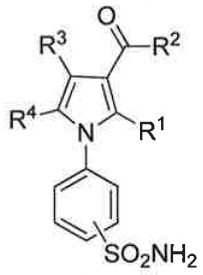
Field of the Invention:

The present invention is related to novel compounds of the general formula I,



I

their tautomeric forms, their stereoisomers, ~~their analogs, their prodrugs,~~ their isotopes, ~~their metabolites,~~ their pharmaceutically acceptable salts, polymorphs, solvates, optical isomers, clathrates, co-crystals, combinations with suitable medicament, pharmaceutical compositions containing them, methods of making of the above compounds , and their use as nicotinic acetylcholine receptor α7 subunit (α7 nAChR) modulator.

Background of the invention:

Cholinergic neurotransmission, mediated primarily through the neurotransmitter acetylcholine (ACh), is a predominant regulator of the physiological functions of the body via the central and autonomic nervous system. ACh acts on the synapses of the neurons present in of all the autonomic ganglia, neuromuscular junctions and the central nervous system. Two distinct classes of ACh target receptors viz. muscarinic (mAChRs) and the nicotinic (nAChRs) have been identified in brain, forming a significant component of receptors carrying its mnemonic and other vital physiological functions.

Neural nicotinic ACh receptors (NNRs) belong to the class of ligand-gated ion channels (LGIC) comprising of five subunits (α2-α10, β2-β4) arranged in heteropentameric (α4β2) or homopertameric (α7) configuration (Paterson D et al.,

TNF-α: tumor necrosis factor alpha.

VTA: ventral tegmental area.

α7 nAChR: nicotinic acetylcholine receptor α7 subunit.

Objective of the Invention:

The main objective of the present invention is therefore to provide novel compounds of the general formula I, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, pharmaceutical compositions containing them, process and intermediates for the preparation of the above said compounds which have α7 nAChR modulatory activity.

Summary of the Invention

According to one aspect of the present invention there is provided compounds represented by the general formula I, its tautomeric forms, its stereoisomers, ~~its analogs, its prodrugs,~~ its isotopes, ~~its metabolites,~~ its pharmaceutically acceptable salts, its polymorphs, its solvates, its optical isomers, its clathrates, its co-crystals, their combinations with suitable medicament and pharmaceutical compositions containing them.

In yet another aspect, the present invention provides a process for the preparation of the compounds of the general formula I.

A further aspect of the present invention is to provide novel intermediates, a process for their preparation and their use in methods of making compounds of the general formula I.

Detailed Description of the invention:

The present invention relates to a compound of the general formula I, its tautomeric forms, its stereoisomers, ~~its analogs, its prodrugs,~~ its isotopes, ~~its metabolites,~~ its pharmaceutically acceptable salts, its polymorphs, its solvates, its

Salts of compound of formula I are obtained by dissolving the compound in a suitable solvent, for example in a chlorinated hydrocarbon, such as methyl chloride or chloroform or a low molecular weight aliphatic alcohol, for example, ethanol or isopropanol, which was then treated with the desired acid or base as described in Berge S.M. et al. "Pharmaceutical Salts, a review article in Journal of Pharmaceutical sciences volume 66, page 1-19 (1977)" and in handbook of pharmaceutical salts properties, selection, and use by P.H.Einrich Stahland Camille G.wermuth , Wiley- VCH (2002).

The stereoisomers of the compounds of formula I of the present invention may be prepared by stereospecific syntheses or resolution of the achiral compound using an optically active amine, acid or complex forming agent, and separating the diastereomeric salt/complex by fractional crystallization or by column chromatography.

The present invention further provides a pharmaceutical composition, containing the compounds of the general formula (I) as defined above, its tautomeric forms, its stereoisomers, ~~its analogs, its prodrugs,~~ its isotopes, ~~its metabolites,~~ its pharmaceutically acceptable salts, its polymorphs, its solvates, its optical isomers, its clathrates and its co-crystals in combination with the usual pharmaceutically employed carriers, diluents and the like are useful for the treatment and/or prophylaxis of diseases or disorder or condition such as Alzheimer's disease (AD), mild cognitive impairment (MCI), senile dementia, vascular dementia, dementia of Parkinson's disease, attention deficit disorder, attention deficit hyperactivity disorder (ADHD), dementia associated with Lewy bodies, AIDS dementia complex (ADC), Pick's disease, dementia associated with Down's syndrome, Huntington's disease, cognitive deficits associated with traumatic brain injury (TBI), cognitive and sensorimotor gating deficits associated with schizophrenia, cognitive deficits associated with bipolar disorder, cognitive impairments associated with depression, acute pain, post-surgical or post-operative pain, chronic pain, inflammation,

inflammatory pain, neuropathic pain, smoking cessation, need for new blood vessel growth associated with wound healing, need for new blood vessel growth associated with vascularization of skin grafts, and lack of circulation, arthritis, rheumatoid arthritis, psoriasis, Crohn's disease, ulcerative colitis, pouchitis, inflammatory bowel disease, celiac disease, periodontitis, sarcoidosis, pancreatitis, organ transplant rejection, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, septic shock, toxic shock syndrome, sepsis syndrome, depression, and rheumatoid spondylitis.

