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An Influence of Aryloxy-/Arylthio-ethyl Fragment on 5-HT$_{1A}$/5-HT$_7$ Receptor Selectivity in a Group of Quinolinesulfonamide Derivatives of Aryloxyethyl- and Arylthioethyl- Piperidines.

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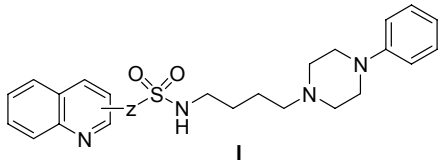
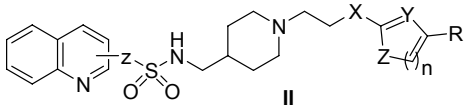
Employing a parallel solid-phase synthesis integrated with virtual combinatorial library design, and followed by multistep virtual screening procedure, allowed us to replace arylpiperazine moieties of LCAP with their flexible biomimetics [1]. In this series of compounds, arylpiperazine moiety was changed into a flexible aryloxy-/arylthio-ethyl fragment, while in the part corresponding to the alkylene spacer of LCAP, different, partially rigidified amines – 3-aminopyrrolidine, 4-aminopiperidine, 4-aminomethylpiperidine were introduced. It was further presented, that the affinity of compounds for the tested monoamine receptors (5-HT$_{1A}$, 5-HT$_6$, 5-HT$_7$, D$_2$) depended upon a kind of a substituent in the aryloxy-/arylthio- ethyl fragments, a distance between the basic nitrogen atom and amide/sulfonamide moiety, and finally a kind of amide/sulfonamide fragment [1].



I



II

X = O, S; Y = CH, N; Z = CH, S;
z = 3, 6, 7, 8; n = 1, 2
Phenyl: Z=Y=CH; n=2

Now we report on the design, synthesis, and biological evaluation for 5-HT$_{1A}$, 5-HT$_6$, and 5-HT$_7$ receptors of a new series of quinolinesulfonamide derivatives of aryl(heteroaryl)oxy-/heteroarylthio-ethyl 4-aminomethylpiperidines. The structural modifications comprised introduction of different quinoline sulfamoyl fragments, to further extend exploration in a group of azinesulfonamides (**I**), variation of different substituents in the phenyl ring of aryloxy-/arylthio- ethyl fragment, as well as a replacement of the central phenyl ring of the aryloxy-/arylthioethyl fragment with five-membered heteroaromatic system. We chose 4-aminomethylpiperidine central core to maintain a distance between tertiary nitrogen atom and sulfonamide bond, corresponding to the four-methylene linker present in the previously reported azinesulfonamide derivatives of LCAP [2]. In particular, we determined an influence of aryl(heteroaryl)oxy-/heteroarylthio- fragment on 5-HT$_{1A}$ and 5-HT$_7$ receptor binding profile.

[1] Zajdel P., et al. : *Eur. Med. Chem*. 2012 (*accepted*)
[2] Zajdel P., et al. : *Bioorg. Med. Chem*. **20** (2012), 1545–1556.

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