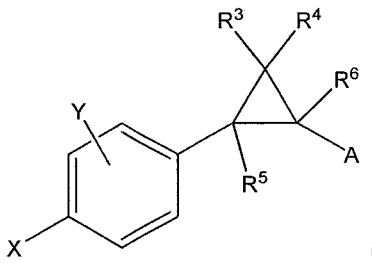
neurotransmission. There are two classs of α7 PAMs, type I and type II, which differ based on the functional properties of modulation. The type I PAMs (e.g. NS1738, see for example, Timmermann *et al. J. Pharmacol. Exp. Ther.* (2007) 323:294-307) predominantly affect the peak current with little or no effect on receptor desensitization, while the type II PAMs (e.g. PNU120596, see for example, Hurst *et al. J. Neurosci.* (2005) 25:4396-4405) markedly delay desensitization of the receptor. Additionally, α7 nAChR PAMs may have improved selectivity over related channel targets, presumably through binding to non-conserved regions of the receptor.

The present invention is directed to a new class of compounds that exhibit positive allosteric modulation of the α7 nAChR.

SUMMARY

The present disclosure relates to novel compounds of formula I and pharmaceutically acceptable salts thereof. These compounds may be useful, either as compounds or their pharmaceutically acceptable salts (when appropriate), in the modulation of the α7 nAChR, the prevention, treatment, or amelioration of disease, particularly disorders of the central nervous system such as cognitive impairments in Alzheimer's disease, Parkinson's disease, and schizophrenia and/or as pharmaceutical composition ingredients. As pharmaceutical composition ingredients, these compounds and their salts may be the primary active therapeutic agent, and, when appropriate, may be combined with other therapeutic agents including but not limited to acetylcholinesterase inhibitors, NMDA receptor antagonists, beta-secretase inhibitors, M4 mAChR agonists or PAMs, mGluR2 antagonists or NAMs or PAMs, 5-HT6 antagonists, histamine H3 receptor antagonists, PDE4 inhibitors, PDE9 inhibitors, HDAC6 inhibitors, antipsychotics, MAO-B inhibitors, and levodopa.

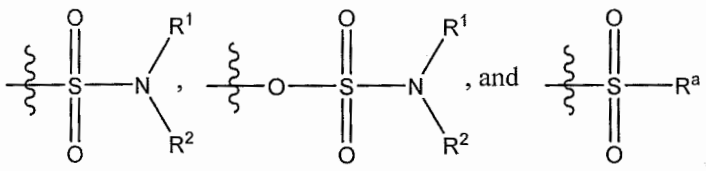
The present disclosure relates to a compound of formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

X is selected from



Y is selected from 1 to 4 substituents, each independently selected from H, (C_1-C_4)alkyl, halogen, and OH, wherein said alkyl is optionally substituted with one or more halogen or OH;

A is a 5-membered heteroaryl ring which is substituted with 1 to 3 R groups each independently selected from OH, oxo, NR^7R^8, CN, alkoxy, halogen, aminoalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein said alkoxy, aminoalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are optionally substituted with one or more substituents independently selected from F, Cl, Br, OH, oxo, CF_3, OCF_3, CN, (C_1-C_6)alkyl, O(C_1-C_4)alkyl, S(C_1-C_4)alkyl, C=O(C_1-C_4)alkyl, (C=O)NR^7R^8, (C=O)OR^7, (C_2-C_4)alkynyl, (C_3-C_6)cycloalkyl, O(C_3-C_6)cycloalkyl, C=O(C_3-C_6)cycloalkyl, aryl, heteroaryl and heterocyclyl, wherein said alkyl, aryl, heteroaryl and heterocyclyl are optionally independently substituted with one or more halogen, CF_3, OH and oxo;

R^1 is H or (C_1-C_4)alkyl;

R^2 is H or (C_1-C_4)alkyl;

R^3 is H, halogen or (C_1-C_4)alkyl, wherein said alkyl is optionally substituted with one or more halogen;

R^4 is H, halogen or (C_1-C_4)alkyl, wherein said alkyl is optionally substituted with one or more halogen;

or, R^3 and R^4 optionally can come to together to form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl ring wherein said ring may be optionally substituted with one or more substituents independently selected from OH, halogen, or (C_1-C_4)alkyl;

