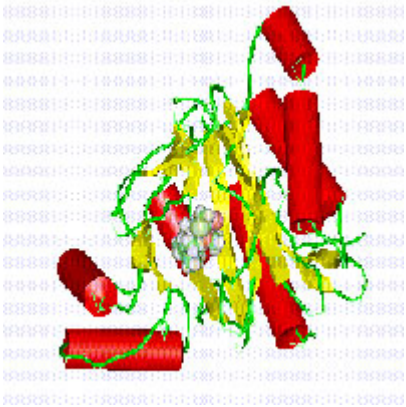

II KONWERSATORIUM CHEMII MEDYCZNEJ

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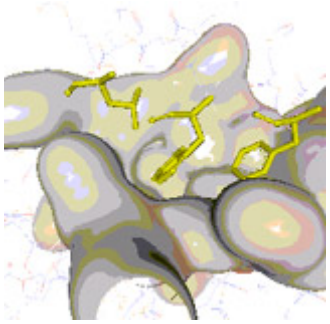

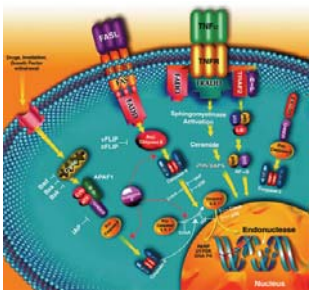

Polskie Towarzystwo Chemii Medycznej

Uniwersytet Medyczny w Lublinie

Komisja Syntezy i Projektowania Nowych Leków
Komitetu Terapii i Nauk o Leku PAN

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

Lublin, 2009

Komitet Naukowy:

Dr hab. Andrzej Bojarski

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Prof. dr hab. Janina Karolak-Wojciechowska

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Prof. dr hab. Dariusz Matosiuk

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Dr Monika Wujec

oraz

dr Monika Aletańska-Kozak

mgr Marcin Hus

dr Marzena Rządkowska

dr Elżbieta Szacoń

Plan Konwersatorium
Wtorek, 08.09.2009
18.00-18.15 – Otwarcie Konwersatorium

Prof. dr hab. Dariusz Matosiuk,

Prof. dr hab. Andrzej Książek, JM Rektor Uniwersytetu Medycznego w Lublinie;

18.15-19.00 – Wykład Inauguracyjny

Prof. dr hab. Lucjan Strekowski,

„Novel near-infrared cyanine dyes: synthesis, bioanalytical, forensic and medicinal applications."

19.45-22.00 – Spotkanie powitalne/Wieczór na Zamku
Środa, 09.09.2009
9.30-11.00 – Sesja wykładowa – Projektowanie leków a inne dyscypliny.

Prowadzący sesję – prof. dr hab. Janina Karolak-Wojciechowska,
prof. dr hab. Józef Dulak

L-1

Prof. dr hab. Marek Główka, Politechnika Łódzka,

„ Practical aspects of drug polimorphism."

L-2

Prof. dr hab. Elżbieta Mikiciuk-Olasik, Uniwersytet Medyczny w Łodzi,

„ Radiopharmacy befor eand today."

L-3

Prof. dr hab. Osman Achmatowicz, Warszawa

„ Synteza substancji aktywnych leków odtwórczych. Przykłady."

11.00-11.30 – przerwa na kawę

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

Prowadzący sesję – prof. dr hab. Katarzyna Kieć-Kononowicz,
prof.dr hab. Marek Główka

L-4

Prof. dr hab. Józef Dulak, UJ w Krakowie,

„ Heme oxygenase-1: a new therapeutic target ."

L-5

Dr hab. Sławomir Filipek, MIBMK, Warszawa

Modelling of the γ-secretase complex: the structure of presenilin and the interfaces with other proteins."

L-6

Prof. dr hab. Zdzisław Chilmonczyk, NIL,Warszawa

„ Docking study of buspirone analogues to a serotonin transporter model."

13.00-14.00 – Lunch

14.00-15.30 – Sesja posterowa i prezentacje posterów

Prowadzący sesję – prof. dr hab. Elżbieta Mikiciuk-Olasik,
prof. dr hab. Stanisław Ryng

PP-1

Mgr Iwona Chlebek, CMUJ, Kraków

„ Synthesis, physico-chemical and anticonvulsant properties of new Mannich bases derived from 3-(2-bromophenyl)-pyrrolidine-2,5-diones."

PP-2

Mgr Anna Dela, CMUJ, Kraków

„ Evaluation of phenylpiperazine derivatives of arylidene hydantoins as ligands of α_1-adrenergic receptors."

PP-3

Mgr Michał Koliński, MIBMiK, Warszawa

„ A proposed agonist/antagonist sensor in opioid receptors."

PP-4

Mgr Anita Płazińska, Uniwersytet Medyczny, Lublin

„ Molecular modeling study of interaction between the β2 adrenergic receptor and fenoterol derivatives."

PP-5

Mgr Katarzyna Targowska-Duda, Uniwersytet Medyczny, Lublin

„ Molecular modeling of interactions between various subtypes of nicotinic acetylcholine receptors and selected allosteric inhibitors."

PP-6

Dr Zbigniew Karczmarzyk, Akademia Podlaska, Siedlce

„ Keto-enol tautomerism for the β-dicarbonyl grouping in 3-acyl-4-oxo/-hydroxy-2-substituted-pyrido[3,2-e][1,2]thiazine 1,1-dioxides."

15.30-16.00 – Przerwa na kawę

16.00-18.00 – Komunikaty ustne

Prowadzący sesję – prof. dr hab. Barbara Malawska,
prof. dr hab. Osman Achmatowicz

PK-1

Dr Mariusz Sterzel, Cyfronet AGH, Kraków

„ Polska infrastruktura informatycznego wspomagania nauki w europejskiej przestrzeni badawczej – PL-GRID.“

PK-2

Dr Tomasz Gośliński, Uniwersytet Medyczny w Poznaniu,

„ Synthesis and optical properties of novel porphyrazines bearing mixed dithienylpyrrolyl and dimethylamino groups in the periphery.”

PK-3

Dr Jadwiga Handzlik, CMUJ, Kraków

„Various hydantoin derivatives as potential tool to combat bacterial multidrug resistance.“

PK-4

Mgr Paulina Płoszaj, Akademia Medyczna we Wrocławiu,

„ Structure and synthesis of the isooxazole derivatives with immuno-modulating activity.”

PK-5

Prof. dr hab. Janina Karolak-Wojciechowska,Politechnika Łódzka

„ Wiązanie wodorowe jako element konstrukcji syntonu supramolekular-nego.”

Czwartek, 10.09.2009

9.30-11.00 – Sesja wykładowa – Projektowanie leków a inne dyscypliny.II.

Prowadzący sesję – prof. dr hab. Lucjan Strekowski,
prof. dr hab. Dariusz Matosiuk

L-7

Dr Danuta Siluk, Uniwersytet Medyczny, Gdańsk

„ Pharmacokinetics and metabolism of (R,R)-methoxyphenoterol in the rat investigation.”

L-8

Dr Elżbieta Pękala, CMUJ, Kraków

“ Alcohol dehydrogenases as tools for the preparation of enantiopure metabolites of drugs with methyl alkyl ketone moiety.”

L-9

Dr Paweł Zajdel, CMUJ, Kraków

„ Combinatorial chemistry on solid support in the search for 5-HT receptor ligands..”

11.00-11.30 – przerwa na kawę

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

Prowadzący sesję – prof. dr hab. Zdzisław Chilmonczyk,
dr hab. Zofia Mazerska

L-10

Dr Beata Kolesińska, Politechnika Łódzka,

“ Bacteriocines.”

L-11

Prof. dr hab. Jan Mazerski, Politechnika Gdańska,

“Małocząsteczkowe ligandy DNA o selektywnosci sekwencyjnej jako potencjalne leki przeciwnowotworowe.”

L-12

Dr Agnieszka Kaczor, Uniwersytet Medyczny, Lublin

„ Allosteric modulation of G protein-coupled receptors as novel approach to the treatment of cns disorders.”

13.00-14.00 – Lunch

14.00-15.30 – Sesja posterowa i prezentacje posterowe

Prowadzący sesję – prof. dr hab. Andrzej Stańczak,
prof. dr hab. Marek Cegła

PP-7

Mgr inż. Ewa Gronek, Politechnika Gdańska

„Synthesis of O-/N-glycoconjugates.”

PP-8

Dr Paweł Szumański, Uniwersytet Medyczny, Łódź

„ N-alkyl-fluorobenzoyl derivatives of tacrine as acetylcholinesterase inhibitors.”

PP-9

Mgr Stafan Mordalski, Instytut Farmakologii PAN, Kraków

„ Homology modelling of metabotropic glutamate receptor 2.”

PU-10

Dr Mariusz Mojzych, Akademia Podlaska, Siedlce

„ Synthesis and X-ray analysis of new derivatives of pyrazolo[4,3-e]-tetrazolo[4,5-b][1,2,4]triazine."

PP-11

Mgr Michał Otręba, Śląski Uniwersytet Medyczny, Katowice

„ 1,4-Dihydro-4-oxo-3-alkanesulfonylquinolones – synthesis and antimicrobial activity evaluation."

PP-12

Mgr Daniel Szulczyk, Uniwersytet Medyczny, Wraszawa

„ Design of new [4 + 2]π cycloadducts of "Phencyclone" and maleimides N-substituted by alkyl-(N-aryl) piperazine moiety as different approach to serotonin receptors family."

15.30-16.00 – Przerwa na kawę

16.00-18.00 – Komunikaty ustne

Prowadzący sesję – dr hab. Sławomir Filipek,
dr hab. Krzysztof Jóźwiak

PK-6

Dr Jarosław Sączewski, Uniwersyte Medyczny w Gdańsku,

„ Synthesis of novel 2-iminoimidazolidine derivatives with potential biological activities."

PK-7

Mgr Aleksandra Redzicka, Akademia Medyczna we Wrocławiu,

„ Synthesis and pharmacological properties of pyrrolo[3,4-c]pyrrole and pyrrolo[3,4-d]pyridazine derivatives."

PK-8

Mgr Ryszard Bugno, Instytut Farmakologii PAN, Kraków

„ The research of the key-structure fragments of arylpiperazine and arylsulfonamide derivatives influences on selectivity towards 5-HT_7 vs 5-HT_{1A} receptors."

PK-9

Mgr Urszula Kijkowska-Murak,Uniwersytet Medyczny w Lublinie,

" Modelling of the human neuropeptide $NPFF_2$ receptor and its interactions with ligands."

19.30-23.00 – Wieczór pożegnalny „Nad Zalewem"

Lista posterów:

PP-1 Chlebek Iwona, mgr
Synthesis, physico-chemical and anticonvulsant properties of new Mannich bases derived from 3-(2-bromophenyl)-pyrrolidine-2,5-diones.

PP-2 Dela Anna, mgr
Evaluation of phenylpiperazine derivatives of arylidene hydantoins as ligands of α_1-adrenergic receptors.

PP-3 Koliński Michał, mgr
A proposed agonist/antagonist sensor in opioid receptors.

PP-4 Płazińska Anita, mgr
Molecular modeling study of interaction between the β2 adrenergic receptor and fenoterol derivatives.

PP-5 Targowska-Duda Katarzyna, mgr
Molecular modeling of interactions between various subtypes of nicotinic acetylcholine receptors and selected allosteric inhibitors.

PP-6 Karczmarzyk Zbigniew, dr
Keto-enol tautomerism for the *β*-dicarbonyl grouping in 3-acyl-4-oxo/hydroxy-2-substituted-pyrido[3,2-*e*][1,2]thiazine 1,1-dioxides.

PP-7 Gronek Ewa, mgr inż.
Synthesis of O-/N-glycoconjugates.

PP-8 Janik Agnieszka, mgr
N-alkyl-fluorobenzoyl derivatives of tacrine as acetylcholinesterase inhibitors.

PP-9 Mordalski Stefan, mgr
Homology modelling of metabotropic glutamate receptor 2.

PP-10 Mojzych Mariusz, dr
Synthesis and X-ray analysis of new derivatives of pyrazolo[4,3-*e*]tetrazolo[4,5-*b*]-[1,2,4]triazine.

PP-11 Otręba Michał, mgr
1,4-Dihydro-4-oxo-3-alkanesulfonylquinolones – synthesis and antimicrobial activity evaluation.

PP-12 Szulczyk Daniel, mgr
Design of new [4 + 2]π cycloadducts of “Phencyclone” and maleimides N-substituted by alkyl-(N-aryl) piperazine moiety as different approach to serotonin receptors family.

P-1 Aletańska-Kozak Monika, dr
Synthesis of new aminoguanidine derivatives.

P-2 Aletańska-Kozak Monika, dr
Application of preparative FLASH chromatography for separation of ureids.

P-3 Bajda Marek, mgr
Search for dual function inhibitors for alzheimer’s disease: synthesis and biological activity of cholinesterases inhibitors derivatives of *n*-benzylpiperidine and their aβ fibril formation inhibition capacity.

P-4 Balewski Łukasz, mgr
Synthesis, structure and biological activities of novel imidazolines and their Cu(II) complexes.

P-5 Baran Marzena, mgr
Investigations on reaction of α-amino-β-bromo heterocyclic compounds with oxirane derivatives.

P-6 Barszcz Konrad, stud.
Bifunctional hybrides of nitrogen mustards with peptide “Address” attached to the 1,3,5-triazine scaffold.

P-7 Bębenek Ewa, dr
Synteza i ocena aktywności cytotoksycznej *in vitro* alkynylowych pochodnych betuliny.

P-8 Chłoń-Rzepa Grażyna, dr
New theophylline derivatives with carboxyl, ester and amide moieties as a potential non-steroidal anti-inflammatory agents.

P-9 Czopek Anna, dr
The acid-base properties of imidazolidine-2,4-dione and imidazo-[2,1-f]theophylline derivatives, containing arylpiperazinylalkyl fragment in the aspect of their serotonin transporter activity.

P-10 Cytarska Joanna, dr
New isophosphoramide mustard analogues as prodrugs for gene therapy.

P-11 Drozdowska Danuta, dr
Solid phase synthesis of carbocyclic distamycin analogues and their biological evaluation.

P-12 Dutkiewicz Zbigniew, dr
Ab initio and DFT studies for alkylation reaction of 2,3-bis[(3-pyridylmethyl)amino]-2(*Z*)-butene-1,4-dinitrile.

P-13 Frączyk Justyna, dr inż.
The interactions of library of artificial receptors with nitrogen mustards attached to the 1,3,5-triazine scaffold.

P-14 Gunia Agnieszka, mgr
Preliminary evaluation of anticonvulsant activity of some aminoalkanol derivatives.

P-15 Handzlik Jadwiga, dr
Chemical modifications and biological activity of 2-methoxy-phenylpiperazine derivatives of phenytoin. Mutagenicity tests *in vitro* and influence on artificial membrane for two α_1-adrenoceptor antagonists with antiarrhythmic properties.

P-16 Kaczor Agnieszka, dr
Allosteric modulation of opioid receptors.

P-17 Karolak-Wojciechowska Janina, prof. dr hab.
Struktura i konformacja 2-tiozebulariny – badania w krysztale i roztworze.

P-18 Kędzierska Ewa, dr
The interactions of new derivatives of 1-aryl-2-iminoimidazolidine with the known antidepressants.

P-19 Kępczyńska Elżbieta, dr
Estimation of the lipophilicity of some xanthone derivatives exhibiting anticonvulsant acitivity.

P-20 Kieć-Kononowicz Katarzyna, prof.dr hab.
A comparison of rat and human adenosine A_{2A} receptor affinity of tricyclic purinediones.

P-21 Koszel Dominik, mgr
Synthesis and lipophilicity determination of bicine derivatives of GlcN-6-P synthase inhibitors.

P-22 Kowalska Alicja, dr
Synthesis of azathioprine derivatives.

P-23 Kowalska Alicja, dr
Lipophilicity of novel anticancer N-acylaminoalkyl- and N-sulfonylaminoalkyl diazaphenothiazines.

P-24 Kuder Kamil, mgr
Search for novel histamine H_3/H_4 receptors ligands in the group of (cyclic)isothiourea derivatives.

P-25 Kurczab Rafał, mgr
The development and validation of a novel virtual screening cascade protocol to identify potential serotonin 5-HT_7R antagonists.

P-26 Latacz Gniewomir, mgr
Application of capillary electrophoresis to the determination *D*-hydantoinase and *N*-carbamoylase activity.

P-27 Łażewska Dorota, dr
Metabolism and pharmacological activity of 1-[3-(4-*tert*-butylphenoxy)propyl]piperidine - potent histamine H_3-receptor antagonist.

P-28 Maniukiewicz Waldemar, dr
Rentgenowska dyfraktometria proszkowa (XRD) w badaniu składu fazowego przeterminowanych leków.

P-29 Mączyński Marcin, dr
Struktura i aktywność immunomodulująca pochodnych izoksazolu.

P-30 Mrozek Agnieszka, dr
Analiza SAR procesu dokowania barwników trimetylofenylowych we wnękach wiążących utworzonych przez N-lipidowane aminokwasy immobilizowane na matrycy celulozowej.

P-31 Niemyjska Maria, dr
Synthesis of 3,3'-diindolilomethane and 3,3'-dithio-bis-indole derivatives with potential antitumor activity.

P-32 Nowaczyk Alicja, dr
Application of computational QSAR analysis for the 1-(3-(4-arylpiperazin-1-yl)-propyl)-pyrrolidin-2-one derivatives as α_1-adrenoceptor antagonists.

P-33 Oracz Monika, mgr
Otrzymywanie kokryształów substancji aktywnych farmakologicznie metodą „solvent-drop grinding".

P-34 Pachuta-Stec Anna, dr
Antimicrobial activity of new derivatives of N-substituted amides of 3-(3-methylthio-1,2,4-triazol-5-yl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid.

P-35 Pachuta-Stec Anna, dr
Synthesis of some 1,6-bis(3-substituted-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)-hexanes with potential biological activities.

P-36 Pachuta-Stec Anna, dr
Synthesis and pharmacological properties of 3-chlorobenzoic acid hydrazide derivatives.

P-37 Płazińska Anita, mgr
Conformational analysis of fenoterol stereoisomers.

P-38 Rosołowski Szymon, mgr
Synthesis and biological activity derivatives of 1-bromo-17-azapentacyclo-[6.6.5.$0^{2,7}$.$0^{9,14}$.$0^{15,19}$]nonadec-2,4,6,9,11,13-heksaen-16,17-dionu.

P-39 Rosołowski Szymon, mgr
New triazole derivatives as compounds with potential biological activity.

P-40 Rządkowska Marzena, dr
Synthesis of new substituted 1-(2-pyridil)imidazo[1,2-a][1,3,5]-triazepines.

P-41 Skowerski Krzysztof, mgr
Isophosphoramide mustard analogues containing benzo[*d*]-isoxazole ring as anticancer prodrugs.

P-42 Sochacka Jolanta, dr
The binding of thiopurine derivatives to serum albumin – lipophilicity dependence.

P-43 Sochacka Jolanta, dr
Interaction of thiopurine derivatives with serum albumin – studying and prediction by means of molecular docking.

P-44 Staroń Jakub, mgr
Azo dyes as potential allosteric modulators of the metabotropic glutamate receptors mGluR4.

P-45 Szczesio Małgorzata, dr
High resolution study on non-stoichiometric gramicidin D complexes with alkali metals salts.

P-46 Szulczyk Daniel, mgr
Synthesis and preliminary evaluation of antimicrobial activity of selected derivatives of 2-benzofurancarboxylic acid.

P-47 Szkaradek Natalia, mgr
Antifungal activity of xanthone derivatives against chosen strains of dermatophytes, yeasts and molds.

P-48 Szymańska Ewa, dr / Karolak-Wojciechowska Janina, prof. dr hab.
Crystallographic studies of *Z* and *E* isomers of 2-amino-5-(2-chlorobenzylidene)-1-methyl-1H-imidazol-4(5H)-one.

P-49 Świątek Piotr, dr
Aktywność przeciwbakteryjna nowej pochodnej izotiazolo[5,4-*b*]pirydyny.

P-50 Trela Marcin, mgr
New derivatives of indole – analogues of MMPIP – an allosteric modulator of the metabotropic glutamatergic receptors mGluR7.

P-51 Więcek Małgorzata, dr
3-(1H-imidazol-4-yl)propyl carbamates as histamine H_3/H_4 receptor ligands.

P-52 Wójcik Tomasz, mgr
Bivalent ligands for adenosine A_{2A} receptors.

P-53 Wysocki Waldemar, mgr
Synthesis and structure of 1-[1-(4-methoxyphenyl)imidazolidyne-2-ylidene]-3-phenethylurea.

P-54 Zagórska Agnieszka, dr
The synthesis of new pyrimido[2,1-f]theophylline derivatives, with potential affinity for CNS receptors.

P-55 Zajdel Paweł, dr
Solid-phase synthesis of novel arylpiperazine-functionalized amino acid amides.

P-56 Żylewski Marek, dr
Observation of ligand – micelle interactions. The attempt to use the NMR spectroscopy as a tool for lipophilicity measurements.

P-57 Sobiak Stanisław, prof. dr hab.
New synthesis of methylthiobenzaldehyde, convenient substrate for synthesis of methylthiostilbenoides.

WYKŁADY

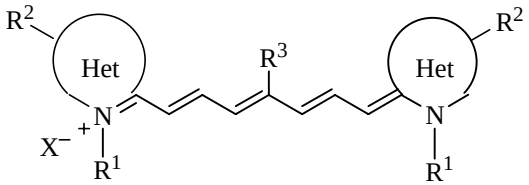
IL

Novel Near-infrared Cyanine Dayes: Synthesis, Bioanalytica, Forensic and Medicinal Applications.

Lucjan Strekowski

Goergia State Universitym Atlanta, Georgia 30302, USA
e-mail: lucjan@gsu.edu

Any biological medium is extensively penetrated by near-infrared (NIR) radiation (> 700 nm). In particular, the highly sensitive fluorescence spectroscopy of NIR cyanine dyes has attracted considerable attention in bioanalytical and medicinal research. Such dyes serve as fluorescent NIR probes and labels for biomolecules (see the general structure below). In the UV-visible region of the electromagnetic
spectrum, the autofluorescence from biomolecules can be significant while very few biomolecules possess intrinsic fluorescence in the NIR region.



Recent developments in the synthetic chemistry of cyanine dyes, including functionalization for covalent attachment to biomolecules and improved aqueous solubility, will be discussed. Other topics include the applications in bioanalytical chemistry such as fluorescent tagging of proteins, DNA sequencing, and monitoring pH in the microenvironment of biomolecules. An important property of several cyanine dyes is their preferential accumulation in tumors, which provides a new approach to cancer detection and localization. Some cyanine dyes show intrinsic anti-cancer properties. A novel use of cyanine dyes in fingerprint visualization will also be presented.

L-1

Practical Aspects of Drug Polimorphism.

Marek Główka, Joanna Bojarska, Monika Oracz, Waldemar Maniukiewicz

Institute of General and Ecological Chemistry, Faculty of Chemistry,
Technical University, Żeromskiego 116, 90-924 Łódź
e-mail: marekglo@p.lodz.pl

Polimorfizm zwany też wielopostaciowością polega na innym ułożeniu elementów strukturalnych fazy skondensowanej. Polimorfizm jest zjawiskiem powszechnym, szczególnie ważnym w przemyśle farmaceutycznym oraz we wszystkich procesach wytwarzania bądź przetwarzania substancji w fazie stałej.
Inne ułożenie w przestrzeni atomów tej samej substancji stałej powoduje zmianę właściwości fizykochemicznych, służących do jej jednoznacznej charakterystyki. Stąd badania właściwości i budowy takich substancji w innych fazach niż stała, odbywające się często w roztworze, nie może dawać żadnej informacji o polimorfizmie. Nawet proste badanie budowy molekularnej związków organicznych w innej fazie też może być mylące (lub co najmniej niepełne) w przypadku układów równowagowych, np. tautomerii. Z drugiej strony możliwość otrzymania tej samej substancji o innych właściwościach fizykochemicznych stwarza szansę wyeliminowania właściwości niekorzystnych lub wzmocnienia właściwości pożądanych, a także może mieć istotne znaczenie komercyjne, związane ze „zdolnością patentową".

Rozwój chemii teoretycznej oraz obecne możliwości obliczeniowe spowodowały również intensywne prace nad przewidywaniem występowania nowych odmian polimorficznych, któremu to zagadnieniu poświęcę nieco czasu. Jak zawsze w takich teoretycznych przypadkach, kluczowym dla sukcesu jest etap praktycznej realizacji pięknych teorii, czyli odpowiedź na oczywiste pytanie: „Jak daną odmianę otrzymać?".

W tego typu wystąpieniu nie może oczywiście zabraknąć omówienia zjawiska pseudopolimorfizmu (tworzenia solwatów), a więc występowania w fazie stałej, obok substancji zasadniczej, także rozpuszczalnika czy też kilku rozpuszczalników. Dalszym rozszerzeniem tego zjawiska jest występowanie w krysztale jeszcze innej substancji stałej z utworzeniem współkryształów (kokryształów). Warto zauważyć, że w zasadzie solwaty od kokryształów różnią się tylko temperaturowo zdefiniowanym stanem skupienia współkrystalizujących substancji oraz ewentualnie dominującą rolą jednej z nich w tworzeniu sieci krystalicznej.

Tak więc będę się starał omówić następujące zagadnienia:

1. Niejednoznaczność definicji odmiany polimorficznej
2. Znaczenie polimorfizmu dla przemysłu farmaceutycznego
3. Krystalochemiczne podstawy i problemy polimorfizmu
4. Otrzymywanie (nowych) odmian polimorficznych
5. Pseudopolimorfizm (solwaty i współkryształy)
6. Przewidywanie występowania polimorfizmu

L-2

Radiopharmacy Before and Today.

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W latach 50-tych XX wieku dynamicznie rozwinęła się medycyna nuklearna. Jest to dziedzina medycyny stosująca związki zawierające izotopy promieniotwórcze do diagnostyki medycznej i terapii wielu chorób np. nerek, dróg żółciowych, mięśnia sercowego oraz ośrodkowego układu nerwowego. Izotopy pierwiastków promieniotwórczych wchodzące w skład związków stosowanych w diagnostyce są zwykle źródłem promieniowania γ (gama), a czas ich połowicznego rozpadu możliwie krótki, aby narażenie radiacyjne pacjenta było możliwie niewielkie. Promieniowanie γ łatwo przenika przez tkanki i jest rejestrowane przez detektory (gammakamery). Metody wykorzystujące to promieniowanie nazywamy metodami scyntygraficznymi, a należą do nich dwie techniki: PET i SPECT. Metody scyntygraficzne polegają na badaniu rozmieszczenia w tkankach żywego ustroju radiofarmaceutyków, czyli związków chemicznych znakowanych izotopami promieniotwórczymi. W terapii natomiast najczęściej stosuje się izotopy, które emitują promieniowanie β. Należy także podkreślić zastosowanie radiofarmaceutyków w leczeniu bólów nowotworowych.
Ponadto radiofarmaceutyki są bardzo użytecznym narzędziem w badaniu mechanizmów działania leków i w badaniach receptorowych.
Stosowane radionuklidy nie niosą zagrożenia dla pacjentów, przyjmuje się, że prawdopodobieństwo zachorowania na chorobę nowotworową pacjenta badanego metodami rentgenowskimi i radioizotopowymi jest takie samo, jak każdego człowieka otrzymującego dawkę promieniowania jonizującego ze źródeł naturalnych.
W latach sześćdziesiątych zwrócono uwagę na izotopy metastabilne (przebywające długi czas w stanie wysokoenergetycznym). Takim właśnie izotopem jest ^{99m}Tc, który ze względu na swoje właściwości (emiter promieniowania γ o energii 140 keV, okres półtrwania 6h) znalazł szerokie zastosowanie w medycynie nuklearnej i obok pochodnych jodu jego związki technetu należą do najczęściej stosowanych radiofarmaceutyków.

L-3

Synthesis of the Active Substances of Generic Drugs. Examples.

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Leki odtwórcze (leki generyczne) są wytwarzane i wprowadzane na rynek od momentu ustania ochrony patentowej dla leków oryginalnych - ich odpowiedników. Lek generyczny musi zawierać tę samą substancję aktywną co jego oryginalny odpowiednik i wykazywać taką samą biorównoważność a w konsekwencji jest stosowany w taki sam sposób co lek innowacyjny. Zaletą leków generycznych jest ich niższa od leków oryginalnych cena. Jej obniżenie jest możliwe m.in. w wyniku ustania ochrony patentowej na lek innowacyjny i pojawia się konkurencji po między wytwórcami.
W przypadku leków generycznych możliwe jest patentowanie ich formulacji i/lub metody syntezy. W wystąpieniu będą przedstawione nowe, oryginalne metody syntezy aktywnych składników trzech leków odtwórczych z różnych obszarów terapeutycznych i zdecydowanie różniących się pod względem chemicznym. Są to:

i. Repaglinid – obniżający poziom glukozy we krwi przez pobudzenie wydzielania insuliny przez trzustkę, stosowany w leczeniu cukrzycy typu II,
ii. Sildenafil – stosowany w leczeniu zaburzeń erekcji oraz w pierwotnym nadciśnieniu płucnym,
iii. Latanoprost – aktywny składnik płynu ocznego stosowanego do kontrolowania postępu jaskry lub nadciśnienia w gałce ocznej.

L-4

Heme Oxygenase-1: a New Terapeutic Target.