The present invention also provides a pharmaceutical composition, containing the compounds of the general formula (I) as defined above, its tautomeric forms, its stereoisomers, ~~its analogs, its prodrugs,~~ its isotopes, ~~its metabolites,~~ its pharmaceutically acceptable salts, its polymorphs, its solvates, its optical isomers, its clathrates and its co-crystals in combination with the usual pharmaceutically employed carriers, diluents and the like are useful for the treatment and/or prophylaxis of diseases or disorder or condition classified or diagnosed as major or minor neurocognitive disorders, or disorders arising due to neurodegeneration.

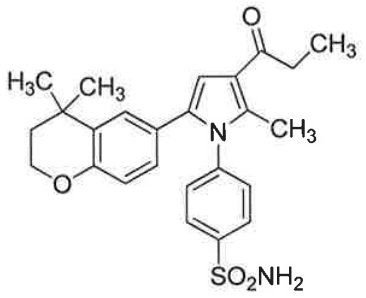
The present invention also provide method of administering a compound of formula I, as defined hereinabove in combination with or as adjunct to medications used in the treatment of attention deficit hyperactivity disorders, schizophrenia, and other cognitive disorders such as Alzheimer's disease, Parkinson's dementia, vascular dementia or dementia associated with Lewy bodies, traumatic brain injury.

The present invention also provide method of administering a compound of formula I, as defined hereinabove in combination with or as an adjunct to acetylcholinesterase inhibitors, disease modifying drugs or biologics for neurodegenerative disorders, dopaminergic drugs, antidepressants, typical or an atypical antipsychotic.

Accordingly, compound of formula I is useful for preventing or treating a disorder mediated by nicotinic acetylcholine receptors. Such compounds can be administered to a subject having such a disorder or susceptible to such disorders in a therapeutically effective amount. The compounds are particularly useful for a method of treating a mammal having a condition where modulation of nicotinic acetylcholine receptor activity is of therapeutic benefit, wherein the method is accomplished by administering a therapeutically effective amount of a compound of formula I to a subject having, or susceptible to, such a disorder. The term 'subject' used herein can be defined as any living organism capable of expressing α7 subunit of nicotinic acetylcholine receptor including mammals.

The following examples are provided to further illustrate the present invention ~~and therefore should not be construed to limit the scope of the present invention~~. All ^{1}HNMR spectra were determined in the solvents indicated and chemical shifts are reported in δ units downfield from the internal standard tetramethylsilane (TMS) and interproton coupling constants are reported in Hertz (Hz).

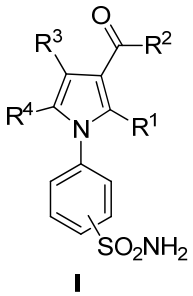
Example 1: Preparation of 4-(5-(4,4-dimethylchroman-6-yl)-2-methyl-3-propionyl-1*H*-pyrrol-1-yl)benzenesulfonamide.



Step 1: 2-Bromo-1-(4,4-dimethylchroman-6-yl)ethanone

CLAIMS

1. A compound of the general formula I, its tautomeric forms, its stereoisomers and its pharmaceutically acceptable salts;



I

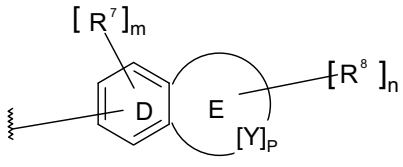
wherein,

R^1 is selected from hydrogen, halogen, optionally substituted alkyl, perhaloalkyl, optionally substituted cycloalkyl, optionally substituted aryl; optionally substituted heterocyclyl, optionally substituted heteroaryl;

R^2 is selected from optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, or $–NR^5(R^6)$, $-A^1R^5$, $-N(R^5)OR^6$;

R^3 is selected from hydrogen, optionally substituted alkyl, halo, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, cyano, nitro or $–NR^5(R^6)$, $-OR^5$;

R^4 is



wherein, phenyl ring 'D' is fused with ring 'E', which is a non-aromatic five to eight member ring inclusive of 'Y' group(s);

Y is independently selected at each repetition from -O-, -S-, -NH-, , or ,

where q = 1 - 4; wherein when Y is selected as –NH- or , it is optionally substituted by $[R^8]_n$;

wherein, R^5 and R^6 are independently selected from hydrogen, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, $R^{9a}C(=A^1)$-;

R^7 is selected independently at each occurrence from the group consisting of halogen, optionally substituted alkyl, optionally substituted cycloalkyl;

R^8 is independently selected at each occurrence from the group consisting of optionally substituted alkyl, R^9A^1-, $R^{9a}C(=A^1)$-;

m = 0 to 2;

n = 0 to 3;

p = 0 to 4;

such that, when p = 0 then $n \neq 0$;

wherein, R^9 wherever it appears, is selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl; and A^1 is selected from O and S;

