BIOISOSTERIC REPLACEMENT IN THE DESIGN AND SYNTHESIS OF LIGANDS FOR NICOTINIC ACETYLCHOLINE RECEPTORS

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Abstract. A series of others containing pyrrolidine and/or pyridine bioisosteres was synthesized and evaluated as nicotinic ligands. The dimethylaminoethoxy pyridines 6 and 7 inhibited the specific binding of (-)[3H]nicotine with Ki values of 300 nM and 450 nM, respectively. Compounds 8 and 9 were found to have Ki values of 3390 nM and 360 nM. These results suggest that dialkylamino and appropriately substituted benzene rings (NO2, 8; OH, 9) are bioisosteric replacements for pyrrolidine and pyridine, respectively.

The endogenous neurotransmitter acetylcholine (ACh) and the alkaloid nicotine bind nonselectively to nicotinic acetylcholine receptor (nAChR) subtypes and elicit a wide range of pharmacological actions. Evidence suggests that nAChR subtypes may serve as novel drug targets for treatment of CNS disorders including Alzheimer's Disease (AD) and Parkinson's Disease (PD). Ligands capable of binding to nAChRs in the CNS could serve as important pharmacological tools and might lead to the development of therapeutic agents.

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Pharmacophoric models are useful in the development of new ligands for nAChRs. Beers and Reich reported that nicotinic ligands should possess a hydrogen-bond acceptor (HBA) group (the lone pair of electrons on the pyridine) and a cationic center (the protonated nitrogen of the pyrrolidine ring). The cationic center is positioned 5.9 Å from the center of the van der Waals surface of the HBA. Later Sheridan et al., used a distance geometry approach to propose a three dimensional model defining the key molecular dimensions of nicotinic ligands. The distance between key functional groups for nicotine ligands in that model was postulated to be 4.8 Å.

Recent data suggest that nicotinic receptors are more heterogeneous than earlier appreciated and that interatomic distances for high affinity nicotinic ligands (e.g., epibatidine, 5.5 Å) exceed those proposed in these early models. A re-evaluation of the nicotine pharmacophore model has resulted in proposals by Glennon, Tønder, Katjusa Breje, Schmitt and others. A review of the recent structure-affinity literature suggests that ligands binding to the α4β2 and α7 receptor subtypes: should include a cationic center which is preferably nitrogenous; favor a HBA and/or π-electron rich moiety; should include a relative separation of cationic and HBA/π moieties of ca. 4-8 Å; exhibit the tendency toward stereospecific interaction; may prefer some degree of HBA-cation coplanarity. Most recently Sixma et al., proposed that the pyridine of nicotine binds to nACHR by hydrogen bonding through a water bridge and that ligands with longer nitrogen to nitrogen distances (7-8 Å) may displace the water molecule and interact directly with specific residues of the receptor. The pharmacophoric requirements for nicotinic receptor ligands continue to evolve as more SAR data become available.

The ether linkage has been shown to be an effective means of connecting the cationic center to the HBA moiety of nicotinic ligands. Our ongoing interest in the design of cholinergic ligands led to the identification of a series of quinuclidine-containing ethers (CLZ-12, CLZ-13; Figure 1) and esters as nACHR ligands. These studies suggest that nitrobenzene and phenol groups may serve as useful bioisosteres for the pyridine ring of nicotinic ligands. As a continuation of that work, a series of ether-linked compounds containing potential pyridine and pyrrolidine bioisosteres has been synthesized. Interatomic distances and the results of receptor binding assays for the compounds are reported.