15:30 Poster 93

New derivatives of thiosemicarbazide and 1,2,4-triazole-5-thione with potential antimicrobial activity

Monika Wujec[1], Urszula Kosikowska[2], Edyta Kuśmierz[1], Agata Siwek[1], Anna Malm[2]

1. *Medical University, Faculty of Pharmacy, Department of Organic Chemistry, Staszica 6, Lublin 20-081, Poland* **2.** *Medical University, Faculty of Pharmacy, Department of Pharmaceutical Microbiology, Chodźki 1, Lublin 20-093, Poland*

e-mail: monika.wujec@am.lublin.pl

1,2,4-Triazoles have been reported to associate with antimicrobial, fungicidal, anti-inflammatory, antiparasitic, insecticidal, herbicidal, antiviral, antitumor, anticonvulsant, antidepressant, hypotensive effects and plant growth regulatory activities. On the other hand, nitroimidazole like metronidazole, ornidazole, secnidazole and tinidazole are widely used in the treatment of diseases caused by protozoa and anaerobic bacteria. Furthermore, some 5-nitroimidazoles have been shown activity against *Helicobacter pylori.* In the design of new compounds, the development of hybride molecules through the combination of different pharmacophores in one frame may lead to compounds with increase antimicrobial activity. Herein, we have synthesized novel compounds containing (4-nitroimidazol-1yl)methyl fragment at the position 3 of the 4-substituted-1,2,4-triazole-5-thiones.

Six compounds were screened for their antimicrobial activity against reference strains of bacteria (9 species) and fungi (5 species). Two compounds inhibited the growth of Gram-positive *Micrococcus luteus* ATCC 10240 with MIC = 250 mg L^{-1} and MIC = 500 mg L^{-1}, respectively. The most effective against Gram-negative bacteria was 4-phenyl-1-[(4-nitroimidazol-1-yl)acetyl]thiosemicarbazide with MIC = 500 mg L^{-1} for *E. coli* ATCC 25922 and about 36 to 65% reduction of the growth of *Klebsiella pneumoniae* ATCC 13883 and *Proteus mirabilis* ATCC 12453 at lower concentrations (7.81 - 250 mg L^{-1}). None of the compounds had influence on the growth of reference strains belonging to *Staphylococcus, Bacillus* or *Pseudomonas* species. The tested compounds had no activity against fungi, besides 4-(4-tolyl)-1-[(4-nitroimidazol-1-yl)acetyl]thiosemicarbazide showing moderate inhibitory effect against *Trichophyton menthagrophytes* ATCC 9533 with MIC = 250 mg L^{-1} and about 30-70% reduction of the growth of this dermatophyte at lower concentrations (7.81 - 125 mg L^{-1}). Moreover, this compound exerted about 0-70% inhibition of the growth of reference strains of *Candida* spp. and *Aspergillus niger* ATCC 16404 at concentrations of 7.81 - 500 mg L^{-1}.

15:30 Poster 94

HPLC as a method for analytical control of synthesis and determination of tolterodine (TD-S)

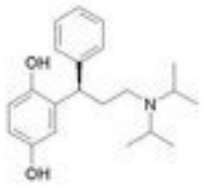
Joanna Zagrodzka, Anna Rosa, Kamila Miłońska, Wojciech Łuniewski, Marcin Cybulski, Paulina Bujak

Pharmaceutical Research Institute (IF), Rydygiera 8, Warszawa 01-793, Poland

e-mail: j.zagrodzka@ifarm.waw.pl

Physical preparation or complex structure of API may cause many analytical problems. Therfore elaboration of suitable analytical methods for both routine manufacturing processes and investigation of novel synthetic routes is very important.

Analytical method used for this purpose must ensure fast and efficient determination of the presence of starting materials, product, impurities and side products. Nowadays, the common and widely applied method which meets these requirements is high performance liquid chromatography, especially in reverse phase mode (RP-HPLC). This technique was used for optimization of synthesis and determination of purity of tolterodine tartrate – an active substance administered in urinary incontinence therapy.