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Heme oxygenase-1 (HO-1) degrades heme to iron, carbon monoxide and biliverdin, which is subsequently reduced to bilirubin by biliverdin reductase. Altough crucial, this is not the only function of this enzyme. HO-1 is recently considered as one of the most important cytoprotectants. It plays significant role in defence of cells against oxidative stress. HO-1 mediates also intracellular signaling. These functions are of particular importance in endothelial cells and during blood vessel formation.
Formation of new blood vessels is prerequisite for the development of organism and is connected with numerous pathologies. Nevascularisation is also crucial for proper executing of the reparative processes such as wound healing. Many pathological conditions, eg. heart ischemia, is related to the bad functions and impaired formation of blood vessels. On the other hand, excessive vascularisation parallels numerous diseases, among which the most important are tumors, atherosclerosis and retinopathies.
Formation of new blood vesseles can be attained by vasculogenesis and angiogenesis. The first one is the creation of capillaries *de novo*, from stem cells, while angiogenesis is the formation of new vessels from preexisting ones.
Our research in the last years has proven the important role of HO-1 in blood vessels formation and discovered the new vasculogenic and angiogenic pathways in which this enzyme is involved (see references below). Those studies have demonstrated the key role of HO-1 in: **1**) VEGF- and **2**) bFGF-dependent proliferation of endothelial cells and progenitor cells; **3)** SDF-1 induced angiogenesis; **4)** SDF-1-dependent postnatal vasculogenesis; and **5)** partial involvement of HO-1 in angiogenesis dependent on IL-8. Those mechanisms are crucial for **6**) wound healing and **7)** tumor growth and in **8)** angiogenesis caused by tissue ischemia. The role of HO-1 in neovascularisation is additionally related to its **9**) cytoprotective activities, protecting endothelial cells and endothelial progenitor cells against oxidative stress.
It can be hypothesised that mechanisms described above can be used for development of new therapies for diseases with excessive or impaired blood vessel formation.

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L-5

Modelling of the γ-Secretase Complex: the Structure of Presenilin and the Interfaces with Other Proteins.

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Presenilins (PS-1 and PS-2) are highly evolutionary conserved integral membrane proteins that – as a part of a large, multiprotein γ-secretase complex - cleave other transmembrane proteins, such as Notch receptor or β-amyloid precursor protein (APP). Presenilins contain ten identified hydrophobic regions (HRs) in their primary structure and nearly all of them, except HR-7, were suggested to form transmembrane helices leading to many topological models of these proteins. Proteolytic processing of APP by the sequential action of β-secretase and γ-secretase releases amyloid-β peptides (Aβ) – highly aggregative components of senile plaques. Presently, more than 170 Alzheimer's Disease (AD) mutations is in the *PSEN1* gene.

We performed the analysis of mutation patterns in all ten HRs using the most up-to-date information about AD mutations and we have built a conceptual model of PS-1 based on the distribution of these mutations. Regarding discordant amino acids in PS-1 vs. PS-2 proteins allowed us to estimate regions less important for the function of presenilins and they proved to be complementary to areas of AD mutations. The obtained model properly distinguishes residues belonging to AD-affected sites and non-pathogenic areas and may be used for classification purposes. It also complies with experimental results such as different accessibilities of the catalytic residues in uncleaved PS-1 and binding of PEN-2 by the PS-1 HR-4 NF motif.

We also constructed a model of interactions between two proteins forming γ-secretase: APH-1 and presenilin. This interface is based on a highly conserved GxxxGxxxG motif in the APH-1 protein. It can form a tight contact with a small-residue AxxxAxxxG motif in presenilin. We proposed and verified four binding modes based on similar structures involving GxxxG motifs in glycophorin and aquaporin. The resulting best model employs antiparallel orientations of interacting helices and is in agreement with the currently accepted topology of both proteins. In the case of analyzed PS-1 – APH-1 interface there is a long network of small residues. Such an arrangement of residues in antiparallel model provides the lowest binding energy suggesting the most probable mode of interaction. This model can be used for further structural characterization of γ-secretase and its components.

L-6

Docking Study of Buspirone Analogues to a Serotonine Transporter Model.

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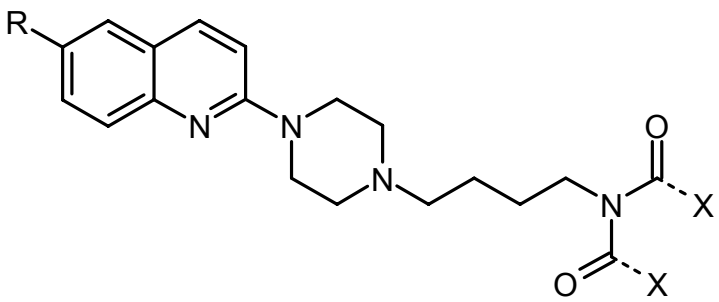
6-Nitroquipazine has been known as one of the most potent and selective inhibitors of the serotonin transporter (SERT). In the present study we examined several buspirone analogues, with known SERT affinities, containing quipazine or 6-nitroquipazine moieties in the aromatic part of a molecule. The compounds were docked to SERT and analyzed using molecular modelling methods. The SERT model was based on the crystal structure of a bacterial homologue of SERT, the leucine transporter ($LeuT_{Aa}$).



R = H; $–NO_2$

The docking indicated that the imide moieties of the high affinity ligands remained in close contacts with - SERT Tyr95 (THM1) and Ser438 (THM8). In such an orientation of nitrated (low affinity) ligands, the nitro groups were in close steric contacts with the hydrophobic amino acids Val^{343} and Lue^{344} in TMH6. It also appeared that nitro groups can occupy the binding place of imide carbonyls. Thus during docking of nitrated ligands to the SERT narrow binding site possible destabilising steric contacts between ligand's polar groups and SERT hydrophoobic amino acids were observed.

This study was partly supported by the PNRF-103-AI-1/07 project "Creating an academia based platform to discover substances acting on serotonergic or glutamatergic system as potential new antidepressant or anxiolytic drugs".

L-7

Pharmacocinetics and Methabolism of R,R-Methoxyphenoterol in the Rat Investigation.

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(R,R)-Metoksyfenoterol (MF) jest pochodną (R,R)-Fenoterolu (F), agonisty receptorów β2-adrenergicznych, który obecnie badany jest w zastoinowej niewydolności serca. W pracy opisano farmakokinetykę i metabolizm MF u szczurów po podaniu dożylnym i doustnym oraz porównano z wynikami otrzymanymi dla F. W porówniu z F dla MF zaobserwowano zwiększoną biodostępność względną (3 razy), zmniejszony klirens (170 *vs*. 52 ml/min/kg), dłuższy biologiczny okres półtrwania (96,4 *vs*. 125 min) oraz niższą objętość dystrybucji (V_{ss} 11,6 *vs*. 7,3 l/kg). MF był wydalany głównie w wyniku procesu sprzęgania z kwasem glukuronowym, który w istotnym stopniu zachodził presystemowo. Obecność metabolitu, glukuronianu MF, potwierdzona została przy pomocy inkubacji z hepatocytami szczurzymi i szczurzymi mikrosomami jelitowymi oraz analizy HPLC z detekcją tandemowej analizy spektrometrii mas.

Po dożylnym i doustnym podaniu MF szczurom w próbkach moczu wykryto F oraz glukuronian F co wskazuje na O-demetylację MF i dalsze sprzęganie z kwasem glukuronowym. Po podaniu *i.v.* sumaryczna ilość F oraz jego glukuronianu wynosiła 3,6% natomiast po podaniu *p.o.* około 0,3%, co wskazuje na silny efekt pierwszego przejścia dla MF. Wyniki te zostały potwierdzone w badaniach *in vitro* na hepatocytach szczurzych, gdzie po inkubacji z MF stwierdzono obecność F oraz glukuronianów zarówno MF jak i F. Natomiast po inkubacji MF z mikrosomami jelitowymi wykryto jedynie glukuronian MF.

L-8

Alcohol Dehydrogenases as Tools for the Preparation of Enantiopure Metabolites of Drugs with Methyl Alkyl Ketone Moiety.

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The interconversion of ketone to the corresponding chiral alcohol and vice versa represents one of the most common redox-reactions in organic chemistry. Whereas traditional synthetic methods predominantly use toxic metals and expensive complex hydrides, biotransformations offer some significant advantages. Various chiral alcohols can be produced by biocatalysis using two methods kinetic resolution of the racemic starting material or direct synthesis from prochiral compounds. The asymmetric reduction of prochiral carbonyl substrate is one example of direct synthesis. The vast majority of dehydrogenases and reductases used for ketone reduction and alcohol oxidation require nicotinamide cofactors, such as NADH and NADPH.

For the synthesis of chiral alcohols, commercially available alcohol dehydrogenases (ADHs) isolated from yeast (NADH dependent Y ADH), horse liver (NADH dependent HLADH) or *Thermoanaerobium brockii* (NADPH-dependent TBADH) can be used for different substrate structures. Horse-liver ADH can be used for the reduction of a broad range of cyclic ketones and 2- or 3-ketoesters, while open-chain methyl and ethyl ketones are the preferred substrates for *T brockii* ADH. An NADPH-dependent ADH from *Rhodococcus erythropolis* (READH) was found that reduces a broad variety of ketones with specific activity, giving (S)-alcohols. Furthermore, an NADPH-dependent ADH was found in *Lactobacillus* that converted similar ketone structures but formed (R)-alcohols. *Lactobacillus kefiri* produces an (R)-ADH *(LKADH)* that accepts a broad variety of ketone substrates - including acetophenone and derivatives (ring halogenated), aliphatic, open-chain ketones, 2-, 3-ketoesters, and cyclic ketones - with a high specific activity. In the majority of cases enzymatic and microbial reductions of the alkyl aryl ketones proceed according to Prelog's rule generating alcohols in the *(S)*-configuration The enzyme transfers the pro-(R) hydrogen of the cofactor to the re-face of ketone. The majority of enzymes, such as HLADH, YADH, TBADH and ADH from *R. erythropolis,* follow this rule, while only a few (e.g. *LKADH)* have been described as possessing enzymes of the opposite specificity, *i.e.* anti-Prelog's specificity (Figure1).

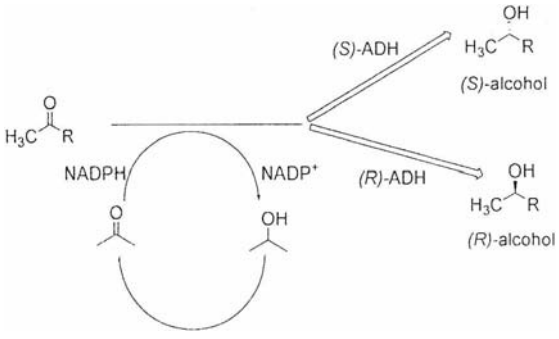

Figure 1 The application of Prelog's rule to the bloreduction performed by ADHs

In this study, we present the results of the enantio-selective bioreduction of drugs *i.e.* pentoxifylline (PTX), propentofylline (PPT) and denbufylline (DBF) using the commercially available dehydrogenases (ADHs) and microbial methods. The drugs tested possess a methyl ketone moiety in their structures were reduced biocatalytically by isolated native alcohol dehydrogenases: ((R)-ADH from *L. kefiri,* (S)-aromatic ADH from *T.* sp., (S)-ADH from *T. brockii)* or by whole cells of the selected strains of microorganisms (strains of baker's of wine' yeasts, strain of *Cunninghamella echinulata* and strain of *Lactobacillus kefirii)*, which were a source of the *(R)* or *(S)*specific ADH.

The chiral products, important, pharmacologically significant metabolites (R)-OHPTX, (R)-OHPPT and (R)-OHDBF were obtained with the maximum biotransformation yield 96-98% and high enantioselectivity *(ee 96-99%).*

L-9

Combinatorial Chemistry on Solid Support in the Search for 5-HT Receptor Ligands.

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The advent of combinatorial chemistry was one of the most important developments, that has significantly contributed to the drug discovery process. Within just a few years, its initial concept aimed at production of libraries containing huge number of compounds, so called screening libraries, has shifted towards preparation of small and medium-sized rationally designed libraries. When applicable, the use of solid supports for the generation of libraries has been a real breakthrough in enhancing productivity. With a limited amount of resin and simple manual workups, the split/mix procedure may generate thousands of bead-tethered compounds. Beads can be chemically or physically encoded to facilitate the identification of a hit after the biological assay. Compartmentalization of solid supports using small reactors like teabags, kans or pellicular discrete supports like Lanterns resulted in powerful sort and combine technologies, relying on codes 'written' on the reactor, and thus reducing the need for automation and improving the number of compounds synthesized. These methods of solid-phase combinatorial chemistry have been recently applied by our research group in the project aimed at discovering bioactive compounds acting on 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptors involved in central nervous system disorders.

L-10

Bacteriocines.

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Bacteriocins first discovered by A. Gratia in 1925 [1] are metabolites produced by gram positive, gram negative *Bacteria* and *Archea* to inhibit the growth of similar or closely related bacterial strains. Previously these were classified as narrow spectrum antibiotics, though this has been debated and recently examples were found demonstrating much broader activity including even cancer and AIDS treatment. According to Tagg's [2] definition bacteriocins are peptide or proteins antagonistic mostly towards related microorganisms. Due to heterogenicity of bacteriocins precise determination of profile of activity is not trivial, because even for the same microorganism some sub-population could be sensitive but other sub-populations could be resistant.

Bacteriocins are categorized in several ways, including the producing strain , genetics (large plasmids, small plasmids, chromosomal), method of production (ribosomal, post ribosomal modifications, non-ribosomal), molecular weight or structure, (large protein, polypeptide, with/without sugar moiety, containing uncoded amino acids), common resistance mechanisms, and mechanism of killing (pore forming, dnase, nuclease, murein production inhibition, etc). The most common method of classification include three groups of bacteriocins:

Class I bacteriocins are small peptide inhibitors and include nisin.

Class IIa-c bacteriocins are small heat-stable proteins.

Class III bacteriocins are large, heat-labile proteins.

Bacteriocins are of interest in medicine because they are also made by non-pathogenic bacteria that normally colonize the human body. Therefore the loss of these harmless bacteria following antibiotic therapy may allow the invasion of opportunistic pathogenic bacteria.

Rapidly growing application of nisin [3], the best known bakteriocin, stimulated the intensive search in this area expecting their application for food conservation as safe, natural fungicide and antimicrobial agents.

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[2] Tagg J., Dajani A. S., Wannamer L.. W.: *Bacteriol. Rev. (1976), 40, 722-756.*

[3] Nisin has a GRAS (Generally Recognized As Safe) status and its application as conserving agent is allowed in more then 50 countries.

L-11

Małocząsteczkowe Ligandy DNA o Selektywności Sekwencyjnej jako Potencjalne Leki Przeciwnowotworowe.

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Poznanie ludzkiego genomu stwarza unikalną możliwość stworzenia nowej generacji leków przeciwnowotworowych o obniżonej toksyczności. Wymaga to z jednej strony znalezienia genów mogących stanowić cel molekularny, a z drugiej ligandów selektywnie blokujących ekspresje tych genów.
Ligandami takimi mogą być zarówno antysensowe oligonukleotydy lub ich analogi jak i małocząsteczkowe ligandy o odpowiednio dobranej selektywności sekwencyjnej. Wobec znanych problemów z terapia antysensową duże nadzieje wiąże się obecnie z ligandami małocząsteczkowymi.
Przedmiotem doniesienia będzie omówienie potencjalnych podstaw selektywności sekwencyjnej takich ligandów. Przyjmuje się powszechnie, że selektywność sekwencyjna ligandów małocząsteczkowych wynikać może z dwóch powodów:

- specyficznej, różnej od helisy B, struktury fragmentów DNA o określonej sekwencji. Ligandy rozpoznawałyby wtedy strukturę helisy, a nie samą sekwencję.
- zdolności ligandu do tworzenia specyficznych oddziaływań fizykochemicznych z parami zasad. Selektywność takich ligandów opierałaby się więc na bezpośredniej zdolności do rozpoznawania sekwencji par zasad.

Zaprezentowane zostaną również przykłady struktur chemicznych potencjalnie zdolnych do sekwencyjnie specyficznego wiązania się DNA oraz metody badań biofizycznych pozwalające na wykrywanie takich oddziaływań.

L-12

Allosteric Modulation of G Protein-Coupled Receptors as Novel Approach to the Treatment of CNS Disorders.

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Despite G-protein-coupled receptors (GPCRs) being among the most fruitful targets for marketed drugs, intense discovery efforts for several GPCR subtypes have failed to deliver selective drug candidates. Historically, drug discovery programmes for GPCR ligands have been dominated by efforts to develop agonists and antagonists that act at orthosteric sites for endogenous ligands. However, in recent years, there have been tremendous advances in the discovery of novel ligands for GPCRs that act at allosteric sites to regulate receptor function. These compounds provide high selectivity, novel modes of efficacy and may lead to novel therapeutic agents for the treatment of multiple psychiatric and neurological human disorders [1].
Allosteric receptor ligands bind to a recognition site that is distinct from the binding site of the endogenous messenger molecule. As a consequence, allosteric agents may attach to receptors that are already transmitter-bound. Ternary complex formation opens an avenue to qualitatively new drug actions at G protein-coupled receptors (GPCRs), in particular receptor subtype selective potentiation of endogenous transmitter action. Consequently, suitable exploitation of allosteric recognition sites as alternative molecular targets could pave the way to a drug discovery paradigm different from those aimed at mimicking or blocking the effects of endogenous (orthosteric) receptor activators. The number of allosteric ligands reported to modulate GPCR function is steadily increasing and some have already reached routine clinical use [2].
Allosteric modulators of G-protein-coupled receptors (GPCRs) offer several advantages over standard orthosteric drugs. GPCR allosteric binding sites can show greater divergence across subtypes of a particular receptor than orthosteric sites, so better selectivity might be obtained. Additional advantages would be preservation of the normal spatial and temporal pattern of physiological signal generation and termination, with the only effect of the modulator being to either ‘tune up’ or ‘tune down’ this pattern of signaling, and reduced potential for toxic effects – modulators would have a ‘ceiling’ to their effect, irrespective of the administered dose. There are also reports of ligands showing mixed, allo- and orthosteric activity, which may result in interesting pharmacological profiles. These ligands have been named 'dualsteric ligands' [3].
The aim of the lecture is to present advantages of allosteric ligands as potential drugs for the treatments of CNS disorders and to consider their possible limitations.

Computations were performed in the framework of computational grant by Interdisciplinary Centre for Mathematical and Computational Modelling, Warsaw, Poland, grant number G30-18.
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[3] see poster by Bartuzi et al.

PREZENTACJE USTNE
KOMUNIKATY

PK-1

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We współczesnym świecie współpraca zespołów naukowych wymaga efektywnego współdzielenia zasobów obliczeniowych należących do rozmaitych instytucji. Technologie gridowe stanowią odpowiedź na wyzwania związane z problematyką jednolitego i sprawnego dostępu do zasobów przy pomocy przyjaznych dla użytkownika mechanizmów wizualizacji i komunikacji. Gridy łączą w jedną całość i umożliwiają dostęp do rozproszonych zasobów i bibliotek danych naukowych podobnie jak sieć WWW umożliwia wymianę oraz dostęp do informacji rozproszonych po Internecie.
PL-Grid jest ogólnopolskim projektem, którego celem jest budowa obliczeniowej infrastruktury gridowej dla potrzeb polskich naukowców. W ramach projektu udostępnione zostaną potężne zasoby obliczeniowe i magazyny danych na potrzeby nauki. Równolegle z udostępnianiem zasobów opracowywane są i wdrażane narzędzia pozwalające projektować i uruchamiać skomplikowane eksperymenty obliczeniowe wykorzystujące różnorakie oprogramowanie naukowe. Projekt jest realizowany przez konsorcjum PL-Grid, utworzone w styczniu 2007r., w skład którego wchodzą następujące instytucje: (1) Akademickie Centrum Komputerowe CYFRONET AGH w Krakowie, (2) Interdyscyplinarne Centrum Modelowania Matematycznego i Komputerowego w Warszawie, (3) Instytut Chemii Bioorganicznej PAN - Poznańskie Centrum Superkomputerowo-Sieciowe w Poznaniu, (4) Centrum Informatyczne Trójmiejskiej Akademickiej Sieci Komputerowej w Gdańsku i (5) Wrocławskie Centrum Sieciowo - Superkomputerowe we Wrocławiu. Projekt PL-Grid jest częściowo finansowany ze środków Europejskiego Funduszu Regionalnego, jako element Programu Operacyjnego Innowacyjna Gospodarka.
Integralną częścią projektu jest Wirtualne Laboratorium – zbiór komponentów i narzędzi, które – używane razem – tworzą rozproszone środowisko współpracy. W jego ramach różnorodne (geograficznie rozproszone) grupy naukowców mogą używać wirtualnego laboratorium do planowania i przeprowadzania eksperymentów numerycznych, jak również dzielić się wynikami swoich prac badawczych. Równolegle z narzędziami Laboratorium oferuje pomoc w zrozumieniu zagadnień związanych z uruchamianiem aplikacji na rozproszonych zasobach PL-Grid, wsparcie technologiczne i informatyczne przy projektowaniu własnych aplikacji naukowych i ich wdrażaniu jak również pomoc techniczną przy adaptacji stosowanych obecnie narzędzi do działania w nowych warunkach. Oferowane narzędzia do zaawansowanej organizacji eksperymentów mogą również być dostosowane do indywidualnych potrzeb grup badawczych.
Eksperymenty uruchamiane w ramach Wirtualnego Laboratorium mogą wykorzystywać jednocześnie zbiory danych i obliczenia numeryczne niezbędne do poszerzenia wiedzy na temat badanego problemu naukowego. Ta zdolność do łączenia heterogenicznych źródeł informacji z oprogramowaniem naukowym wykorzystującym maszyny dużej mocy w celu wspólnego opracowywania wartościowych rezultatów prac badawczych tworzy z niego podstawowe narzędzie pracy dla nowoczesnej nauki.

PK-2

Synthesis and Optical Properties of Novel Porphyrazines Bearing Mixed Dithienylpyrrolyl and Dimethylamino Groups in the Periphery.

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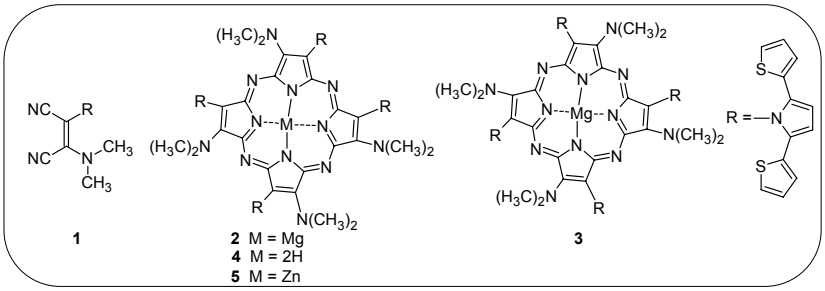
The synthesis and characterization of unsymmetrical porphyrazines (pzs) with peripheral 2,5-dimethylpyrrolyl and methyl(3-pyridylmethyl)amino groups possessing interesting optical and electrochemical properties has been reported lately [1]. This work was extended to the synthesis of novel pzs bearing 2,5-di(2-thienyl)-1*H*-pyrrole and dimethylamino substituents in the periphery [2].



The Paal-Knorr reaction of diaminomaleonitrile with 1,4-di(2-thienyl)-1,4-butanedione followed by methylation led to the novel dinitrile system **1** (Scheme). The Linstead macrocyclization of **1** gave unsymmetrical magnesium porphyrazine **2** as the major product, accompanied by one isomer **3**. Demetallation of **2** gave the free base porphyrazine **4**. When a harsh method of macrocyclization was used ($Zn(OAc)_2$-DBU-pentanol), the pz **5** was isolated as the only product.
All pzs **2**-**5** were purified by column chromatography and fully characterized by NMR. The asymmetry imposed by the non-alternate order of peripheral substituents, breaking C_4 symmetry, resulted in the non-equivalence of ^1H and ^{13}C NMR signals for pzs **2**, **4** and **5**. Further recrystallization of **2** led to crystals suitable for single crystal X-ray analysis. In the UV-Vis spectrum of pz **2** significant solvatochromic changes in various solvents were observed. Novel pzs may find diverse applications as both precursors to optical materials and photosensitizers for photodynamic therapy.

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Acknowledgements

This study was supported by the Polish Ministry of Science and Higher Education Grant No. N405 031 32/2052. T.G. thanks the British Council and the Polish Ministry of Science and Higher Education for the opportunity to participate in the British-Polish Young Scientists Programme.

PK-3

Various Hydantoin Derivatives as Potential Tool to Combat Bacterial Multidrug Resistance.

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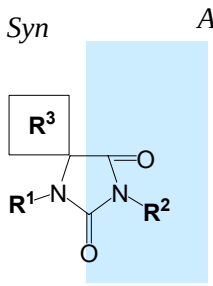
Multidrug resistance is a great challenge for current medicinal science as it is a seriously limiting factor in various diseases therapy including bacterial infections treatment, antifungal and also anticancer therapy. Microbial drug efflux proteins play an important role in MDR. They contribute in both natural insensitivity to antibiotics and to emerging antibiotics resistance and so are potential targets for the development of new antibacterial agents [1]. According to the newest lines of evidence, blocking the efflux capacity of bacterial cell is one of the main strategies to overcome bacterial resistance [2]. Aromatic hydantoin derivatives seem to be an interesting target in pharmacological strategies for overcoming multidrug resistance. Our recent-years researches gave several groups of hydantoin derivatives [3] that can be considered as potential anti-MDR agents (**Fig. 1**)

Modification I (Syn)

R^1 = amine-alkyl

R^2 = H, alkyl, ester, carboxylic acid

R^3 = substituents with aromatic fragments



Modification II (Anti)

R^1 = H, alkyl, ester, carboxylic acid

R^2 = amine-alkyl

R^3 = substituents with aromatic fragments

Fig. 1. Chemical modifications of hydantoin.

The compounds were examined on their capability to increase antibiotic susceptibility to resistant pathogens as *Enterobacter aerogenes* involved in human infections. The microbiological assays were carried out on two *E. aerogenes* strains: ATCC13048 as reference and the derivative CM64 strain which over produces AcrAB-TolC efflux pump. Selected compounds induced an increase of chloramphenicol, nalidixic acid and sparfloxacin activity. Among anti-derivatives, benzylidene and 5,5-diphenyl hydantoins with amine-alkyl chain are especially promising. In group of syn-derivatives, 5-methoxyphenyl-5-methylhydantoin derivative with phenylpiperazinealkyl chain displayed the best anti-MDR activity.

The work was partly supported by grants: 501/N-COST/2009/0, COST action BM0701.

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PK-4

Structure and Synthesis of the Izoxazole Derivatives with Immunomodulating Properties.

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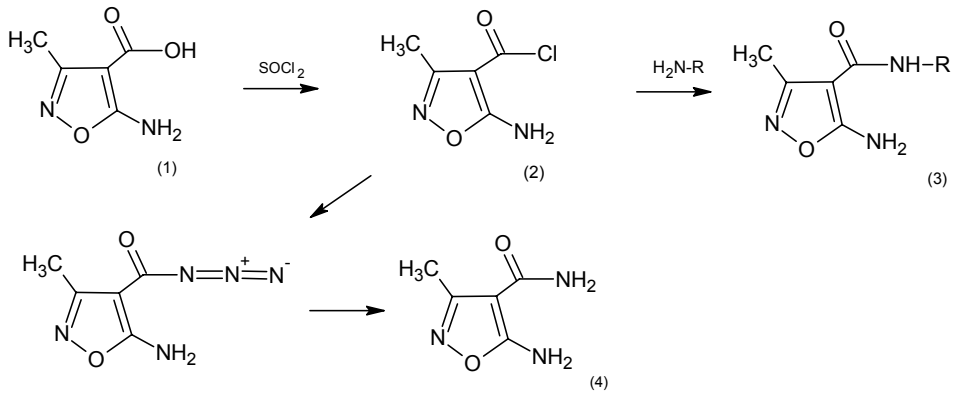
W ostatnich latach obserwuje się znaczny wzrost zachorowań na choroby związane z pierwotnym lub nabytym deficytem immunologicznym. Do zwalczania niedoborów immunologicznych poszukuje się efektywnych substancji immunostumulujących. Przedmiotem zainteresowania alergologów, transplantologów oraz onkologów są natomiast struktury wykazujące działanie immunosupresyjne.
Kilkunastoletni okres badań zaowocował opracowaniem syntezy nowych pochodnych izoksazolu o właściwościach zarówno immunostumulujących jak i immunosupresyjnych. W toku prac prowadzonych w Katedrze i Zakładzie Chemii Organicznej Akademii Medycznej we Wrocławiu otrzymano pochodne, wykazujące aktywność immunostymulującą większą od Lewamisolu oraz immunosupresory efektywniejsze od Cyklosporyny A. Wśród immunostymulantów najbardziej aktywną grupę, przy relatywnie niskiej toksyczności, stanowią amidy kwasu 5-amino-3-metyloizoksazolo-4-karboksylowego (1) otrzymane trzema sposobami: przez działanie chlorku kwasowego na kwas (2), na drodze kondensacji kwasu z odpowiednią aminą (3) oraz w reakcji redukcji azydu kwasu 5-amino-3metyloizoksazolo-4-karboksylowego (4) [1].



W celu otrzymania pochodnych izoksazolu o działaniu immunosupresyjnym (potwierdzonym w badaniu *in vitro*) użyto azydu kwasu 5-amino-3-metyloizoksazolo-4-karboksylowego, który na skutek przegrupowania Curtiusa, tworzy odpowiedni izocjanian, a ten w reakcjach z aminami aromatycznymi przechodzi w pochodne ureilenowe Pochodnym tym przypisuje się większą aktywność immunosupresyjną w porównaniu z lekami referencyjnymi.

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PK-5

Wiązanie Wodorowe jako Element Konstrukcji Syntonu Supramolekularnego.

