Abstract

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Department of: Inorganic and Organic chemistry

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Title of Thesis: Design and synthesis of potential M_1 muscarinic acetylcholine receptor dualsteric modulator

Dualsteric ligands can modulate activity of receptors connected with G-proteins, also known as G-protein coupled receptor. These ligands are interesting for their use as pharmacological tools to clarify activity-induced conformational transitions. Moreover, dualsteric ligands can serve like a concept for design of new drugs. It was already prove that dualsteric compounds containing orthosteric ligand, which can act as agonist or antagonist, and allosteric part, which act as address determining target receptor via own selectivity, have affected affinity to receptor. Further, dualsteric binding can serve to introduce receptor subtype selectivity.

Muscarinic acetylcholine receptors are related to G-proteins. Until now five subtypes of these receptors (usually marked as $M_1 – M_5$) are known. Activation of single muscarinic acetylcholine receptors subtypes induce different replies. Muscarinic acetylcholine receptors are widely represent in entire organism and are important targets for some drugs. Unfortunately due to similar structure of binding sites it is hard to achieve functional selectivity, which causes different side effects. So far selective agonists of M_2 muscarinic acetylcholine receptor – iper-6-phtp and iper-6-naph - were prepared.

In my diploma thesis I dealt with the preparation of compounds selective to M_1 receptor and which affects this receptor as agonist. As suitable structures for this compound were chosen fluorinated derivate of benzyl quinolone carboxylic acid and derivate of oxotremorine linked with appropriate spacer (Fig. 1).

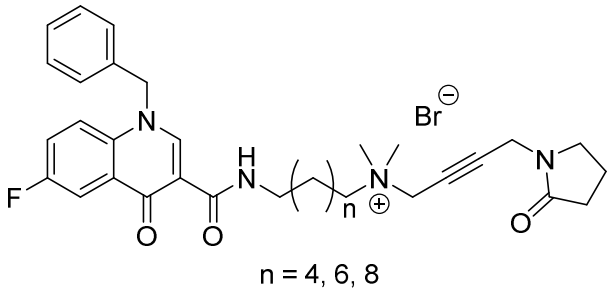

Fig. 1: Structure of potential M_1 selective dualsteric modulators.

There are assumptions that selective agonists of M_1 muscarinic acetylcholine receptor could be used in therapy of schizophrenia and impaired cognitive functions such as in Alzheimer's disease, where these compounds can improve symptoms of these diseases. Moreover there are assumptions that these agonists can positively affect pathophysiological processes related with Alzheimer's disease.