R^{9a} wherever it appears, is selected from optionally substituted C_{1-6} alkyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl;

wherein,

"optionally substituted alkyl", means a alkyl group optionally substituted with 1 to 6 substituents selected independently from the group consisting of oxo, halogen, nitro, cyano, aryl, hereroaryl, cycloalkyl, $R^{10a}SO_2$-, $R^{10}A^1$-, $R^{10a}OC(=O)$-, $R^{10a}C(=O)O$-, $(R^{10})(H)NC(=O)$-, (R^{10})(alkyl)$NC(=O)$-, $R^{10a}C(=O)N(H)$-, $(R^{10})(H)N$-, (R^{10})(alkyl)N-, $(R^{10})(H)NC(=A^1)N(H)$-, (R^{10})(alkyl)$NC(=A^1)N(H)$-;

"optionally substituted heteroalkyl" means a heteroalkyl group optionally substituted with 1 to 6 substituents selected independently from the group consisting of oxo, halogen, nitro, cyano, aryl, hereroaryl, cycloalkyl.

"optionally substituted cycloalkyl" means a cycloalkyl group optionally substituted with 1 to 6 substituents selected independently from the group consisting of oxo, halogen, nitro, cyano, aryl, hereroaryl, alkyl, $R^{10a}C(=O)$-, $R^{10a}SO_2$-, $R^{10}A^1$-, $R^{10a}OC(=O)$-, $R^{10a}C(=O)O$-, $(R^{10})(H)NC(=O)$-, (R^{10})(alkyl)$NC(=O)$-, $R^{10a}C(=O)N(H)$-, $(R^{10})(H)N$-, (R^{10})(alkyl)N-, $(R^{10})(H)NC(=A^1)N(H)$-, (R^{10})(alkyl)$NC(=A^1)N(H)$-;

"optionally substituted aryl" means (i) an aryl group optionally substituted with 1 to 3 substituents selected independently from the group consisting of halogen, nitro, cyano, hydroxy, C_1 to C_6 alkyl, C_3 to C_6 cycloalkyl, C_1 to C_6 perhaloalkyl, alkyl-O-, perhaloalkyl-O-, alkyl-N(alkyl)-, alkyl-N(H)-, H_2N-, alkyl-SO_2-, perhaloalkyl-SO_2-, alkyl-C(=O)N(alkyl)-, alkyl-C(=O)N(H)-, alkyl-N(alkyl)C(=O)-, alkyl-N(H)C(=O)-, $H_2NC(=O)$-, alkyl-N(alkyl)SO_2-, alkyl-N(H)SO_2-, H_2NSO_2-, 3 to 6 membered heterocycle containing 1 to 2 heteroatoms selected from N, O and S optionally substituted with alkyl or alkyl-C(=O)-, (ii) an aryl ring optionally fused with

cycloalkane or heterocycle across a bond optionally substituted with oxo, alkyl or alkyl-C(=O)-;

"optionally substituted heterocyclyl" means a (i) heterocyclyl group optionally substituted on ring carbons with 1 to 6 substituents selected independently from the group consisting of oxo, halogen, nitro, cyano, aryl, hereroaryl, alkyl, $R^{10}A^1$-, $R^{10a}OC(=O)$-, $R^{10a}C(=O)O$-, $(R^{10})(H)NC(=O)$-, (R^{10})(alkyl)NC(O)-, $R^{10a}C(=O)N(H)$-, $(R^{10})(H)N$-, (R^{10})(alkyl)N-, $(R^{10})(H)NC(=A^1)N(H)$-, (R^{10})(alkyl)$NC(=A^1)N(H)$-; (ii) heterocyclyl group optionally substituted on ring nitrogen(s) with substituents selected from the group consisting of aryl, hereroaryl, alkyl, $R^{10a}C(=O)$-, $R^{10a}SO_2$-, $R^{10a}OC(=O)$-, $(R^{10})(H)NC(=O)$-, (R^{10})(alkyl)NC(=O)-;

"optionally substituted heteroaryl" means a heteroaryl group optionally substituted with 1 to 3 substituents selected independently from the group consisting of halogen, nitro, cyano, hydroxy, C_1 to C_6 alkyl, C_3 to C_6 cycloalkyl, C_1 to C_6 perhaloalkyl, alkyl-O-, perhaloalkyl-O-, alkyl-N(alkyl)-, alkyl-N(H)-, H_2N-, alkyl-SO_2-, perhaloalkyl-SO_2-, alkyl-C(=O)N(alkyl)-, alkyl-C(=O)N(H)-, alkyl-N(alkyl)C(=O)-, alkyl-N(H)C(=O)-, $H_2NC(=O)$-, alkyl-N(alkyl)SO_2-, alkyl-N(H)SO_2-, H_2NSO_2-, 3 to 6 membered heterocycle containing 1 to 2 heteroatoms selected from N, O and S optionally substituted with alkyl or alkyl-C(=O)-;

