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Allosteric Modulation of Receptors: A Way to Enhance the Ligand Binding to Muscarinic Receptor

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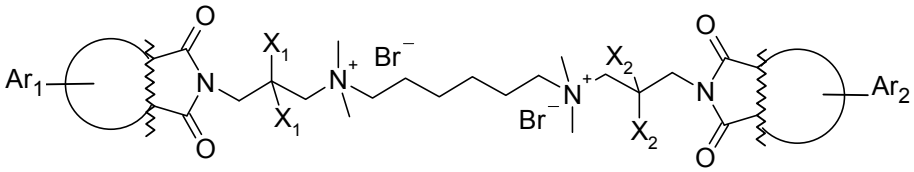
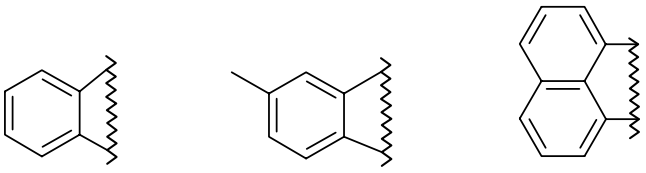
Allosteric modulators of receptor binding are found for a variety of receptors. In the case of the muscarinic receptor a huge selection of structural divergent modulators are described for the different receptor subtypes. Alkane-bisammonio-type compounds carrying lateral phthalimido substituents are known to have a high affinity for the common allosteric binding site of the acetylcholine M_2 receptor which is already occupied by the conventional antagonist N-methylscopolamine. The resulting allosteric inhibition of the dissociation of [^{3}H]N-methylscopolamine from the M_2 receptors in porcine cardiac homogenates served to indicate binding of the test compounds to the allosteric site. Along with this, the allosteric modulators can strongly influence the equilibrium binding: it can be reduced, left unaltered or elevated, encoded as negative, neutral and positive cooperativity, respectively. Interestingly, often symmetrical compounds were considered as allosteric modulators. In order to find out whether symmetry is a prerequisite for high allosteric potency, a series of symmetrical and non-symmetrical compounds was synthesized whose phthalimide residues were replaced with variously substituted imide moieties.

The compounds showing the highest allosteric potency, i. e. the 1,8-naphthalimido, the 5-methylphthalimido (see Fig.) and, for sake of comparison, the phthalimido substituted compounds were intensively studied with regard to their cooperativity. Methylation of lateral propyl chains induced a high positive cooperativity which is correlated with a high allosteric potency. Quantitative structure-activity relationships will be derived to explain the connection between the affinity to the free and liganded receptor, the cooperativity and the inhibition of the antagonist dissociation.





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