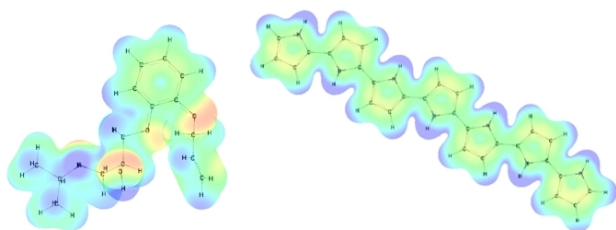


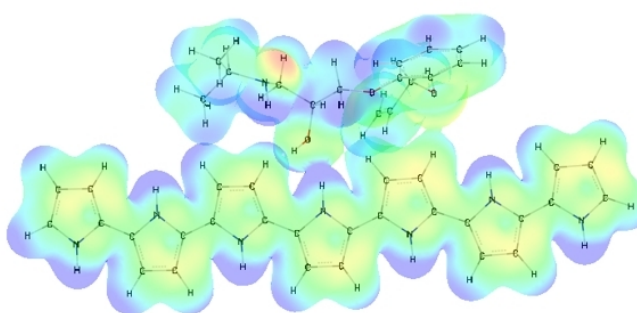
The solid phase microextraction (SPME) developed by Pawliszyn [1] allows one to monitor the drug concentration in blood by the simple and effective way. In this work we have investigated the nature of interaction between oxprenolol (**1**) and polypyrrole (**2**) on the theoretical level. The former is a beta-adrenergic antagonist drug used in treatment of hypertension, angina pectoris, and arrhythmias. The later is a polymer used as an active sorbent of the drug.



1

2

As a representative for the polypyrrole we have used the  $\alpha$ -a N-anti heptamer. Geometries of separated molecules were optimized on the DFT B3LYP/6-31G\*\* level of theory. The Interaction were determined by the minimization of the energy of system consist of two separated molecules (**1**) and (**2**), and analysis of the electrostatic potential distribution in resulting complex (**3**).



3

[1] J. Pawliszyn, *Solid-phase Microextraction: Theory and practice*, Wiley-VCH, New York, USA, 1997

This work was financially supported by professor's subsidy awarded (BB) by the Foundation for Polish Science (FNP)

15:30	Poster	58
-------	--------	----

### Molecular modeling explains differences in binding affinity of new potent and selective 5-HT<sub>1A</sub> ligands: arylpiperazinylalkylthiobenzoxazole derivatives

Mateusz Nowak<sup>1</sup>, Andrzej J. Bojarski<sup>1</sup>, Loredana Salerno<sup>2</sup>, Maria N. Modica<sup>2</sup>, Maria A. Siracusa<sup>2</sup>

**1.** Polish Academy of Sciences, Institute of Pharmacology, Department of Medicinal Chemistry, Smełna 12, Kraków 31-343, Poland **2.** Dipartimento di Scienze Farmaceutiche, Università di Catania, viale A. Doria 6, Catania 95125, Italy

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

Binding modes of series of new compounds containing a benzoxazole moiety bridged to an arylpiperazine by different thioether chains to 5-HT<sub>1A</sub> receptor were investigated by means of molecular docking. The correlation of the binding affinity with the length of thioether spacer was observed experimentally: three-unit spacer caused at least 100-fold decrease in K<sub>i</sub> compared to longer spacers. Automated docking with pharmacophoric constraints revealed the structural cause of this correlation. Possible interactions between Tyr7.43 and thioether fragment of the spacer caused the weakening of interactions from arylpiperazine part of the ligand. Additionally, the benzoxazole moiety of three-unit spacer compounds could hardly form any interactions with the transmembrane part of the receptor. On the contrary, for the compounds with longer spacers, not only the arylpiperazine moiety occupied optimal position in the binding pocket, but also benzoxazole was shown to form favorable interactions (H-bonds,  $\pi$ - $\pi$  stacking) with residues in the third and seventh transmembrane helices. It is also shown, that the extended conformations for those flexible, long-chain molecules are both observed by MNR measurements and predicted by modeling techniques.

#### REFERENCES:

- [1] Siracusa M.A., Salerno L., Modica M.N., Pittalà V., Romeo G., Amato M.E., Nowak M., Bojarski A.J., Mereghetti I., Cagnotto A., Mennini T. *Synthesis of New Arylpiperazinylalkylthiobenzimidazole, Benzothiazole, or Benzoxazole Derivatives as Potent and Selective 5-HT<sub>1A</sub> Serotonin Receptor Ligands*, submitted to J. Med. Chem.
- [2] Kołaczowski M., Nowak M., Pawłowski M., Bojarski A.J. *Receptor-based Pharmacophores for Serotonin 5-HT<sub>7R</sub> Antagonists – Implications to Selectivity*. J. Med. Chem., 2006, 49(23): 6732-41
- [3] Nowak M., Kołaczowski M., Pawłowski M., Bojarski A.J. *Homology modeling of the serotonin 5-HT<sub>1A</sub> receptor using automated docking of bioactive compounds with defined geometry*. J. Med. Chem. 2006, 49(1): 205-214

15:30

Poster

59

### Pharmacophore model of group II metabotropic glutamate receptor modulators

Mateusz Sikora, Mateusz Nowak

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

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

Metabotropic glutamate receptors (mGluRs) are members of large G-protein coupled receptor (GPCR) family, activated by L-glutamate, an excitatory neurotransmitter. They are responsible for normal signal transduction in central nervous system as well as pathophysiological processes. No crystal structure of complete metabotropic glutamate receptor is known so far, although it is believed, that all mGluRs manifest similar three-dimensional organization. They consist of large extracellular domain with glutamate binding site, a cysteine-rich linker and typical for GPCR's trans-helical domain containing allosteric site [1]. mGluR group II receptors are potential targets for anti-schizophrenic drugs, as well as for generalised anxiety disorder [2]. The orthosteric ligand binding site has been extensively studied and shown limited usability as a drug target, because of marginal selectivity between receptor types. Another, allosteric binding site located on extracellular part of trans-membrane domain exhibits