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Wiązania wodorowe są najważniejszymi z szerokiego wachlarza nie-kowalencyjnych oddziaływań międzycząsteczkowych. To one są odpowiedzialne zarówno za rozpoznanawanie się czasteczek jak i za ich samoorganizację. To wiązania wodorowe biorą istotny udział w powstawaniu biologicznych supraczasteczek, takich jak DNA czy kompleksy pomiędzy receptorem biologicznym i właściwym ligandem. Równocześnie to właśnie wiązania wodorowe kształtują motywy upakowania cząsteczek w prawie wszystkich kryształach związków organicznych. Z punktu widzenia koncepcji chemii supramolekularnej, każdy monokryształ należy traktować jako jedną supraczasteczkę, zbudowaną z powtarzających się elementów zwanych „syntoniami supramolekularnymi" albo „motywami struktury".
Najwięcej informacji o geometrii i topologii wiazań wodorowych różnego typu otrzymuje się z danych krystalograficznych. To na ich podstawie identyfikuje się supramolekularne syntony charakterystyczne dla danej grupy związków. Analizując określony typ wiązań wodorowych nie należy ograniczać się tylko do badań strukturalnych dla wybranej grupy związków. Należy także wykorzystać Cambridge Structural Database (CSD) jako źródłem statystycznych informacji o wybranym motywie w syntonach innych związków. Włącza się w to także wiązania wodorowe kwadrupulowe, w których zawarte są wielokrotne oddziaływania tworzące sieci wiązań wodorowych.

PK-6

Synthesis of Novel 2-Iminoimidazolidine Derivatives with Potential Biological Activities.

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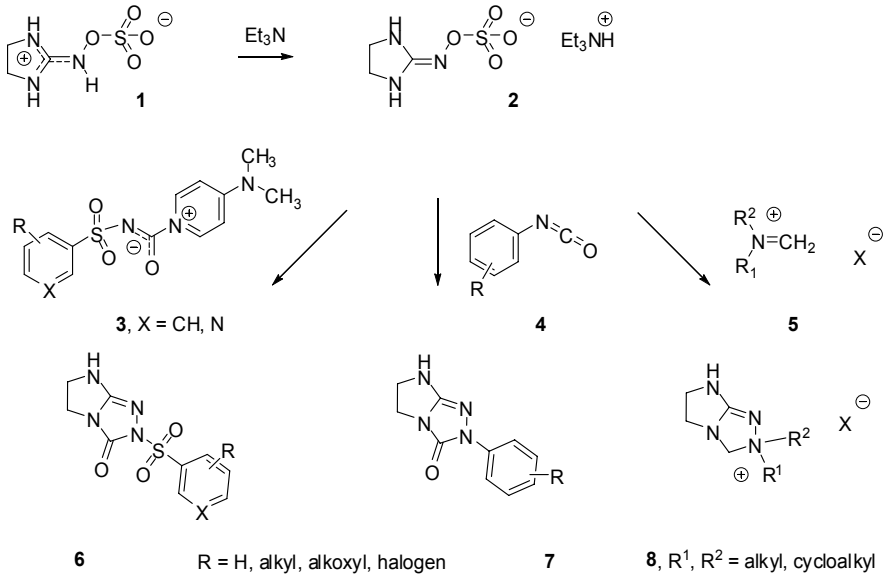
The chemistry presented in this communication pertains to our previous reports describing application of 2-hydroxyimino-imidazolidine derivatives to the synthesis of novel fused heterocyclic ring systems with potential biological activities [1]. Now we have found that triethylaminium 2-hydroxyliminoimidazolidine-*O*-sulfonate (**2**) generated from betaine **1** may be successfully applied to the synthesis of variously substituted imidazo[2,1-*c*]triazoles via the tandem nucleophilic addition - electrophilic amination reactions with either carbamoylides **3** [2], aryl isocyanates **4** or Eschenmoser salts **4** [3]. In this communication we will discuss the possible mechanisms of the formation of 2-(aryl-sulfonyl)-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol-3(5*H*)-ones (**6**), 2-aryl-6,7-dihydro-2*H*-imidazo[2,1-*c*][1,2,4]triazol 3(5*H*)-ones (**7**) and cyclic quaternary hydrazonium salts **8**:



The newly prepared compounds **6** representing cyclic analogues of amidino-arylsulfonylureas may behave as neuropeptide Y receptor (NPY) antagonists useful for the treatment of anxiety, obesity, hypertension and/or regulation of coronary tone [4].

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[4] Ling A. L.: *Expert Opinion on Therapeutic Patents 1999, 9, 375-384.*

PK-7

Synthesis and Pharmacological Properties of Pyrrolo[3,4-*c*]pyrrole and Pyrrolo[3,4-*d*]pyridazine Derivatives.

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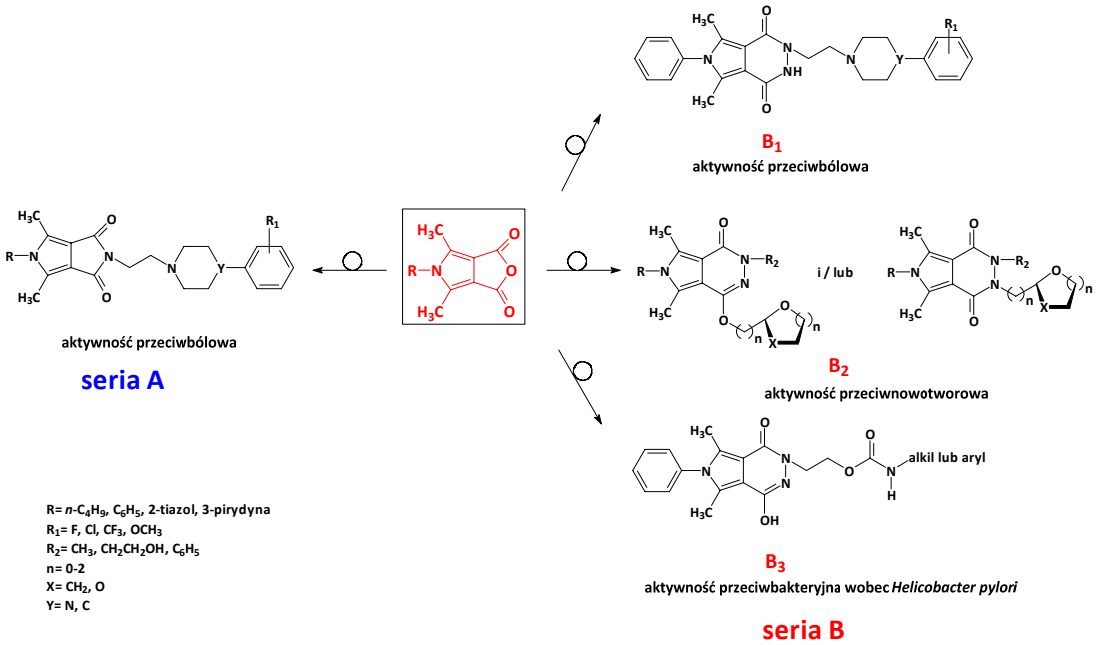
Syntezę nowych pochodnych pirolo[3,4-*c*]pirolu i pirolo[3,4-*d*]pirydazyny (schemat) nakierowano na uzyskanie preparatów o przewidywanej aktywności przeciwbólowej (seria **A**, **B**$_1$), przeciwnowotworowej (seria **B**$_2$) względnie przeciwbakteryjnej (seria **B**$_3$).



SCHEMAT

Testy przeciwbólowe wykazały, że związki serii **A** i **B**$_1$ posiadają silną aktywność analgetyczną. Połączenia serii **A** w teście „przeciągania się" były ~1.5-5 razy bardziej aktywne niż kwas acetylosalicylowy zastosowany jako lek referencyjny. Pirolopirydazynony serii **B**$_1$ wykazały jednak jeszcze silniejsze działanie przeciwbólowe. Najbardziej interesujący preparat serii **B**$_1$, w teście „przeciągania się", był około 900 razy skuteczniejszy od ASA (ED_{50}=39.15 mg/kg) oraz 60 razy skuteczniejszy od morfiny (ED_{50}=2.44 mg/kg). Trzy związki serii **B**$_1$, ze względu na znaczącą aktywność analgetyczną są przedmiotem zgłoszeń patentowych.
Zakładana aktywność przeciwnowotworowa połączeń serii **B**$_2$ i przeciwbakteryjna serii **B**$_3$ nie została potwierdzona wynikami farmakologicznymi.

PK-8

The Research of the Key-Structure Fragments of Arylpiperazine and Arylsulfonamide Derivatives Influences on Selectivity Towards 5-HT_7 *vs* 5-HT_{1A} Receptors.

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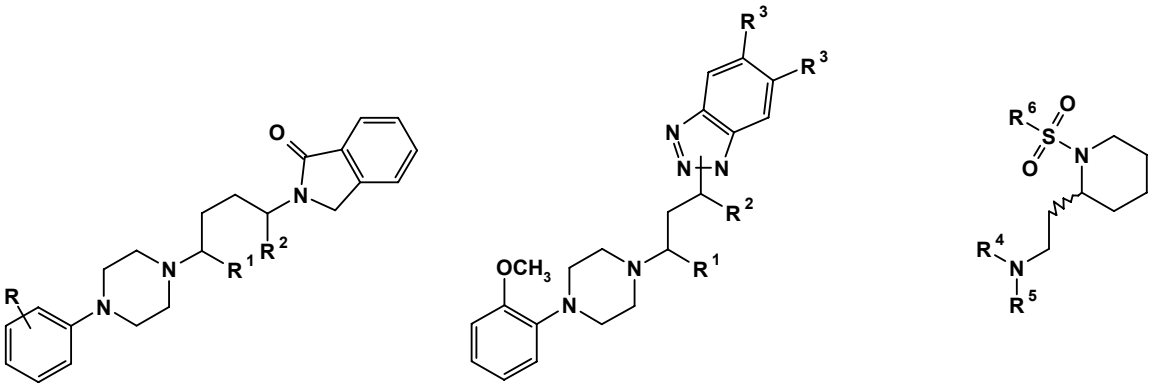
The discovery of 5-HT_7 receptor ligands with mixed 5-HT_{1A}/5-HT_7 receptor profile, especially in the group of LCAPs (*Long Chain ArylPiperazines*), raised a problem of selectivity. Recognition of structural factors influencing affinity towards both receptors can be helpful in process of designing new ligands with improved selectivity profile and – due to their potential application as a valuable pharmacological tools – broaden knowledge about these important drug targets.
One of the main research topics realized in the Department of Medicinal Chemistry, is the discovery of ligands of different types of serotoninergic receptors, among others, within the group of LCAP derivatives. The structure – 5-HT_{1A} receptor activity relationships of this type of derivatives is well–known and described in degree which permits the designing of compounds with desired activity, however, suitable requirements regarding the 5-HT_7 receptor are, until now, considerably less accessible.
In this context, the presented research is concentrated on the synthesis of the new arylpiperazine and arylsulfonamide derivatives and investigations of the structural elements of 5-HT_7 receptor ligands determining the selectivity over 5-HT_{1A} receptors.



Acknowledgements:
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PK-9

Modelling of the Human Neuropeptide $NPFF_2$ Receptor and Its Interactions with Ligands.

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Neuropeptide FF is a member of the RFamide family of peptides and is derived from pro-$NPFF_A$ peptide. It has an interesting array of pharmacological effects - may have anti-opioid activity when administred intracerebroventricularly and pro-opioid activity at intrahecal administration. Moreover, NPFF is involved in feeding process, insulin release, cardiovascular events and electrolyte imbalance [1]. Thus, NPFF receptor antagonists are potential drugs for the treatment of pain and hyperalgesia, withdrawal symptoms for alcohol, psychotropics and nicotine dependencies, for improvement or cure of said dependencies, for regulation of insulin excretion, food intake, memory functions, blood pressure, electrolyte and energy management and for the therapy of urinary incontinence [2]. More recently, two G protein-coupled receptors, $NPFF_1$ and $NPFF_2$, have been cloned and characterized as specific NPFF receptors. These receptors are related to the neuropeptide Y (NPY) and orexin receptor family. While distribution of $NPFF_1$ receptors in rodents is restricted to supraspinal regions, $NPFF_2$ receptors are detected in the brain and spinal cord [1]. There are several peptide and non-peptide ligands of NPFF receptors available, but their binding site has not been defined jet. The lack of mutagenesis data on the receptor as well as a crystal structure has also hindered the understanding of ligand recognition at the receptor level. Generally, pro-$NPFF_A$ and pro-$NPFF_B$ derived peptides have been found to be selective for $NPFF_2$ and $NPFF_1$ receptor, respectively. In particular, pro-$NPFF_A$ derived NPAF (AGEGLSSPFWSLAAPQRFa) show high selectivity for $NPFF_2$, while pro-$NPFF_B$ derived NPVF is moderately selective for $NPFF_1$ [1].
Thus, the aim of presented work was to model human $NPFF_2$ receptor applying homology modeling with Modeller9v5. Multiple alignment of $NPFF_2$ receptor and several other GPCRs sequences was performed with CLUSTAL2W and used for generation of the population of 100 $NPFF_2$ receptor model. 2RH1 and 3EML were used as templates. As the extracellular loops 2 and 3 are longer in neuropeptide FF_2 receptor than in adrenergic and adenosine receptors and there are segments with no template, dope-loop module of Modeller9v5 was used to refine those loops. The final model of $NPFF_2$ receptor with the lowest value of Modeller objective function was applied for molecular docking of its peptide ligand NPAF and non-peptide ligands: BIBP3226, Gomisin G and its derivatives - active components of *Schizandra chinensis*, followed by molecular dynamics simulations. Receptor modeling and the analysis of ligand-receptor interaction allowed to characterize the activity of the receptor on the molecular level. Docking results allowed also to describe the binding pocket of the receptor and the mechanism of ligand-binding cavity interactions.

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PREZENTACJE USTNE
POSTERY

PP-1

Synthesis, Physicochemical and Anticonvulsant Properties of New Mannich Bases Derived from 3-(2-Bromophenyl)-pyrrolidine-2,5-diones.

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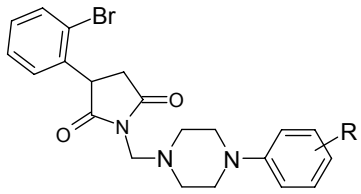
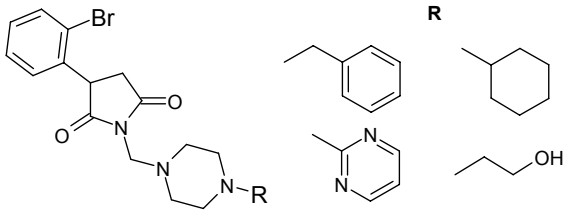
The aim of the present study is the synthesis of new N-Mannich bases with an expected anticonvulsant activity. This work is a continuation of our previous study in a group of 3-substituted pyrrolidine-2,5-diones with 4-substituted piperazine moiety connected to the imide nitrogen atom by alkylene space. The most active, in this series, were compounds with the methylene linker between two nitrogen atoms [1]. Taking into consideration the above findings, as part of our efforts to search new anticonvulsant agents, in the present study we have designed and synthesized a small library of N-(4-substituted-piperazin-1-yl)-methylene derivatives of 3-(2-bromophenyl)-pyrrolidine-2,5-dione. The structures are presented below.



cmpd **1**-**7**

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



cmpd **8**-**11**

All obtained compounds were tested for their anticonvulsant activity within the Antiepileptic Drug Development (ADD) Program in Epilepsy Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Rockville, MD, USA
The results obtained revealed that some of compounds exhibited protection in the MES tests after *ip.* administration to mice, as well as, when dosed orally to rats.
This work was supported by the grant from Jagiellonian University, Medical College, No K/ZDS/000711

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PP-2

Evaluation of Phenylpiperazine Derivatives of Arylidene Hydantoins as Ligands of α_1-Adrenergic Receptors.

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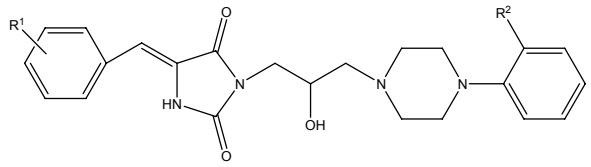
In recent years α_1-ARs have been the subject of intense research because of their potential role in arrythmias mechanism, especially in ischemic arrhythmia. [1] The α_1-adrenoreceptors are the family of G-protein-coupled seven-transmembrane helix receptors. Studies of receptor binding have shown that the numerous compounds with affinity for α_1-AR contain arylpiperazine moieties.
In our research several 1-N-(phenyl piperazine derivatives) of 5,5-diphenyl hydantoin were obtained. [2,3] Such compounds have shown nano- to submikro affinity to α_1 – ARs. In the present work, a group of phenylpiperazine derivatives of arylidene hydantoin was designed, obtained and evaluated on their affinity for α_1-ARs. Their structures were in accordance with the pharmacophore model of α_1-ARs antagonists developed by Barbaro et. al. in 2001. [4]



R^1 – H, Cl, $N(CH_3)_2$, OCH_3, diOCH_3
R^2 – H, OCH_3, OC_2H_5

Fig.1

This work was focused on the modification of substituents at C5 and N3 position of hydantoin ring (**Fig 1**). Arylidene ring was substituted with Cl, dimethyloamino or methoxy substituents and derivatives of (alkoxy)phenyl piperazines were obtained. The synthesis consisted of four steps: Knoevenagel condensation, Mitsunobu reaction, microwave irradiation and transfer of the obtained basic derivatives into the hydrochloric form.
The new compounds were evaluated on their affinity for α_1-adrenoreceptors using [^{3}H]prazosin as α_1-AR radioligand. For chosen compounds their pharmacological profile was examinated in functional bioassays.
SAR-sudies have shown a great influence of C5 and N3 substituents on α_1-AR affinity. Their affinity was in broad range (from nano- to mikromalor concentration). It was noticed the profitable influence of methoxyl group in aryl- and arylidene fragment of the examinated compounds on α_1-AR affinities.
The work was partly supported by grant: K/ZDS/000727.

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PP-3

A Proposed Agonist/Antagonist Sensor in Opioid Receptors.

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Opioid receptors belong to large and diverse family of G Protein Coupled Receptors (GPCRs) which are responsible for transduction of a signal across the plasma membrane. Activated receptor goes through series of conformational changes ruled by molecular switches. Drugs that interact with opioid receptors cause multiple effects including analgesia, sedation, euphoria and physical dependence. Therefore, discovery of more potent and selective ligands for mu, delta and kappa opioid receptor subtypes should suppress the unwanted side effects. Drug design is mostly limited by the scarcity of structural information on receptor proteins. Up to date, structures of only two members of GPCR family have been reported: rhodopsin and beta2-adrenergic receptor. The mechanisms of activation of GPCRs, including conformational changes which occur upon ligand binding, are sill not clearly understood.

Agonist binding is the first step in ligand-induced receptor activation. To investigate the relationship between the final movements of a ligand in a binding site and the first steps of the activation process in opioid receptors we chose a set of rigid ligands (analogs of morphine) with the structural motif of tyramine. The structures of three opioid receptors were built using homology/comparative modeling techniques based on crystallographic structure of inactive rhodopsin. Series of agonists and antagonists were docked to the receptor models and the complexes were simulated in water and lipid environment. Based on conducted molecular dynamics simulations and on available mutagenesis data we proposed different binding modes for agonists and antagonists. They all initially bind to Y3.33 but only agonists are able to move deeper to H6.52. The movement from Y3.33 to H6.52 induces breaking of the TM3-TM7 connection as was observed for complexes of an agonists or an antagonist - naltrexone forced to bind to H6.52. For the first time a correlated motion of W6.48 and H6.52 was observed to act in analogous way as a rotamer toggle switch CWxPxF in beta2-adrenergic receptor.

PP-4

Molecular Modeling Study of Interaction Between the β2 Adrenergic Receptor and Fenoterol Derivatives.

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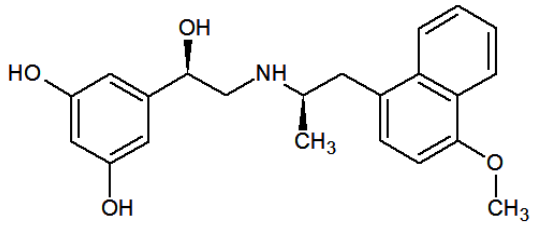
The β_2 adrenergic receptor (β_2-AR) has become a model system for studying the ligand recognition process and the mechanism of GPCR activation. The β_2-AR agonist binding site is well characterized, and there is a wealth of structurally related ligands with functionally diverse properties. Fenoterol is a selective β_2-AR agonist existing as four stereoisomers which significantly differ in β_2-AR binding affinities and selectivities. The clinically used drug, *rac*-fenoterol, is a racemic mixture of (R,R)-fenoterol and (S,S)-fenoterol, and this mixture is used for the treatment of asthma. In the present study we use stereoisomers of fenoterol and some of its derivatives as a molecular probe to identify differences in stereo-recognition of structurally similar agonists. Fenoterol stereoisomers and derivatives were docked to the three molecular models of β_2-AR: 1) "de novo" model built by homology to the rhodopsin structure [1]; 2) the X-ray crystallography structure of engineered β_2-AR cocrystalized with an inverse agonist – carazolol [2] and 3) the newly proposed model combining some features of each of above models. Docking analysis demonstrated differences between binding modes of ligands to each model.

Molecular modeling allowed to design and synthesize a set of new structures with optimized affinity towards β_2-AR. One of these new compounds, (R,R)-4-methoxy-1-naphthylfenoterol (Figure 1), appeared as very effective and very selective agonist of the receptor. It is promising lead compound with potential use in the treatment of the congestive heart failure.



K_i β_2-AR	2.8×10^{-7} M
K_i β_1-AR	1.6×10^{-4} M
β_1/β_2 selectivity	573
cAMP accumulation EC_{50}	3.9×10^{-9} M
cardiomyocyte contractility EC_{50}	1.6×10^{-8} M

Figure 1. (R,R)-4-methoxy-1-naphthylfenoterol

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PP-5

Molecular Modeling of Interactions Between Various Subtypes of Nicotinic Acetylcholine Receptors and Selected Allosteric Inhibitors.

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Nicotinic acetylcholine receptor (nAChR) is archetypical member of the Cys-loop Ligand Gated Ion Channels superfamily. Several neuronal subtypes of nAChR poses a promising target for treatment of such disorders as nicotine addiction, cognition deficits, depression or schizophrenia. Large group of commonly used drug molecules and their metabolites affect the function of neuronal nAChR by a mechanism of non-competitive inhibition associated with physical blocking of the actual ion channel. In our studies molecular models of nAChR channel domain are used to simulate interactions with inhibitors molecules. Homology models representing different subtypes of the receptor are used to study subtype selective aspects of these interactions.

In presents studies we use a molecular models of the nAChR membrane domain obtained from *Torpedo marmorata* (PDB id: 2BG9). This model was further modified to a represent models of the human muscular subtype of nAChR or the human neuronal subtypes: $\alpha_3\beta_4$, $\alpha_3\beta_2$, $\alpha_4\beta_2$, α_7. The model of *Torpedo marmorata* was also used for docking.

Docking simulations of the flexible group of ligand into the rigid models of the receptors' channel was performed and allowed classification of the ligand in respect to the binding energies.

Obtained result indicated that ligand molecules stably interact with the surface of the channel formed by an assembly of five transmembrane helices M2. Estimated Free Energy of Binding assessed in docking was related to experimental binding affinity data [1,2] and statistically valid correlations were obtained.

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PP-6

Keto-enol Tautomerism for the *β*-Dicarbonyl Grouping in 3-Acyl-4-oxo/hydroxy-2-substituted-pyrido[3,2-*e*][1,2]thiazine 1,1-Dioxides.

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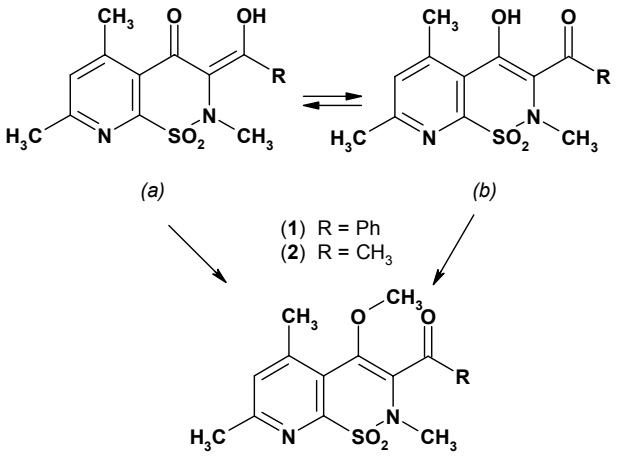
The 3-acyl-4-oxo/hydroxy-2-substituted-pyrido[3,2-*e*][1,2]thiazine 1,1-dioxides were synthesized for pharmaceutical reasons [1, 2]. The spectral data of these compounds suggested that *β*-dicarbonyl grouping partially incorporated into structure of the thiazine ring may exist in two tautomeric forms (***a***) or (***b***).



In order to determine the keto/enol tautomeric equilibrium of the *β*-dicarbonyl grouping the ^{13}C NMR analyses, X-ray crystal structure determinations and theoretical calculations were undertaken using pyridothiazines (**1**) – (**3**) as model compounds. Results of our investigation indicates that the co-existence of both possible keto/enol tautomers (***a***) and (***b***) with visible predominance of the 4-keto form is observed for pyridothiazines (**1**) and (**2**) [3]. The obtained data may be helpful in structure-activity relationship (SAR) studies within class of our analgesic 2-substituted pyridothiazines [4] closely related to (**1**) and (**2**).

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PP-7

Synthesis of O-/N-Glycoconjugates.

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The link between sugar and another molecules is known as a glycoconjugates. The major sugar chains of glycoproteins can be classified into two groups: O-linked and N-linked. In nature an O-linked sugar chain contains an *N*-acetylgalactosamine residue at its reducing terminus, which is linked to the hydroxyl group of either serine or threonine residue in a polypeptide chain. N-linked sugar chains are linked to the amide group of asparagine residues of a polypeptide chain. This sugar chain contains an *N*-acetylglucosamine residue at its reducing terminus [1-3].
Searching for the new and effective drugs can be led by direct chemical modification of existing group of compounds or by attaching them to specific carriers. This kind of approach is called prodrug strategy. One of examples of such carrier can be carbohydrates with attention on its structures. Sugars are unparalleled in the number of structures they can adopt. Variety caused by ring size, branching, anomeric configuration and increased functionality (acylation, phosphorylation) gives carbohydrates almost unlimited potential for diversity [4-5]. This inherent structural variation gives them a role in reducing probability of developing antimicrobial resistance which creates the huge possibilities to project a new chemotherapeutics.
The formation of glycosidic bonds is important to synthesis of this structure. We obtain four types of glycoconjugates: *O*-glycans, amide-, ester- bond and sugar-serine-molecule complex. This immense structural variety the development of a universal glycosylation reaction has failed, and every glycosylation has to be regarded as a unique problem, demanding considerable systematic research.

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PP-8

N-Alkilo-Fluorobenzoyl Derivatives of Tacrine as an Acetylcholinesterase Inhibitors.

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Alzheimer disease (AD) is progressing neurodegenerative illness, in spite of 100 years was described first time. To this time AD is incruable. A considerable decrease in cholinergic neurotransmission associated with the loss of neurons in some parts of the brain has been found in this disorder (Bartus theory - 1981). The basic group of drugs removing symptoms of that disease are acetylcholinesterase inhibitors. These components inhibits the enzymes and affect the level of acetylcholine in synaptic cleft. Because of this, compounds stimulate cholinergic system and have improved clinical symptoms of AD.

The aim of the research was to obtain new derivatives of acetylcholinesterase inhibitors that could be used in therapy and after elaborate new method of exchange “cold fluorine” in radioactive isotope to diagnostics of the Alzheimer’s disease.
On the basis of the gathered information, and earlier research in our Department Pharmaceutical Chemistry and Drug Analyses, the series of n-alkilofluoorbenzoyl derivatives tacrine were designed. These structures contain pharmacophore groups, which occur in currently used drugs. Next, we worked out synthesis of new compounds and a method of their purification. The structures of the derivatives weres confirmed with NMR, IR, MS and MS- HR analyses.
Next, strength and kind of binding of new derivatives were measured with colorimetric method (Ellman’s method).
The last part of this work focused on analyses strucktre activity by molecular modeling with software Cache.

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

PP-9

Homology Modeling of Metabotropic Glutamate Receptor 2.

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Many studies show involvement of metabotropic glutamate receptors (mGluRs) in synaptic excitation transudation. The mGluR family consists of eight proteins divided into three groups corresponding to sequence similarities, pharmacology and physiological role. These groups are: I (mGluR1, -5), II (mGluR2, -3) and III (mGluR4, -6, -7, -8). Group II lies in field of our interest due to its potential as therapeutic target for stroke and pain drugs. Primary goal of this research is to create viable virtual model of transmembrane domain of mGluR2 receptor capable of binding reference ligands. This model will be used for further research.

Our approach is based on homology modeling. Since mGluRs are part of superfamily of G protein coupled receptors (GPCRs) and thus their sequence is similar to Rhodopsin, we have chosen Rhodopsin crystal structure as a template for homology modeling of mGluR2 receptor. We have prepared sequence alignment of mGluR family with Rhodopsin and confronted it with alignments available in literature. Created models were verified using mutagenesis data available.

Acknowledgments
The study was partly supported by the Polish Ministry of Science and Higher Education (MNiSW), Grant No. N N405 184635.

PP-10

Synthesis and X-ray Analysis of New Derivatives of Pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine.