R^5 is H or (C_1-C_4)alkyl;

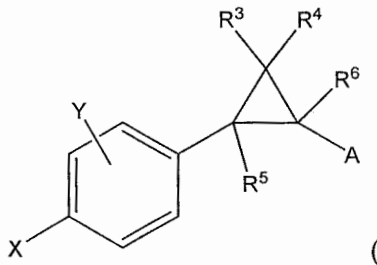
R^6 is H or (C_1-C_4)alkyl;

R^7 is H or (C_1-C_4)alkyl;

R^8 is H or (C_1-C_4)alkyl; and

R^a is H or (C_1-C_4)alkyl.

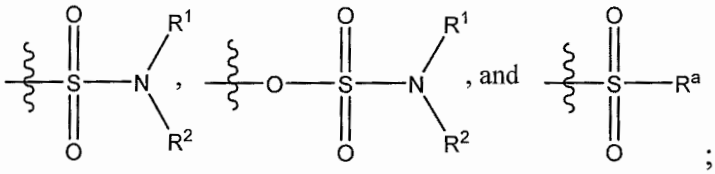
In one aspect, the present disclosure relates to a compound having the formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

X is selected from



;

Y is 4 substituents, each independently selected from H, $(C_1\text{-}C_4)$alkyl, halogen, and OH, wherein said alkyl is optionally substituted with one or more halogen or OH;

A is a 5-membered heteroaryl ring which is substituted with 1 to 3 R groups each independently selected from OH, oxo, NR^7R^8, CN, alkoxy, halogen, aminoalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl, wherein said alkoxy, aminoalkyl, hydroxyalkyl, alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are optionally substituted with one or more substituents independently selected from F, Cl, Br, OH, oxo, CF_3, OCF_3, CN, $(C_1\text{-}C_6)$alkyl, $O(C_1\text{-}C_4)$alkyl, $S(C_1\text{-}C_4)$alkyl, $C{=}O(C_1\text{-}C_4)$alkyl, $(C{=}O)NR^7R^8$, $(C{=}O)OR^7$, $(C_2\text{-}C_4)$alkynyl, $(C_3\text{-}C_6)$cycloalkyl, $O(C_3\text{-}C_6)$cycloalkyl, $C{=}O(C_3\text{-}C_6)$cycloalkyl, aryl, heteroaryl and heterocyclyl, wherein said alkyl, aryl, heteroaryl and heterocyclyl are optionally independently substituted with one or more halogen, CF_3, OH and oxo;

R^1 is H or $(C_1\text{-}C_4)$alkyl;

R^2 is H or $(C_1\text{-}C_4)$alkyl;

R^3 is H, halogen or $(C_1\text{-}C_4)$alkyl, wherein said alkyl is optionally substituted with one or more halogen;

R^4 is H, halogen or $(C_1\text{-}C_4)$alkyl, wherein said alkyl is optionally substituted with one or more halogen;

or, R^3 and R^4 optionally can come to together to form a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl ring wherein said ring may be optionally substituted with one or more substituents independently selected from OH, halogen, or $(C_1\text{-}C_4)$alkyl;

R^5 is H or $(C_1\text{-}C_4)$alkyl;

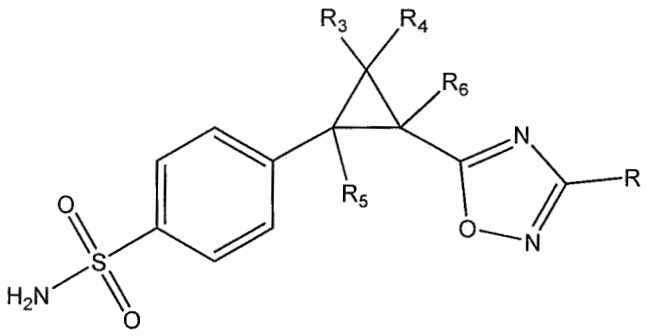
R^6 is H or $(C_1$-$C_4)$alkyl;

R^7 is H or $(C_1$-$C_4)$alkyl;

R^8 is H or $(C_1$-$C_4)$alkyl; and

R^a is H or $(C_1$-$C_4)$alkyl.

