Novel pharmacological tools which activate mAChRs: a question of "dualsterism"

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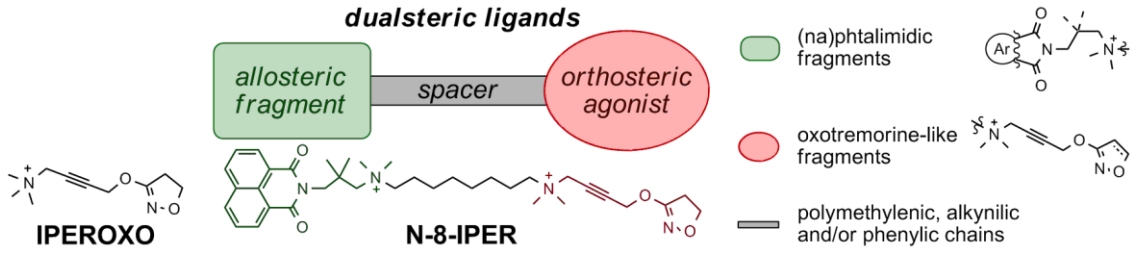
Muscarinic acetylcholine receptors (mAChRs) represent an excellent model system to study orthosteric and allosteric interactions. The high sequence homology shown by orthosteric sites of mAChRs has hampered the development of subtype selective agonists. On the other hand, allosteric recognition sites are less conserved among the various mAChR subtypes.

We synthesized a series of hybrid ligands designed to simultaneously interact with both orthosteric and allosteric sites ("dualsteric" compounds) by fusing orthosteric activators with M_2-selective allosteric fragments (W84 and Naphmethonium). In particular, among the oxotremorine-like orthosteric agents, iperoxo emerged as a potent agonist with supraphysiological efficacy but devoid of subtype selectivity.[1] To explore the whole chemical space of the binding region, we modified the structure of the three component parts (orthosteric and allosteric moieties and spacer) of dualsteric ligands.[2]

These ligands permitted to prove for the first time that GPCR's allosteric vestibule is able to control the extent of receptor movement to govern a hierarchical order of G-protein coupling.[3] In addition, they were found to dynamically switch between two distinct binding orientations, engendering both active and inactive populations of receptors bound by a given ligand.[4] More recently, some of these ligands (notably N-8-IPER) revealed interesting antinociceptive properties and good tolerability.[5] The synthetic approaches together with relevant results and implications of the biological investigation will be presented.



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