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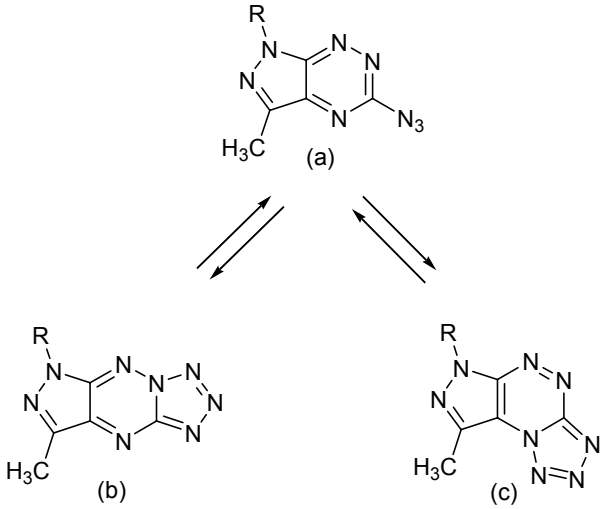
1,2,4-Triazines are well-known class of heterocyclic compounds and have been tested for use in agrochemistry, medicine or as ligands for metal ion complexation.[1,2]
As a part of our ongoing research program into formation of pyrazolo[4,3-*e*][1,2,4]triazines fused with tetrazole ring we report herein synthesis and X-ray analysis of 5,7-dimethyl-5*H*-pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine (**1**) and 5-benzyl-7-methyl-5*H*-pyrazolo[4,3-*e*]tetrazolo[4,5-*b*][1,2,4]triazine (**2**).[3,4]



R = CH_3 (**1**), CH_2Ph (**2**)

^{1}H-NMR spectra for compounds **1** and **2** clearly shown ring-chain tautomerism between azide form (a) and tetrazolo-fused tautomer (b) or (c). In order to establish whether we are dealing with linear (b) or angular (c) form it became necessary to confirm its structure by X-ray crystallography.

References:
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PP-11

Design of New [4 + 2]$_\pi$ Cycloadducts of "Phencyclone" and Maleimides N-substituted by Alkyl-(N-Aryl) Piperazine Moiety as Different Approach to Serotonin Receptors Family.

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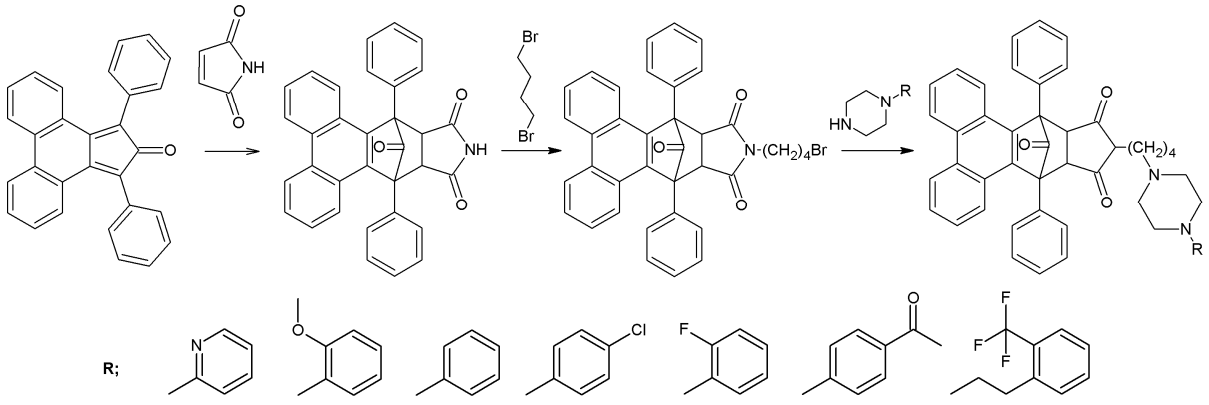
It is well known that cyclopentadienone and analogues are very reactive in Diels-Alder reactions, also gives high peri- and regiospecificity especially in cycloadditions between "Phencyclone" and dienophiles such as maleimides for example.[1,2] Series of compounds, which have phenanthrene-condensed bicyclo[2.2.1]heptene-7-one framework has been synthesized to observe inclusion and clathrate forming abilities that can be useful to find a new class of 5-HTRs. Derivatives of arylpiperazines, initially discovered as 5-HT$_{1A}$R ligands, show also good affinities for 5-HT$_7$Rs, most probably due to the strong similarities between the binding sites of these receptors.[3] Cycloimides, especially N-substituted has show miscellaneous biological, microbiological and antiviral activity. The strategy of synthesis was to combine all interatomic interactions, inclusion, and eventual ability of forming clathrates with affinity to serotonin receptors of arylpiperazines, furthermore to find other pharmacological activity.



All derivatives structures has been established on the basis of elemental analysis, MS and ^{1}H NMR. For crystalline compounds with potential highest affinity to 5-HTRs full X-ray analyze has been made.

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PP-12

4-Oxo-1,4-dihydro-3-alkanesylfonylquinolines – Organic Synthesis and Antimicrobial Activity.

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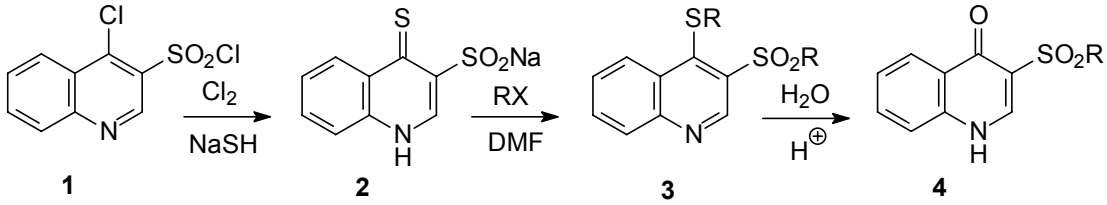
Simple and effective synthesis of thioquinantrene from quinoline prompted us to study properties and preparation of 4-chloro-3-quinolinesulfonyl chloride [1].
We found that the sulfochloride **1** was transformed into sodium 1,4-dihydro-4-thioxo-3-quinolinesulfinate **2** by the reaction with sodium hydrosylfate. Compound **2** was next alkylated in water or dimethylforamide to 4-alkylthio-3-alkanesylfonylquinolines **3** [2]. Sulfones **3** were hydrolyzed with 1% hydrochloric acid into 1,4-dihydro-4-oxo-3-alkanesulfonylquinolines **4**.



R = $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH{=}CH_2$, $-CH_2C_6H_5$;

As compounds with 3-quinolinesulfonyl or 4-quinolone subunits exhibited potent biological activity, drug-sensitivity of microorganisms on received compounds **4** were tested by the use of disc-diffusion method. For this purpose American Type Culture Collection straines (*Pseudomonas auroginosa* ATCC 27853, *Staphylococcus aureus* ATCC 25923 and *Candida albicans* ATCC 10231) were used. Various concentrations of compounds were analysed to determine acquiring changes size of growth invibition are and compared with some quinolones usually used in treatment. Possibility of acquiring resistance to tested compounds was also researched [3]. Only methyl, ethyl and n-propyl derivatives of the 1,4-dihydro-4-oxo-3-alkanesulfonylquinolines **4** compounds showed antimicrobial effect on the tested microorganisms. From above derivatives the best activity has 1,4-dihydro-4-oxo-3-ethane-sulfonylquinoline **4**. To compare that derivative with norfloxacin for used strain of *Enterococcus faecalis* the research results were following:

- 10 μg of norfloxacin on tested disc resulted in 15 mm diameter of growth inhibition area.
- 0.83 mg, 1.27 mg, 1.67 mg, 2.08 mg and 2.5 mg of ethyl derivative on tested discs resulted in 12 mm, 15 mm, 17 mm, 19 mm and 20 mm diameter of growth inhibition area respectively.

References:

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PREZENTACJE POSTEROWE

P-1

Synthesis of New Aminoguanidine Derivatives.

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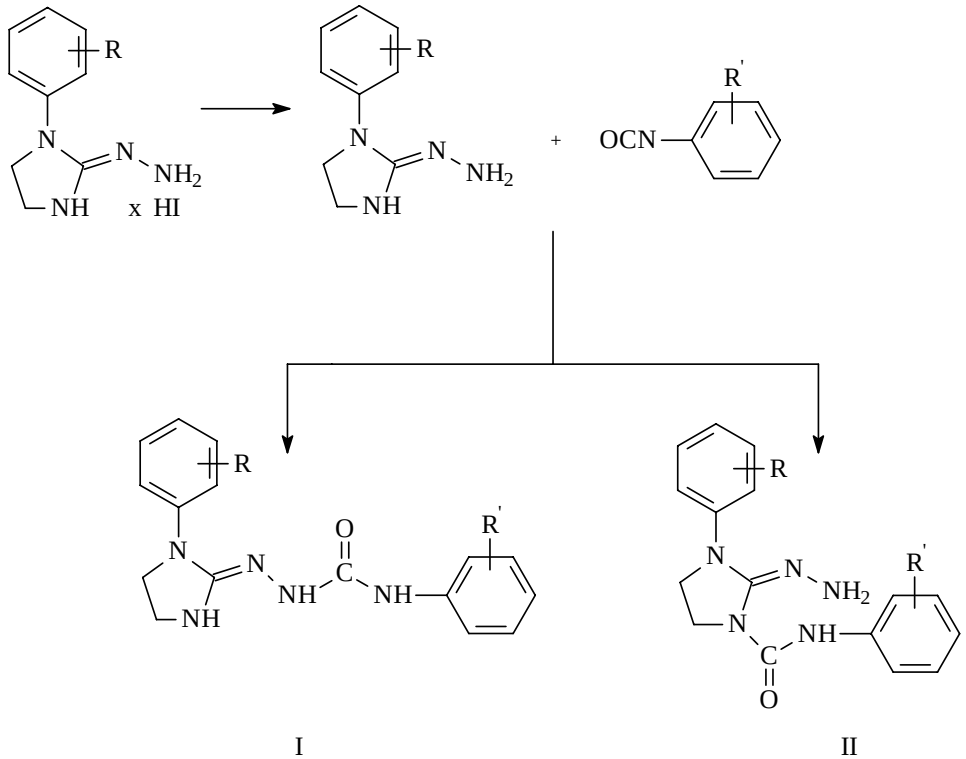
In search of new compounds with potential pharmacological activity new aminoguanidine derivatives were obtained. For this purpose the reaction of derivatives of 1-aryl–2-hydrazoneimidazolidines (obtained from 1-aryl–2-hydrazoneimidazolidines hydroiode) with aryl isoocyanate were carried out. In the course of this reaction 1-(1-arylimidazolidyn-2-yliden)-4-phenylsemicarbazides (I) and 1-aryl-2-hydrazone-3-arylaminocarbonylimidazolidines (II) were obtained. Structure of new compounds were described on the basis of spectral analysis.



I II

R = H; 2-CH_3; 2,3-diCH_3; 2,6-diCl; 4-Cl; 4-OCH_3
R' = 3-Cl; 2,6-diCl

P-2

Application of Preparative FLASH Chromatography for Separation of Ureids.

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Compared to crystallization techniques of purification, purification of organic compounds with application of FLASH chromatography is a fast, convenient and economic method. All the components of the mixture may be isolated, identified and analysed during the process of purification.
The aim of work was to separate the products of reaction of free 1-aryl-2-amineimidazolines-2 with aryl isocyanates. Considering the presence of two reactive nitrogen atoms in the 1-aryl-2-amineimidazolines-2 substrates, it was expected to obtain the mixture of isomeric products which differ with the position of arylaminecarbonyl moiety. The formation of two or three different products was confirmed by thin-layer chromatography method.
The separation of isomeric ureids was performed using toluene-ethyl acetate (3:1 or 7:1) as the eluent. After separation the purity of fractions was verified with TLC method and the structure of isolated compounds was confirmed with ^{1}H NMR.

P-3

Search for Dual Function Inhibitors for Alzheimer's Disease: Synthesis and Biological Activity of Cholinesterases Inhibitors Derivatives of *N*-Benzylpiperidine and Their Aβ Fibril Formation Inhibition Capacity.

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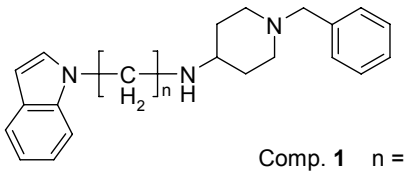
Alzheimer's disease (AD) is neurodegenerative brain disorder which is still an important social and medical problem. AD is characterized by progressive dementia caused by the deficits in the cholinergic system in the brain areas related to memory and learning, and brain deposits of amyloid beta (A□) peptide and neurofibrillary tangles. Actually, for the treatment of AD four drugs have been used: donepezil, rivastigmine, galantamine and memantine. Three of them, were introduced into a clinic according to cholinergic hypothesis. Cholinesterases exert secondary functions among which the mediating the processing and deposition of Aβ peptide seems to be crucial for the development of the AD. Identification of the peripheral anionic binding site (PAS) of AChE as a fragment responsible for binding with Aβ and resulting fibrillogenesis caused the interest in synthesis of dual binding site AChE inhibitors.

In view of the development of new cholinesterases inhibitors as drugs capable of reducing the symptoms of AD, the capacity of newly synthesized *N*-benzylpiperidine derivatives to inhibit the AChE and BuChE was examined [1]. The most interesting series of inhibitors were hybrid molecules bearing two moieties: 1-benzylpiperidino-4-amino group and heterocyclic indol ring or izoindolino-1,2-dion (phthalimido group) linked by alkyl chain. These compounds displayed moderate to good inhibitory activity against both AChE and BuChE. The most promising compounds have been tested in a thioflavin T fluorescence assay for their ability to block Aβ fibril formation [2, 3].



Comp. **1** n = 5
Comp. **2** n = 8

We found derivatives with five (**1**) and eight methylene groups (**2**) to possess the inhibitory effect of cholinesterases and the inhibitory effect on fibril formation. Molecular modeling studies and docking of compounds **1** and **2** into AChE and BuChE active site revealed main interactions between examined molecules and active sites of enzymes.

[1] Więckowska A.: The new carbamates and *N*-benzylpiperidine derivatives with expected cholinestarases inhibiting activity. PhD thesis.Jagiellonian Unversity Poland, 2008.
[2] Goldsbury C. S., Wirtz S., Müller S. A., Sunderji S., Wicki P., Aebi U., Frey P.: *J. Struct. Biol. 130 (2000), 217-231.*
[3] Alptüzün V., Prinz M., Hörr V., Scheiber J., Radacki K., Engels B., Braunschweig H., Erciyas E., Holzgrabe U.: *J. Med. Chem*; (*in preparation*)

P-4

Synthesis, Structure and Biological Activities of Novel Imidazolines and Their Cu(II) Complexes.

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[b] Institut für Pharmazie der Ernst-Moritz-Arndt-Universität Greifswald, Germany
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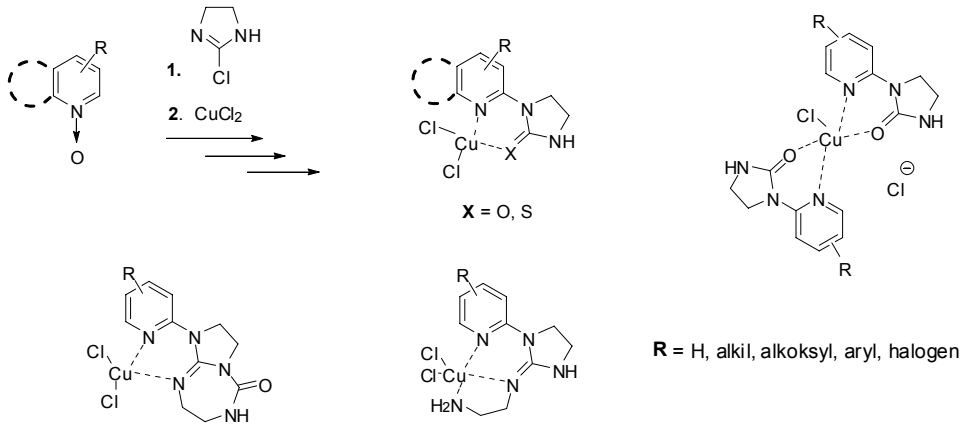
As a continuation of our previous investigations aimed at the synthesis of novel imidazoline derivatives and their complexes [1,2] with potential biological activities, we have now prepared several new series of compounds incorporating pyridine, quinoline or isoquinoline ring at the position N1. Such ligands are susceptible to the reaction with $CuCl_2$ giving rise to the formation of corresponding complexes. According to literature data [2-5], the designed compounds may exhibit both antitumor and superoxide dismutase (SOD)-mimicking properties.
In this communication we will discuss the course of some unusual reactions of 2-chloroimidazoline with heteroaromatic *N*-oxides leading to novel 2-imidazoline derivatives and their Cu(II) complexes:



Structures of the above presented ligands were confirmed by IR and NMR spectroscopic data, while single crystal X-ray analysis was used to confirm the structures of corresponding Cu(II) complexes. Antitumor activities of both the ligands and corresponding complexes have been investigated at the Department of Medicinal Chemistry, University of Greifswald, Germany.

[1] Sączewski F., Foks H.: *Synthesis*, *(1986), 751.*
[2] Sączewski F., Dziemidowicz-Borys E., Bednarski P.J. *et.al.*: *J.Inorg.Biochem.*, *100 (2006), 1389-1398.*
[3] Adsule S., Barve V. *et.al.*: *J.Med.Chem.*, *49 (2006), 7242-7246.*
[4] Cao R., Travieso N. *et al.*: *J. Inorg. Biochem.*, *66 (1997), 213-217.*
[5] Pierre J. L., Chautemps P. *et al.*: *J. Am. Chem. Soc.*, *117 (1995), 1965-1973.*

P-5

Investigations on Reaction of α-Amino-β-Bromo Heterocyclic Compounds with Oxirane Derivatives.

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Studies on the asymmetric synthesis of 8-amino-7-(2-hydroxy-3-morpholinopropyl)theophylline allowed us to obtain tricyclic heterocyclic compounds containing oxazole and oxazine moiety [1,2]. In order to confirm assumed reaction mechanism and to elucidate a new method for synthesis of potentially biological active substances, a series of synthetic reactions have been carried out, using substrates with analogical chemical structure. Firstly, the starting set of substrates was: 2-bromobenzimidazole as a heterocycle and N-(2,3-epoxypropyl)indoline and N-(2,3-epoxypropyl)-morpholine as oxirane derivatives. In both cases two products were obtained. One of them contained three carbon chain, which was formed during the process of opening oxirane ring and its addition to NH group of heterocyclic system. The second product was a tricyclic compound with oxazole ring.
In the next stage of our investigations, we used 6-bromopyridin-2(1*H*)-one as a heterocyclic system while N-(2,3-epoxypropyl)morpholine and N-(2,3-epoxypropyl)-N'-phenylpiperazine as oxirane derivatives were used. In both cases one product was obtained, a bicyclic compound with oxazole moiety.
The structure of obtained compounds was confirmed by one- and two-dimensional NMR spectra and MS spectra.

References:
[1] Cegła M.T., Potaczek J., Żylewski M., Strekowski L.: *Tetrahedron Lett. 46 (2005), 3561-3563*.
[2] Cegła M.T., Potaczek J., Żylewski M., Strekowski L.: *J. Heterocyclic Chem. 46 (2009), 191-194*.

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

P-6

Bifunctional Hybrides of Nitrogen Mustards with Peptide "Address" Attached to the 1,3,5-Triazine Scaffold.

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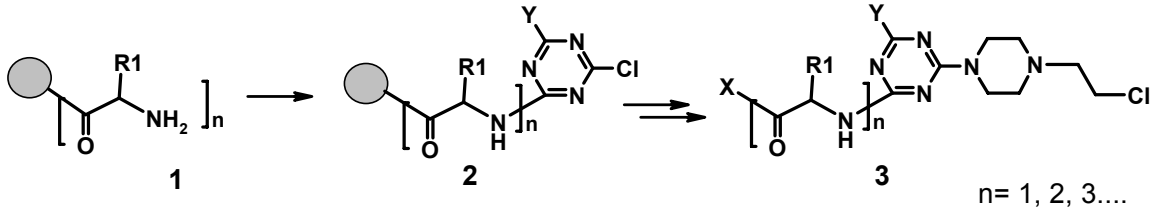
[b] *Department of Organic Chemistry, Medical University, Białystok*
e-mail: zbigniew.kaminski@p.lodz.pl

In our studies we found that triazines substituted even with single 2-chloroethylamine moiety cause apoptosis and inhibition of growth of standard cell line of mammalian tumor MCF-7 [1]. Since classical NM drugs do not operate selectivity, causing high levels of inadvertent DNA damage in normal cells, toxic and mutagenic side effects, and in some cases, leading to secondary malignancies, we attempted to modify structures of two other substituents of triazine scaffold, searching for more selectively acting analogues. To achieve this goal, we designed the bifunctional NM by introducing into triazine ring peptide "address" *via* N-terminus expecting enhanced selectivity of modified structure.
Bifunctional hybrids **3** were prepared on the Wang resin, starting with synthesis of peptide fragment **1** followed by attachment of 2,4-dichloro-6-substituted-1,3,5-triazine scaffold.



The effect of deactivation of chlorine atoms in **2** caused by the conjugation of lone pair of electrons of amino group was weakened by our new synthetic approach based on umpolung of substituent effect [2] and by using excessive amounts of triazine. The final transformation of **2** into hybrid NM structure was done directly on the resin by treatment with excess of DABCO, followed by spontaneous decomposition of intermediate quaternary ammonium chloride into **3**.

References:
[1] Kolesińska B., Kamiński Z. J., Wąsikowska K., Drozdowska D.: Polish Patent Appl. **P-385126**.
[2] Kolesińska B., Kamiński, Z. J.: *Tetrahedron 65 (2009), 3573–3576.*

P-7

Synteza i Ocena Aktywności Cytotoksycznej *in vitro* Alkynylowych Pochodnych Betuliny.

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[b] *Zakład Onkologii Doświadczalnej, Instytut Immunologii i Terapii Doświadczalnej PAN, ul. R. Weigla 12, 53-114 Wrocław*

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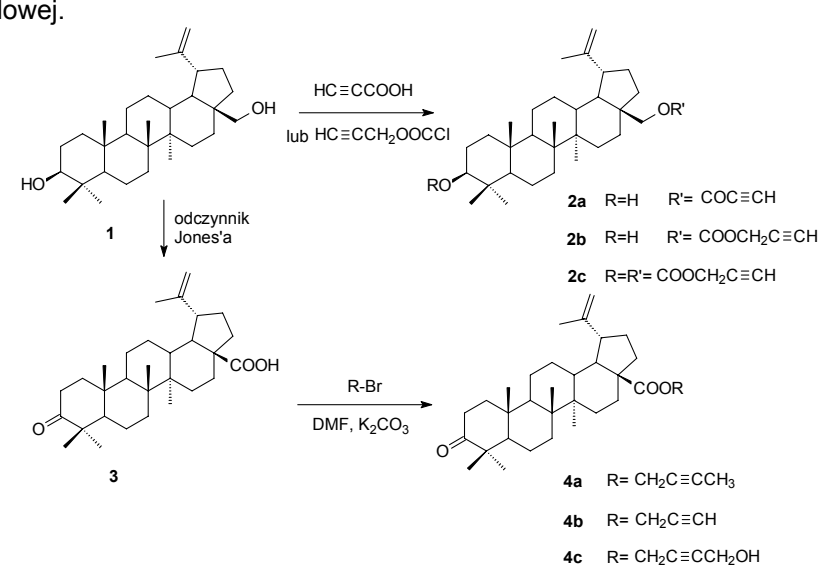
Betulina [lup-20(29)-en-3□,28-diol] **1** jest powszechnie występującym w przyrodzie triterpenem pentacyklicznym typu lupanu. Duże jej ilości znajdują się w zewnętrznej warstwie kory białych gatunków brzozy (zawartość 25-30%), stąd też kora stanowi łatwo dostępny surowiec do otrzymywania **1** w procesie ekstrakcji nie wymagającym wielkich nakładów finansowych [1]. Betulina **1** i jej pochodne wykazują szerokie spektrum aktywności biologicznej, takie jak: przeciwnowotworowe, przeciwbakteryjne, przeciwwirusowe, przeciwzapalne, hepatoochronne, przeciwkamicze i inne [2]. Z aktywnych ugrupowań betulina **1** posiada dwie grupy hydroksylowe przy C-3 i C-28 oraz grupę izopropenylową przy C-19, dzięki czemu ta interesująca struktura farmakoforowa, znana od ponad 200 lat, jest w dalszym ciągu poddawana rozmaitym modyfikacjom chemicznym celem otrzymania nowych pochodnych o lepszych właściwościach farmakologicznych [2].

W prezentowanej pracy przedstawiono syntezę i ocenę aktywności cytotoksycznej *in vitro* nowych alkynylowych pochodnych betuliny **1**. Wyizolowaną z kory brzozy, na drodze ekstrakcji dichlorometanem, betulinę **1** poddano reakcjom z kwasem propiolowym i chloromrówczanem propargilowym otrzymując mono- i diestry **2**. Reakcja utleniania betuliny **1** za pomocą odczynnika Jonesa doprowadziła do powstania kwasu betulonowego **3**, który pod wpływem bromków alkynylowych w środowisku DMF\K_2CO_3 ulega transformacji do pochodnych **4**. Związek **3** przekształcono również, poprzez chlorek kwasu betulonowego, w reakcji z propargiloaminą do pochodnej amidowej.



Oznaczono aktywność cytotoksyczną *in vitro* związków **2** i **4** wobec komórek nowotworowych.

[1] Tomaszkiewicz-Potępa A., Piękoś M.: *Wiad.Chem.*, *56 (2002) 986.*

[2] Tolsikova T. G., Sorokina I. V., Tolsikov G. A., Flekhter O. B.: *Russ. J. Bioorg. Chem.*, *32 (2006) 37*.

P-8

New Theophylline Derivatives with Carboxyl, Ester and Amide Moieties as a Potential Non-steroidal Anti-inflammatory Agents.

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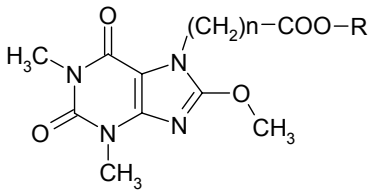
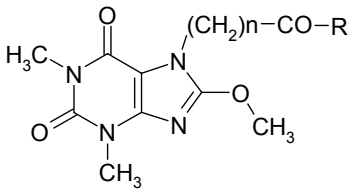
Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used of all therapeutic worldwide i.e. for the alleviation of minor aches and pains, in the symptomatic treatment of rheumatic fever, rheumatoid arthritis (RA) and osteoarthritis (OA). In general all of these analgesic, antipyretic and anti-inflammatory effects are related to the primary action of these drugs – inhibition of arachidonate cyclooxygenase and thus inhibition of the production of prostaglandins and thromboxanes. NSAIDs include a variety of different agent from various chemical classes.
The chemical structure of NSAIDs contain various lipophylic heterocyclic or aromatic core with a free carboxylic or enol groups, what is very important for the biomolecular activity of these drugs. Often the active free carboxylic group is deprotected from the ester or amide precursors during the biotransformation.
According to the structure – activity relationships in the group of NSAIDs we designed and synthesized a new class of 7-alkyltheophylline derivatives with carboxyl, ester or amide terminal groups.



R = H, CH_3
n = 1, 3



R = benzylamine, phenylpiperazine, 4-fluorophenylpiperazine

n = 1, 3

To increase the lipophilicity of these compounds the methoxy substituent was introduced in the 8-position.
The structures of the new compounds were confirmed by examination of their ^{1}H-NMR, IR spectra as well as by elemental analyses.
The anti-inflammatory and analgesic effects of the new compounds will be evaluated in some behavioral models *in vivo* (writhing and formalin tests).

P-9

New Isophosphoramide Mustard Analogues as Prodrugs for Gene Therapy.

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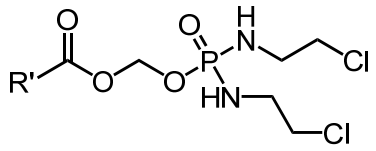
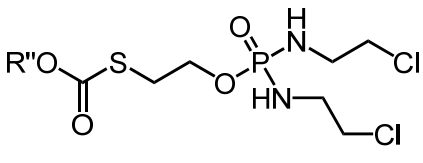
Isophosphoramide mustard (iPAM) is active, cytotoxic metabolite of ifosfamide (IF), anticancer alkilating drug widely used in the clinic. Poor selectivity of cytostatic drugs currently used in conventional cancer chemotherapy lead to attempts to employ gene therapy. One of this type therapy is Gene-Directed Enzyme Prodrug Therapy (GDEPT) [1]. This methodology requires prodrugs, which release highly cytotoxic drugs at the tumor after activation by an exogenous enzyme expressed in tumor cells.

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

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





R' = Me, *t*-Bu, Ph

R'' = Me, Et, *i*-Pr, Bz

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

This research was supported by Nicolaus Copernicus University, grant 70/2009.

[1] Niculescu-Duvaz I., Friedlos F., Niculescu-Duvaz D., Davies J., Springer C. J.: *Anticanc. Drug Des. 14 (1999), 517-538.*

P-10

The Acid-Base Properties of Imidazolidine-2,4-dione and Imidazo-[2,1-f]theophylline Derivatives, Containing Arylpiperazinylalkyl Fragment in the Aspect of Their Serotonin Transporter Activity.