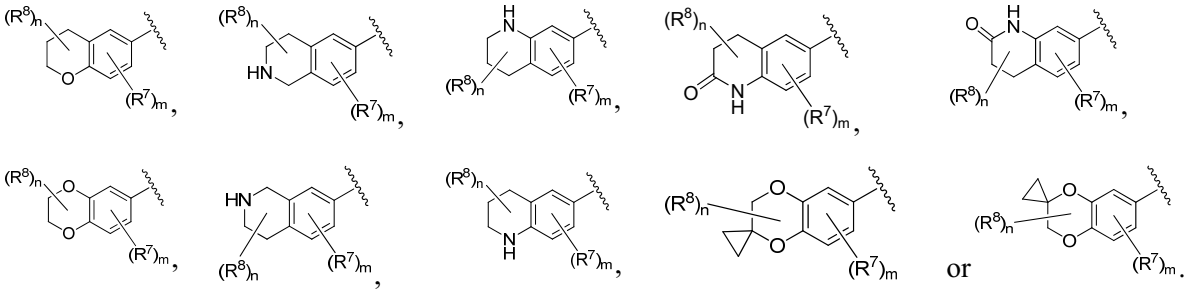
wherein R^{10} is selected from hydrogen, alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl; and A^1 is selected from S and O; and R^{10a} is selected from alkyl, perhaloalkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl.

2. The compound of formula I as claimed in claim 1, wherein R^1 is selected as methyl.

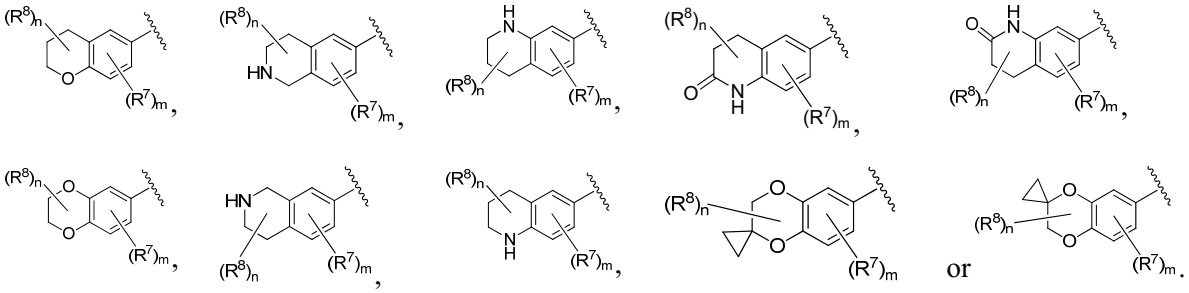
3. The compound of formula I as claimed in claim 1, wherein R^2 is selected from ethyl and ethoxy.

4. The compound of formula I as claimed in claim 1, wherein R^3 is selected from hydrogen and methyl.

5. The compound of formula I as claimed in claim 1, wherein R^4 is selected from



6. The compound of formula I as claimed in claim 1, wherein R^1 is selected from methyl, R^2 is selected from ethyl and ethoxy, R^3 is selected from hydrogen and methyl, and R^4 is selected from



7. The compound of formula I as claimed in claim 1, wherein the compound is selected from-

4-(5-(4,4-dimethylchroman-6-yl)-2-methyl-3-propionyl-1*H*-pyrrol-1-yl)benzenesulfonamide;

4-(5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3,5-dimethyl-4-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

Ethyl 5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2,4-dimethyl-1-(4-sulfamoylphenyl)-1H-pyrrole-3-carboxylate;

4-(5-(2,2-dimethylchroman-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(8-fluoro-4,4-dimethylchroman-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(2-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(2-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-methyl-3-propionyl-5-(3H-spiro[benzo[b][1,4]dioxine-2,1'-cyclopropan]-7-yl)-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-methyl-3-propionyl-5-(3H-spiro[benzo[b][1,4]dioxine-2,1'-cyclopropan]-6-yl)-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(1-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(1-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

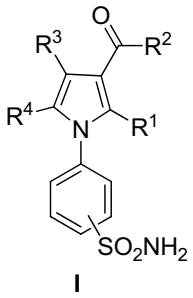
4-(5-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-methyl-3-propionyl-5-(1,4,4-trimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrrol-1-yl)benzenesulfonamide.

8. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

9. ~~A method of~~ Use of compound of claim 1 for the manufacture of a medicament for preventing or treating a disease or its symptoms or a disorder mediated partially or completely by nicotinic acetylcholine receptors~~, said method comprising administering to a subject having or susceptible to said disease or its symptoms or disorder with a therapeutically effective amount of a compound of claim 1~~.

10. ~~A method of treating a disease or disorder or condition, comprising administration of a therapeutically effective amount of a~~ Use of compound of formula (I), its tautomeric forms, its stereoisomers, and its pharmaceutically acceptable salts,



I

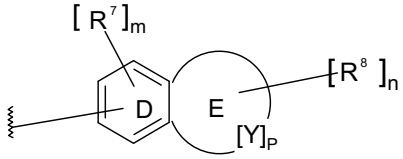
wherein,

R^1 is selected from hydrogen, halogen, optionally substituted alkyl, perhaloalkyl, optionally substituted cycloalkyl, optionally substituted aryl; optionally substituted heterocyclyl, optionally substituted heteroaryl;

R^2 is selected from optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, or $–NR^5(R^6)$, $-A^1R^5$, $-N(R^5)OR^6$;

R^3 is selected from hydrogen, optionally substituted alkyl, halo, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, cyano, nitro or $–NR^5(R^6)$, $-OR^5$;

