Synthesis of novel nicotinic ligands with multimodal action: Targeting Acetylcholine ?4?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 ?4?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 ?4?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 ?4?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.

Affinity

Allosteric modulators

Allosteric modulators

DAT

NAChR

SERT

?4?2

acetylcholine

dopamine

dopamine receptor stimulating agent

dopamine transporter

ester

ligand

nicotine

nicotinic agent

nicotinic receptor

nicotinic receptor alpha4beta2

pyrrolidine

pyrrolidine derivative

serotonin transporter

allosterism

binding site

chemistry

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