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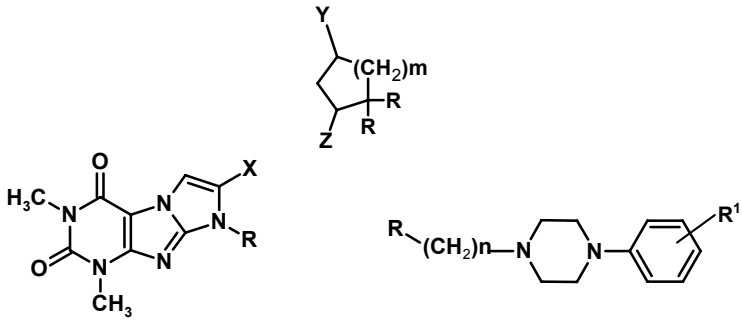
Serotonin has an aliphatic amino group and a phenolic function with pK_a values of 9.8 and 10.73, respectively. Thus there are four ionic species of serotonin possible at neutral to alkaline pH: the cation, the anion, the ampholytic ion and the neutral form. Under physiological condition the serotonin transporter (5-HTT) interact with the cationic form of serotonin [1].
Taking above into a consideration, the dissociation constant (K_a) of the arylpiperazinylalkyl derivatives of imidazolidine-2,4-dione and imidazo[2,1-f]theophylline (fig. 1) were undertaken. Title compounds exhibit multireceptor profile as potent 5-$HT1_A$ and 5-$HT2_A$ receptor ligands and diversified affinity for the serotonin transporter [2,3,4].
The aim of this work was to determine the dissociation constans (K_a) of some arylpiperazinylalkyl derivatives of imidazolidine-2,4-dione and imidazo[2,1-f]theophylline, using potentiometric titration method. The obtained pK_a values were compared with the data calculated by a module of the Pallas program [5]. The biological activity data (5-HTT) were also correlated with the received pK_a values.



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

The work was partly supported by grants: K/ZBW/000479 and K/ZBW/000480.

[1] Rudnick G., Kirk K. I., Fishkes H., Schuldiner S.: *J. Biol. Chem., 1989, 14865-14868.*
[2] Czopek A., Byrtus H., Pawłowski M., Dybała M., Nowak G., Tatarczyńska E., Wesołowska A., Chojnacka-Wójcik E.: poster, *The Fifth Multidisciplinary Conference on Drug Research, Darłówko Wschodnie, 15-17.05.2006, p-32*.
[3] Zagórska A., Pawłowski M., Dybała M., Nowak G., Nikiforuk A., Tatarczyńska E., Chojnacka-Wójcik E.: poster, *The Fifth Multidisciplinary Conference on Drug Research, Darłówko Wschodnie, 15-17.05.2006, p-112*.
[4] Zagórska A., Pawłowski M., Dybała M., Nowak G.: poster, *The Fifth Multidisciplinary Conference on Drug Research, Darłówko Wschodnie, 15-17.05.2006, pp-112-113*.
[5] Pallas 3.2.1, Demo Version, CompuDrug International.

P-11

Solid Phase Synthesis of Carbocyclic Distamycin Analogues and Their Biological Evaluation.

Danuta Drozdowska

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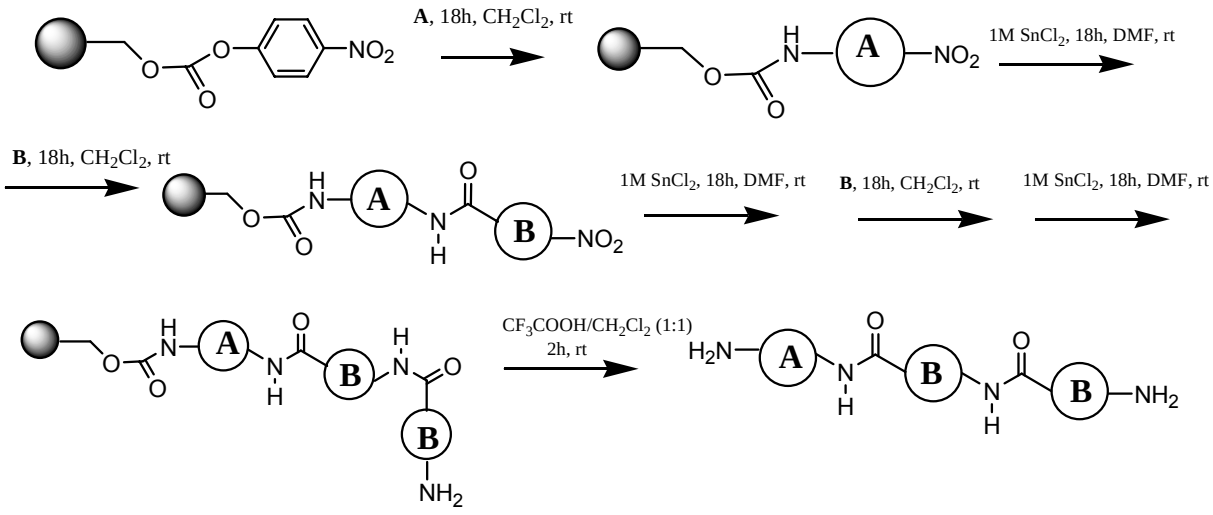
The clinical significance of DNA-binding compounds can hardly be overstated, as many anticancer regimens include a compound that binds to and/or modifies DNA.
Netropsin, distamycin or bis-amidines (e.g. pentamidine) has been extensively studied due to their ability to bind to the minor groove of DNA double helix in sequence-specific manner and have served as models for biochemical and physical studies of drugs that bind to the DNA minor groove. In particular, it has been shown that they bind DNA reversibly through hydrogen bonds, van der Waals contacts, and electrostatic interactions at sequences of four or more consecutive A-T pair and strongly discriminate against G-C pairs.
In the investigations led in Department of Organic Chemistry of Medical University in Białystok, we got series carbocyclic analogues of netropsin and distamycin, having benzene in place N-methylpyrrole rings. Carbocyclic analogues of netropsin and distamycin are readily available, can be modified easily, and are stable under most experimental conditions.
Here we present a solid phase synthesis of carbocyclic distamycin analogues. We chose different aromatic amines **A**, which annexation to polystyrene grains begun the solid phase synthesis (Scheme 1). Obtained on this way compounds were reduced and acylated by 3-nitrobenzoyl chloride **B**. The steps of reduction and acylating were repeated. At the end, using of trifluoroacetic acid solution led to obtainment the trimmers **ABB**, analogues of distamycin, free from polystyrene grains. Their biological activity was investigated.



P-12

Ab initio and DFT Studies for Alkylation Reaction of 2,3-Bis[(3-pyridylmethyl)amino]-2(*Z*)-butene-1,4-dinitrile.

Zbigniew Dutkiewicz, Stanisław Sobiak, Tomasz Gośliński

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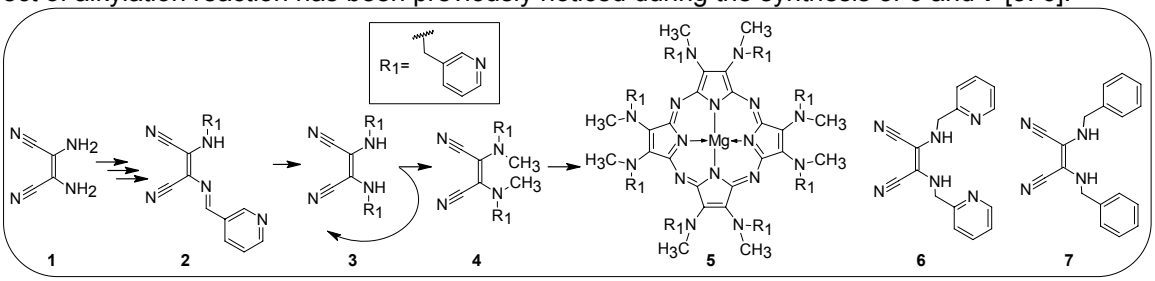
Diaminomaleonitrile (**1**) has been considered as one of the versatile precursors to various types of heterocyclic compounds [1]. Its derivatives have received recognition in the construction of self-assembled materials through metal coordination [2] and red light emitter for electroluminescence devices [3]. Finally, the derivatives of diaminomaleonitrile have been extensively utilized in the synthesis of various macrocyclic systems, including porphyrazines [4].
The synthesis of porphyrazine **5** requires template macrocyclisation reaction using dinitriles as substrates (Scheme 1). Dinitrile **3** was synthesized by sequential double – reductive alkylation of **1**. Attempts to alkylate **3** to **4** with dimethyl sulphate in some conditions (temp > 0 °C) resulted in reaction returning to **2**. Dinitrile **3** seems to act more like a hydride donor than a nucleophile. Similar effect of alkylation reaction has been previously noticed during the synthesis of **6** and **7** [5. 6].



Scheme 1. The molecular structure of **3** disodium salt

The aim of our current *ab initio* and DFT studies was to explore unusual chemical behaviour observed during the alkylation of **3**. The condensed Fukui functions were applied to explain both directions observed during alkylation reaction. These functions were calculated at HF/6-31G(d,p) and B3LYP/6-31G(d,p) levels of theory using Mulliken (MPA) and Löwdin (LPA) population analyses for molecular geometry of **3** in form of its disodium salt and optimized at the MP2/6-31G(d,p) level. The values for f_k^- and f_k^+ calculated from Mulliken and Löwdin populations are presented in table 1.

Atom	MPA (B3LYP)		LPA (B3LYP)	
	f^-	f^+	f^-	f^+
N14, N21	0.066	–0.029	0.095	–0.014
C11, C22	–0.027	–0.009	0.004	0.000
H12, H24	0.048	0.000	0.022	0.000
H13, H23	0.042	0.020	0.021	0.022

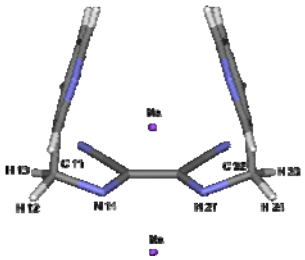


Table 1. The condensed Fukui functions for **3** disodium salt calculated from Mulliken and Löwdin population analyses at B3LYP/6-31G(d,p) level.

The calculated data pleasingly correspond to the experimental observations. While the dinitrile **3** disodium salt was treated with dimethyl sulphate at lower temperature ~ –30 °C the alkylation reaction prevailed (see f^- at N14, N21), whereas at higher temperature ~0 °C alkylating agent acted as hydride anion acceptor, which favoured elimination reaction (see f^- at H12, H24).

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P-13

The Interactions of Library of Artificial Receptors with Nitrogen Mustards Attached to the 1,3,5-Triazine Scaffold

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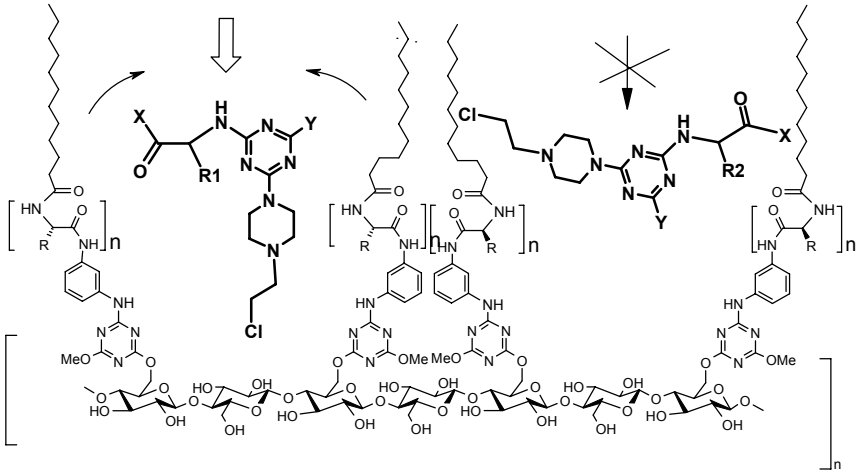
The hybrid drugs, combining two drugs in a single molecule, in many cases are creating a chemical entity more medically effective than its individual components. Both drug-like fragments have independent modes of action that make the emergence of drug resistance less likely. Moreover, in several cases the collected data provide the amplification of effects of fragments, increase of selectivity or even the extraordinary biological effects not attributed to any of the individual partner of the hybrid construct [1].

In order to increase the selectivity and activity of nitrogen mustard (NM) we prepared the hybrid of classic nitrogen mustards (NM) attached to the triazine scaffold with oligopeptide “address” attached *via* N-terminus as new generation of anticancer drug.

Herein we present the studies on interactions of these hybrid with the artificial receptors formed by self-organization of N-lipidated peptide immobilised on the cellulose support.



It is expected that the interactions between the hybrids and the library of receptors could be used as the new tool for the *in vitro* screening of effects of structural modifications initiated by variation of oligopeptide fragment.

References:

[1] Just recently, it has been found that several relatively simple melamine analogues substituted within amino group are potent inhibitors of topoisomerase, telomerase, histone deacetylase, phosphatidiloinositol kinase, protein kinase CK2 etc.

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P-14

Preliminary Evaluation of Anticonvulsant Activity of Some Aminoalkanol Derivatives.

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Epilepsy is one of the most frequent neurological disorder affecting 0.4-1% world's human population [1]. Despite continuous progress in its pharmacotherapy up to 30% of patients are still insufficiently treated by means of antiepileptic drugs (AEDs) which may be caused by among others a development of resistance [2]. AEDs exert their action by different mechanisms and what is more some of them can act by more than one mechanism. The drug can influence the inhibitory or excitatory neurotransmitters' systems or transmembrane transport of ions. Among AEDs different chemical classes can be found. Taking into consideration those facts new anticonvulsant compounds are discovered through conventional screening and/or structure modification rather than the design based on mechanism of action [3, 4]. This approach requires chemical or biotechnological synthesis of a great number of new substances followed by screening procedures.

While searching for new prototype antiepileptic drugs we have noticed that several N-substituted aminoalkanol derivatives posses anticonvulsant activity in different models of seizures. Among chiral structures relationship between configuration and activity is noticeable. It is worth to mention that both amine and their amide analogues exhibit anticonvulsant activity. Former works succeeded among others with patent application of series of aminoalkanol derivatives with anticonvulsant activity of which (*R*)-2-[(2,6-dimethylphenoxy)-ethyl]-amine-1-propanol and its amide analogue (*R*)-2-[(2,6-dimethylphenoxy)-acetyl]-amine-1-propanol have ED_{50} value in MES test of 5.34 and 97.93 with the protection index PI=5.51 and 1.43 respectively (*i.p*. mice) [5]. Another aminoalkanol derivative (*S*)-2-[(2,6-dimethylphenoxy)-ethyl]-amine-1-butanol hydrochloride showed ED_{50} value of 7.57 and PI=4.55 in MES test (i.p. mice) [6].

As a continuation of our former work we herein report on the results of preliminary pharmacological studies on anticonvulsant activity of newly synthesized aminoalkanol derivatives and their amide analogues. It is worth to mention that among the screened compounds both structural and optical isomers can be found. All substances were evaluated in the maximal electroshock (MES) and subcutaneous pentylenetetrazole (ScMet) induced seizures tests and for neurotoxicity (TOX) in the rotorod test in mice after *i.p.* administration. Tests were run according to the Antiepileptic Drug Development (ADD) program at Epilepsy Branch, National Institute of Neurological Disorders and Stroke, National Institute of Health, Rockville, MD 20852, USA [7, 8]. The compounds which showed good anticonvulsant activity in screening procedures were also evaluated in other tests e.g. MES, ScMet, TOX after *p.o.* administration in rats, preliminary hippocampal kindling test in rats, *in vitro* hippocampal slice culture neuroprotection assay (NP), pilocarpine-induced status in rats. Oral administration to rats of the most promising compounds (**1**, **2**) resulted in ED_{50} in MES test with the values of 31.01 and 22.8 mg/kg (after 0.5 h) as compared with a value of 23.2 mg/kg for phenytoin in the same assay. It should be emphasized that compounds **1** and **2** did not show any neurotoxicity (TD_{50}>500 mg/kg). ED_{50} for *R* enantiomer of **2** in the same model of seizures after *i.p.* administration in mice (after 0.5 h) was 76.7 mg/kg which is more than for phenytoin (6.48 mg/kg) and carbamazepine (9.85 mg/kg) but less than for valproate (287 mg/kg) [9]. At the same dose no neurotoxicity was observed (TD_{50}=208.3, 0.25 h).

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P-15

Chemical Modifications and Biological Activity of 2-Methoxyphenyl-piperazine Derivatives of Phenytoin. Mutagenicity Tests *in vitro* and Influence on Artificial Membrane for Two α_1-Adrenoceptor Antagonists with Antiarrhythmic Properties.

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During the search for new antiarrhythmic agents, a number of active amine-alkyl phenytoin derivatives have been obtained [1,2] Among other, phenylpiperazine derivatives displayed interesting antiarrhythmic properties in adrenaline-induced arrhythmia model corresponding to their α_1-adrenoceptor antagonistic properties. One of the most interesting, compound TD-11, showed significant affinity for α_1-adrenoceptor and selectivity in respect to α_2-adrenoceptor in radioligand binding assay [2], promising selective antiarrhythmic activity in adrenaline model and was not active in barium chloride induced model of arrhythmia [1]. Interesting pharmacological properties of compounds TD-11 prompted us to modify its structure within two areas responsible for activity and selectivity (ester moiety at N3 and 2-hydroxypropyl linker, Fig.1). As a result, compound GG-5 was obtained within three-steps synthesis. The new compound was evaluated on its affinity for α_1-adrenoceptor and antiarrhythmic properties. Both compounds were tested on their mutagenicity with applying the test by using the *Vibrio harveyi* strains: BB7 (wild type) and BB7M, BB7XM, BB7X (genetically modified strains). The influence of both compounds on artificial cell membrane was examined by the use of mixed Langmuir monolayers model.

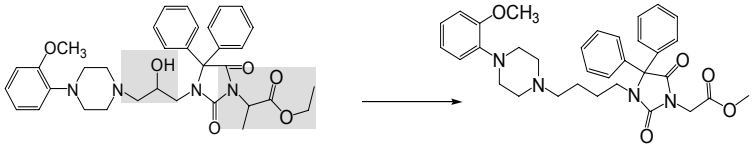

Fig. 1. Compound **GG-5** a chemical modification of compound **TD-11** (two area of modification in grey).

Radioligand binding assay with ^{3}[H]-Prazosin, as selective radioligand, indicated that compound GG-5 had five-fold higher affinity for α_1-adrenoceptor than that of TD-11. In contrary, the ED_{50} (antiarrhythmic activity in adrenaline model) was lower in the case of TD-11. Compound TD-11 showed significant mutagenicity, whereas the GG-5 was not mutagenic. Results of interaction of the compounds with lipids in mixed Langmuir monolayers partly explained some differences in biological activity of the compounds TD-11 and GG-5. Authors thank to Prof. Grzegorz Węgrzyn from University of Gdańsk for *Vibrio harveyi* strains. The work was partly supported by financial program K/ZBW/000473.

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P-16

Allosteric Modulation of Opioid Receptors.

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Allosteric modulators of G-protein-coupled receptors (GPCRs) interact with binding sites topographically distinct from the orthosteric site, and so, they offer several advantages over standard orthosteric drugs. GPCR allosteric binding sites can show greater divergence across subtypes of a particular receptor than orthosteric sites, so better selectivity might be obtained. Additional advantages would be preservation of the normal spatial and temporal pattern of physiological signal generation and termination, with the only effect of the modulator being to either 'tune up' or 'tune down' this pattern of signaling, and reduced potential for toxic effects – modulators would have a 'ceiling' to their effect, irrespective of the administered dose [1]. There are also reports of ligands showing mixed, allo- and orthosteric activity, which may result in interesting pharmacological profiles. These ligands have been named 'dualsteric ligands' [2].

The aim of work was to investigate the mode of interaction of the unique ligands [3-6] (with no pharmacophoric protonable nitrogen atom) with MOR and DOR opioid receptors. Models of the receptors were obtained with the method of homology modelling, with application of Modeller 9v5 software, using β2-adrenergic receptor as a template. These models were assessed by both rigid and flexible docking (by PatchDock and Sybyl 8.0, respectively) of rigid ligands of opioid receptors (SIOM and naloxone). Additionally, docking of N-desmetyloclozapine was carried out, in purpose of initial selection of the δ opioid receptor models with a ligand binding pattern most familiar with that of the crystallographically obtained β2-adrenergic receptor structure.

Detailed analysis of the results have shown that investigated compounds could be bound in the orthosteric binding site, as well as in two other pockets on the extracellular receptor's surface near the orthosteric pocket. Those hypothetical binding sites are located close enough to the orthosteric binding site to affect it allosterically. Moreover, the hypothetical pocket located between extracellular parts of TM1, TM2 and TM7 seems to share important amino acids with the orthosteric pocket, and some docking results reveal possibility of interaction of one molecule of investigated unique ligands with both ortho- and allosteric pocket at the same time, which could be called a dualsteric interaction. The other hypothetical binding site is located in e2 region, and seems to be analogical to allosteric binding site discovered recently in muscarinic M2 receptor structure [7].

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Computations were performed under computational grant by Interdisciplinary Centre for Mathematical and Computational Modeling, Warsaw, Poland, grant number G30-18.

P-17

Struktura i Konformacja 2-Tiozebulariny – Badania w Krysztale i Roztworze.

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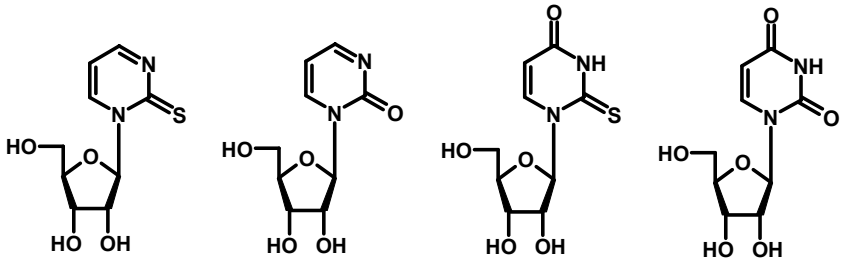
2-Tiozebularyna (**1**) jest analogiem 1-*β*-D-rybofuranozydu 2-pirymidynonu, zwanego zebularyną - związku o dobrze udokumentowanej aktywności w procesie inhibicji metylotransferaz DNA. Hamowanie metylowania DNA jest istotnym celem w epigenetycznej terapii przeciwnowotworowej [1,2].
Przedmiotem niniejszego komunikatu są badania konformacyjne **1** w krysztale i w roztworze za pomocą technik rentgenostrukturalnych i NMR oraz porównanie struktury **1** z parametrami konformacyjnymi zebularyny (**2**), 2-tiourydyny (**3**) i urydyny (**4**).



2-tiozebularyna zebularyna 2-tiourydyna urydyna

2-Tiozebularynę (**1**) otrzymano metodą sililową tworzenia wiązania N-glikozydowego w reakcji 1-*O*-acetylo-2,3,5-tri-*O*-benzoilo-D-rybozy z sililową pochodną 2-merkaptopirymidyny i następczej deprotekcji grup benzoilowych zabezpieczających fukcje hydroksylowe rybozy za pomocą roztworu metanolanu sodu w metanolu. Czystość i budowa modyfikowanego nukleozydu została potwierdzona za pomocą technik chromatograficznych (TLC, HPLC) oraz spektroskopowych (FAB-MS, UV oraz ^{1}H i ^{13}C NMR).
2-Tiozebularyna **1** w roztworze metanolu krystalizuje w układzie jednoskośnym i grupie przestrzennej $P2_1$. W krysztale pierścień rybozy posiada konformację krzesłową *C2'-egzo*/*C3'-endo*, zasada heterocykliczna jest w położeniu *anti* a konformacja wiązania C4'-C5' *trans*. Interesującym wynikiem badań konformacji 2-tiozebularyny w roztworze jest całkowite usztywnienie reszty cukrowej nukleozydu w konformacji *C3'-endo*, w stopniu nie obserwowanym w strukturach zebularyny i 2-tiourydyny [3].

Badania finansowane z funduszu grantu Nr 68/E-61/BWSN-0126/2008.

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P-18

The Interactions of Derivatives of 1-Aryl-2-iminoimidazolidine with the Known Antidepressants.

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Affective states are regulated mainly by serotonin and noradrenaline. However the opioid system has been also related to antidepressant-induced mood improvement. The new substances synthesised - 1-aryl-2-iminoimidazolidine derivatives named DM-1, DM-6, DM-12 and DM-13 contain the urea moiety (which suggests affinity toward serotonin receptors), on the other hand they contain carbonyl groups and this feature can be found in opioid analgesics such as fentanyl and petidine. The results of the pharmacological studies showed that these compounds exerted a significant influence on the central nervous system (CNS) of animals and suggest potential antinociceptive and antidepressant-like activity.

Thus, in the present study, the antidepressant-like effect of the new compounds and their interactions with known antidepressants were evaluated in the forced swim test (FST), commonly applied to predict a potential antidepressant activity.

All tested compounds DM series administered at the dose of 0.1 LD_{50} reduced the immobility time of mice in the FST. The positive results of pharmacological tests and biochemical study (showing the affinity of tested derivatives to 5-HT_2 receptors), suggesting possible antidepressant-like properties of DM series prompted us to examine the interactions of the new substances with the known antidepressants: imipramine, citalopram, reboxetine and tianeptine.

The antidepressant effect of threshold dose of imipramine and citalopram was significantly increased by DM-6 and DM-13 compound. DM-13 compound increased also antidepressant effect of reboxetine, and DM-1 – that of tianeptine. Concurrently, studied derivatives, at the same dose (0.1 LD_{50}) reduced the locomotor activity in mice [1-3], but administered concomitantly with antidepressants do not affect significantly their locomotor activity. These findings indicate that changes in motor activity of animals do not participate in the antidepressant-like effect of the compounds tested.

Although the precise mechanism involved in the observed antidepressant-like activity is not clear, the experimental observations suggest a possible direct or indirect facilitation of the central serotonergic and noradrenergic transmission for the studied compounds. In addition we can not exclude the involvement of central opioid system in the antidepressant activity of these new compounds.

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P-19

Estimation of the Lipophilicity of Some Xanthone Derivatives Exhibiting Anticonvulsant Acitivity.

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The xanthone derivatives show varied pharmacological properties, for example analeptic, antiallergic, antitumor, antimycotics, antimicrobial and anticonvulsant.
In the structure-activity-relationship (SAR) studies lipophilicity is one of the most often used parameters as the predominant descriptor of pharmacodynamic, pharmacokinetic and cytotoxic aspects of a drug acitivity.
Here we report on evaluation of the lipophilicity of some xanthone derivatives exhibiting anticonvulsant activity. The lipophilicity was estimated by the method of planar chromatography on revered phase. The chromatographic data were determined on the aluminum sheets covered with modified silica gel RP-18 F_{254S} (Merck). Two mixtures were used as a mobile phase. The first mixture consists of methanol, water and ammonia and the second consists of acetone, water and ammonia.
The lipophilicity was also estimating theoretically by computing the values of logarithm of partition coefficient (logP) and correlation of them with chromatographic parameter R_{M0}.

P-20

A Comparison of Rat and Human Adenosine A_{2A} Receptor Affinity of Tricyclic Purinediones.

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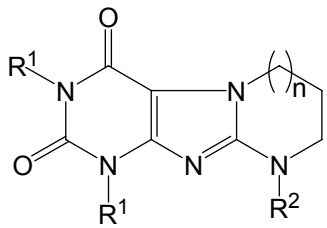
The physiological effects of extracellular adenosine are mediated by four G-protein coupled receptors: A_1, A_{2A}, A_{2B}, A_3 ARs. Adenosine A_{2A} receptor antagonists may be useful for the treatment of acute and chronic neurodegenerative disorders such as cerebral ischemia, Parkinson's and Huntington's disease, as drugs controlling motor functions and exhibiting neuroprotective properties. The closest to its widespread clinical application is styrylxanthine derivative, istradefylline (KW-6002), adenosine A_{2A} receptor antagonist.

Obtained by us (Fig.1) tricyclic anelated xanthines – tricyclic purinediones exhibited high submicromolar affinity to A_{2A} ARs [1-3]. Their activity was tested in radioligand binding assays at rat adenosine A_{2A} receptor.

Figure 1



R = 0, 1
R^1 = CH_3, 
R^2 = cycloalkyl, (un)substituted aryl, arylalkyl

This work was focused on the comparison of the rat and human adenosine A_{2A} receptor affinity. Kiesman et al [4] observed that affinity of xanthine derivatives at rA_1 was generally higher than that for hA_1 receptor. In contrast, no trend was observed between affinities for the rA_{2A} and hA_{2A} receptors [4,5] In our results the tendency of weaker human A_{2A} in comparison to rat A_{2A} receptor affinity was noticed. The obtained results of hA_{2A}/rA_{2A} ratios were in the range of 2,5-16. These ratios are better than noticed for reference compound KW-6002 (hA_{2A}/rA_{2A} ratio = 17.6) [1-4]. Among examined compounds was also one with almost equal affinity for both kinds of receptors (hA_{2A}/rA_{2A} ratio = 0.93), similarly to the literature data [5].

Partly supported by Polish Ministry of Science and Higher Education- grant No N N405 297 896

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P-21

Synthesis and Lipophilicity Determination of Bicine Derivatives of GlcN-6-P Synthase Inhibitors.

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Glucosamine-6-phosphate synthase (GlcN-6-P) is a key enzyme that catalyses formation of D-glucosamine-6-phosphate. GlcN-6P is finally converted into macromolecules containing aminosugars: lipopolisaccharides in bacteria, chitin in fungi and glycoproteins in mammals. Inactivation of GlcN-6-P synthase in fungal cells induces morphological changes and lysis, while in mammals temporary depletion of enzyme activity is acceptable. Therefore GlcN-6-P synthase may be a potential target for antimicrobial chemotherapy [1]. One of the most strong and specific inhibitor of GlcN-6-P synthase is FMDP. FMDP is non-peptide amnino acid and is poorly transported by amino acid permeases into the cells. Consequently FMDP exhibits relatively poor anticandidal activity.
In order to overcome this problem we have synthesized prodrugs containing FMDP and bicine (bis-N,N-(2-hydroxyethyl)glycine), which could by transported into cells by free diffusion. That kind of approach base on the finding that $t_{1/2}$ hydrolysis of bis-N,N-(2-hydroxyethyl)glycinamide was determined to be 3h [2]. Therefore hydrolysis of prodrug containing FMDP and bicine (connected by amide bond) regenerate FMDP in a predictable manner. The esterification of hydroxyl groups of bicine increase lipophilic properties of prodrug. Lipophilicity and ability to diffuse through the cell membrane was measured using a HPLC chromatographic column IAM.PC.DD 2, which mimic fluid cell membranes.