R^4 is



wherein, phenyl ring 'D' is fused with ring 'E', which is a non-aromatic five to eight member ring inclusive of 'Y' group(s);

Y is independently selected at each repetition from -O-, -S-, -NH-, , or , where q = 1 - 4; wherein when Y is selected as –NH- or , it is optionally substituted by $[R^8]_n$;

wherein, R^5 and R^6 are independently selected from hydrogen, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, $R^{9a}C(=A^1)$-;

R^7 is selected independently at each occurrence from the group consisting of halogen, optionally substituted alkyl, optionally substituted cycloalkyl;

R^8 is independently selected at each occurrence from the group consisting of optionally substituted alkyl, R^9A^1-, $R^{9a}C(=A^1)$-;

m = 0 to 2;

n = 0 to 3;

p = 0 to 4;

wherein, R^9 wherever it appears, is selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl; and A^1 is selected from O and S;

R^{9a} wherever it appears, is selected from optionally substituted C_{1-6} alkyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl;

wherein,

"optionally substituted alkyl", means a alkyl group optionally substituted with 1 to 6 substituents selected independently from the group consisting of oxo, halogen, nitro, cyano, aryl, hereroaryl, cycloalkyl, $R^{10a}SO_2$-, $R^{10}A^1$-, $R^{10a}OC(=O)$-, $R^{10a}C(=O)O$-, $(R^{10})(H)NC(=O)$-, $(R^{10})(alkyl)NC(=O)$-, $R^{10a}C(=O)N(H)$-, $(R^{10})(H)N$-, $(R^{10})(alkyl)N$-, $(R^{10})(H)NC(=A^1)N(H)$-, $(R^{10})(alkyl)NC(=A^1)N(H)$-;

"optionally substituted heteroalkyl" means a heteroalkyl group optionally substituted with 1 to 6 substituents selected independently from the group consisting of oxo, halogen, nitro, cyano, aryl, hereroaryl, cycloalkyl.

"optionally substituted cycloalkyl" means a cycloalkyl group optionally substituted with 1 to 6 substituents selected independently from the group consisting of oxo, halogen, nitro, cyano, aryl, hereroaryl, alkyl, $R^{10a}C(=O)$-, $R^{10a}SO_2$-, $R^{10}A^1$-, $R^{10a}OC(=O)$-, $R^{10a}C(=O)O$-, $(R^{10})(H)NC(=O)$-, $(R^{10})(alkyl)NC(=O)$-, $R^{10a}C(=O)N(H)$-, $(R^{10})(H)N$-, $(R^{10})(alkyl)N$-, $(R^{10})(H)NC(=A^1)N(H)$-, $(R^{10})(alkyl)NC(=A^1)N(H)$-;

"optionally substituted aryl" means (i) an aryl group optionally substituted with 1 to 3 substituents selected independently from the group consisting of halogen, nitro, cyano, hydroxy, C_1 to C_6 alkyl, C_3 to C_6 cycloalkyl, C_1 to C_6 perhaloalkyl, alkyl-O-, perhaloalkyl-O-, alkyl-N(alkyl)-, alkyl-N(H)-, H_2N-, alkyl-SO_2-, perhaloalkyl-SO_2-, alkyl-C(=O)N(alkyl)-, alkyl-C(=O)N(H)-, alkyl-N(alkyl)C(=O)-, alkyl-N(H)C(=O)-, $H_2NC(=O)$-, alkyl-N(alkyl)SO_2-, alkyl-N(H)SO_2-, H_2NSO_2-, 3 to 6 membered heterocycle containing 1 to 2 heteroatoms selected from N, O and S optionally substituted with alkyl or alkyl-C(=O)-, (ii) an aryl ring optionally fused with cycloalkane or heterocycle across a bond optionally substituted with oxo, alkyl or alkyl-C(=O)-;

"optionally substituted heterocyclyl" means a (i) heterocyclyl group optionally substituted on ring carbons with 1 to 6 substituents selected independently from the group consisting of oxo, halogen, nitro, cyano, aryl, hereroaryl, alkyl, $R^{10}A^1$-,

$R^{10a}OC(=O)$-, $R^{10a}C(=O)O$-, $(R^{10})(H)NC(=O)$-, $(R^{10})(alkyl)NC(O)$-, $R^{10a}C(=O)N(H)$-, $(R^{10})(H)N$-, $(R^{10})(alkyl)N$-, $(R^{10})(H)NC(=A^1)N(H)$-, $(R^{10})(alkyl)NC(=A^1)N(H)$-; (ii) heterocyclyl group optionally substituted on ring nitrogen(s) with substituents selected from the group consisting of aryl, hereroaryl, alkyl, $R^{10a}C(=O)$-, $R^{10a}SO_2$-, $R^{10a}OC(=O)$-, $(R^{10})(H)NC(=O)$-, $(R^{10})(alkyl)NC(=O)$-;

