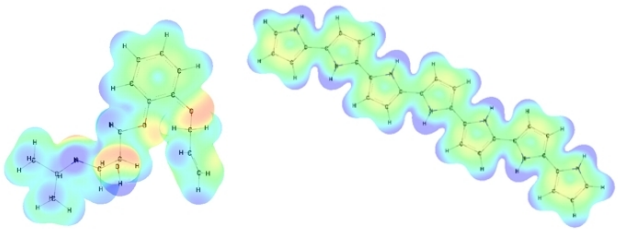
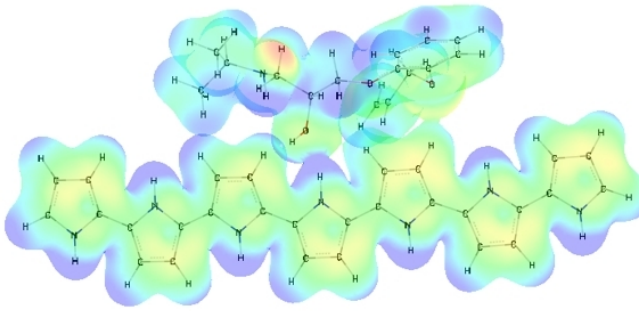
The solid phase microextraction (SPME) developed by Pawliszyn [1] allows one to monitor the drug concentration in blood by the simple and effective way. In this work we have investigated the nature of interaction between oxprenolol (**1**) and polypyrrole (**2**) on the theoretical level. The former 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 a-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**).



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Molecular modeling explains differences in binding affinity of new potent and selective 5-HT$_{1A}$ ligands: arylpiperazinylalkylthiobenzoxazole derivatives

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Binding modes of series of new compounds containing a benzoxazole moiety bridged to an arylpiperazine by different thioether chains to 5-HT$_{1A}$ 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_i 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, π-π 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.

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Pharmacophore model of group II metabotropic glutamate receptor modulators

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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 patophysiological 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

more diversity, and thus specificity. The search for mgluR modulators (i.e. compounds showing the affinity to allosteric site) yielded vast amount of pharmacological data, facilitating computer-assisted approaches. Until today, pharmacophore models for metabotropic glutamate receptors has been elucidated only for mGluR I [3].
We created a pharmacophore model of positive mGluR II modulator using openly available bio-assay results. For creating a 3-D model we utilized Catalyst software from Accelrys. Some key interactions responsible for binding and specificity were proposed. The mapping of pharmacophore on the 3D model of the binding site is also presented.

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Synthesis and anticonvulsant activity of new N-[(4-arylpiperazin-1-yl)-methyl]-3-phenyl-pyrrolidine-2,5-dione derivatives

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As has been shown in our previous investigations on the search for new anticonvulsant agents in a group of *N*-[(4-arylpiperazin-1-yl)-alkyl] 3-substituted pyrrolidine-2,5-diones, the introduction of aromatic area at the position-3 of the imide ring caused considerable growth of anti-seizure activity. It was especially noticeable in case of molecules with chloro atom attached at position-2 to the phenyl ring. In this series of compounds the most active were *N*-[4-(3-chloro-phenylpiperazin-1-yl)-methyl]-3-(2-chlorophenyl)-pyrrolidine-2,5-dione which showed ED_{50} value of 14.18 mg/kg in the MES test [1]. Following these finding, in the present work, we have synthesized two series of analogues, containing the chloro atom at the position-3 of the phenyl ring as well as molecules without substituents at the aromatic fragment (**Fig**. **1**).

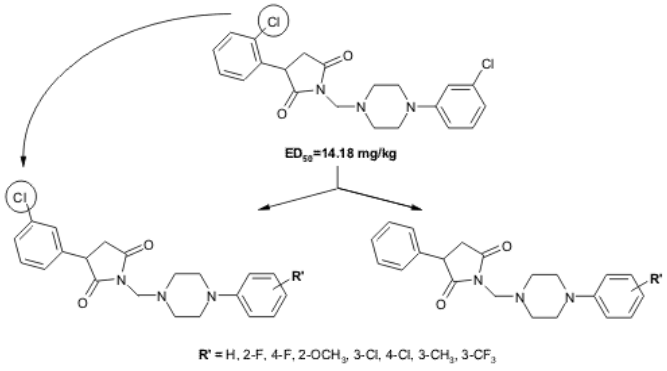

Fig. **1**.

The initial pharmacological screening was performed within the Antiepileptic Drug Development (ADD) Program in Epilepsy Branch, National Institutes of Health, National Institute of Neurological Disorders and Stroke (NIH/NINDS), Bethesda, MD, USA [2]. The results obtained revealed that anticonvulsant activity depended on the presence of chloro atom at position-3 of the phenyl ring as well as the kind of substituents at the 4-arylpiperazine fragment.

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[1] J. Obniska, A. Zagórska, *Il Farmaco***2003**, *58*, 1227-1234.
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Synthesis of novel, peptidic kinase inhibitors with cytotoxic activity

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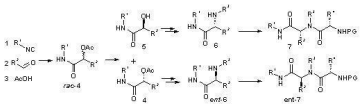
The promising use of small peptides as therapeutics suffers seriously from the problems with farmacokinetics of these compounds. They include: proteolytic instability and high polarity, which prevents small peptides from crossing cell membranes. The synthesis of peptidomimetics aims at the solution of these problems. The changes, which are usually introduced into the structure of the peptide are: *N*-alkylation of peptide bond [1], introduction of non-coded amino acids [2] and introduction of special functional groups at the terminae of the peptide [3].

A novel method for the preparation of peptidomimetics **7** has been recently developed in our laboratory (**Scheme 1**) [4]. It uses Passerini multicomponent reaction for the preparation of racemic scaffold **rac-4** which is then enantioselectivelly hydrolyzed by hydrolytic enzymes to enantiomerically enriched alcohols **5.** These compounds are functionalised towards amines **6**, which are used as substrates in the synthesis of peptidomimetics **7**.



This methodology was applied for the synthesis of novel, peptidic kinase inhibitors with cytotoxic activity towards tumor cells. Studies on the influence of main structural features of studied compounds on biological activity will be presented. The efforts to determine which enantiomer is responsible for the activity will also be presented.

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