Minimal structural changes determine full and partial nicotinic receptor agonist activity for nicotine analogues

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Neuronal ?4?2 nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels (LGIC) that have been implicated in nicotine addiction, reward, cognition, pain disorders, anxiety, and depression. Nicotine has been widely used as a template for the synthesis of ligands that prefer ?4?2 nAChRs subtypes. The most important therapeutic use for ?4?2 nAChRs is as replacement therapy for smoking cessation and withdrawal and the most successful therapeutic ligands are partial agonists. In this case, we use the N-methylpyrrolidine moiety of nicotine to design and synthesize new ?4?2 nicotinic derivatives, coupling the pyrrolidine moiety to an aromatic group by introducing an ether-bonded functionality. Meta-substituted phenolic derivatives were used for these goals. Radioligand binding assays were performed on clonal cell lines of h?4?2 nAChR and two electrode voltage-clamp experiments were used for functional assays. Molecular docking was performed in the open state of the nAChR in order to rationalize the agonist activity shown by our compounds.

Docking

Partial agonist

Pyrrolidine ethers

?4?2 nAChR

nicotine

nicotinic agent

nicotinic receptor

protein binding

binding competition

chemical structure

chemistry

conformation

dose response

human

kinetics

molecular docking

molecular dynamics

structure activity relation

Binding, Competitive

Dose-Response Relationship, Drug

Humans

Kinetics

Molecular Conformation

Molecular Docking Simulation

Molecular Dynamics Simulation

Molecular Structure

Nicotine

Nicotinic Agonists

Protein Binding

Receptors, Nicotinic

Structure-Activity Relationship