"optionally substituted heteroaryl" means a heteroaryl group optionally substituted with 1 to 3 substituents selected independently from the group consisting of halogen, nitro, cyano, hydroxy, C_1 to C_6 alkyl, C_3 to C_6 cycloalkyl, C_1 to C_6 perhaloalkyl, alkyl-O-, perhaloalkyl-O-, alkyl-N(alkyl)-, alkyl-N(H)-, H_2N-, alkyl-SO_2-, perhaloalkyl-SO_2-, alkyl-C(=O)N(alkyl)-, alkyl-C(=O)N(H)-, alkyl-N(alkyl)C(=O)-, alkyl-N(H)C(=O)-, $H_2NC(=O)$-, alkyl-N(alkyl)SO_2-, alkyl-N(H)SO_2-, H_2NSO_2-, 3 to 6 membered heterocycle containing 1 to 2 heteroatoms selected from N, O and S optionally substituted with alkyl or alkyl-C(=O)-;

wherein R^{10} is selected from hydrogen, alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl; and A^1 is selected from S and O; and R^{10a} is selected from alkyl, perhaloalkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl,
for the manufacture of a medicament for treating a disease, disorder, or condition mediated partially or completely by nicotinic acetylcholine receptor.

11. ~~The method~~ Use of compound of claim 10, wherein the compounds are selected from,

4-(5-(4,4-dimethylchroman-6-yl)-2-methyl-3-propionyl-1*H*-pyrrol-1-yl)benzenesulfonamide;

4-(5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3,5-dimethyl-4-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

Ethyl 5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2,4-dimethyl-1-(4-sulfamoylphenyl)-1H-pyrrole-3-carboxylate;

4-(5-(2,3-dihydro-1H-inden-4-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(2,2-dimethylchroman-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(8-fluoro-4,4-dimethylchroman-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(2-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(2-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-methyl-3-propionyl-5-(3H-spiro[benzo[b][1,4]dioxine-2,1'-cyclopropan]-7-yl)-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-methyl-3-propionyl-5-(3H-spiro[benzo[b][1,4]dioxine-2,1'-cyclopropan]-6-yl)-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(1-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(1-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-methyl-3-propionyl-5-(1,4,4-trimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-methyl-3-propionyl-5-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrrol-1-yl)benzenesulfonamide.

12. ~~The method~~ Use of compound of claim 10, wherein the disorder or condition or disease is selected from the group comprising of Alzheimer's disease, mild cognitive impairment, senile dementia, vascular dementia, dementia of Parkinson’s disease, attention deficit disorder, attention deficit hyperactivity disorder, dementia associated with Lewy bodies, AIDS dementia complex, Pick's disease, dementia associated with Down's syndrome, Huntington's disease, cognitive deficits associated with traumatic brain injury, cognitive and sensorimotor gating deficits associated with schizophrenia, cognitive deficits associated with bipolar disorder, cognitive impairments associated with depression, acute pain, post-surgical or post-operative pain, chronic pain, inflammation, inflammatory pain, neuropathic pain, smoking cessation, need for new blood vessel growth associated with wound healing, need for new blood vessel growth

associated with vascularization of skin grafts, and lack of circulation, arthritis, rheumatoid arthritis, psoriasis, Crohn's disease, ulcerative colitis, pouchitis, inflammatory bowel disease, celiac disease, periodontitis, sarcoidosis, pancreatitis, organ transplant rejection, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, septic shock, toxic shock syndrome, sepsis syndrome, depression, and rheumatoid spondylitis, comprising the step of administering a compound of formula I.

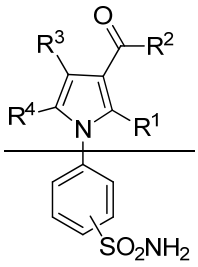
13. ~~The method~~ Use of compound of claim 10, wherein the disease or disorder or condition is selected from the group classified or diagnosed as major or minor neurocognitive disorders, or disorders arising due to neurodegeneration.

14. ~~The method~~ Use of compound of claim 10, comprising administering a compound of formula I in combination with or as adjunct to medications used in the treatment of attention deficit hyperactivity disorders, schizophrenia, and other cognitive disorders such as Alzheimer's disease, Parkinson’s dementia, vascular dementia or dementia associated with Lewy bodies, traumatic brain injury.

15. ~~The method~~ Use of compound of claim 10, further comprising administering a compound of formula I in combination with or as an adjunct to acetylcholinesterase inhibitors, disease modifying drugs or biologics for neurodegenerative disorders, dopaminergic drugs, antidepressants, typical or an atypical antipsychotic.

16. Use of ~~a therapeutically effective amount of a~~ compound of claim 1 for the manufacture of a medicament for preventing or treating a disease or its symptoms or a disorder mediated partially or completely by nicotinic acetylcholine receptors, comprising administration of therapeutically effective amount of a compound of claim 1 to a subject having or susceptible to said disease or its symptoms or disorder.