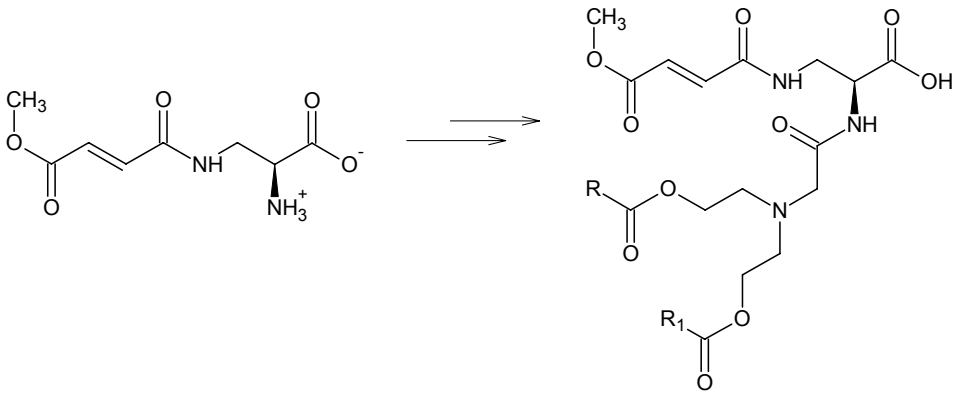

Fig 1. FMDP and bicine derivatives of FMDP.

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P-22

Synthesis of Azathioprine Derivatives.

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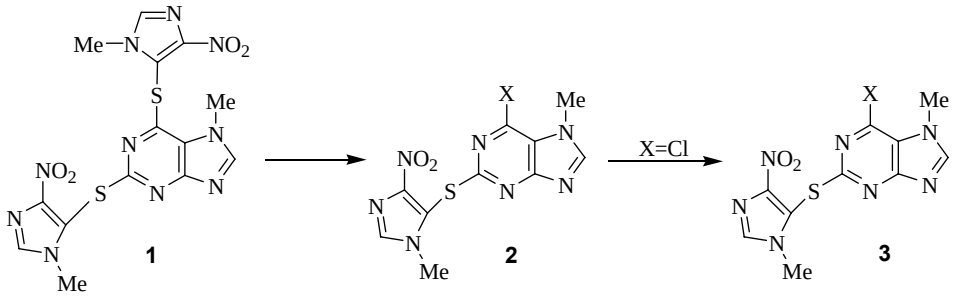
Azathioprine, 6-(1-methyl-4-nitroimidazol-5-ylthio)purine is a thiopurine prodrug clinically used for immunosuppression in the treatment of inflammatory diseases and in pharmacological regimens of organ transplantation.[1,2] As a continuation of our research[3] in the synthesis of azathioprine analogs, very interesting 7-methyl-2,6-di(1-methyl-4-nitroimidazol-5-ylthio)purine **1**, containing three imidazole rings, was obtained.[3] This compound shows promising potential cytostatic, immunosuppressive, antimetabolite, antineoplastic and cytokine modulator acivity and could be useful as anti-inflammatory, anticancer, antiarthritic and dermatologic agent.[4] X-ray analysis of compound **1** shows an unusual conformation of the imidazolylthio groups. Despite that both substituted imidazolylthio groups are being quite large substituents, they are directed to one another (and to N_1 atom), but alternately.



A different reactivity of the imidazolylthio groups towards nucleophilic reagents gave possibility to transform bis(imidazolylthio)purine **1** into 6-alkoxy derivatives **2** in reaction with alcohols or 6-oxo derivatives **2** in reaction of alkaline hydrolysis. 6-Chloro-2-imidazolylthio-7-methylpurine **2** was obtained in three routes: from 6-oxo derivative with phosphorus oxychloride ($POCl_3$), from 6-alkoxy compounds in reaction with phenyldichlorophosphate or directly from di(imidazolylthio)purine **1** with $POCl_3$/DMF mixture and with phenyldichlorophosphate. 6-Chloro derivative was transformed into thioxo compound **3** in the reaction with thiourea and further into the 6-alkylthio derivatives in 82-86% yield.

The structure of all new isomeric analogs of azathioprine being 6-substituted derivatives of 7-methyl-2-(1-methyl-4-nitroimidazol-5-ylthio)purines **2** and **3** were confirmed by spectral ^{1}H NMR and CI-MS analysis.

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P-23

Lipophilicity of Novel Anticancer N-Acylaminoalkyl- and N-Sulfonylaminoalkyl Diazaphenothiazines.

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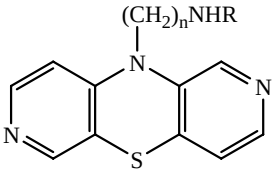
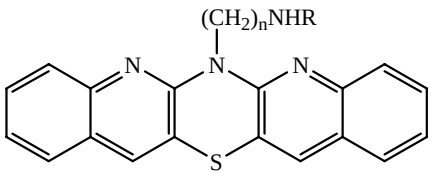
Phenothiazines are known for varied important biological activities. Recent reports deal with anticancer activities, reversal of multidrug resistance and potential treatment in Alzheimer's and Creutzfeldt-Jakob diseases [1]. The most significant modifications of the phenothiazine structures were made by introduction of new pharmacophoric substituents at the thiazine nitrogen atom and by substitution of the benzene ring with an azine ring to form azaphenothiazines [2,3]. In continuation of our search for pharmacoactive pyridine and quinoline derivatives we modified the phenothiazine structure with the pyridine and quinoline rings to form new types of azaphenothiazines: dipyrido-1,4-thiazines (2,7-diazaphenothiazines) **1** and the linear fused diquino-1,4-thiazines (dibenzo-1,9-diazaphenothiazines) **2**. The structure of the all novel compounds were determined by ^{1}H NMR and FAB MS from N-unsubstituted compounds via aminoalkyl derivatives.



1 n = 3,4



2 n = 2,3,4

R = H, $COCH_3$, $COOC_2H_5$, COC_6H_5, $CONHC_2H_4Cl$, SO_2CH_3, $SO_2C_6H_4CH_3$

For the exact *Structure-Activity-Relationship* (SAR) studies, the lipophilicity is one of the most often used parameters as the predominant descriptor of pharmacodynamic, pharmacokinetic and cytotoxic aspects of a drug activity. The lipophilicity of the new compounds was estimated theoretically using commercial programs [4] and was also determined by the method of planar chromatography on reversed phase and next correlated with biological activity. The calculated and determined experimentally lipophilic parameters of diazaphenothiazines **1** were lower and for diazaphenothiazines **2** were higher than the parameters for neuroleptic phenothiazines.
We calculated *in silico* (using PreADMET ver 2.0 [5]) blood-brain barrier (BBB) for these compounds. The new azaphenothiazines exhibit the lower parameter BBB than neuroleptic phenothiazines.
The novel azaphenothiazines exhibit promising anticancer activities against human cell lines of lung, colon, breast, renal, ovarian, prostate and CNS cancers, melanoma and leukemia determined in National Cancer Institute in Bethesda, in USA [6].

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[5] http://preadmet.bmdrc.org/
[6] Pluta K., Morak-Młodawska B., Jeleń M.: National Cancer Institute Developmental Therapeutics Program, In-Vitro Testing Results, Bethesda, USA.

P-24

Search for Novel Histamine H_3/H_4 Receptors Ligands in the Group of (Cyclic)isothiourea Derivatives.

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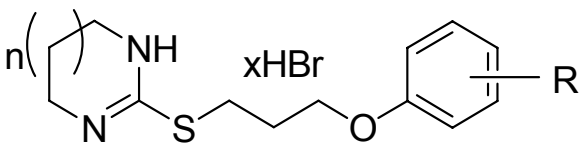
Histamine H_3 receptors are constitutively active Gi-protein coupled receptors described as presynaptically located auto- and heteroreceptors, that modulate the levels of histamine as well as that of other neurotransmitters such as: ACh, NA, 5-HT. Therefore, blockade of these receptors could be useful in the treatment of different CNS disorders [1,2]

The "youngest" histamine receptor: H_4 receptor, has been discovered in 2000 [3]. Its expression could be observed on mast cells, basophiles, eosinophiles and T-dendritic cells that could suggest its role in immunological response.

The first known ligands for the histamine H_3 receptor: thioperamide, clobenpropit, as well as histamine H_4 receptor ligands, eg.: imetit, dimaprit and VUF8430 consisted of (iso)thiourea scaffold. Therefore our aim of research was to obtain compounds containing the isothiourea group, closed in the ring, that would serve as a heterocyclic part for the planned structures (Fig. in text). For comparison non cyclic derivative was obtained too.



The (cyclic)isothiourea propoxy derivatives were obtained and evaluated on the influence of the thiourea group on histamine H_3 receptor affinity. The novel compounds were tested for histamine H_3 receptor affinity *in vitro* in the binding assay for the hH_3 receptor stably expressed in HEK-293 cells. Additionally the compounds were also tested for histamine H_4 receptor *in vitro* affinity on SF9 cells stably expressing hH_4 receptor co-expressed with different G-protein subunits.

The (cyclic)isothiourea propoxy derivatives showed lack of affinity at histamine H_3- and weak affinity at H_4 receptors. It could be concluded, that introduction of the (cyclic)isothiourea group is not tolerated for both histamine H_3 and H_4 receptors in this series.

This work was performed in frame of COST Action BM0806

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P-25

The Development and Validation of a Novel Virtual Screening Cascade Protocol to Identify Potential Serotonin 5-HT_7R Antagonists.

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The 5-HT_7 receptor is a well known target for the treatment of CNS disorders. In attempt to identify new potential ligands for this receptor, we performed a multistep virtual screening (VS) based on two-dimensional (2D) pharmacophore similarity, physico-chemical scalar descriptors, ADME/Tox filter, three-dimensional (3D) pharmacophore searches and docking protocol. The six chemical classes of 5-HT_7R antagonists [1] were used as a query structures in double-path virtual screening scheme. The Enamine screening database [2] consisting of approximately 730 000 commercially available compounds was adopted and used in this study. The binding mode of selected virtual hits are shown in comparison to that of known antagonists [1].

This study was partly supported by the Network "Synthesis, structure and therapeutic properties of compounds and organic substances" coordinated by the Institute of Organic Chemistry Polish Academy of Sciences.

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[2] http://www.enamine.net/

P-26

Application of Capillary Electrophoresis to the Determination D-Hydantoinase and *N*-Carbamoylase Activity.

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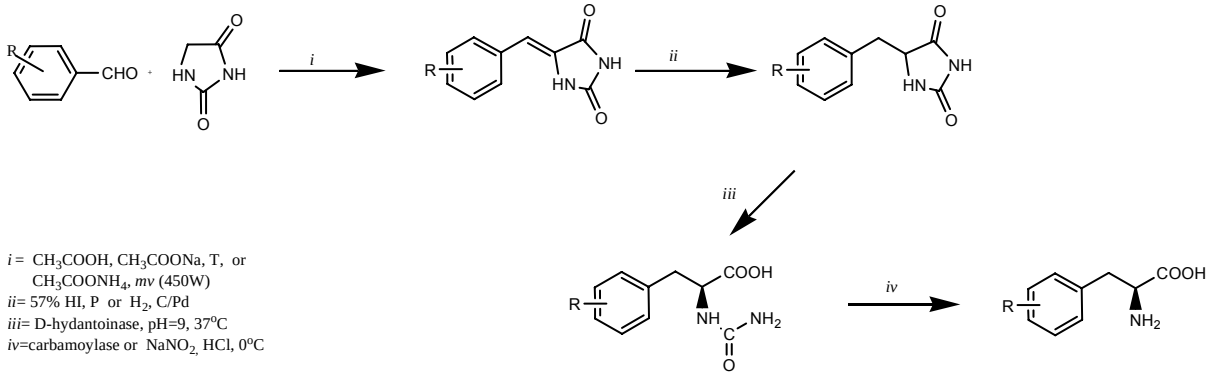
D-amino acids are important chiral building blocks for biologically active compounds including: pesticides, peptidomimetics and semisynthetic antibiotics [1]. Many of the D-amino acids can be incorporated in place of the natural L-amino acids, either at a specific position, or throughout the whole peptide to increase peptides stability toward proteases. Nonnatural amino acids may also increase *in vivo* half life time and potency of peptides. Because of the non-polar nature and steric bulkiness of its side chain phenylalanine is one of the preferred amino acids in peptidomimetics [2]. Several enantiomers of hydroxy- or carboxy- derivatives of phenylglycine or phenylalanine have been described as potent agonists or antagonists at glutamate receptors of the central nervous system. Up to date the only one glutamate receptor active phenylalanine derivative, (S)-α-methyl-3-carboxyphenylalanine, has been described as mGluR8 antagonist [3][4].
For the preparation of optically pure D-amino acids v*ia* two-steps hydantoinase method two enzymes: D-hydantoinase and *N*-carbamoylase were applied. We used and compared an activity of two D-hydantoinases: immobilized, recombinant, cloned and expressed in *Escherichia coli* (Fluka) one and D- Hydantoinase from *Vigna angularis* (Fluka).



Also is reported an enzymatic route mediated by *N*-carbamoylase which enables the subsequent hydrolysis of *N*-cabamoyl-D-phenylalanine derivatives to corresponding D-amino acids. Plasmid pAH71 containing the *N*-carbamoylase gene used in this study was kindly donated by Prof. Yun-Peng Chao from *Department of Chemical Engineering, Feng Chia University, Taiwan* [5].
Within this study an application of P/ACE MDQ Beckman Capillary Electrophoresis System as a rapid and highly efficient method to analyze the enzyme activity and substrate specificity were described.

Project co-financed from the European Social Fund and national budget in the frame of The Integrated Regional Operational Programme.
Partly supported by Polish Ministry of Health and Higher Education grant: N405 2518 33

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P-27

Metabolism and Pharmacological Activity of 1-[3-(4-*tert*-Butylphenoxy)propyl]piperidine - Potent Histamine H_3-Receptor Antagonist.

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Histamine H_3 receptors (H_3Rs) are constitutively active receptors, mostly expressed in CNS. They are either presynaptic autoreceptors regulating the CNS levels of histamine or heteroreceptors controlling the release of other neurotransmitters (e.g. Ach, NA, DA, 5-HT). Histamine H_3Rs antagonists/inverse agonists may be useful for the treatment of a wide range of CNS disorders including ADHD, Alzheimer's disease, dementia, epilepsy, narcolepsy or schizophrenia [1].
Our research group is involved in the search for active histamine H_3Rs ligands. Some of the compounds showed moderate to good histamine H_3R affinities both *in vitro* and *in vivo* [2-4].
1-[3-(4-*tert*-butylphenoxy)propyl]piperidine hydrogen oxalate, potent histamine H_3 receptor antagonist tested *in vitro* (hK_i: 22 ± 3 nM) and *in vivo* (ED_{50}: 2.8 ± 0.4 mg/kg p.o.), was chosen for further studies [2]. The results of metabolism simulation *in silico* and under biotransformation with *Saccharomyces cerevisiae* will be presented as well as the results of pharmacokinetic behavior in rats after oral and intravenous administration.
This compound was also tested for an anticonvulsant activity at BETHESDA (MES and scMET tests) and in maximal electroshock test (MES) showed 75% protection in the dose of 100 mg/kg.

The work was partly supported by program K/ZDS/000727.

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P-28

Rentgenowska Dyfraktometria Proszkowa (XRD) w Badaniach Składu Fazowego Przeterminowanych Leków.

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Leki należą do grupy podstawowych produktów decydujących o rozwoju współczesnej cywilizacji. Niestety, mogą one mieć także ujemny wpływ na współczesny świat np. ich obecność w środowisku niekorzystnie oddziaływuje na ekosystemy wodne i glebowe. Pomimo, że są one wprowadzane w małych stężeniach do środowiska, to posiadają często bardzo wysoką aktywność biologiczną [1]. Stąd leki przeterminowane i niewykorzystane zaliczone zostały do odpadów niebezpiecznych [2].
Głownym celem prezentowanej pracy było badanie metodą rentgenowskiej dyfraktometrii proszkowej (XRD) zmian składu fazowego popularnych leków (tj. polopiryna, ibuprofen, ranigast, pyralgina, nifuroksazyd, pyralgina, loperamid) o różnym stopniu przeterminowania. Pomiary XRD zostały wykonane przy użyciu wielozadaniowego dyfraktometru polikrystalicznego X'Pert PRO MPD firmy PANanalytical wykorzystując promieniowanie CuKα uzyskane w wyniku monochromatyzacji promieniowania rentgenowskiego na filtrze niklowym. Zastosowano skan ciągły (krok 0,033º), czas pomiaru jednego kroku trwał 20 sekund. Pomiary wykonano w zakresie kątów 2θ od 3 do 80º. Podczas analizy wyników wykorzystano programy X'Pert HighScore Plus oraz bazę wzorców proszkowych ICDD PDF2 (ver. 2004).

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P-29

Structure and Immunomodulating Activity of Isooxazole Derivatives.

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W trakcie wielu lat badań otrzymaliśmy małocząsteczkowe pochodne izoksazolu wykazujące aktywność immunomodulującą. Zsyntezowaliśmy kilka serii związków wywodzących się z hydrazydu kwasu 5-amino-3-metylo-4-izoksazolokarboksylowego. N'-podstawione hydrazydy kwasu 5-amino-3-metylo-4-izoksazolo-karboksylowego to immunosupresory, silniejsze działanie od Cyklosporyny A (CsA) wykazał N'-(4-chlorobenzylideno)hydrazyd kwasu 5-amino-3-metylo-4-izoksazolo-karboksylowego w modelu odpowiedzi proliferacyjnej splenocytów mysich na konkanawalinę A [1]. Semikarbazydy i tiosemikarbazydy kwasu 5-amino-3-metylo-4-izoksazolokarboksylowego wykazały szeroko pojętą aktywność immunomodulującą [2-4]. Modyfikacja podstawnika w pozycji 4 izoksazolu rozszerzyła profil aktywności. Oprócz działania immunosupresyjnego tych związków, kilka pochodnych nabyło zdolności immunostymulujących. Na największe zainteresowanie zasługują 4-fenylotiosemikarbazyd oraz 4-(4-nitrofenylo)semikarbazyd, które w dawce 100μg/ml bardzo silnie stymulowały proliferację splenocytów mysich indukowaną konkanawaliną A (ConA).
5-podstawione pochodne 3-metyloizoksazolo[5,4-*d*]-1,2,3-triazyn-4-onu to związki immunosupresyjne, aktywniejszy od CsA jest 5-etylidenoamino-3-metyloizoksazolo[5,4-*d*]-1,2,3-triazyn-4-on w modelu humoralnej i komórkowej odpowiedzi immunologicznej oraz 5-(4-chlorobenzylideno)amino-3-metyloizoksazolo[5,4-*d*]-1,2,3-triazyn-4-on w modelu humoralnej odpowiedzi immunologicznej u myszy [5-6]. 5-podstawione pochodne 3-metylo-izoksazolo[5,4-d]pirymidyn-4-onu to immunosupresory, aktywniejszy od CsA w modelu nadwrażliwości typu opóźnionego (DTH) mierzonej testem obrzęku łapy był 5-(2-chloro-benzylideno)amino-3-metyloizoksazolo[5,4-*d*]pirymidyn-4-on [7]. Cyklizacja N'-podstawionych hydrazydów do związków bicyklicznych nie zniosła działania immunosupresyjnego. Pochodne 3,5-dimetylo-izoksazolo[5,4-e][1,2,4]triazepin-4-onu podstawione jak i niepodstawione w pozycji 7 wykazały bardzo silne przeciwstawne aktywności immunologiczne. RM-33 to bardzo silny immunosupresor [8-10], a RM-11 to bardzo silny immunostymulator [11-12].

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P-30

Analiza SAR Procesu Dokowania Barwników Trimetylofenylowych we Wnękach Wiążących Utworzonych przez N-Lipidowane Aminokwasy Immobilizowane na Matrycy Celulozowej.

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Wykonana analiza jest fragmentem pracy, której podstawowym celem było zaprojektowanie struktury sztucznego receptora, który umożliwi dynamiczne dopasowanie wnęki wiążącej do struktury ligandu, a przy tym struktura wnęki zapewni wiązanie ligandu oddziaływaniami identycznymi do występujących w receptorach naturalnych. W jednym z etapów pracy wykorzystano bibliotekę
N–lipidowanych aminokwasów do zbadania zależności określających intensywność wiązania grupy barwników trimetylofenylowych. Różnice w budowie poszczególnych barwników są stosunkowo niewielkie i polegają na zróżnicowaniu podstawników w pierścieniach fenylowych. Dla poznania wpływu podstawników znajdujących się w szkielecie trifenylometylowym dokowaniu poddano pięć barwników: błękit bromotymolowy, błękit bromochlorotymolowy, purpurę bromokrezolową, czerwień fenolową oraz zieleń bromokrezolową.
Z otrzymanych zależności wywnioskowano, że wnęki stosowanych receptorów są stosunkowo małych rozmiarów, o czym świadczy obniżona zdolność dokowania barwników z podstawnikami rozbudowanymi przestrzennie. Zaskakujące jest, że obecność grup hydroksylowych, które są donorami wiązania wodorowego, w nieznaczny sposób wpływa na proces dokowania do wnęk receptorowych biblioteki.
Analizując intensywności wybarwień przy zmieniających się strukturach aminokwasowych i fragmentach lipidowych stwierdzono, że wpływ fragmentu aminokwasowego na oddziaływania pomiędzy wnęką a barwnikiem jest dominującym, zaś fragment lipidowy wpływa na oddziaływania i na zdolność dokowania do wnęki N-lipidowanych aminokwasów w znacznie mniejszym stopniu. Wiązanie ligandu prawdopodobnie odbywa się w bezpośrednim kontakcie z fragmentem aminokwasowym, co potwierdziło założenia wstępne pracy.

P-31

Synteza Pochodnych 3,3'-Diindolilometanu oraz 3,3'-Ditio-bis-indolu o Potencjalnej Aktywności Przeciwnowotworowej.

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Ogromny postęp w zakresie rozpoznawania i leczenia nowotworów ciągle nie zapewnia możliwości opanowania problemu nowotworów złośliwych. Obecnie wykorzystywane metody terapeutyczne nie są dostatecznie swoiste i efektywne. Liczba chorych na nowotwory zarówno w Polsce jak i na świecie stale rośnie. Proces nowotworowy nazwany karcynogenezą prowadzi do licznych zmian w komórkach, których wynikiem jest pojawienie się tzw. „cech szczególnych" komórek nowotworowych. Do cech tych zaliczamy: zdolność do wzmożonej proliferacji czyli zbyt częstych podziałów komórkowych, unikanie apoptozy, zdolność do angiogenezy oraz inwazyjność i przerzuty. Poznanie wspomnianych wyżej cech charakteryzujących komórki nowotworowe oraz mechanizmów umożliwiających ich rozwój w większym stopniu umożliwia opracowanie leków działających przeciwnowotworowo w sposób bardziej wybiórczy. Jeśli w pewnym uproszczeniu założymy, że choroba nowotworowa polega na utracie kontroli organizmu nad przebiegiem szeroko rozumianych procesów metabolicznych w określonej komórce, a zwłaszcza nad jej zdolnością do podziałów, to potencjalnie każdy element łańcucha reakcji odpowiadającego za tę nieprawidłową cechę komórki może stać się miejscem działania leku przeciwnowotworowego. Każde z ogniw tego łańcucha jest badane pod kątem możliwości wykorzystania go jako potencjalnego punktu uderzenia terapii celowanej.
W Katedrze i Zakładzie Chemii Organicznej od kilku lat syntetyzowane są pochodne 3,3'-diindolilometanu (DIM-u) /1,2,3/ oraz 3,3'-ditio-bis-indolu /4/, których aktywność przeciwnowotworową *in vitro* potwierdziły badania przeprowadzone w NCI. Pochodne indolu wpływają na hamowanie wielu procesów prowadzących do rozwoju komórek nowotworowych. Pochodne DIM-u hamują proliferację komórek nowotworowych przez wpływ na stosunek Bax/Bcl-2 oraz mogą oddziaływać z DNA zarówno w obszarach bogatych w pary zasad AT jak i GC. Pochodne ditio-*bis*-indoli są inhibitorami kinazy tyrozynowej. Pochodne 3,3'-diindolilometanu otrzymano przez kondensację 5-podstawionych indoli z formaldehydem w środowisku wodno-etanolowym. Pochodne 3,3'-ditio-*bis*-indoli w reakcji 5-podstawionych indoli z tiomocznikiem w obecności jodu. Budowę wszystkich otrzymanych związków potwierdzono analizą widm IR i NMR ^{1}H, ^{13}C, HETCOR a także ^{13}C CP/MAS w ciele stałym. Strukturę większości otrzymanych związków zdefiniowano metodą dyfrakcji rentgenowskiej. Obecnie syntezy ukierunkowane są na uzyskanie asymetrycznych pochodnych 3,3'-diindolilometanu.

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P-32

Application of Computational QSAR Analysis for the 1-(3-(4-Arylpiperazin-1-yl)-propyl)-pyrrolidin-2-one Derivatives as α_1-Adrenoceptor Antagonists.

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A number of quantitative structure – activity relationship (QSAR) studies have been reported in the medical research, which use calculated molecular descriptors in predicting anticancer, anti-inflammatory and CNS activity, as a set of physicochemical, pharmacological or toxicological properties of the substance. However, there are relatively few publications reporting the application of QSAR analysis to α_1-Adrenergic receptors antagonists (α_1-ARs) species.

In the course of our studies in the field of new α_1-AR antagonists, which pyrrolidin-2-one derivatives, we have previously reported synthesis details and pharmacological results, and a number of molecular modelling studies on 1-(3-(4-arylpiperazin-1-yl)-propyl)-pyrrolidin-2-one derivatives [1-4]. A number of these compounds showed high in vitro affinity for α_1-AR, and displayed antiarrhythmic and antihypertensive activities in in vivo studies. In this context the objective of this work, being a part of our drug design project, is to find a model explaining the α_1-AR activity of a series of 1-[3-(4-arylpiperazin-1-yl)-propyl]-pyrrolidin-2-one derivatives applying the quantitative relationship between structural parameters and the α_1-ARs antagonist effect. The activity of various 1-(3-(4-arylpiperazin-1-yl)-propyl)-pyrrolidin-2-ones α_1-adrenergic receptors (α_1-ARs) antagonists, was described using the QSAR model by applying it to 49 compounds. The molecular descriptors of the α_1-ARs antagonists were obtained by quantum chemical calculations combined with molecular modelling calculations. The obtained model explains more than 88% of the variance and it was successfully validated by four tests (LOO, LMO, external test and Y-scrambling test). Statistical analysis shows that the α_1-ARs activity of the studied compounds depends mainly on the PCR and Qindex descriptors [5].

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P-33

Otrzymywanie kokryształów substancji aktywnych farmakologicznie metodą „solvent-drop grinding".

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Substancje aktywne farmakologicznie są współcześnie stosowane w lecznictwie w postaci różnych odmian polimorficznych ewentualnie w postaci solwatów. Poza wymienionymi formami związki te mogą tworzyć również kokryształy. Kokryształ to wieloskładnikowy kryształ molekularny zbudowany z dwóch (rzadziej z większej liczby) składników zachowujących względem siebie wzajemny stosunek stechiometryczny w sieci krystalicznej. Kokryształy farmaceutyczne do niedawna nie budziły większego zainteresowania. Obecnie, ze względu na możliwość opatentowania stały się one atrakcyjnym przedmiotem badań dla firm farmaceutycznych. Dodatkowo, podstawową zaletą wykorzystania kryształów wieloskładnikowych w medycynie jest możliwość modyfikacji obecnych na rynku leków w kierunku poprawy ich właściwości fizyko-chemicznych (t.j. rozpuszczalność, stabilność, biodostępność). W kryształach tego typu jeden ze składników musi być substancją aktywną farmakologicznie, natomiast pozostałe mogą być dowolnymi, farmaceutycznie akceptowalnymi substancjami [1,2]. Cząsteczki tworzące kokryształ mogą dodatkowa stabilizować jego strukturę poprzez tworzenie wiązań wodorowych lub/i inne poprzez oddziaływania międzycząsteczkowe.
Klasyczną metodą otrzymywania kokryształów jest krystalizacja z roztworu. Od niedawna coraz większe zainteresowanie budzą również metody mechaniczno-chemiczne m.in. polegające na ucieraniu. Technika ta, podobnie jak same kokryształy, znana jest już od ponad 160 lat, jednak do syntezy kokryształów zaczęto ją wykorzystywać na większą skalę dopiero w ostatnich latach. Szczególnie interesującą odmianą techniki ucierania jest metoda „solvent-drop grinding", w której składniki kokryształu są mechanicznie ucierane z dodatkiem kilku kropel rozpuszczalnika. Mechanizm wpływu niewielkiej ilości rozpuszczalnika na otrzymywanie kokryształów nie został jeszcze w pełni poznany. Najczęściej stosowane rozpuszczalniki to: metanol, woda, octan etylu lub acetonitryl. Przyjmuje się, że wszystkie lub przynajmniej jeden ze składników powinien być rozpuszczalny w wybranym do ko-krystalizacji rozpuszczalniku [3].
Metoda „solvent-drop grinding" stanowi ciekawą alternatywę w stosunku do klasycznej krystalizacji, głównie z powodu możliwości uzyskania wymiernych korzyści ekonomicznych i ekologicznych. Podstawowe zalety tej techniki to: niewielkie zużycie rozpuszczalników, szybka możliwość otrzymania nowych form krystalicznych badanych substancji, często niedostępnych metodą tradycyjnej krystalizacji oraz niski koszt aparatury [4]. Głównym celem prezentacji będzie przedstawienie skuteczności otrzymania kokryształów metodą „solvent-drop grinding" na podstawie badań własnych oraz doniesień literaturowych, np. Trask i współpracownicy [5] otrzymali tą techniką m.in. kokryształy kofeiny z kwasem glutarowym.

