Synthesis of novel nicotinic ligands with multimodal action: Targeting Acetylcholine \(\beta_4\beta_2\), Dopamine and Serotonin Transporters

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Nicotinic acetylcholine receptors (nAChRs), serotonin transporters (SERT) and dopamine transporters (DAT) represent targets for the development of novel nicotinic derivatives acting as multiligands associated with different health conditions, such as depressive, anxiety and addiction disorders. In the present work, a series of functionalized esters structurally related to acetylcholine and nicotine were synthesized and pharmacologically assayed with respect to these targets. The synthesized compounds were studied in radioligand binding assays at \(\beta_4\beta_2\) nAChR, h-SERT and h-DAT. SERT experiments showed not radioligand [3H]-paroxetine displacement, but rather an increase in the radioligand binding percentage at the central binding site was observed. Compound 20 showed Ki values of 1.008 ± 0.230 µM for h-DAT and 0.031 ± 0.006 µM for \(\beta_4\beta_2\) nAChR, and [3H]-paroxetine binding of 191.50% in h-SERT displacement studies, being the only compound displaying triple affinity. Compound 21 displayed Ki values of 0.113 ± 0.037 µM for \(\beta_4\beta_2\) nAChR and 0.075 ± 0.009 µM for h-DAT acting as a dual ligand. Molecular docking studies on homology models
of ?4?2 nAChR, h-DAT and h-SERT suggested potential interactions among the compounds and agonist binding site at the ?4/?2 subunit interfaces of ?4?2 nAChR, central binding site of h-DAT and allosteric modulator effect in h-SERT. © 2019 by the authors.
HEK293 cell line
human
molecular docking
radioassay
structure activity relation
synthesis
Acetylcholine
Allosteric Regulation
Binding Sites
Dopamine
Dopamine Agonists
Dopamine Plasma Membrane Transport Proteins
Esters
HEK293 Cells
Humans
Ligands
Molecular Docking Simulation
Nicotine
Nicotinic Agonists
Pyrrolidines
Radioligand Assay
Receptors, Nicotinic
Serotonin Plasma Membrane Transport Proteins
Structure-Activity Relationship