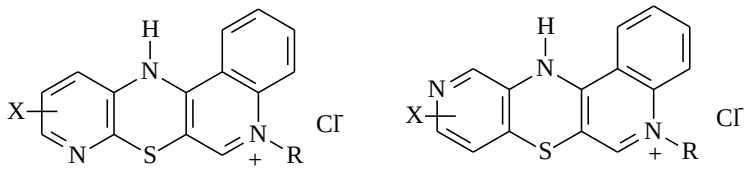
A series of new diazafentothiazine derivatives was obtained. Studies have been carried out on the mechanism of 1,4-thiazine ring formation and the influence of substituents on the cyclization mechanisms and the direction of substitution in the pyridine ring.



X = H, F, Cl, Br, J, CH_3, OCH_3

Antiproliferative activity of the synthesized compounds was studied using cultured neoplastic cells (MDA-MB-231, SNB-19, and C-32 cell lines) (IC50 range 0.1 - 15 µg/mL). Based on the results of CVDE, WST-1 and LDH test it may be concluded that exposition to all compounds causes concentration-dependent reduction in the number of cultured cells.
The observed antiproliferative effect is not the result of cytotoxic action of these derivatives, leading to cell death, but is rather the consequence of inhibiting cell proliferation. The inhibition appears to be the result of these compounds' binding to cell DNA. Selected compounds were investigated in more detail for cytotoxicity and antiproliferative effect. Transcriptional activity of genes regulating cell cycle (TP53), apoptosis (BAX, BCL-2) as well as proliferation (H3) were assessed. Finally, ability of the selected compounds to bind DNA was checked in the presence of ethidium bromide. The influence of selected compounds on the antiproliferative activity of cisplatin was tested. Some of the compounds tested increase the activity of cisplatin.

[1] Zięba A., Latocha M., Sochanik A., Nycz A., Kuśmierz D. *Molecules* 21 (2016) 1-14

P140

The effect of metoxy substituent position on antimicrobial activities and crystal structures of 1,6-diphenyl-4-methyl-2[1*H*]-pyrimidineselenone derivatives

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Staphylococcus is a Gram-positive bacteria including at least 40 species. Most are harmless and reside normally on the skin and mucous membranes of humans and other organisms. However, some species e.g. *S. aureus*, *S. epidermidis* are responsible for a wide spectrum of human diseases [1,2]. *S. aureus* causes mainly skin and soft tissue infections, while *S. epidermidis* is the most frequent cause of device-related infections occurring in the hospital setting.

The interest of our group is focused on synthesis of selenoorganic compounds towards their antimicrobial activities. Based on previous research [3], we have modified leading structure with the highest antimicrobial activities. We present three new crystal structures of 1,6-diphenyl-4-methyl-2[*1H*]-pyrimidineselenone derivatives with different positions of metoxy substituent at a phenyl ring, and their antimicrobial activities. The activity against *S. aureus* is increased only for metoxy substituent in *para*-position, while in the case of *S. epidermidis* a higher activity for each *ortho*-, *metha*- and *para*-derivative is observed, with the best value for *ortho*-metoxy derivative.

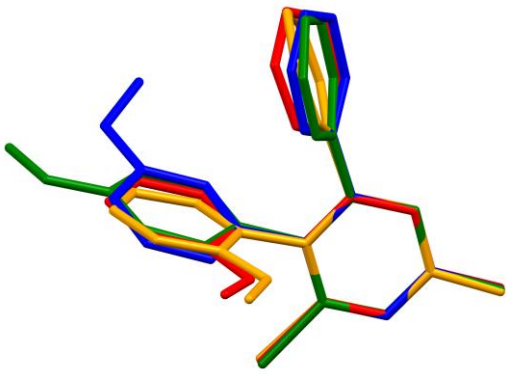

Fig. 1. The overlap of pyrimidineselenone rings of four molecules: o-OMe - red and orange, m-OMe - blue and p-OMe – green

Compound with *ortho*-metoxy substituent crystallizes with two molecules in the asymmetric unit, while the other two with one molecule. The conformations of investigated compounds differ slightly in mutual orientations of aromatic and pyrimidineselenone rings (Fig. 1). The most active compound shows the most close angles to 90° between the aromatic rings and heterocyclic ring. The packing of molecules in the crystal structures can be characterized by weak C-H···O and C-H···Se intermolecular interactions. The arrangement of the molecules in the crystal lattice is different for these derivatives.

