NEW DEVELOPMENT IN ALFA-1 ADRENERGIC RECEPTORS ANTAGONISTS

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α_1-Adrenoceptors constitute a heterogeneous family of receptors belonging to the superfamily of G-protein coupled receptors. They own therapeutic interest because of their important role in control of blood pressure, contraction and growth of smooth and cardiac muscle.

α_1-Adrenoceptors antagonists belong to a various chemical groups thus, quinazolines, phenylalkylamines, piperidines, dihydropirydines, and arylpiperazines. Currently, the arylpiperazines represent one of the most studied class of their antagonists. The typical α_1-antagonist contains arylpiperazine moiety connects with one or two additional fragment of molecule. It was found that the protonatable nitrogen atom of piperazine ring play a crucial role in interaction with the receptor site. Moreover, an aryl moiety (preferentially substituted at the *ortho*- position with halogen or alkoxy group) connected to the second nitrogen atom of piperazine is the second structural feature which is needed for interacting with receptor. Finally, the basic nitrogen atom is bound to the spacer which is usually represented by polymetylene chains (substituted or not) with different number of methylene units. It is also important to note that the arylpiperazine and the terminal groups should be located at the proper distance to interact with the receptor counterparts.

In the course of our studies on α_1-adrenoceptor antagonists, we designed and synthesized new arylpiperazine derivatives found to have affinity towards α_1-adrenoceptors. We have chosen compounds whose common structural features are a substituted phenylpiperazine, the second terminal group is represented by pyrrolidin-2-one bounds to the second piperazine nitrogen atom with substituted or not substituted three methylene units chain. The compounds obtained displayed affinity to α_1- and α_2-adrenoreceptors, and possessed antiarrhythmic and hypotensive activity. Physicochemical properties such as lipophilicity determined using immobilized artificial membrane stationary phase, as well as calculated log D and pKa values have been evaluated for these new compounds. Preliminary molecular modeling study of new arylpiperazinepropylpyrrolidin-2-one derivatives enable to verify structural requirements of defined pharmacophore model of α_1-adrenceptor antagonists.