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P-34

Antimicrobial Activity of New Derivatives of N-Substituted Amides of 3-(3-Methylthio-1,2,4-triazol-5-yl)bicyclo[2.2.1]hept-5-ene-2-Carboxylic Acid.

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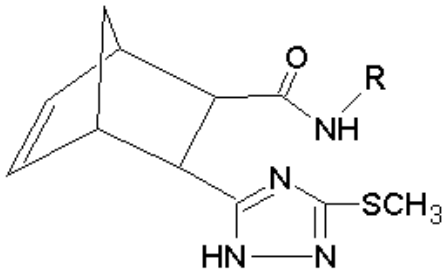
1,2,4-triazoles and its derivatives are an important group of compounds in modern heterocyclic chemistry. They show a wide range of biological activities. Some of them posses antifungal, antimicrobial, anti-inflammatory, antidepressant and antiviral properties. In addition they have therapeutic properties and are used as drug in modern medicine.
We present here antimicrobial activity of new derivatives of N-substituted amides of 3-(3-methylthio-1,2,4-triazol-5-yl)bicyclo[2.2.1]hept-5-ene-2-carboxylic acid I-IX.



I-IX

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

Compounds (I – IX) were screened for their antimicrobial activity *in vitro* against the reference strains of 8 species of aerobic bacteria and 6 species of fungi from American Type Culture Collection (ATCC), routinely used for evaluation of antimicrobials. Microbial suspensions were prepared in sterile saline (0.85% NaCl) with an optical density of McFarland standard 0.5 (150 x 10^6 CFU [Colony Forming Units)/mL]). All stock solutions of the tested compounds were dissolved in dimethyl sulfoxide (DMSO). Antimicrobial activity of the newly synthesized compounds were screened by an agar well diffusion method on the basis of the average diameter of the growth inhibition zone surrounding the well containing the compounds at concentration 1000 mg/L and for potentially active IV or VIII compounds - by broth microdilution technique (with 1:10 diluted suspension) on the basis of MIC (minimal inhibitory concentration) values. Mueller-Hinton medium without or with 2% glucose was used for growth of bacteria or fungi, respectively.
According to our preliminary results based on the agar well diffusion method, among the tested agents IV compound showed activity against *M. luteus* ATCC 10240 or *E. coli* ATCC 25922, as monitored by total growth inhibition zone around the well ranging from 13 to 15 mm and MIC values ranging from 250-500 mg/L. The compound VIII affected the growth of fungi belonging to yeasts (*C. albicans* ATCC 10231, *C. albicans* ATCC 2091, *C. parapsilosis* ATCC 22019) with partial growth inhibition around the wells and MIC values ranging from 250 – 500 mg/L.

P-35

Synthesis of Some 1,6-bis-(3-Substituted-4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)hexanes with Potential Biological Activities.

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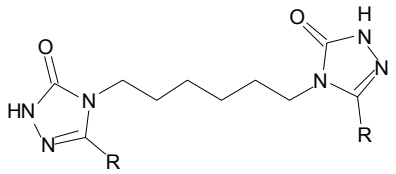
The synthesis of 1,2,4-triazoles and investigation of their chemical and biological behavior have gained more importance in recent decades for biological, medicinal and agricultural reasons. In the present investigation, we show biological study of new 1,6-bis(3-substituted 4,5-dihydro-1*H*-1,2,4-triazol-5-on-4-yl)hexanes **1-3**.



R = CH_3(**1**), C_6H_5(**2**), 1-methylpyrrol-2-ylmethyl(**3**)

Anticancer activity *in vitro* for new obtained compounds were evaluated by BrdU method for human lung and breast carcinoma cell lines (A549, T47D) and normal human skin fibroblasts (HSF). Compounds **2** and **3** were found to be the most effective against human lung carcinoma cells . Compound **1** had the most antiproliferative effect on breast carcinoma cell line. The non cytotoxicity or stimulation effect of compound **3** of the all examined compounds on normal cell line HSF and several-fold higher against the two observed carcinoma cell lines were ascertained. The most antiproliferative and antitumor effects were observed for compound **1** on lung and breast carcinoma cells *in vitro*.

Determination of in vitro antibacterial and antifungal activity of the tested compounds was performed using the microdilution method. The results indicated that the activities of compound **1** and **2**, at the concentrations 3,75 µg/ml and 1,87µg/ml respectively were observed against tested *Candida* strains. It may suggest that the higher concentrations of the compounds derivates may have antifungal properties. As the cytotoxicity of those compounds is low, it would be useful to perform additional test in this course.

P-36

Synthesis and Pharmacological Properties of 3-Chlorobenzoic Acid Hydrazide Derivatives.

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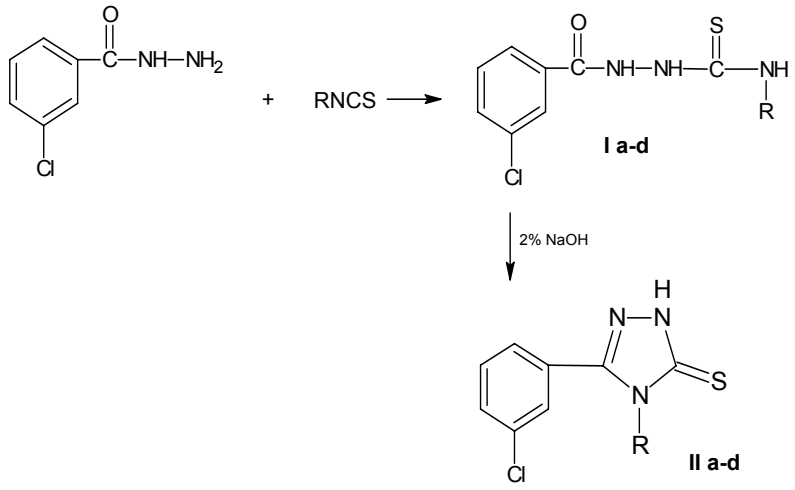
Certain 1,4-disubstituted thiosemicarbazide and 1,2,4-triazole-3-thione derivatives have been reported to exhibit antibacterial, antiviral and antifungal activities. The influence on the central nervous system is also well known. Thiosemicarbazide derivatives were afforded by the reaction of 3-chlorobenzoic acid hydrazide with substituted isothiocyanates. The cyclization of obtained compounds in the presence of 2% NaOH resulted in the formation of substances containing 1,2,4-triazole ring. All synthesized compounds were screened for their antimicrobial activity. Moreover, analgesic, anticonvulsant and antidepressive properties have been investigated.



R = $-C_2H_5$ (a), $4\text{-}CH_3\text{-}C_6H_4$ (b), $4\text{-}OCH_3\text{-}C_6H_4$ (c), $4\text{-Br-}C_6H_4$ (d)

All tested compounds displayed antinociceptive effect in the „writhing syndrome" test. Compound **IId** was more active, because in doses of 0.0125 to 0.1 LD_{50} significantly decreasing the number of writhing episodes induced by 0.6 % acetic acid in mice. Besides, all compounds in doses 0.05 and 0.1 LD_{50} produced anticonvulsive effects in mice.

P-37

Conformational Analysis of Fenoterol Stereoisomers.

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Fenoterol is relatively long acting β_2 selective agonist of adrenergic receptor (β_2-AR) used in the treatment of asthma. The molecule contains two stereogenic centers and the compound exists as four stereoisomers. The clinically used drug, *rac*-fenoterol, is a racemic mixture of (R,R)-fenoterol and (S,S)-fenoterol. Our previous research [1] indicated that stereoisomers significantly differs in affinity, selectivity and functional activity on the β_2-AR. Radioligand displacement studies indicated that (R,R)-isomer showed the strongest affinity and selectivity followed by (R,S)- and (S,R)-forms while the (S,S)-isomer was the weakest. Molecular modeling and docking simulations suggest that stereochemistry significantly influences the orientation of the molecule within the binding site and its internal conformation.

Conformational search analysis of all four isomers were performed by monitoring the potential energy change with gradual rotation of each rotatable dihedral angle. Local minimum was selected for each dihedral and used to constructed optimized molecule. The molecule was further subjected to energy minimization and molecular dynamic simulations in vacuo and in water.

The procedure allowed to define conformations representing global minimum of energy for each stereoisomer. These conformations can be compared with internal conformation of each stereoisomer in complex with β_2-AR model. Among stereoisomers, the conformation of (R,R)-fenoterol in complex with β_2-AR shows the closest correspondence with the conformation representing the global minimum. Thus, binding of (R,R)-isomer is additionally promoted by lowest increase of internal energy associated with adopting the receptor induced conformation upon binding.

[1] Jozwiak K., Khalid C., Tanga M. J., Berzetei-Gurske I., Jimenez L., Kozocas J. A., Woo A., Zhu W., Xiao R. P., Abernethy D. R., Wainer I. W.: *J. Med. Chem. 50(12) (2007), 2903-2915.*

P-38

Synthesis and Biological Activity Derivatives of 1-Bromo-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}]nonadec-2,4,6,9,11,13-heksaen-16,17-dione.

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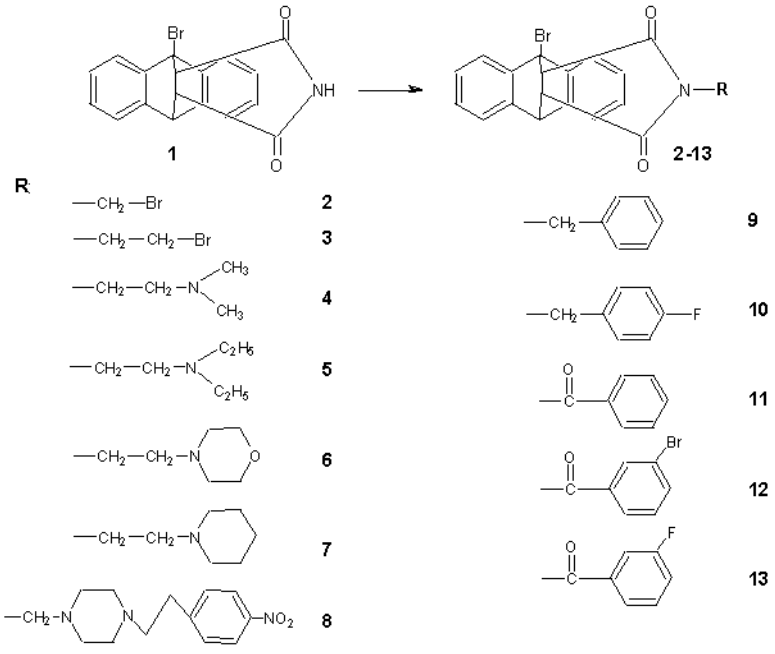
It is well-known derivative N-substituted imide of show biological activity [1,2] therefore, we designed and synthesized of new N-alkyl-, aminoalkyl-, benzyl- and benzoyl derivatives with an expected biological activity.

The starting compound was 1-bromo-17-azapentacyclo[6.6.5.0^{2,7}.0^{9,14}.0^{15,19}]nonadec-2,4,6,9,11,13-heksaen-16,17-dione which was obtained earlier in Diels-Alder reaction. This compound was condensed with dibromoethane, dibromomethane in acetonitryl, appropriate alkylamines and substituted chlorobenzyl and chlorobenzoyl derivatives in acetone.

Scheme:



The structure of the all compounds obtained were confirmed by ^{1}HNMR and ESI MS.

All new compounds were tested for their antibacterial activities. In this study were used Gram-positive (*S. aureas*) and Gram-negative (*E. coli*) bacterial strains and *Candida albicans*. Only two compounds **4**, **5** were active against *C. albicans*.

[1] Bisi A. et al.: *J. Med. Chem 49 (2006), 3049-3051.*
[2] Zentz F. et al.: *Farmaco 59(11) (2004), 879-886.*

P-39

New Triazole Derivatives as Compounds with Potential Biological Activity.

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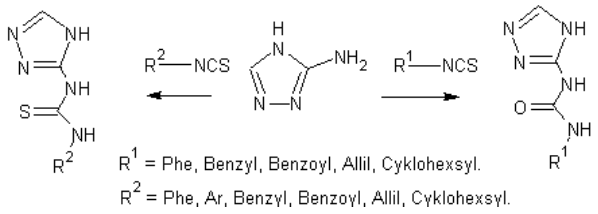
Derivatives of 1,2,4-triazole show wide biological activity. We could mention antibacterial, antifungal, anticancer, antiasthmatic or anticholinergic properties [2,3]. They also function as ligands of 5-HT_{1A} receptor [1]. In the midst of leading triazole drugs we could point at Itraconazole, Fluconazole or Voriconazole. Those chemicals are very helpful in treatment of hard mycotic infections. Many scientific papers shows that urea and tiourea derivatives of triazoles also have anti-HIV and sedative properties (selective ligands of 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors - strong influence on the central nervous system) [4 - 8].

Those information lead us to get series urea and tiourea derivatives in reaction between 3-amino-1,2,4-triazole and suitable isocyanates and isotiocyanates (*Scheme 1*). New compounds that we received (and also confirmed by the ^{1}H NMR and MS spectra) were tested on antibacterial and anti-HIV activity and also their cytotoxicity were determined. We get very promising results. Many of our synthesized new compounds has impressive activity for gram-positives bacteria (MIC: 6,25÷200 μg mL^{-1}) with very low cytotoxicity. The next advantage is a very simple synthesis from the reagents which are generally available.

New triazole's derivatives that were synthesized may be a medical future of this arm of 5-HTRs or in any other biological activity that was mentioned.



Scheme 1: Reaction between 3-amino-1,2,4-triazole and suitable isocyanates and isotiocyanates.

[1] Salerno, Siracusa, Guerrera, Romeo: *ARKIVOC 2004, 312-324.*
[2] El-Zemity, El-Shazly, Kadous: *J. Appl. Sci. Res. 2(12) (2006), 1314-1318.*
[3] El-Sayed: *Grasas y Aceites 57(2) (2006), 180-188*.
[4] Forbes I. T., Ham P., Booth D. H., Martin R. T., Thompson M., Baxter G. T., Blackburn T. P., Glen A., Kennet G. A., Wood M. D.: *J. Med. Chem. 25 (1995), 2524.*
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[7] Fludzinski P., Wittenauer L. A., Schenck K. W., Cohen M. L.: *J. Med. Chem. 29 (1986), 2415.*
[8] Audia J. E., Evrard D. A., Murdoch G. R., Droste J. J., Nissen J. S., Schenck K. W., Fludziński P., Lucaites V. L., Nelson D. L., Cohen M. L.: *J. Med. Chem. 39 (1996), 2773.*

P-40

Synthesis of New Substituted 1-(2-Pirydynyl)imidazo[1,2-a]-[1,3,5]triazepin.

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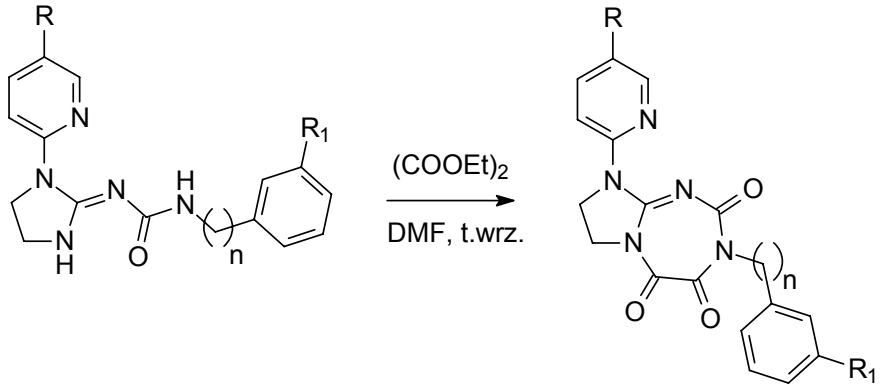
The aminocarbonyl derivatives of 1- aryl-2-imidazolidine-2 have significant antinociceptive activity connected with activation of the MOP (mu opioid protein) receptor [1-3].
The syntnetic derivatives of triazepine form are various and important group of medicine.
In the search for new derivatives with potential pharmacological activity received of new imidazo [1,2-a][1,3,5]triazepine
New 1-(2-pirydynyl)-6-fenyl(benzyl)-5,6,8(1H)-tioxoimidazo[1,2-a][1,3,5]triazepine and 1-[2-(5-nitro)pirydynyl]-6-fenyl(benzyl)-5,6,8(1H)-trioxoimidazo[1,2-a][1,3,5]triazepine were synthesised in reaction of adequate substituted 1-[(2-pirydynyl)imidazolidine-2-ylideno]-3-fenyl(benzyl)urea with diethyl oxalic acid ester.



R = H, n = 0, R_1 = H, Cl R = H, n = 2, R_1 = H
R = 4-NO_2, n = 0, R_1 = H, Cl R = 4-NO_2, n = 2, R_1 = H

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

[1] Matosiuk D., Fidecka S., Antkiewicz-Michaluk L., Dybała I., Kozioł A. E.: *Eur. J. Med.. Chem. 36 (2001), 783.*
[2] Matosiuk D., Fidecka S., Antkiewicz-Michaluk L., Lipkowski J., Dybała I., Kozioł A. E.: *Eur. J. Med.. Chem. 37 (2002),761.*
[3] Sztanke K., Fidecka S., Kędzierska E., Karczmarzyk Z., Pihlaja K., Matosiuk D.: *Eur. J. Med.. Chem. 40 (2005),127.*

P-41

Isophosphoramide Mustard Analogues Containing Benzo[*d*]isoxazole Ring as Anticancer Prodrugs.

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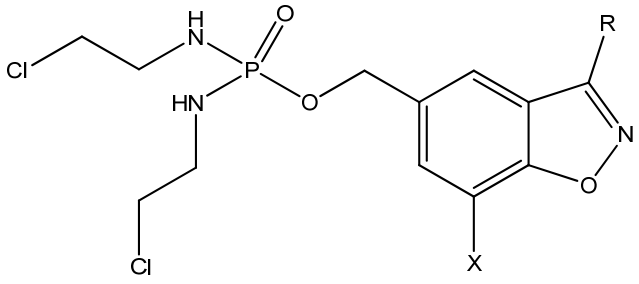
Rapidly growing solid tumors contain regions with low oxygen concentration, so-called hypoxic regions. This effect is due to inefficient vascular network and high interstitial pressures. Hypoxic regions are responsible for chemo- and radioresistance of solid tumors and for tumor aggressiveness and metastasis as well. Nevertheless hypoxia phenomenon can be exploit to design of tumor selective prodrugs. Such a prodrugs ought to be activated only in regions with low oxygen concentration and an active metabolite should demonstrate a potent bystander effect in order to kill oxygenated tumor tissue as well providing high therapeutic effect with low systemic toxicity. A wide range of compounds have been explored as bioreductive hypoxia selective agents (HSA), including: aromatic and aliphatic N-oxides, nitro-aromatics, quinones, and metal complexes. Up to now non of the HSA has been registered as a drug, but same of them are intensively investigated in clinical trials (tirapazamine, AQ4N, TH-302) [1].
Zonisamide, an antiepileptic drug which possesses benzo[*d*]izoxazol ring, is metabolized by endogenous enzymes (probably CYP 3A4 and aldehyde oxygenase) preferentially under hypoxic condition. This metabolic pathway leads to N-O bond cleavage and hydrolysis of formed imine to an appropriate ketone. Isophosphoramide mustard (iPAM) is an active metabolite of ifosfamide, a widely used anticancer drug. We designed and synthesized a series of iPAM analogs **1** – **8**, containing a benzo[*d*]izoxazol ring. These prodrugs should be, based on the literature report [2], selectively activated under hypoxic conditions with a release of iPAM.



1 - 8

1 : X=H, R=CH_3; **2** : X=H, R= CH_2Cl; **3** : X=H, R= $CHBr_2$; **4** : X=H, R=CF_3,
5 : X=Cl, R=CH_3; **6** : X=Cl, R=CH_2Cl; **7** : X=Cl, R=$CHCl_2$, **8** : X=Br, R=CF_3

[1] Duan J.-H., Jian H., Kaizerman J., Stranton T., Evans J. W., Lan L., Lorenta G., Banica M., Jung D., Wang J., Ma X., Li X., Yang Z., Hoffman R. M., Ammons W. S., Hart Ch. P., Matteucci M.: *J. Med. Chem. 51 (2008), 2412-2420.*
[2] Jain M., Kwon Ch.-H.: *J. Med. Chem. 46 (2003), 5428-5436.*

P-42

Interaction of 6-Thioguanine with Human Serum Albumin. Experiments and Prediction by Means of Molecular Docking

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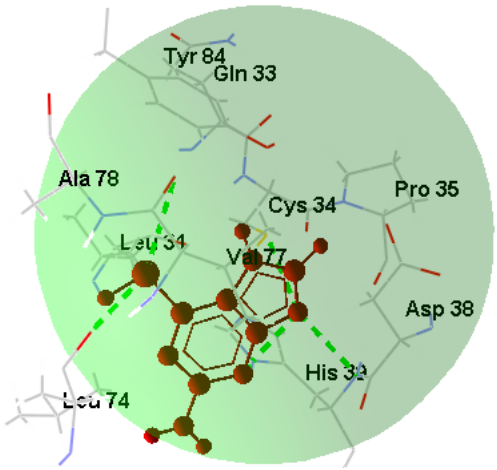
Human serum albumin (HSA) consists of three structurally homologous domains (I, II, III) and each domain is formed by two subdomains (A and B). The subdomains IIA and IIIA are two the most important binding sites, which are structurally characterized by the presence of a buried hydrophobic cavity capped by charged and polar residues. The ability of HSA to bind different substrates is related to the presence of highly reactive residues. The single Trp 214 is situated in the subdomain II, where Lys 195, Lys 199 and His 242 play a key role in the albumin-ligand interaction. The Tyr 411 and Arg 410 are the most important residues of the IIIA subdomain binding site. The single unpaired Cys 34 is present as a free thiol in domain I and binds a range of drugs and metal ions.
In this study the interaction of 6-Thioguanine (6-TG) with HSA was examined by fluorescence and circular dichroism (CD) spectroscopy and molecular docking (Molegro Virtual Docker, MVD 2008. 3.2.1.) method.
6-TG quenches the albumin fluorescence, induces a red shift of maximum fluorescence and causes a decrease of the two negative bands intensity of the far-UV CD spectra. This indicates that 6-TG alters the albumin tertiary structure and provokes changes in the α-helical structure of protein. The results obtained from modeling showed that the binding of 6-TG in domain I, II and III of HSA is possible.



The interaction mode between 6-TG and HSA. The residue of HSA and the 6-TG structure are represented using line and ball and stick model, respectively, and the hydrogen bond between 6-TG and HSA is represented using dashed green line (Molegro Virtual Docker, MVD 2008. 3.2.1.)

P-43

The Binding of Thiopurine Derivatives to Serum Albumin – Lipophilicity and Ionization Dependence.

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Human serum albumin (HSA) has two high-affinity binding sites which are located in hydrophobic cavities in the IIA (site I) and IIIA (site II) subdomains. The subdomain IIIA has the primary binding activity whereas subdomain IIA is more specialized. The small heterocyclic and aromatic negatively charged ligands bind principally in regions located in subdomain IIA and/or IIIA.
In this work, the binding affinity for 6-Mercaptopurine, 6-Thioguanine, Azathioprine and series of 2,6-disubstituted 7-methylpurines to HSA was analyzed. The lipophilicity and ionization dependence of the binding of purine series to HSA was also examined. The binding pocket for thiopurines on albumin has been identified by the use of fluorescence probes specific for site I – region Ia: warfarin, region Ib: 5-dimethylaminonaphtalene-1-sulfonamide (DNSA), region Ic: n-butyl *p*-amino-benzoate (ABE) and for site II – 8-anilino-1-naphtalenesulfonic acid (ANS). The percentage displacement of the probe from its binding site in albumin was calculated. The lipophilicity (log*P*) of thiopurines has been determined by reversed-phase thin-layer chromatography using water-methanol mixtures as eluents. The pK_a values and ion fraction of compounds at pH 7.4 were calculated by use of software ADME Boxes vs 3.5 (Pharma Algorithms 2008).
Using the fluorescence probes for the determination of the binding sites of thiopurines in HSA allows us to conclude that thiopurines competed with probes for hydrophobic sites of HSA. The competition is weaker for ANS – probe for site II and stronger for warfarin – probe for site I (region Ic). The lipophilicity correlates with binding affinities of thiopurines for site II, however only for compounds in non-ionized forms in aqueous solution, pH 7.4.

P-44

Azo Dyes as Potential Allosteric Modulators of the Metabotropic Glutamate Receptors mGluR4.

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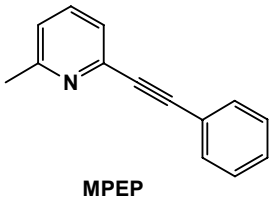
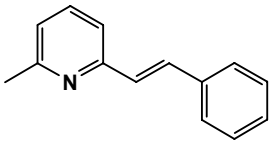
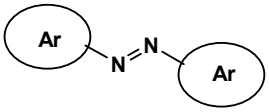
The glutamatergic system regulation by the metabotropic receptors (mGluR) appears as promising new therapy of central nervous system disorders. Until now, drug discovery programs have mainly focused on group I (mGluR1 and 5) and II (mGluR2 and 3). However, recent publications revealed high therapeutic potential of metabotropic glutamatergic receptor ligands of group III e.g. mGluR4, 7, and 8. Especially it seems that the non-competitive ligands (positive and negative allosteric modulators), which bind to the transmembrane heptahelical domain of mGlu receptors may have potential antidepressant properties. Moreover, the allosteric modulation of mGluR gives possibilities to more selective interactions with individual subtypes of mGluR family and increased tolerance in comparison to competitive agonists/antagonists.
The research progress of allosteric modulation of receptors group III is hampered mainly due to the very limited number of specific compounds.
The Department of Medicinal Chemistry is currently engaged in project (acronym “ModAll”) concerning among others discovery of mGluR4 selective modulators. On the basis of known non-competitive mGluR5 agonists – MPEP and SIB-1893, which are classified also as positive allosteric modulators of mGluR4 [1], a series of azo dyes – structural analogues of SIB-1893 – was designed and synthesized. The received compounds are currently evaluated in pharmacological tests.



MPEP



SIB-1893



This study is supported by project UDA-POIG.01.03.010-12-100/08-00 "Allosteric modulation – new strategy in pharmacotherapy. Identification of psychotropic properties of glutamatergic receptor ligands group III" co-financed by European Union from the European Fund of Regional Development (EFRD).

[1] Mathiesen J. M. et al.: *Br. J. Pharmacol. 138 (2003)*, 1026-1030.

P-45

High Resolution Study on Non-Stoichometric Gramicidin D Complexes with Alkali Metals Salts.

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Gramicidin D is a naturally occurring ionophoric antibiotic produced by *Bacillus brevis* [1]. This linear gramicidin is a natural antibiotic, acting against Gram+ species by incorporation in a membrane cytoplasm [2,3] in form of an intramembrane channel specific for monovalent cations transportation. Formation of helical gramicidin channels is due to the alternate D-L configuration of gramicidin pentadecapeptide having a sequence formyl-Val(Ile)-Gly-Ala-D-Leu-Ala-D-Val-Val-D-Val-Trp-D-Leu-Trp(Phe,Tyr)-D-Leu-Trp-D-Leu-Trp-ethanolamine [4].
High-resolution (synchrotron radiation, low-temperature) structures of gramicidin complexes with alkali metals salts reveal details [5,6], which were needed to understand the nature of the ion coordination in the channel and to gain insight into the mechanism of ion transport. There are four crystallographically independent molecules of gramicidin in the studied crystal, forming two pairs of helical right-handed strands intertwined in an anti-parallel.

[1] Dubos R. J.: *J. Exp. Med. 70 (1939), 1-10.*
[2] Hotchkiss R. D.: *Adv. Enzymol. 4 (1944), 153-199*.
[3] Gross E., Witkop B.: *Biochemistry 4 (1965), 2495-2501*.
[4] Sarges R., Witkop B.: *J. Am. Chem. Soc. 87 (1965), 2011-2020.*
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[6] Olczak A., Główka M., Szczesio M., Bojarska J., Duax W. L., Burkhart B. M., Wawrzak Z.: *Acta Crystallogr. D63 (2007), 319-327.*

P-46

Synthesis and Preliminary Evaluation of Antimicrobial Activity of Selected Derivatives of 2-Benzofurancarboxylic Acid.