In another aspect, the present disclosure relates to a compound having the formula:



(Ib),

or a pharmaceutically acceptable salt thereof, wherein;

R is selected from $(C_1$-$C_4)$alkyl, $(C_3$-$C_6)$cycloalkyl, phenyl, indanyl, piperidinyl, pyridinyl, furanyl, oxazolyl, benzoxazinyl, cyclopentalpyrrolyl, thienopyrrolyl, thiazolyl, imidazolyl, azetidinyl, pyrrolyl, pyrazinyl, quinolinyl and benzothiazolyl wherein each are optionally substituted with one or more substituents independently selected from F, Cl, Br, OH, oxo, CF_3, OCF_3, CN, $(C_1$-$C_4)$alkyl, $O(C_1$-$C_4)$alkyl, $S(C_1$-$C_4)$alkyl, $C{=}O(C_1$-$C_4)$alkyl, $(C_2$-$C_4)$alkynyl, $(C_3$-$C_6)$cycloalkyl, $O(C_3$-$C_6)$cycloalkyl, $C{=}O(C_3$-$C_6)$cycloalkyl, phenyl, O-phenyl, imidazolyl, pyrazinyl, furanyl, oxazolidinyl, pyrrolidinyl, and benzoxazolyl, wherein said alkyl, phenyl, oxazolidinyl, pyrrolidinyl, and benzoxazolyl are optionally independently substituted with one or more F, Cl, CF_3 and oxo;

R^3 and R^4 are independently H, F or methyl; and

R^5 and R^6 are independently H or methyl.

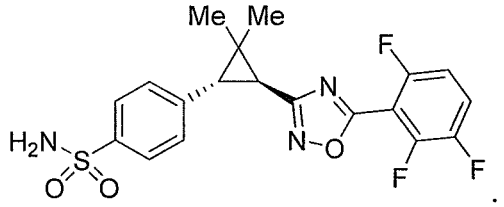
In another aspect, the present disclosure relates to a pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier and (ii) a compound as disclosed herein or a pharmaceutically acceptable salt thereof.

In another aspect, the present disclosure relates to a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

In another aspect, the present disclosure relates to a use of the compound as disclosed herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment of cognitive impairments associated with Alzheimer's disease, Parkinson's disease, and schizophrenia.

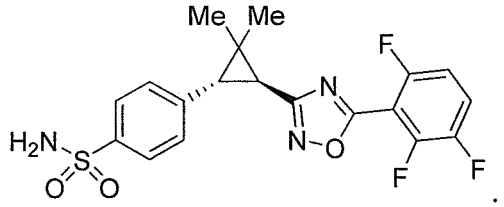
In another aspect, the present disclosure relates to a compound as disclosed herein, or a pharmaceutically acceptable salt thereof, for use in treating a patient with cognitive impairments associated with Alzheimer's disease, Parkinson's disease, and schizophrenia.

In another aspect, the present disclosure relates to a compound which is



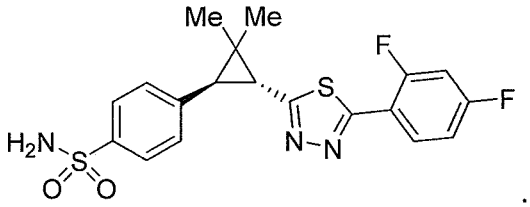
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In another aspect, the present disclosure relates to a pharmaceutically acceptable salt of a compound which is



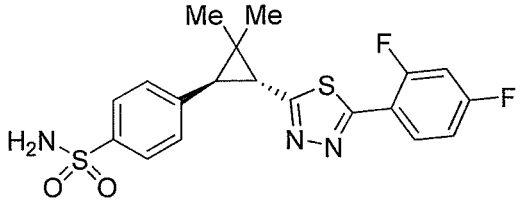
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In another aspect, the present disclosure relates to a compound which is



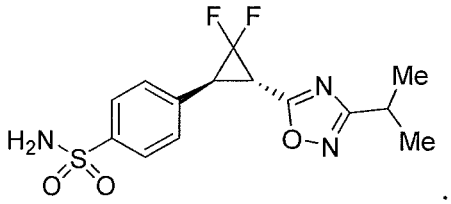
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In another aspect, the present disclosure relates to a pharmaceutically acceptable salt of a compound which is



