



(51) International Patent Classification:

C07D 401/04 (2006.01) *A61P 1/00* (2006.01)
C07D 207/333 (2006.01) *A61P 17/00* (2006.01)
A61K 31/31 (2006.01) *A61P 31/00* (2006.01)
A61K 31/4439 (2006.01) *A61P 37/00* (2006.01)
A61P 25/00 (2006.01) *A61P 19/00* (2006.01)

(21) International Application Number:

PCT/IB2014/062268

(22) International Filing Date:

16 June 2014 (16.06.2014)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

2049/MUM/2013 17 June 2013 (17.06.2013) IN

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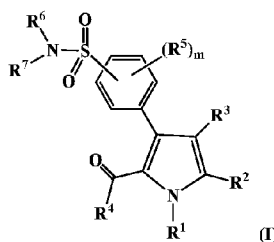
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: PYRROLE DERIVATIVES AS ALPHA 7 NACHR MODULATORS



(57) Abstract: Disclosed are compounds of the formula (I), wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and m are as described herein, as modulators of the nicotinic acetylcholine receptors, particularly the $\alpha 7$ subtype, their tautomeric forms, stereoisomers, and their pharmaceutically acceptable salts, pharmaceutical compositions thereof, and combinations thereof with suitable other medicaments. Also disclosed are a process of preparation of the compounds and the intended uses thereof in therapy, particularly in the prophylaxis and/or treatment of disorders such as Alzheimer's disease, mild cognitive impairment, and senile dementia.

PYRROLE DERIVATIVES AS ALPHA 7 NACHR MODULATORS

FIELD OF THE INVENTION

[1] The present invention relates to pyrrole derivatives, their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, pharmaceutical compositions comprising one or more such compounds, and their use as nicotinic acetylcholine receptor $\alpha 7$ subunit ($\alpha 7$ nAChR) modulators.

CROSS-REFERENCE TO A RELATED APPLICATION

[2] The present application claims the benefit of Indian Provisional Patent Application No. 2049/MUM/2013 filed on 17th June 2013 the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[3] 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 all of 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 the brain, forming a significant component of receptors carrying out its mnemonic and other vital physiological functions.

[4] Neural nicotinic ACh receptors (NNRs) belong to the class of ligand-gated ion channels (LGIC) comprising five subunits ($\alpha 2$ - $\alpha 10$, $\beta 2$ - $\beta 4$) arranged in heteropentameric ($\alpha 4\beta 2$) or homopentameric ($\alpha 7$) configuration (David Paterson et al., Progress in Neurobiology, 61(2000), 75-111). $\alpha 4\beta 2$ and $\alpha 7$ nAChR constitute

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the predominant subtypes expressed in the mammalian brain. $\alpha 7$ nAChR has attained prominence as a therapeutic target due to its abundant expression in the learning and memory centres of brain, hippocampus and the cerebral cortex (F. Rubboli et al., *Neurochem. Int.*, 1994, 25(1), 69-71). Particularly, $\alpha 7$ nAChR is characterized by a high Ca^{2+} ion permeability, which is responsible for neurotransmitter release and consequent modulation of excitatory and inhibitory neurotransmission (Manickavasagam Alkondon et al., *European Journal of Pharmacology*, 393 (2000), 59-67; Federico Dajas-Bailador et al., *TRENDS in Pharmacological Sciences*, 2004, 25(6), 317-324). Furthermore, high Ca^{2+} ion influx also has implications on the long-term potentiation of memory via alterations in gene expression (Robert S. Bitner et al., *The Journal of Neuroscience*, 2007, 27(39), 10578-10587; Bruce E. McKay et al., *Biochemical Pharmacology*, 74 (2007), 1120-1133).

[5] Several recent studies have confirmed the role of $\alpha 7$ nAChR in neural processes like attention, memory and cognition (Huibert D. Mansvelder et al., *Psychopharmacology*, (2006), 184, 292-305; Wai Kit Chan et al., *Neuropharmacology*, 52 (2007), 1641-1649; Jared W. Young et al., *European Neuropsychopharmacology*, (2007), 17, 145-155). Gene polymorphisms associated with the $\alpha 7$ nAChR protein *CHRNA7* have been implicated in the genetic transmission of schizophrenia, related neurophysiological sensory gating deficits and resultant cognitive impairment (Robert Freedman et al., *Biol. Psychiatry*, 1995, 38, 22-33; Debby W. Tsuang et al., *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, 105, 662-668 (2001)). Also, preclinical studies in $\alpha 7$ nAChR knock-out and anti-sense oligonucleotide treated mice have demonstrated impaired attention and defective cognition underscoring the prominent role of $\alpha 7$ nAChR in cognition (Peter Curzon et al., *Neuroscience Letters*, 410 (2006), 15-19; Jared W. Young et al., *Neuropsychopharmacology*, (2004), 29, 891-900). Additionally, pharmacological blockade of $\alpha 7$ nAChR impairs memory and its activation enhances the same in preclinical rodent models, thereby implicating $\alpha 7$

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nAChR as a target for cognitive enhancement (Kenji Hashimoto et al., *Biol. Psychiatry*, 2008, 63, 92-97).

