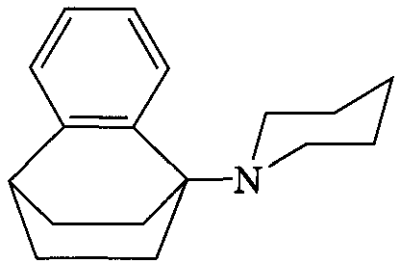
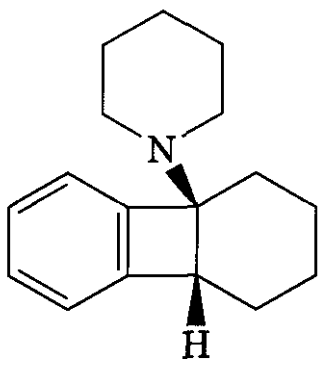


(33)



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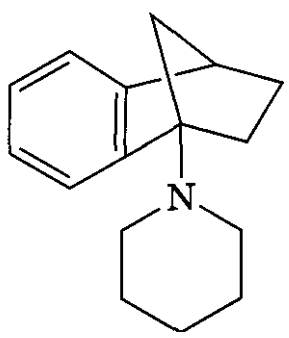

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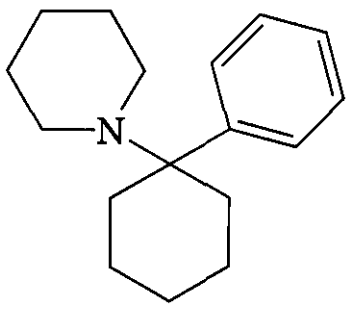
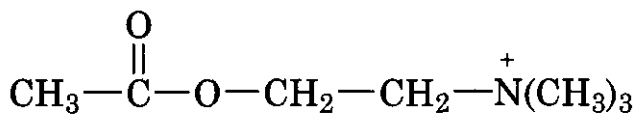


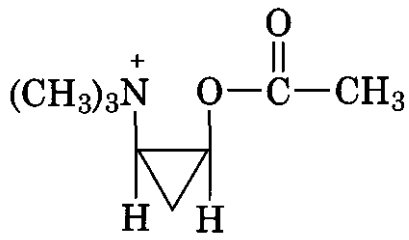
(36)

ture and an attached piperidine ring that is free to rotate. All three rigid analogs showed low to no affinity for the PCP receptor, but they had good affinity in a a-receptor-binding assay (25). These binding data were proposed to be useful in defining a model for the $\sigma$-receptor pharmacophore. This study also provided additional evidence that the a-receptor is independent of the PCP-binding site (cf. Ref. 26 and references therein).

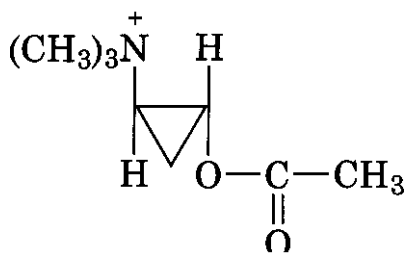
Incorporation of the choline portion of acetylcholine (37) into a cyclopropane ring system resulted in cis- and *trans*-1,2-disubstituted molecules, (38) and (39), in which the



(37)



(38)



(39)

acetylcholine molecule is locked into folded ("cisoid") and extended ("transoid") conformations.

The (1*S*),(2*S*)-(+)-*trans*-isomer (39) was somewhat more potent than acetylcholine itself in tissue and whole-animal assays for muscarinic agonism (27) and it was an excellent substrate for acetylcholinesterase. The (1*R*),(2*R*) enantiomer of (39) was exponentially less potent than its (1*S*),(2*S*) enantiomer in the assays cited, but it was a good substrate for acetylcholinesterase. The (2)-cis-isomer (38) was almost inert at nicotinic and muscarinic receptors and it was a poor substrate for acetylcholinesterase. These data were taken as evidence that the flexible acetylcholine molecule interacts with muscarinic receptors in an extended geometry of the chain of atoms (28). When this semirigid analog strategy was applied to a cyclobutane ring system (compound 40), there was a marked loss of pharmacologic effect (29). This result is enigmatic; differences in interatomic distances and bond angles in the pharmacophoric moiety as well