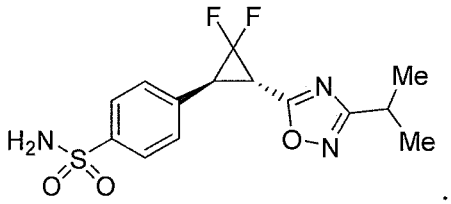
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In another aspect, the present disclosure relates to a compound which is



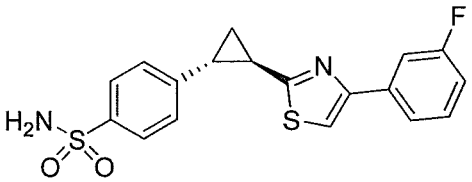
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In another aspect, the present disclosure relates to a pharmaceutically acceptable salt of a compound which is



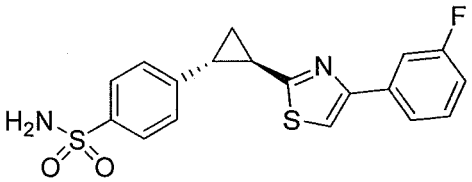
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In another aspect, the present disclosure relates to a compound which is



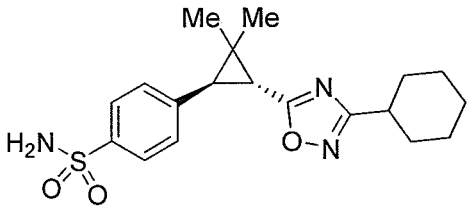
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In another aspect, the present disclosure relates to a pharmaceutically acceptable salt of a compound which is



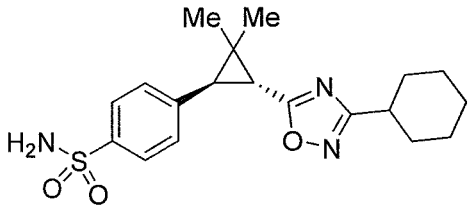
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In another aspect, the present disclosure relates to a compound which is



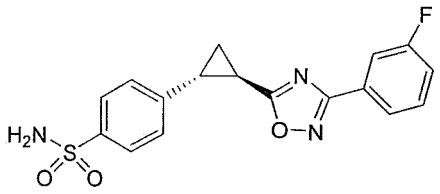
.

In another aspect, the present disclosure relates to a pharmaceutically acceptable salt of a compound which is

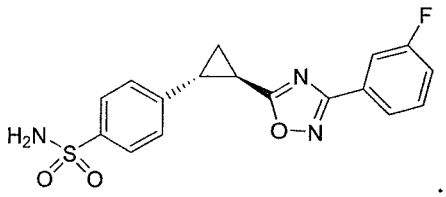


.

In another aspect, the present disclosure relates to a compound which is



In another aspect, the present disclosure relates to a pharmaceutically acceptable salt of a compound which is



In another aspect, the present disclosure relates to a pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier and (ii) the compound as disclosed herein.

In another aspect, the present disclosure relates to a pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier and (ii) the pharmaceutically acceptable salt as disclosed herein.

In another aspect, the present disclosure relates to use of a compound as disclosed herein in the manufacture of a medicament for the treatment of mild to moderate dementia of the Alzheimer's type.

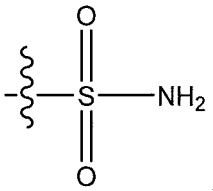
The present disclosure also includes pharmaceutical compositions containing a compound of the present disclosure and methods of preparing such pharmaceutical compositions. The present disclosure further includes methods of preventing, treating, or ameliorating the

cognitive impairments associated with Alzheimer's disease, Parkinson's disease, and schizophrenia.

Other embodiments, aspects and features of the present disclosure are either further described in or will be apparent from the ensuing description, examples and appended claims.

