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The Multiobjective Based Design, Synthesis and Evaluation of the Arylsulfonamide/amide Derivatives of Arylxyethyl- and Arylthioethyl Piperidines and Pyrrolidines as a Novel Class of Potent 5-HT$_7$ Receptor Antagonists.

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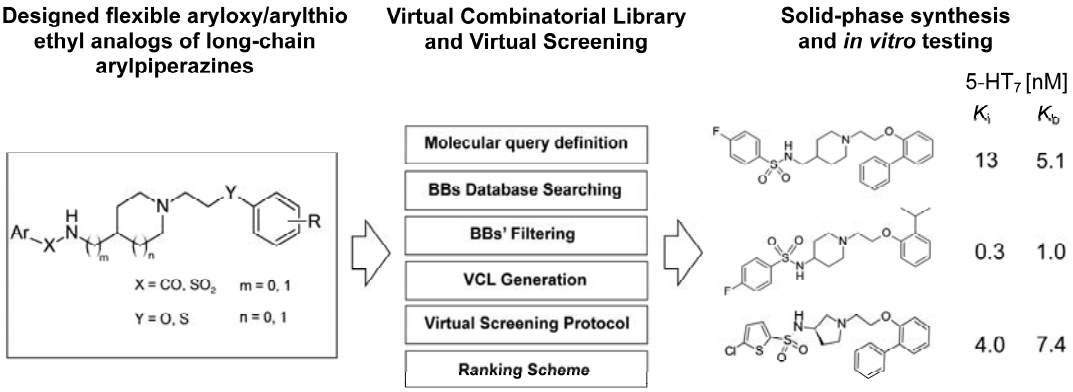
A computational approach involving a combinatorial library design and a multistep virtual screening [1], followed by post-docking filtering and building block ranking within compounds satisfying the desired 5-HT$_7$R binding pattern allowed us to identify critical molecular substructures and provided rationale data for designing 72-member library of the arylamide and arylsulfonamide derivatives of aryloxyethyl- and arylthioethyl- piperidines and pyrrolidines [2]. All compounds were synthesized according to an elaborated parallel solid-phase method and were biologically evaluated for their affinity for 5-HT$_7$. Additionally, the targeted library members were tested for 5-HT$_{1A}$, 5-HT$_6$, and D$_2$ receptors.



Selected compounds of particular interest were examined for their intrinsic activity at 5-HT$_7$R in vitro employing a cAMP assay. The study allowed us to identify compound **68** (4-fluoro-*N*-(1-{2-[(propan-2-yl)phenoxy]ethyl}piperidin-4-yl) benzenesulfonamide) as a potent 5-HT$_7$R ligand (K_i = 0.3 nM) with strong antagonistic properties (K_b = 1 nM) and a 1450-fold selectivity over 5-HT$_{1A}$Rs.

[1] Kurczab R., *et al.*: *Bioorg. Med. Chem. Lett.* **20** (***2010***), 2465–2468.
[2] Zajdel P., *et al.*: *Eur. J. Med. Chem.* **2012** (*accepted*).

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