~~17.~~ ~~Use of a therapeutically effective amount of a compound of formula I for treating a disease or disorder or condition, comprising administration of a therapeutically effective amount of a compound of formula I,~~



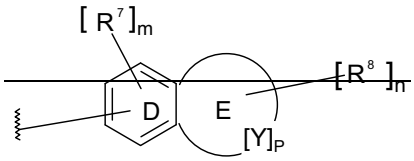
~~wherein,~~

~~R^1 is selected from hydrogen, halogen, optionally substituted alkyl, perhaloalkyl, optionally substituted cycloalkyl, optionally substituted aryl; optionally substituted heterocyclyl, optionally substituted heteroaryl;~~

~~R^2 is selected from optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, or $-NR^5(R^6)$, $-A^1R^5$, $-N(R^5)OR^6$;~~

~~R^3 is selected from hydrogen, optionally substituted alkyl, halo, optionally substituted cycloalkyl, optionally substituted aryl, optionally substituted heterocyclyl, optionally substituted heteroaryl, cyano, nitro or $-NR^5(R^6)$, $-OR^5$;~~

~~R^4 is~~



wherein, phenyl ring 'D' is fused with ring 'E', which is a non-aromatic five to eight member ring inclusive of 'Y' group(s);

Y is independently selected at each repetition from –O–, –S–, –NH–, , or ;

where q = 1 – 4; wherein when Y is selected as –NH– or , it is optionally substituted by $[R^8]_n$;

wherein, R^5 and R^6 are independently selected from hydrogen, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, $R^{9a}C(=A^1)$–;

R^7 is selected independently at each occurrence from the group consisting of halogen, optionally substituted alkyl, optionally substituted cycloalkyl;

R^8 is independently selected at each occurrence from the group consisting of optionally substituted alkyl, R^9A^1–, $R^{9a}C(=A^1)$–;

m = 0 to 2;

n = 0 to 3;

p = 0 to 4;

wherein, R^9 wherever it appears, is selected from hydrogen, optionally substituted C_{1-6} alkyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl; and A^1 is selected from O and S;

R^{9a} wherever it appears, is selected from optionally substituted C_{1-6} alkyl, optionally substituted heteroalkyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted cycloalkyl, and optionally substituted heterocyclyl;

wherein,

"optionally substituted alkyl", means an alkyl group optionally substituted with 1 to 6 substituents selected independently from the group consisting of oxo, halogen, nitro, cyano, aryl, hereroaryl, cycloalkyl, $R^{10a}SO_2$-, $R^{10}A^1$-, $R^{10a}OC(=O)$-, $R^{10a}C(=O)O$-, $(R^{10})(H)NC(=O)$-, $(R^{10})(alkyl)NC(=O)$-, $R^{10a}C(=O)N(H)$-, $(R^{10})(H)N$-, $(R^{10})(alkyl)N$-, $(R^{10})(H)NC(=A^1)N(H)$-, $(R^{10})(alkyl)NC(=A^1)N(H)$-;

"optionally substituted heteroalkyl" means a heteroalkyl group optionally substituted with 1 to 6 substituents selected independently from the group consisting of oxo, halogen, nitro, cyano, aryl, hereroaryl, cycloalkyl.

"optionally substituted cycloalkyl" means a cycloalkyl group optionally substituted with 1 to 6 substituents selected independently from the group consisting of oxo, halogen, nitro, cyano, aryl, hereroaryl, alkyl, $R^{10a}C(=O)$-, $R^{10a}SO_2$-, $R^{10}A^1$-, $R^{10a}OC(=O)$-, $R^{10a}C(=O)O$-, $(R^{10})(H)NC(=O)$-, $(R^{10})(alkyl)NC(=O)$-, $R^{10a}C(=O)N(H)$-, $(R^{10})(H)N$-, $(R^{10})(alkyl)N$-, $(R^{10})(H)NC(=A^1)N(H)$-, $(R^{10})(alkyl)NC(=A^1)N(H)$-;

"optionally substituted aryl" means (i) an aryl group optionally substituted with 1 to 3 substituents selected independently from the group consisting of halogen, nitro, cyano, hydroxy, C_1 to C_6 alkyl, C_3 to C_6 cycloalkyl, C_1 to C_6 perhaloalkyl, alkyl O-, perhaloalkyl O-, alkyl N(alkyl)-, alkyl N(H)-, H_2N-, alkyl SO_2-, perhaloalkyl SO_2-, alkyl C(=O)N(alkyl)-, alkyl C(=O)N(H)-, alkyl N(alkyl)C(=O)-, alkyl N(H)C(=O)-, $H_2NC(=O)$-, alkyl N(alkyl)SO_2-, alkyl N(H)SO_2-, H_2NSO_2-, 3 to 6 membered heterocycle containing 1 to 2 heteroatoms selected from N, O and S optionally substituted with alkyl or alkyl C(=O)-, (ii) an aryl ring optionally fused with

cycloalkane or heterocycle across a bond optionally substituted with oxo, alkyl or alkyl-C(=O)-;