Tolterodine

Synthesis of the active substance – tolterodine - was conducted in two different ways: first one consisted of seven synthetic steps, and second one of eight steps. The method described in this poster is useful for both synthetic pathways and suitable for determination of product purity, as well as separation and identification of impurities and side products.

15:30 Poster 95

Solid-phase synthesis and preliminary biological investigation of arylpiperazine library as 5-HT$_{1A}$ and 5-HT$_{2A}$ receptor ligands

Paweł Zajdel[1], Joanna Król[1], Andrzej J. Bojarski[2], Beata Duszyńska[2], William Scott[3], Ziniu Zhou[3], Matrin J. O'Donnell[3], Maciej Pawłowski[1]

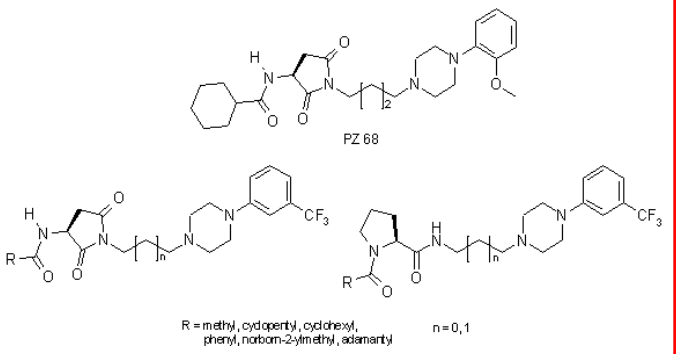
1. *Jagiellonian University, Medical College, Department of Medicinal Chemistry, Medyczna 9, Kraków 30-688, Poland* **2.** *Institute of Pharmacology Polish Academy of Sciences, Department of Medicinal Chemistry, Smętna 12, Kraków 31-343, Poland* **3.** *Department of Chemistry and Chemical Biology, Indiana University Purdue University Indianapolis, 402 N. Blackford Street, Indianapolis 46202, United States*

e-mail: mfzajdel@cyf-kr.edu.pl

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 amino acid fragments [1,2]. It was found, that the kind of substituent at aromatic ring influenced receptor affinity and compounds in vivo 5-HT$_{1A}$ intrinsic activity. Finally, the project allowed selecting a lead compound (PZ 68), pre- and postsynaptic 5-HT$_{1A}$ agonist, which demonstrated distinct anxiolytic-like and antidepressant-like effects in the respective animal models.

Taking advantage of the solid-phase chemistry for quick generation

of compound libraries, we have designed and synthesized analogs of previously reported long-chain arylpiperazines containing N-acylated amino acid fragments (aspartic acid, proline).



A 24 member library of trifluromethyl derivatives was synthesized on solid-support. The previously reported synthetic methodology was now adopted for a BAL-type PL-MBHA 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} and 5-HT_{2A} receptor affinities. The results obtained followed by the discussion on the influence of the modifications applied on receptor affinity will be presented.

References

[1] Zajdel, P. *et al.J. Comb. Chem.* **2004**, *6*, 761-767.
[2] Zajdel, P. *et al.Bioorg. Med. Chem.* **2007**, *15*, 2907-2919.
[3] Scott, W. L. *et al.* U.S. Patent 5,785,927, July 28, 1998. Available from Leads Metal Products, PO Box 441186, Indianapolis, IN, 46244-1186(larry@leadsmetal.com).

15:30 Poster 96

Oxidation status of ALDH3A1 and antioxidant capacity correlation for human saliva.

