hypothesis of Alzheimer's Disease is linked to both β-amyloid and hyperphosphorylated tau protein. Formation of β-amyloid may impair the coupling of the muscarinic receptor with G-proteins. Stimulation of the M1 muscarinic receptor has been shown to increase formation of the neuroprotective αAPPs fragment, thereby preventing the formation of the Aβ peptide. Thus, M1 agonists may alter APP processing and enhance αAPPs secretion. *See* Fisher, *Jpn J Pharmacol*, 2000, 84:101-112.

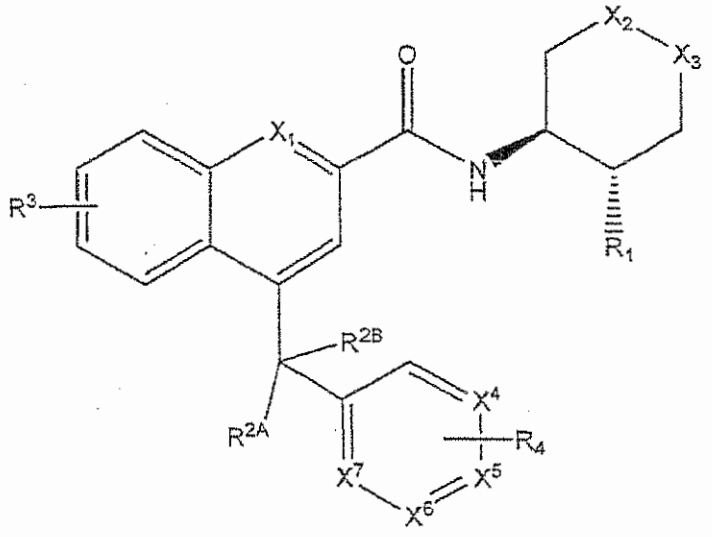
However, M1 ligands which have been developed and studied for Alzheimer's Disease have produced side effects common to other muscarinic receptor ligands, such as sweating, nausea and diarrhea. *See* Spalding et al, *Mol Pharmacol*, 2002, 61:6, 1297-1302.

The muscarinic receptors are known to contain one or more allosteric sites, which may alter the affinity with which muscarinic ligands bind to the primary binding or orthosteric sites. *See, e.g.*, S. Lazareno et al, *Mol Pharmacol*, 2002, 62:6, 1491-1505; S. Lazareno et al, *Mol Pharmacol*, 2000, 58, 194-207.

Thus the compounds of the invention, which are muscarinic M1 receptor positive allosteric modulators, are believed to be useful in the treatment of Alzheimer's Disease and other diseases mediated by the muscarinic M1 receptor.

SUMMARY ~~OF THE INVENTION~~

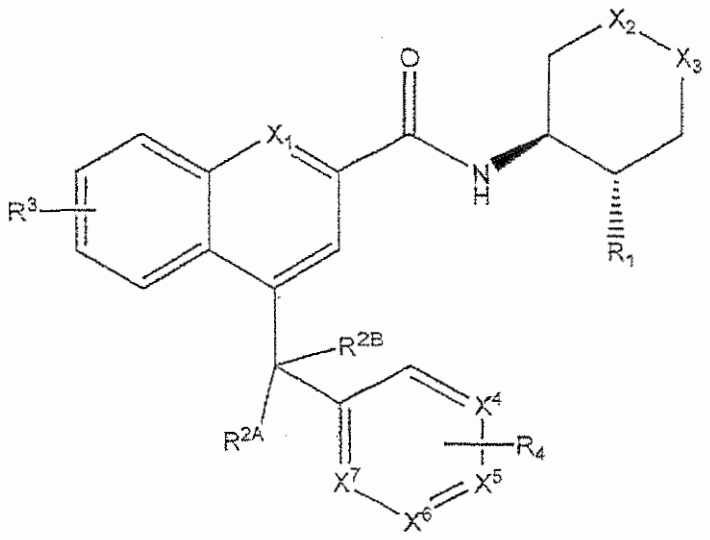
The present ~~invention~~disclosure is directed to quinoline amide compounds of generic formula (I)



(I)

or a pharmaceutically acceptable salt thereof, which is useful as an M1 receptor positive allosteric modulator.

In a first aspect, there is provided a compound of formula (I):



(I)

wherein

X^1 is selected from the group consisting of

(1) N, and

(2) N→O;

X^2-X^3 is selected from the group consisting of

(1) -CH_2-CH_2-,

(2) -O-CH_2-,

(3) -CH_2-O-, or

(4) -CH_2-;

X^4, X^5, X^6 and X^7 are each selected from the group consisting of

(1) N,

(2) N→O,

(3) CH,

(4) O

provided that one of X^4, X^5, X^6 and X^7 may be absent, thereby forming a five-membered ring;

R^1 is selected from the group consisting of

(1) hydrogen,

(2) halogen,

(3) –C_{1-6} alkyl,

(4) –C_{2-6} alkynyl,

(4) phenyl,
(5) =O,
(6) $=CH_2$,
(7) hydroxyl,
wherein the R^1 alkyl, alkynyl or phenyl group is optionally substituted with one or more
(a) hydroxyl, or
(b) halogen;

R^{2A} and R^{2B} are independently selected from the group consisting of
(1) hydrogen,
(2) hydroxyl, and
(3) halogen,
or R^{2A} and R^{2B} together form =O;

