Synthesis, docking, 3-D-qsar, and biological assays of novel indole derivatives targeting serotonin transporter, dopamine D2 receptor, and mao-a enzyme: In the pursuit for potential multitarget directed ligands

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Abstract
A series of 27 compounds of general structure 2,3-dihydro-benzo[1,4]oxazin-4-yl)-2-{4-[3-(1H-3indolyl)-propyl]-1-piperazinyl}-ethanamides, Series I: 7(a-o) and (2-{4-[3-(1H-3-indolyl) -propyl]-1-piperazinyl}-acetylamine)-N-(2-morfolin-4-yl-ethyl)-fluorinated benzamides Series II: 13(a-l) were synthesized and evaluated as novel multitarget ligands towards dopamine D_2 receptor, serotonin transporter (SERT), and monoamine oxidase-A (MAO-A) directed to the management of major depressive disorder (MDD). All the assayed compounds showed affinity for SERT in the nanomolar range, with five of them displaying Ki values from 5 to 10 nM. Compounds 7k, Ki = 5.63 ± 0.82 nM, and 13c, Ki = 6.85 ± 0.19 nM, showed the highest potencies. The affinities for D_2 ranged from micro to nanomolar, while MAO-A inhibition was more discrete. Nevertheless, compounds 7m and 7n showed affinities for the D_2 receptor in the nanomolar range (7n: Ki = 307 ± 6 nM and 7m: Ki = 593 ± 62 nM). Compound 7n was the only derivative displaying comparable affinities for SERT and D_2 receptor (D_2/SERT ratio = 3.6) and could be considered as a multitarget lead for further optimization. In addition, docking studies aimed to rationalize the molecular interactions and binding modes of the designed compounds in the most relevant protein targets were carried out. Furthermore, in order to obtain information on the structure-activity relationship of the synthesized series, a 3-D-QSAR CoMFA and CoMSIA study was conducted and validated internally and externally (q^2 = 0.625, 0.523 for CoMFA and CoMSIA and r^2_{ncv} = 0.967, 0.959 for CoMFA and CoMSIA, respectively).

Author keywords
3-indolylpropylpiperazines
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