Małgorzata Bogucka[1], Katarzyna Zawada[2], Piotr Wroczyński[1]

1. *Medical University of Warsaw, Department of Drugs Analysis, Żwirki i Wigury 61, Warsaw 02-091, Poland* **2.** *Medical University of Warsaw, Faculty of Pharmacy, Department of Physical Chemistry, Banacha 1, Warszawa 02-097, Poland*

e-mail: katarzyna.zawada@am.edu.pl

Aldehyde dehydrogenase isozyme (ALDH3A1) is an enzyme oxidizing mainly long- and medium-chain aliphatic as well as aromatic aldehydes. The salivary aldehyde dehydrogenase was postulated to play an important role in deactivation of higher aldehydes of plant origin, and may be involved in the prevention of chemical carcinogenesis [1,2].

It is also well documented that ALDH3A1 can be induced several-hundred-fold in some neoplastic states of different cancers e.g. liver, breast, colon and oral [3].

Activity of ALDH is unstable in the absence of thiols, but can be stabilized by 1 mM glutathione. Inactivated enzyme can be re-activated within 10 minutes by treatment of 0.5 mM DTT [4].

Saliva samples were collected to buffer stock solution containing various thiols, and assayed in the presence of fluorogenic substrate 6-methoxy-2-naphthaldehyde and NAD^+.

The oxidative stress has been associated with increased risk of many diseases, including different kinds of cancer. It can be measured by many methods, like ORAC (Oxygen Radical Absorbing Capacity) method [5], which gives information about total antioxidant capacity of body fluids. ORAC-FL test uses fluorescein as a fluorophore. The decay of the fluorescence emission over time due to exposition to the peroxyl radical source (AAPH) is measured. In the presence of diluted saliva sample the fluorescence decay is delayed due to the presence of antioxidants present in the saliva.

In present studies the ORAC value of human saliva of oral cavity surgical patients and healthy subjects was correlated with the ALDH3A1 activity.

We observed no distinct direct correlation between antioxidant capacity and ALDH3A1 oxidation status of human saliva in all healthy patients. However, in smoking patients and in patients with definite diet the correlation was observed.

[1] Vasiliou V, Pappa A, Estey T. Role of human ALDH in endobiotic and xenobiotic metabolism. Drug Metab Rev 2004; 36:279-299
[2] Sladek NE. Human aldehyde dehydrogenase: Potential pathological, pharmacological, and toxicological impact. J Biochem Mol Toxicol 2003; 17:7-23
[3] Sreerama L., Hedge M.W., Sladek N.E.: Clin. Can. Res. 1, 1153 (1995).
[4] Wroczyński P., Wierzchowski J., Rakowska A., Chimkowska M., Targoński J. (2004) Aldehyde Dehydrogenase in Human Saliva – Evaluation of Its Oxidation Status**,** Acta Poloniae Pharmaceutica – Drug Research.
[5] Ou B., Hampsch-Woodill M., Prior RL (2001) Development and Validation of an Improved Oxygen Radical Capacity Assay Using Fluorescein as the Fluorescent Probe. J. Agric. Food Chem. 49; 4619-4626

15:30 Poster 97

"Preliminary study of silicone gel sheets containing onion (Allium cepae) extract for treatment of scars"

Maria E. Żebrowska[1], Marzena Jamrógiewicz[2], Loretta Pobłocka-Olech[3], Jerzy Łukasiak[2], Mirosława Krauze-Baranowska[3], Małgorzata Sznitowska[1]

1. *Medical University of Gdańsk, Department of Pharmaceutical Technology, Hallera 107, Gdańsk 80-416, Poland* **2.** *Medical University of Gdańsk, Department of physical chemistry, Gen. J. Hallera 107, Gdańsk 80-416, Poland* **3.** *Medical University of Gdańsk, Department of Pharmacognosy, Gen. J. Hallera 107, Gdańsk 80-416, Poland*

e-mail: mariazebrowska@amg.gda.pl

Hypertrophic scars and keloids are formed during abnormal scarring process and result from excessive collagen deposition. Creams containing onion extract are very common in therapy of the scars and lately occlusive silicone dressings become a popular treatment option. However, the mode of pharmacological action of such preparations still remains unclear.

Although silicone preparations are used since 1983, there has been no reports about adhesive silicone-based sheet containing any