"optionally substituted heterocyclyl" means a (i) heterocyclyl group optionally substituted on ring carbons with 1 to 6 substituents selected independently from the group consisting of oxo, halogen, nitro, cyano, aryl, hereroaryl, alkyl, $R^{10}A^1$-, $R^{10a}OC(=O)$-, $R^{10a}C(=O)O$-, $(R^{10})(H)NC(=O)$-, $(R^{10})(alkyl)NC(O)$-, $R^{10a}C(=O)N(H)$-, $(R^{10})(H)N$-, $(R^{10})(alkyl)N$-, $(R^{10})(H)NC(=A^1)N(H)$-, $(R^{10})(alkyl)NC(=A^1)N(H)$-; (ii) heterocyclyl group optionally substituted on ring nitrogen(s) with substituents selected from the group consisting of aryl, hereroaryl, alkyl, $R^{10a}C(=O)$-, $R^{10a}SO_2$-, $R^{10a}OC(=O)$-, $(R^{10})(H)NC(=O)$-, $(R^{10})(alkyl)NC(=O)$-;

"optionally substituted heteroaryl" means a heteroaryl group optionally substituted with 1 to 3 substituents selected independently from the group consisting of halogen, nitro, cyano, hydroxy, C_1 to C_6 alkyl, C_3 to C_6 cycloalkyl, C_1 to C_6 perhaloalkyl, alkyl-O-, perhaloalkyl-O-, alkyl-N(alkyl)-, alkyl-N(H)-, H_2N-, alkyl-SO_2-, perhaloalkyl-SO_2-, alkyl-C(=O)N(alkyl)-, alkyl-C(=O)N(H)-, alkyl-N(alkyl)C(=O)-, alkyl-N(H)C(=O)-, $H_2NC(=O)$-, alkyl-N(alkyl)SO_2-, alkyl-N(H)SO_2-, H_2NSO_2-, 3 to 6 membered heterocycle containing 1 to 2 heteroatoms selected from N, O and S optionally substituted with alkyl or alkyl-C(=O)-;

wherein R^{10} is selected from hydrogen, alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl; and A^1 is selected from S and O; and R^{10a} is selected from alkyl, perhaloalkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl.

18. The use of claim 17, wherein the compounds are selected from,

4-(5-(4,4-dimethylchroman-6-yl)-2-methyl-3-propionyl-1*H*-pyrrol-1-yl)benzenesulfonamide;

4-(5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-3,5-dimethyl-4-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

Ethyl 5-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2,4-dimethyl-1-(4-sulfamoylphenyl)-1H-pyrrole-3-carboxylate;

4-(5-(2,3-dihydro-1H-inden-4-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(2,2-dimethylchroman-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(8-fluoro-4,4-dimethylchroman-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(2-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(2-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-methyl-3-propionyl-5-(3H-spiro[benzo[b][1,4]dioxine-2,1'-cyclopropan]-7-yl)-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-methyl-3-propionyl-5-(3H-spiro[benzo[b][1,4]dioxine-2,1'-cyclopropan]-6-yl)-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(1-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(1-acetyl-4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(5-(4,4-dimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-7-yl)-2-methyl-3-propionyl-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-methyl-3-propionyl-5-(1,4,4-trimethyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-1H-pyrrol-1-yl)benzenesulfonamide;

4-(2-methyl-3-propionyl-5-(5,6,7,8-tetrahydronaphthalen-2-yl)-1H-pyrrol-1-yl)benzenesulfonamide.

19. The use of claim 17, wherein the disorder or condition or disease is selected from the group consisting of Alzheimer's disease, mild cognitive impairment, senile dementia, vascular dementia, dementia of Parkinson’s disease, attention deficit disorder, attention deficit hyperactivity disorder, dementia associated with Lewy bodies, AIDS dementia complex, Pick's disease, dementia associated with Down's syndrome, Huntington's disease, cognitive deficits associated with traumatic brain injury, cognitive and sensorimotor gating deficits associated with schizophrenia, cognitive deficits associated

~~with bipolar disorder, cognitive impairments associated with depression, acute pain, post-surgical or post-operative pain, chronic pain, inflammation, inflammatory pain, neuropathic pain, smoking cessation, need for new blood vessel growth associated with wound healing, need for new blood vessel growth associated with vascularization of skin grafts, and lack of circulation, arthritis, rheumatoid arthritis, psoriasis, Crohn's disease, ulcerative colitis, pouchitis, inflammatory bowel disease, celiac disease, periodontitis, sarcoidosis, pancreatitis, organ transplant rejection, acute immune disease associated with organ transplantation, chronic immune disease associated with organ transplantation, septic shock, toxic shock syndrome, sepsis syndrome, depression, and rheumatoid spondylitis, comprising the step of administering a compound of formula I.~~

~~20.~~ ~~The use of claim 17, wherein the disease or disorder or condition is selected from the group classified or diagnosed as major or minor neurocognitive disorders, or disorders arising due to neurodegeneration.~~

~~21.~~ ~~The use of claim 17, comprising administering a compound of formula I in combination with or as adjunct to medications used in the treatment of attention deficit hyperactivity disorders, schizophrenia, and other cognitive disorders such as Alzheimer's disease, Parkinson's dementia, vascular dementia or dementia associated with Lewy bodies, traumatic brain injury.~~

~~22.~~ ~~The use of claim 17, further comprising administering a compound of formula I in combination with or as an adjunct to acetylcholinesterase inhibitors, disease modifying drugs or biologics for neurodegenerative disorders, dopaminergic drugs, antidepressants, typical or an atypical antipsychotic.~~