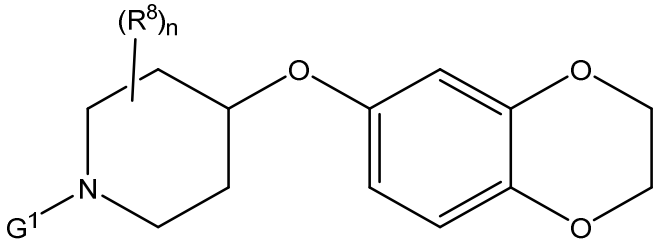
approach to circumvent problems associated with targeting the highly conserved orthosteric ACh binding site is developing compounds that act at allosteric sites on mAChRs that are removed from the orthosteric site and are less highly conserved. In the case of mAChRs, a major goal has been to develop allosteric ligands that selectively increase activity of mAChR M_4 or other mAChR subtypes. Allosteric activators can include allosteric agonists, that act at a site removed from the orthosteric site to directly activate the receptor in the absence of ACh as well as positive allosteric modulators (PAMs), which do not activate the receptor directly but potentiate activation of the receptor by the endogenous orthosteric agonist ACh. Also, it is possible for a single molecule to have both allosteric potentiator and allosteric agonist activity.

[0008] More recently, muscarinic agonists including xanomeline have been shown to be active in animal models with similar profiles to known antipsychotic drugs, but without causing catalepsy (Bymaster *et al.*, *Eur. J. Pharmacol.* 1998, 356, 109, Bymaster *et al.*, *Life Sci.* 1999, 64, 527; Shannon *et al.*, *J. Pharmacol. Exp. Ther.* 1999, 290, 901; Shannon *et al.*, *Schizophrenia Res.* 2000, 42, 249). Further, xanomeline was shown to reduce psychotic behavioral symptoms such as delusions, suspiciousness, vocal outbursts, and hallucinations in Alzheimer's disease patients (Bodick *et al.*, *Arch. Neurol.* 1997, 54, 465), however treatment induced side effects, e.g., gastrointestinal effects, have severely limited the clinical utility of this compound.

[0009] Despite advances in muscarinic acetylcholine receptor research, there is still a scarcity of compounds that are potent, efficacious, and selective activators of the M_4 mAChR and also effective in the treatment of neurological and psychiatric disorders associated with cholinergic activity and diseases in which the muscarinic M_4 receptor is involved.

SUMMARY

[0010] In one example, disclosed are compounds of formula (I), or a pharmaceutically acceptable salt thereof

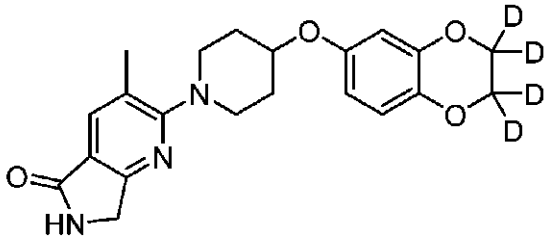


(I)

wherein:

R^7 is C_{1-4}alkyl, hydrogen, halogen, cyano, C_{1-4}fluoroalkyl, C_{2-4}alkenyl, $–OR^{7a}$, $–C_{1-3}$alkylene–OR^{7a}, CO_2R^{7a}, COR^{7a}, or C_{3-6}cycloalkyl;
alternatively, R^6 and R^7, together with the atoms to which they are attached, form an aromatic or non-aromatic ring consisting of 5-7 carbon atoms;
R^{7a} is hydrogen, C_{1-4}alkyl, C_{1-4}fluoroalkyl, C_{3-4}cycloalkyl, or $–C_{1-3}$alkylene–C_{3-4}cycloalkyl;
R^8, at each occurrence, is independently halogen, C_{1-4}alkyl, C_{1-4}fluoroalkyl, or C_{3-4}cycloalkyl; and
n is 0, 1, 2, 3, or 4;
wherein at least one hydrogen in the compound is the isotope deuterium (^2H).

[0010a] In one aspect, the present disclosure refers to a compound



, or a pharmaceutically acceptable salt thereof.

[0011] In another example, the disclosure provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. In one aspect, the present disclosure refers to a pharmaceutical composition comprising the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0011a] In one aspect, the present disclosure refers to a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein, for use in therapy.

[0012] Another example provides a method of treating a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal, comprising administering to the mammal a therapeutically effective amount of the compound of formula (I), or pharmaceutically acceptable salt or composition thereof.

[0013] Another example provides a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof, for use in the treatment of a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal.

[0014] Another example provides use of a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof, for the preparation of a medicament for the treatment of a neurological and/or psychiatric disorder associated with muscarinic acetylcholine receptor dysfunction in a mammal. In one aspect, the present disclosure refers to use of a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition as disclosed herein, in the manufacture of a medicament for the treatment of a neurological and/or psychiatric disorder, wherein the disorder is selected from Alzheimer's disease, schizophrenia, a sleep disorder, a pain disorder, and a cognitive disorder.

[0015] In another example, the disclosure provides kits comprising a compound of formula (I), or a pharmaceutically acceptable salt or composition thereof, and instructions for use.

BRIEF DESCRIPTION OF THE DRAWING

[0016] The FIGURE shows the effects of Compound 3 in an amphetamine-induced hyperlocomotion assay.