Neonicotinic analogues: Selective antagonists for ?4?2 nicotinic acetylcholine receptors

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Nicotine is an agonist of nicotinic acetylcholine receptors (nAChRs) that has been extensively used as a template for the synthesis of ?4?2-preferring nAChRs. Here, we used the N-methyl-pyrrolidine moiety of nicotine to design and synthesise novel ?4?2-preferring neonicotinic ligands. We increased the distance between the basic nitrogen and aromatic group of nicotine by introducing an ester functionality that also mimics acetylcholine (Fig. 2). Additionally, we introduced a benzyloxy group linked to the benzoyl moiety. Although the neonicotinic compounds fully inhibited binding of both [?-125I]bungarotoxin to human ?7 nAChRs and [3H]cytisine to human ?4?2 nAChRs, they were markedly more potent at displacing radioligand binding to human ?4?2 nAChRs than to ?7 nAChRs. Functional assays showed that the neonicotinic compounds behave as antagonists at ?4?2 and ?4?2?5 nAChRs. Substitutions on the aromatic ring of the compounds produced compounds that displayed marked selectivity for ?4?2 or