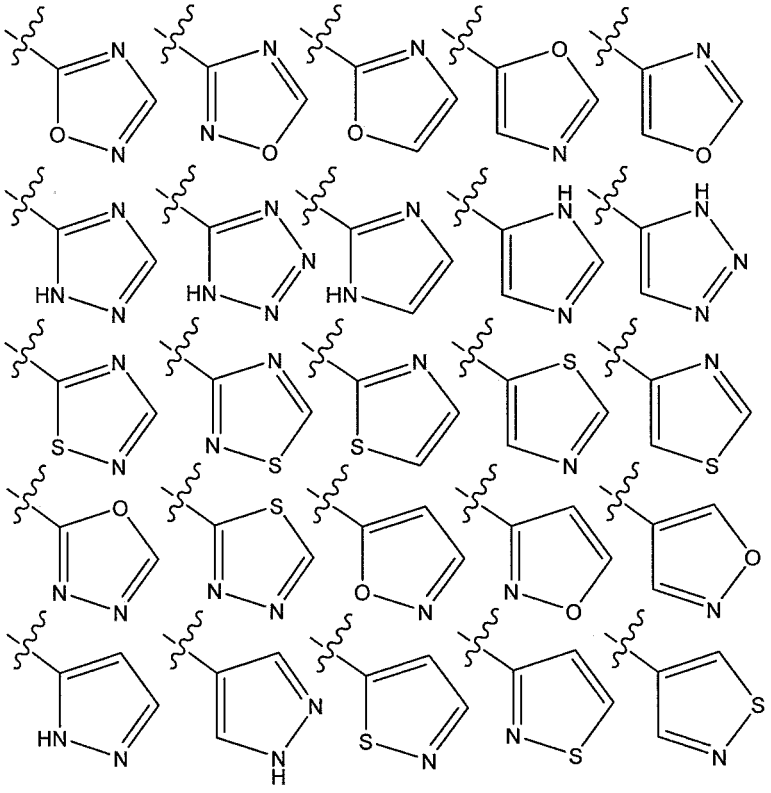
DETAILED DESCRIPTION OF THE INVENTION

The present invention includes compounds of formula I above, and pharmaceutically acceptable salts thereof. The compounds of formula I are positive allosteric modulators of α7 nAChR.

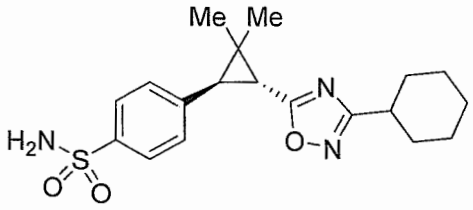
In a first embodiment of the invention, X is , and the other groups are as provided in the general formula above.

In a second embodiment of the invention, Y is H and the other groups are as provided in the general formula above, or as in the first embodiment.

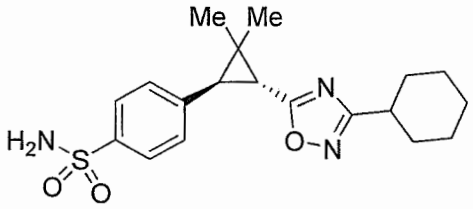
In a third embodiment of the invention, A is selected from



36. A compound which is



37. A pharmaceutically acceptable salt of a compound which is

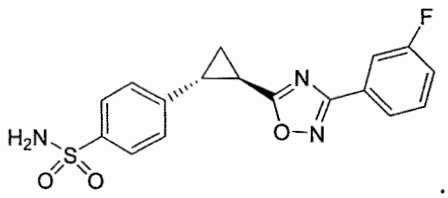


38. A pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier and (ii) the compound of claim 36.

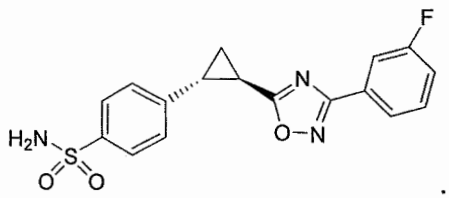
39. A pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier and (ii) the pharmaceutically acceptable salt of claim 37.

40. Use of a compound of claim 36 in the manufacture of a medicament for the treatment of mild to moderate dementia of the Alzheimer's type.

41. A compound which is



42. A pharmaceutically acceptable salt of a compound which is



43. A pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier and (ii) the compound of claim 41.

44. A pharmaceutical composition comprising (i) a pharmaceutically acceptable carrier and (ii) the pharmaceutically acceptable salt of claim 42.

45. Use of a compound of claim 41 in the manufacture of a medicament for the treatment of mild to moderate dementia of the Alzheimer's type.