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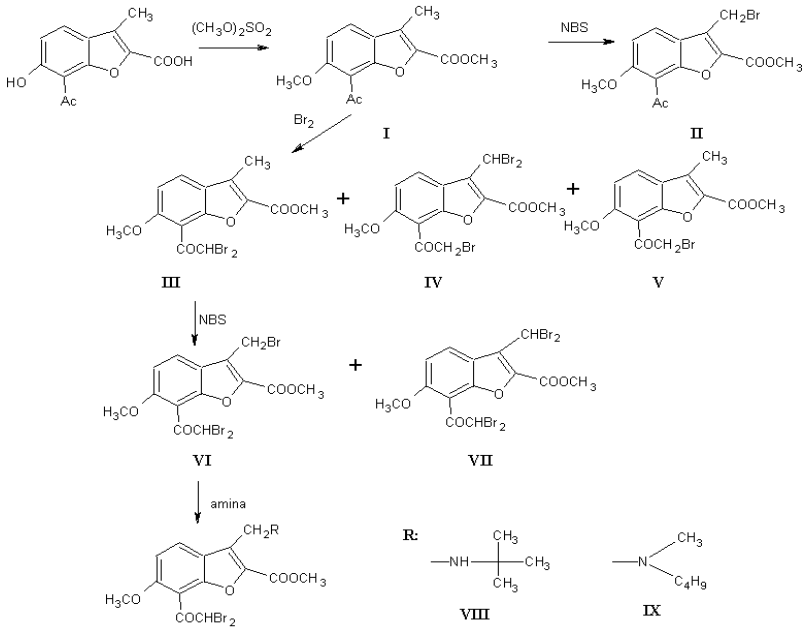
Many compounds containing a benzofuran arrangement show biological activity, such as antiarrythmic (e.g. Amiodaron, Benzaron); spazmolitic, antiviral, anticancer, antifungal and antiinflammable [1-2]. Our previous studies show that introducing of halogen to the benzofuran system increase its biological activity [3]. Taking into account this fact we synthesized the new derivatives including bromine in a system (Scheme). The starting material was 7-acetyl-6-hydroxy-3-methyl-1-benzofuran-2-carboxylic acid. The compound **I** was obtained in the reaction with excess $(CH_3O)_2SO_2$. Next the bromo derivatives were prepared in the reaction with Br_2 and /or NBS.



The structure of the all compounds obtained were confirmed by ^{1}HNMR and elemental analysis. All derivatives were tested for antimicrobial activity. Microorganisms used in this study were as follows: Gram-positive (*S. aureas*) and Gram-negative (*E. coli*) bacterial strains and *Candida albicans.* Compound **VIII** showed antimicrobial activity.

[1] Kodama I. et al.: *Am. J. Cardiol. 84(9A) (1999), 20R-28R.*
[2] Sun W. et al.: *Circulation 100(22) (1999), 2276-2281.*
[3] Kossakowski J. et al.: *Il Farmaco 60 (2005), 519-527.*

P-47

Antifungal Activity of Xanthone Derivatives Against Chosen Strains of Dermatophytes, Yeasts and Molds.

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Xanthones comprise interesting class of naturally occurring and synthetic compounds with documented, diverse biological activity including antimalarial [1], antimycobacterial [2, 3], antibacterial [4] and antifungal [5, 6] properties.
The aim of the present study was evaluation of antifungal efficacy of the newly synthesized xanthone derivatives. Our interest in this area was connected with currently observed outbreak of fungal infections, partially linked to immunosystem failure caused by ageing, diseases (e. g. AIDS, cancer) [7], immunosuppressive drugs administered in chemotherapy [8], or the transplantation process [9]. Natural xanthone derivatives were widely reported as antifungal agents e.g. 1,3,5,6-tetrahydroxy-2-(3,3-dimethylallyl)-9H-xanthen-9-one (MIC a 10 μg/mL against *Candida glabrata*) [10]. In contrast, investigations in the group of synthetic xanthone derivatives seem to be insufficient.
Taking into account these facts and our former establishments that:

- substitution of xanthone rings in position 2 is more favourable than in position 4,
- chlor is more potent than methoxyl substituent,
- carbonyl group is responsible for the lack of activity, as well as hydroxyl group in side chain,
- the most effective amine fragments are methyl-, ethyl- or allylamine moieties [11],

There were synthesized five new allylamine and methylamine type xanthones. They were evaluated according to the disc-diffusion method against 16 representative strains of dermatophytes, yeasts and molds. Obtained results confirmed our former structure-activity establishments. Three of the tested compounds demonstrated significant antifungal activity, especially against *Trychopython mentagrophytes*, *Trichophyton rubrum*, *Microsporum gypseum*, *Microsporum canis*, *Epidermophyton floccosum*. Zones of growth inhibition ranged up to 40mm. This value is smaller than values obtained for commercially available drugs with allyl and / or methylamine moieties (eg. terbinafine revealed growth inhibition zone ranging 85 mm) but bigger than values obtained for triazoles (e. g. fluconazole revealed growth inhibition zone ranging 13 mm) [12].

[1] Portela C., et al.: *Bioorg. Med. Chem. 12 (2004), 3313-3321*. [2] Pickert M., Schaper K. J., Frahm A. W.: *Arch. Pharm. (Weinheim) 331(5) (1998), 193-197*. [3] Szkaradek N., et al.: *Acta. Polon. Pharm. – Drug Res. 65 (2008), 21-28*. [4] Panthong K., et al.: *Phytochemistry 67 (2006), 999-1004*. [5] Salmoiraghi I., et al.: *Arch. Pharm. Pharm. Med. Chem. 331 (1998), 225-227*. [6] Moreau S., et al.: *Eur. J. Med. Chem. 37 (2002), 237-253*. [7] Shen Y. Z., et al.: *Mycoses 50 (2007), 475-480*. [8] Staber P., et al.: *Wien Med. Wochenschr. 157 (2007), 503-510*. [9] Kobayashi R., et al.: *J. Pediatr. Hematol. Oncol. 29 (2007), 786-791*. [10] Fukai T., et al.: *J. Nat. Prod. 66 (2003), 1118-1120*. [11] Marona H., et al.: *Arch. Pharm. Chem. Life Sci.*, *342 (2009), 9–18.* [12] Karaca N., Koç A. N.: *Diagn. Microbiol. Infect. Dis.*, *48 (2004), 259–264.*

P-48

Crystallographic Studies of *Z* and *E* Isomers of 2-Amino-5-(2-chlorobenzylidene)-1-methyl-1H-imidazol-4(5H)-one.

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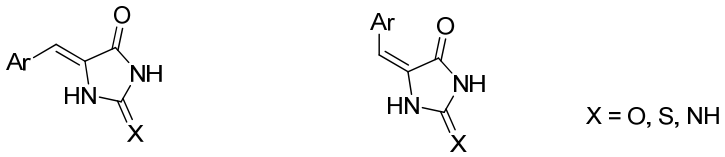
Both natural and synthetic compounds based on imidazolidine-4-one scaffold show a wide range of biological activity, among others anticonvulsant, antiarrhythmic, antihypertensive, antibacterial or fungicidal properties. The group of 5-arylidene-imidazolidine-4-one derivatives, including hydantoin, 2-thiohydantoin and creatinine analogs (Fig. 1), presents an interesting target for studies on structure-activity relationship and molecular structure assignment. For each of possible geometric *E*/*Z* isomers equilibrium of two or even three possible tautomeric forms may be observed.

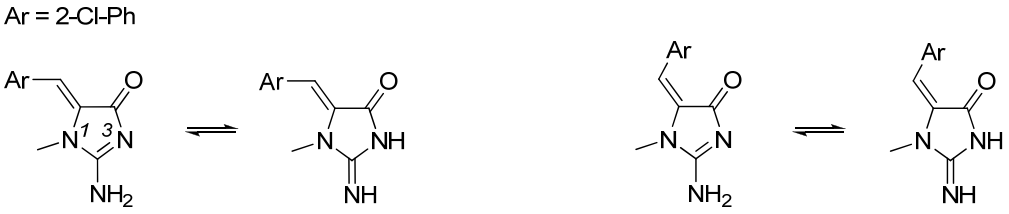
Fig. 1



(*Z*)-isomer (*E*)-isomer

The structure determination among 5-arylidene-imidazolidine-4-one derivatives has been the subject of extensive structural studies using both spectral and crystallographic methods also in our group. The spectroscopic consideration on the tautomerism equilibrium observed for this series prompted us to the synthesis of new derivative, the 2-chlorobenzylidene-creatinine. Due to the methyl substituent at N1, the tautomeric equilibrium of creatinines is limited to two possible forms (Fig. 2). During the synthesis of 2-chlorobenzylidene-creatinine two geometric isomers - *Z* and *E* - were isolated. In our present work the results of X-ray studies, supported with spectral data provided for both isomers are reported.

Fig.2



P-49

Aktywność Przeciwbakteryjna Nowej Pochodnej Izotiazolo[5,4-*b*]pirydyny.

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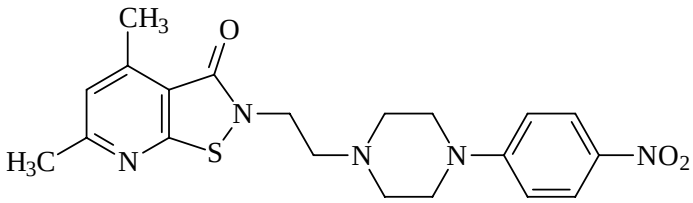
W komunikacie zaprezentowano wyniki badań mikrobiologicznych nowej pochodnej izotiazolo[5,4-*b*]pirydyny przedstawionej na poniższym rysunku. W odróżnieniu od pochodnych izotiazolo[5,4-*b*]pirydyn-3(2*H*)-onu zamieszczonych w literaturze a patentowanych jako potencjalne czynniki przeciwtrądzikowe [1-3], związek otrzymany w naszym zespole zawiera w podstawniku w pozycji 2 ugrupowanie arylopiperazynowe oraz posiada w pozycji 4,6 macierzystego układu grupy metylowe.



Prezentowany związek w badaniach mikrobiologicznych *in vitro*, w zakresie stężeń 0.25-100 μg/ml, hamował w 90-99% wzrost szczepu *Propionobacterium acnes*. Bakteria ta uważana jest za jeden z czynników biorących udział w patogenezie zmian trądzikowych. Szczegółowe badania mikrobiologiczne dowiodły, że nowa pochodna izotiazolopirydyny najwyższą efektywność wykazuje w stężeniu 0.5-0.25 μg/ml, przewyższając skutecznością erytromycynę zastosowaną jako lek referencyjny.
Prezentowany związek jest przedmiotem zgłoszenia patentowego zarejestrowanego pod numerem P 386302.

[1] DE 3,313,778(1984); CA: **100**, 121052k
[2] DE 3,342,538 (1984); CA: **101**, 116736c
[3] FR 2,555,450 (1985); CA: **103**, 215279d

P-50

New Derivatives of Indole – Analogues of MMPIP – an Allosteric Modulator of the Metabotropic Glutamatergic Receptors mGluR7.

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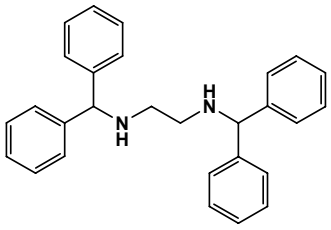
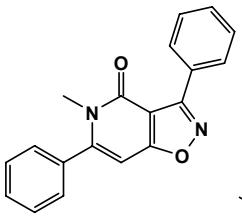
The mGluRs have recently become attractive therapeutic targets for drug development for the treatment of CNS diseases. So far, major drug discovery programs have largely focused on group I (mGlu1 and 5) and II (mGlu2 and 3) mGlu receptors, which have been implicated in neuropathological and various psychiatric disorders. The mGluR4, 7 and 8 belongs to III group of metabotropic glutamate receptors are especially promising, however, they were significantly less studied, mainly due to the limited number of specific agents. Recent advances in the identification of selective or specific compounds, and the generation of transgenic animals have, however, revealed important insights into the potential role of group III receptors in the pathophysiology of neurological and mood disorders.

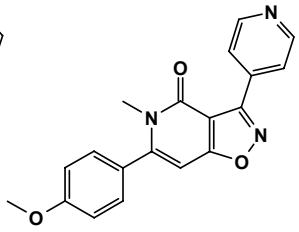
One of the main topic of the project ModAll, currently realized in the Institute of Pharmacology PAS, is the discovery of new selective allosteric modulators of mGluR7. Only a few selective mGlu7 receptor non-competitive agents are reported to date. The first selective mGluR7 allosteric agonist – AMN082 and antagonist – MDIP were identified by random high-throughput functional screening of chemical library, whereas MMPIP was obtained by subsequent chemical modification of MDIP [1,2]. In our approach, based on the MMPIP pattern, the new series of indole derivatives were designed and synthesized. The new compounds are currently under pharmacological evaluation.



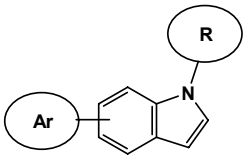
AMN082



MDIP



MMPIP



This study is supported by project UDA-POIG.01.03.010-12-100/08-00 "Allosteric modulation – new strategy in pharmacotherapy. Identification of psychotropic properties of glutamatergic receptor ligands group III" co-financed by European Union from the European Fund of Regional Development (EFRD)

[1] Mitsukawa K. et al.: *Proc. Natl. Acad. Sci. USA 102(51) (2005)*, 18712-7.
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P-51

3-(1H-Imidazol-4-yl)propyl Carbamates as Histamine H_3/H_4 Receptor Ligands.

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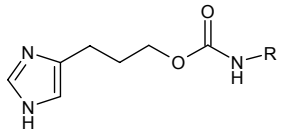
Histamine has been found to exert tremendous influence over variety of physiological processes. So far, there are known four histamine receptor subtypes: H_1, H_2, H_3 and H_4. The H_1 and H_2 receptor antagonists are for many years in clinical use, in the treatment of allergic conditions and gastric ulcers respectively. The histamine H_3 receptors (H_3R) have been known since 1983 and are constitutivly active receptors mostly expressed in CNS. They are identified as mainly presynaptic autoreceptors, regulating the release of histamine, as well as heteroreceptors on non-histaminergic neurons controlling the release of many other important neurotransmitters, such as acetylcholine, norepinephrine, dopamine and serotonin. Given theirs localisation and theirs ability to affect multiple neurotransmitter systems it is supposed that H_3R antagonists could be useful for the treatment of a wide range of central nervous system disorders such as Alzheimer's disease, attention-deficit hyperactivity disorder (ADHD), sleep disorders, pain and obesity [1]. Histamine H_3R ligands (inverse agonists, antagonists) belong to two general groups: imidazole-based compounds and non-imidazole derivatives [2, 3]. The histamine H_4 receptor (H_4R) has only recently (2000) been discovered independently by several research groups. The human H_4R is closely related to the human H_3R. The two proteins have a sequence identity of 31%. Their homology in the transmembrane region is 58% and both have a long third intracellular loop. The H_4Rs are mainly expressed in bone marrow and peripheral leukocytes. Potential therapeutic indications for histamine H_4R ligands include asthma, allergic rhinitis, pain, inflammatory bowel disease and cancer [4].
Our investigation deals with the search for histamine H_3 receptor antagonists in the class of 3-(1H-imidazol-4-yl)propyl carbamates.



The impact of the substituent on carbamate nitrogen in these compounds on H_3 receptor antagonist activity was studied. These compounds were tested for their effects at histamine H_3 receptors *in vitro* (at isolated guinea pig ileum and at cloned human H_3 receptors) and *in vivo* after oral administration to mice. Moreover for some compounds *in vitro* affinity for H_4Rs was evaluated.
These compounds showed good *in vivo* activity and the high affinity for human H_3R (in the nanomolar concentration range), and displayed moderate, weak or the lack of potency for human H_4R.

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P-52

Bivalent Ligands for Adenosine A_{2A} Receptor.

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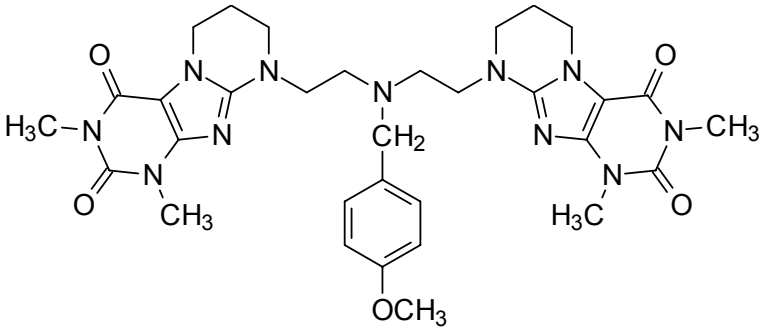
Many deseases must be treated by combining therapeutic approaches trough multiple targets. One strategy is to develop a single chemical entity that is able to modulate multiple targets simultaneously [1]. This can be adequate especially for G-protein coupled receptors ligands, which are proved to exist as dimers (homo- or heteromers) or higher order oligomers. Multicomponent conjugate of ligands for each oligomer unit can provide optimal effect with lower risk of drug-drug interactions compared to cocktail of single target drugs. Over the past few decades bivalent ligands have been developed for a variety of G-protein coupled receptors, including opioid, adrenergic, dopaminergic, serotoninergic and muscarinic receptors [2].



In our research, we developed the series of bivalent pyrimido[2,1-*f*]purinedione derivatives. Affinity for adenosine A_{2A} receptors and selectivity over adenosine A_1 receptors were evaluated for the structure presented above with radioligand binding assay (using [^{3}H]2-chloro-N^6-cyclopentyladenosine and [^{3}H]1-propargyl-3-(3-hydroxypropyl)-7-methyl-8-(*m*-methoxystyryl)xantine as adenosine A_1 and A_{2A} receptor radioligands respectively). Then influence on human adenosine A_{2A} receptors was assessed by time-resolved fluorescence lifetime measurements in FRET analyses. Ligand-rec eptor interaction was also modeled *in silico* by molecular docking studies. As a result it was concluded that linker length seems to be key issue for optimal multivalent GPCR ligand development. Based on the obtained results we are going to focus on heteromeric adenosine A_{2A}, dopaminergic D_2 and glutaminergic $mGlu_5$ receptors oligomers [3]. It could provide the new therapeutic approach for the treatment of Parkinson's and other neurodegenerative deseases.

The work was partly supported by grant N405 304 136

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P-53

Synthesis and Structure of (E)-1-[1-(4-Methoxyphenyl)imidazolidyn-2-ylidene]-3-phenethylurea.

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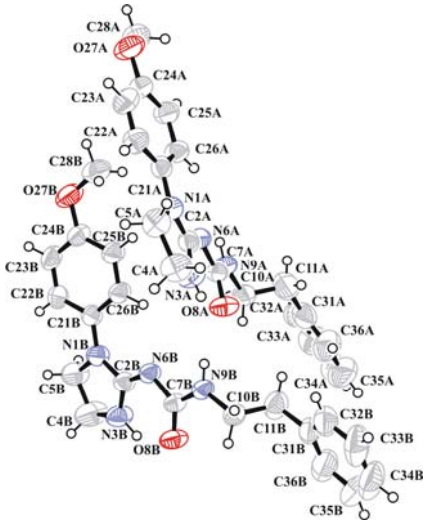
From the previous research raports it was confirmed that 1-(imidazoli-2-yl)-3-arylurea derivatives exhibit significant activity in central nervous system. The most interesting was antinociceptive and antidepressant activity [1]. Very interesting pharmacological effect was also observed concerning positive modulation of the low dose activity for both morphine and imipramine. It can suggest allosteric action on MOP and DOP opioid receptors and amelioration of the pain stimuli and depression respectively [2].
Farther investigation on derivatives with aliphatic linker attached between aromatic ring and N3 nitrogen atom lead to finding of even more active ones. The most active derivative was 1-[1-(4-methoxyphenyl)imidazoline-2-yl]-3-phenethylurea. It was synthesized from 1-(4-methoxy)-2-amino-imidazoline-2 and 2-phenethylisocyanate by the method described elsewhere [1].
To check its active conformation which would help in further bioinformatic analyses of the whole set activity x-ray crystallography was performed.



Crystallographic data (**1**): $C_{19}H_{22}N_4O_2$, M_r = 338.41, Monoclinic, *C*2/c, a = 19.283(4), b = 8.513(2), c = 43.901(9) Å, β = 91.29(3)°, V = 7205(3) $Å^3$, Z = 16, D_x = 1.248 gcm^{-3}, μ = 0.671 mm^{-1}, CuKα, λ = 1.54178 Á, T = 293 K, R = 0.0526 for 5206 reflections.

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P-54

The Synthesis of New Pyrimido[2,1-f]theophylline Derivatives with Potential Affinity for CNS Receptors.

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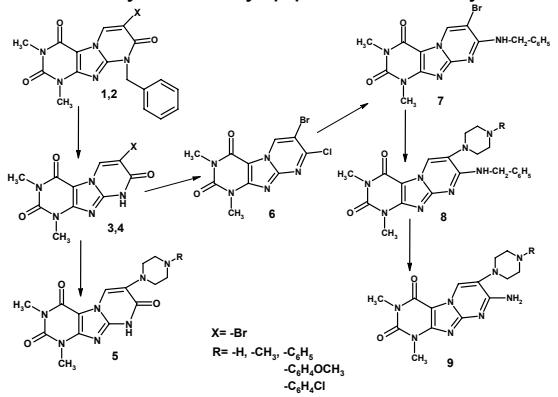
Long chain arylpiperazines (LCAP) with an amide moiety have been found as serotonin receptor ligands in particular 5-HT_{1A} and 5-HT_{2A} ones. Although the terminal amide fragment significantly affects binding of 1-arylpiperazine derivatives for serotonin receptors, its role is not clear yet .The significance of the terminal part in ligand-receptor interaction has been the subject of many structure-activity relationships studies. On the other hand, we have found that annellation of six or seven membered ring at the 7,8-position of the theophylline changed the profile of its central nervous system activity. In comparison to the reference compound, derivatives with pyrimidine or diazepine, lactam or non lactam ring fused in the 7,8-position of theophylline, demonstrated sedative, hypotermizing and neuroleptic-like effects on the CNS [1,2]. In the course of exploring structure-activity relationships in the group of tricyclic theophylline derivatives, the aim of this work was to develop a synthetic procedures to obtain new heterocyclic system: 8-chloro; 8-benzylamino or 8-amino-pyrimido[2,1-f]theophylline, with piperazine, N-methyl- or N-aryl-piperazine moiety.



The starting material for synthesis pyrimido[2,1-f]theophylline derivatives were 1,3-dimethyl-9-benzyl-pyrimido[2,1-f]purine-2,4,8(1H,3H,9H)trione (**1**) and 1,3-dimethyl-7-bromo-9-benzyl-pyrimido[2,1-f]purine-2,4,8(1H,3H,9H)trione (**2**) prepared according to the procedures described earlier [3]. Compounds **4** was treated with phosphorus oxychloride to obtain 1,3-dimethyl-7-bromo-8-chloro-pyrimido[2,1-f]purine-2,4,8(1H,3H,9H)dione (**6**). This compound in two steps, was converted to the 1,3-dimethyl-7-piperazynyl-8-amino-pyrimido[2,1-f]purine-2,4,8(1H,3H,9H)dione derivatives. Compounds **4** was also converted by coupling him with appropriate arylpiperazines (**5**). Further detailed studies are presently being undertaken on pyrimido[2,1-f]theophylline derivatives for their 5-HT_{1A}/5-HT_{2A} receptor affinity.

The work was partly supported by grant: K/ZDS/000722

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[3] Pawłowski M., Katlabi J., Rys B., Szeler E.: *Pharmazie 52 (1997), 279-282.*

P-55

Solid-Phase Synthesis of Novel Arylpiperazine-Functionalized Amino Acid Amides.

Paweł Guzik [a], Katarzyna Grychowska [a], Paweł Zajdel [a], Marek Żylewski [b], Beata Duszyńska [c], Andrzej J. Bojarski [c], Maciej Pawłowski [a]

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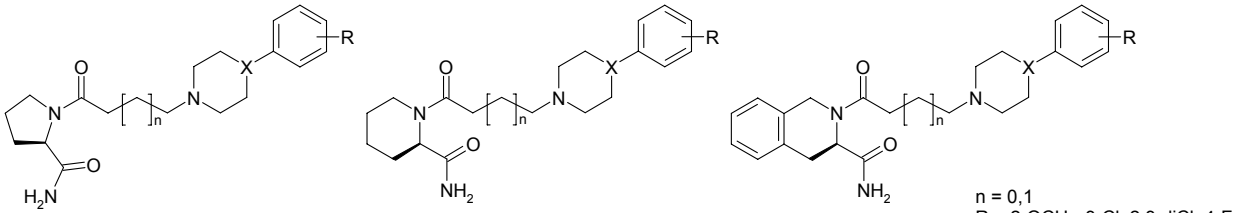
We have previously reported on successful application of combinatorial chemistry techniques for generation of rationally designed libraries of serotonin receptor ligands, namely arylpiperazine derivatives containing N-acylated proline fragments [1, 2]. Encouraged by these findings, we have designed and synthesized a library of aryl piperidine- or piperazine analogs containing amino acid amides (pyrrolidine-2-carboxamide, piperidine-2-carboxamide, tetrahydroisoquinoline-3-carboxamide).



A 19 member library of derivatives was synthesized on Rink-Amide polystyrene resin. Library generation was performed manually by using Bill-Board set [3]. This equipment keeps the solid-phase reactions organized in a grid and simplifies repeated cycles of reactions, washings, cleavage, and finally solvent evaporation step. Selected library representatives were evaluated for their 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptor affinities. The results obtained followed by the discussion on the influence of the modifications applied on receptor affinity will be presented.

References

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P-56

Observation of Ligand - Micelle Interactions. The Attempt to use the NMR Spectroscopy as a Tool for Lipophilicity Measurements.

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Surfactants are well known class of compounds consisting of polar “head” and non polar, usually long hydrocarbon chain. Their characteristic property is formation in aqueous solutions of so called micelles, which occurs after reaching enough high concentration. This concentration is called critical micelle concentration – CMC and depends on structure of surfactant. CMC can be varied after addition of other compound into solution due to hydrophobic interactions. More hydrophobic compounds should have bigger affinity to interior of the micelle and this phenomena can induce earlier (for lower concentrations of surfactant) formation of micelles. Our assumption is, that it is possible to use CMC as a measure of lipophilicity of added compounds.
CMC can be obtained using various methods. NMR spectroscopy is one of the newest used for that purpose. Elucidation of CMC is based on changes of chemical shifts of protons caused by changing of surfactant's molecule neighborhood due to formation of micelle system. Our recent investigations showed that it is possible to observe the influence of additives on CMC of investigated surfactant.
The aim of present study is to elucidate the influence of various xanthon derivatives on CMC of sodium dodecyl sulfate and to compare of obtained CMC values with other lipophilicity parameters of investigated additives.

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P-57

New Synthesis of Methylthiobenzaldehyde, Convenient Substrate for Synthesis of Methylthiostilbenoides

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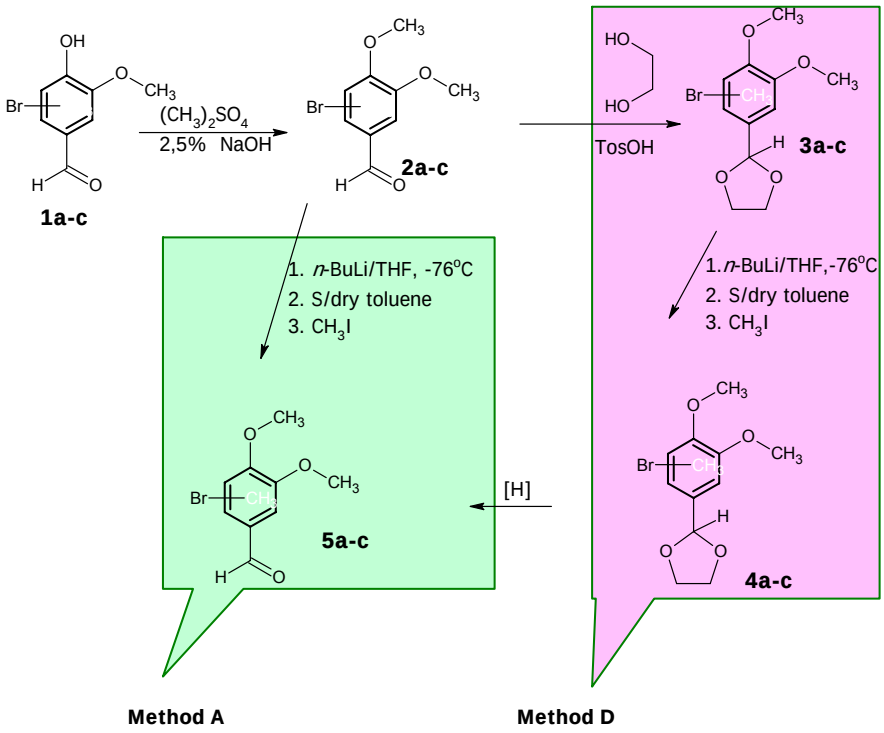
In our previous study [1] on stilbenoide analogues, we made an observation that selected 4'-thio-polymethoxy *trans* stilbenes showed high potency toward CYP1A1, CYP1A2 and CYP1B1. SAR analysis allowed to reach a conclusion that activity of synthesized compounds strongly depend on presence of methylthio substituent. Among compounds tested, 2-methoxy-4'-thiomethyl-trans-stilbene and 3-methoxy-4'-thiomethyl-trans-stilbene demonstrated the most potent and selective inhibitory effect on CYP1A1 and CYP1B1 activities. It very much seems as if methylotio group play a key role in mechanism of activity of these compounds towards enzyme active center. In order to explain real reason of higher activity of methylthio derivatives of stilbene in comparison with natural polymethoxy *trans*-stilbenes (e.g. resveratol), the new project of synthesis methylthio derivatives of stilbene have been created. The main goal of this project was the synthesis population of stilbene enriched with methylthio groups substituted into various position of phenyl rings of stilbene. In the first attempts we started with synthesis of 2- 5 or 6-bromo-waniline (**1a-c**) which after conversion into bromoveratraldehyde (**2a-c**), aldehyde group was blocked by ethylene glycol to obtain compounds (**3a-c)**. Both groups of compounds **2a-c** and **3a-c** were transformed to final products **5a-c**. The average yield obtained products **5a-c** by two steps ***Method A*** were 11%, whereas; in the case of ***Method B*** products 5a-c yields were 53%. This observation leads us to the conclusion that *Method B* is better than ***method A***. Structure of all synthesized compounds were confirmed by H and ^{13}C NMR and HRMS.



[1] Mikstacka R., Baer-Dubowska W., Wieczorek M., Sobiak S.: *Mol. Nutr. Food Res. 52 (2008), S77 – S8*

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