R^3 is optionally present at one or more of the ring carbon atoms, and is independently selected from the group consisting of
(1) halogen,
(2) –O-C_{1-6} alkyl,
(3) –S-C_{1-6} alkyl, or
(4) a heteroaryl group, which is an aromatic cyclic group, having from five to twelve ring atoms, said ring atoms selected from C, O, N, N→O or S, at least one of which is O, N, N→O or S, wherein the heteroaryl is optionally substituted with C_{1-6} alkyl;

R^4 is optionally present at one or more of the ring atoms, and is selected from the group consisting of
(1)hydroxyl,
(2) halogen,
(3) –C_{1-6} alkyl,
(4) –O-C_{1-6} alkyl,
(5) –S-C_{1-6} alkyl,
(6) –C_{3-8} cycloalkyl,
(7) –C_{6-10} aryl,
(8) –CN,
(9) a heteroaryl group, which is an aromatic cyclic group, having from five to twelve ring atoms, said ring atoms selected from C, O, N, N→O or S, at least one of which is O, N, N→O or S,
(10) -NR^AR^B,
wherein R^A and R^B are selected from the group consisting of
(a) hydrogen, or
(b) –C_{1-6} alkyl,

or R^A and R^B are linked together with the nitrogen to which they are attached to form a 4-6 membered carbocyclic ring, wherein one or two of the ring carbon atoms is optionally replaced by a nitrogen, oxygen or sulfur, and the ring is optionally substituted with one or more

(a) halogen,

(b) hydroxyl,

(c) C_{1-6} alkyl,

(d) $-O-C_{1-6}$ alkyl,

(e) $-C(=O)-(O)_n-C_{1-6}$ alkyl;

wherein n is 0-1; and the alkyl, cycloalkyl, aryl or heteroaryl R^4 group is optionally substituted with one or more

(a) halogen,

(b) hydroxy,

(c) $-O-C_{1-6}$ alkyl,

(d) $-C_{1-6}$ alkyl,

(e) $-S-C_{1-6}$ alkyl, or

(f) a heteroaryl group, which is an aromatic cyclic group, having from five to twelve ring atoms, said ring atoms selected from C, O, N, N→O or S, at least one of which is O, N, N→O or S,

wherein the alkyl, aryl or heteroaryl moiety is optionally substituted with one or more

(i) halogen,

(ii) hydroxy,

(iii) $-O-C_{1-6}$ alkyl, or

(iv) $-C_{1-6}$ alkyl;

or two R^4 groups are linked together to form a three or four atom fused ring heteroaryl group, said ring atoms selected from C, O, N, N→O or S, at least one of which is O, N, N→O or S,

or a pharmaceutically acceptable salt thereof.

The ~~invention~~disclosure is further directed to methods of treating a patient (preferably a human) for diseases or disorders in which the M1 receptor is involved, such as Alzheimer's disease,

cognitive impairment, schizophrenia, pain disorders and sleep disorders, by administering to the patient a therapeutically effective amount of a compound of general formula (I), or a pharmaceutically acceptable salt thereof. The ~~invention~~disclosure is also directed to pharmaceutical compositions which include an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, and the use of the compounds and pharmaceutical compositions of the ~~invention~~disclosure in the treatment of such diseases.

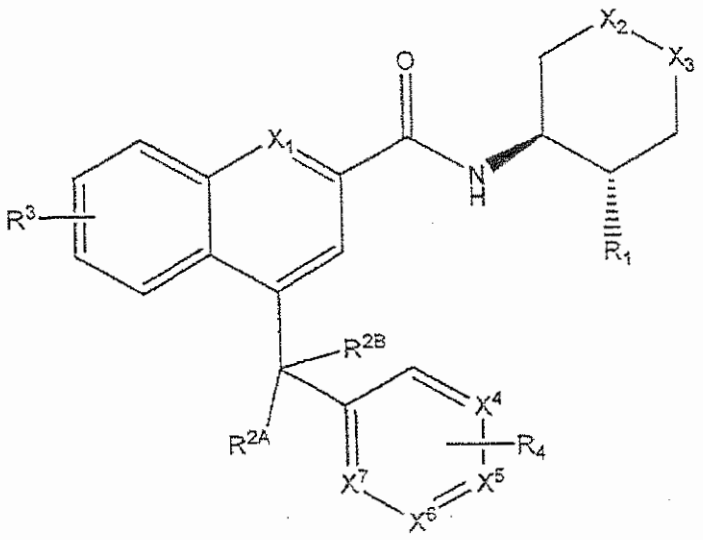
In a second aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined above or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a third aspect, there is provided a pharmaceutical composition for the treatment of a disease or disorder mediated by the muscarinic M1 receptor, wherein said disease or disorder is selected from the group consisting of Alzheimer's disease, schizophrenia, pain or sleep disorders, comprising a therapeutically effective amount of a compound as defined above or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

In a fourth aspect, there is provided the use of a compound as defined above or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, for the manufacture of a medicament for the treatment of a disease or disorder mediated by the muscarinic M1 receptor, wherein said disease or disorder is selected from the group consisting of Alzheimer's disease, schizophrenia, pain or sleep disorders.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the invention is directed to quinoline amide compounds of general formula (I)



(I)

and pharmaceutically acceptable salts thereof, wherein

X^1 is selected from the group consisting of

(1) N, and

(2) N→O;

X^2-X^3 is selected from the group consisting of

(1) -CH_2-CH_2-,

(2) -O-CH_2-,

(3) -CH_2-O-, or

(4) -CH_2-;