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Systematic study reveals new potent and selective 5-HT6R ligands based on indole scaffold

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Herein we summarize the development of new series of 5-HT_6R ligands. Based on pharmacological profile of a published compound [2-(4-iodo-2,5-dimethoxyphenyl)ethyl][(2-methoxyphenyl)methyl] amine[1,2] (Cimbi-5), it has been assumed that structural modifications could possibly retain or modify its 5-HT_{2A}R and 5-HT_6R activity while keeping high selectivity over related targets intact (K_i = 0.044 nM at 5-HT_{2A}R, K_i = 73 nM at 5-HT_6R; $K_i \geq$ 500 nM was reported for receptors: 5-HT_{1A}, D_3, H_2, 5-HT_{1D}, α_{1A} adrenergic, δ opioid, 5-HT_{5A}, 5-HT_{1B}, D_2, 5-HT_7, D_1, 5-HT_3, 5-HT_{1E}, D_5, muscarinic M_1-M_5, H_3, and transporters: DAT, SERT[3,4]). Incorporation of 3-methylindole in place of benzyl group was considered. Three pilot compounds AH-120, AH-122 and AH-125 were synthesized and their affinities towards 5-HT_{1A}, 5-HT_{2A}, 5-HT_6, 5-HT_7 and D_2 receptors were determined in radioligand assays. While the 5-HT_{2A}R activities were found at least four orders of magnitude lower in comparison to the parent compound, the 5-HT_6R binding affinities were favourable (39 nM $\leq K_i \leq$ 87 nM). New ligands (AH-184, AH-185 and 186) were subsequently synthesized to check the pharmacological profile of raw core substructure of the pilot series. It became clear that the substitution patterns in AH-120, AH-122 and AH-125 do not contribute significantly to their 5-HT_6R activity. In the next step we prepared database of available aromatic aldehydes and arylethylamines; the C-N bond between these reagents can be readily formed via reductive amination to yield more derivatives of the investigated group of ligands. All the 3364 structures of virtual library were docked to 5-HT_{2A}, 5-HT_{2C} and 5-HT_6 receptor homology models using Glide software. Virtual docking will be used to search for additional ligand-aminoacid interactions that can arise after incorporation of specific functional groups. Compounds from the sets are to be synthesized in our search of potent and selective 5-HT_6 receptor ligands; it is likely that further improvements in binding affinity will be reached as soon as appropriate substitution patterns in both aromatic systems are found.

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