[1] Tong S.Y.C et. al. *Clin. Microb. Rev.* 28 (2015) 603-661
[2] Widerström M. *J. Clin. Microb*. 54 (2016) 1679-1681
[3] Żesławska E. et al. *J. Mol. Struct*. 1142 (2017) 261-266

P141

Molecular modelling of dopamine D_2 receptor in the active conformation

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Dopamine D_2 receptor belongs to aminergic G protein-coupled receptors and is the main molecular target for current antipsychotics as well as one of drug targets in Parkinson's disease [1].
The aim of our studies was to construct homology models of human D_{2LONG} and D_{2SHORT} receptor (the isoforms including long and short intracellular loops 3, IL3) in active conformation in complex with G_{i1} or G_{i2} protein and to use these models to investigate their interaction with dopamine.
The homology models of D_{2LONG} and D_{2SHORT} receptors in complex with respective G proteins were built using Modeller applying the X-ray structures of β_2 adrenergic receptor in complex with G_s (PDB ID: 3SN6) as a template for helix bundle and G proteins, as well as X-ray structures of dopamine D_2, D_3 and D_4 receptors in inactive conformation (PDB ID: 6CM4, 3PBL and 5WIU, respectively) as additional templates. Yasara software was used to generate a short and long receptor IL3 loop models, consisting of 110 and 139 residues, respectively, which were refined using Modeller based on their predicted secondary structure. Dopamine was docked to the receptor models using Molegro software.
Molecular dynamics simulations using Gromacs were performed to study the effect of dopamine on the receptor. To properly simulate subtle effects, emphasis on native-like conditions was put. For this purpose, the active-state models with G proteins were immersed in an asymmetrical membrane composed of 8 types of lipids in proportions appropriate to membrane rafts. Amber force field was used to describe the interactions of protein and ligands while the Slipids were used to describe the cell membrane. The trajectories were analyzed using the Principal Component Analysis and Mutual Information methods.

[1] Fuxe K, Marcellino D, Genedani S, Agnati L: Adenosine A2A receptors, dopamine D2 receptors and theirinterac-tions in Parkinson's disease. *Mov Disord*, 2007, 22,1990-2017

P142

Comparative Molecular Field Analysis (CoMFA) and molecular dynamics studies for FAAH inhibitors

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The endocannabinoid signaling system (ECS) regulates diverse physiologic processes and has attracted significant attention as a potential drug target. The key ligands of the endocannabinoid system are the lipid transmitters N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG), which activate the two major cannabinoid receptors, CB_1 and CB_2. According to the current knowledge, life-time of 2-AG is regulated by three enzymes belonging to the metabolic serine hydrolase family. From these, monoacylglycerol lipase (MGL) is on a quantitative basis the main 2-AG hydrolase. Fatty acid amide hydrolase (FAAH) is a key enzyme responsible for the degradation of the endocannabinoid anandamide. FAAH inactivation is emerging as a strategy to treat several CNS and peripheral diseases, including inflammation and pain. The search for effective FAAH inhibitors has thus become a key focus in present drug discovery.

We have recently reported a series of 1,2,5-thiadiazole carbamates as potent FAAH inhibitors. Here we present Comparative Molecular Field Analysis (CoMFA) and molecular dynamics studies of these compounds. 34 compounds (characterized with IC_{50}) were prepared with LigPrep and docked with Glide to the humanized rat X-ray structure of FAAH (PDB ID: 3QK5). Selected poses (among those where a ligand interacts with Ser241 from the catalytic triad) were used for CoMFA alignment. CoMFA model was constructed using Sybyl-X. The compounds were divided into the training set (28 molecules) and the test set (6 molecules). Selected inhibitor-enzyme complexes were subjected to molecular dynamics studies with Desmond.

The CoMFA model gave a cross-validated coefficient Q^2 of 0.46 and R^2 of 0.98. The field contributions of parameters were 46% and 54% for the steric field and the electrostatic field descriptor, respectively. These statistical parameters indicate that the CoMFA model is statistically significant. As the first step in validation, the IC_{50} of the 6 compounds from the test set was predicted with R^2 of 0.95. Furthermore, a progressive scrambling test was performed as an additional validation. The CoMFA fields were mapped onto the FAAH binding site which enabled to discuss the structure activity relationship based on ligand-receptor interactions. The CoMFA model was applied to predict potential activity of novel FAAH inhibitors.

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