[6] Pathological brain function in sensory-deficit disorders has been associated with nicotinic cholinergic transmission particularly through $\alpha 7$ receptors (Robert Freedman et al., *Biol. Psychiatry*, 1995, 38, 22-33; T Debby W. Tsuang et al., *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, 105, 662-668 (2001); Robyn Carson et al., *Neuromol., Med.* (2008), 10, 377-384; S. Leonard et al., *Pharmacology Biochemistry and Behaviour*, 70 (2001), 561-570; Robert Freedman et al., *Current Psychiatry Report*, 2003, 5, 155-161; Tyrone D. Cannon et al., *Current Opinion Psychiatry*, 2005, 18, 135-140). A defective pre-attention processing of sensory information is understood to be the basis of cognitive fragmentation in schizophrenia and related neuropsychiatric disorders (Steven C. Leiser et al., *Pharmacology & Therapeutics*, 122(3), (2009), 302-311). Genetic linkage studies have traced sharing of the $\alpha 7$ gene locus for several affective, attention, anxiety and psychotic disorders (S. Leonard et al., *Pharmacology, Biochemistry and Behaviour*, 70 (2001), 561-570; Suemaru K. Folia et al., *Folia Pharmacol. Jpn.*, 119, 295-300 (2002)).

[7] Perturbations in the cholinergic and glutamatergic homeostasis have long been implicated as causative factors for a host of neurological diseases, including dementia(s) (Eran Nizri et al., *Drug News Perspect.*, 2007, 20(7), 421-429). Dementia is a severe, progressive, multi-factorial cognitive disorder affecting memory, attention, language, and problem solving. Nicotinic ACh receptor, particularly the interaction of $\alpha 7$ receptor with $\alpha\beta_{1-42}$, is implicated as an upstream pathogenic event in Alzheimer's disease, which is a major causative factor for dementia (Hoau-Yan Wang et al., *The Journal of Neuroscience*, 2009, 29(35), 10961-10973). Moreover, gene polymorphisms in CHRNA7 have been implicated in dementia with Lewy bodies (DLB) and Pick's disease (Agnes Feher et al., *Dement. Geriatr. Cogn. Disord.*, 2009, 28, 56-62).

[8] Disease modification potential of the nAChRs, particularly the $\alpha 7$ receptor, has been recognized. For example, disease-modification of Alzheimer's disease (AD) and Parkinson's disease (PD) has been proposed by enhancing neuron survival and preventing neurodegeneration (Hoau-Yan Wang et al., *The Journal of Neuroscience*, 2009, 29(35), 10961-10973; R. G. Nagele et al., *Neuroscience*, 2002, 110(2), 199-211; G. Jeyarasasingam et al., *Neuroscience*, 2002, 109, 275-285). Additionally, it has been proposed that $\alpha 7$ nAChR induced activation of anti-apoptotic (BCL-2) and anti-inflammatory pathways in the brain could have neuroprotective effects in neurodegenerative diseases (Mario B. Marrero et al., *Brain Research*, 2009, 1256, 1-7). Dopamine-containing neurons of the ventral tegmental area (VTA) and laterodorsal tegmental nucleus (LDT) are known to express nicotinic ACh receptors, particularly the $\alpha 4$, $\alpha 3$, $\beta 2$, $\beta 3$, and $\beta 4$ subunits (Alexander Kuzmin et al., *Psychopharmacology*, (2009), 203, 99-108). Nicotinic ACh receptors $\alpha 4\beta 2$ and $\alpha 3\beta 4$ have been identified by the candidate-gene approach to have a strong mechanistic link for nicotine addiction (Robert B. Weiss et al., *PLoS Genetics*, 2008, 4(7), e1000125). $\alpha 7$ nAChR has particularly been studied for a putative role in cannabis addiction (Marcello Solinas et al., *The Journal of Neuroscience*, 2007, 27(21), 5615-5620). Varenicline, a partial agonist of $\alpha 4\beta 2$, has demonstrated better efficacy in reducing smoking addiction and relapse prevention than bupropion (Jon O. Ebbert et al., *Patient Preference and Adherence*, 2010, 4, 355-362).

[9] The presence of a high-affinity nicotine binding site at $\alpha 4\beta 2$ nAChR in the descending inhibitory pathways from the brainstem has sparked interest in the antinociceptive properties of nicotinic ACh receptor agonists like epibatidine (Michael Decker et al., *Expert Opin. Investig. Drugs*, (2001), 10(10), 1819-1830). Several new developments have opened the area for the use of nicotinic modulators in pain therapy (Michael C. Rowbotham et al., *PAIN*, 146, (2009), 245-252).

[10] Another key role of the $\alpha 7$ nAChR is its ability to modulate the production of pro-inflammatory cytokines, like interleukins (IL), tumor necrosis factor alpha (TNF- α), and high mobility group box (HMGB-1) in the central nervous

system. Consequently, anti-inflammatory and antinociceptive effects have been demonstrated in pain disorders (M. Imad Damaj et al., *Neuropharmacology*, 39 (2000), 2785-2791). Additionally, 'cholinergic anti-inflammatory pathway' has been proposed to be a regulator of local and systemic inflammation and neuro-immune interactions through neural and humoral pathways (Margot Gallowitsch-Puerta et al., *Life Sci.*, 2007, 80(24-25), 2325-2329; Mauricio Rosas-Ballina et al., *Mol. Med.*, 15(7-8), 195-202 (2009); M. Rosas-Ballina et al., *J. Intern. Med.*, 2009, 265, 663-679). Selective modulators of nicotinic ACh receptors, particularly the $\alpha 7$ type, like GTS-21, attenuate cytokine production and IL-1 β after endotoxin exposure. Furthermore, $\alpha 7$ nAChR are understood to have a central role in arthritis pathogenesis and potential therapeutic strategy for treatment of joint inflammation (M. Westman et al., *Scandinavian Journal of Immunology*, 2009, 70, 136-140). A putative role for $\alpha 7$ nAChR has also been implicated in severe sepsis, endotoxemic shock and systemic inflammation (Y. Jin, et al., *International Journal of Immunogenetics*, 37, 361-365; Chong Liu et al., *Crit. Care Med.*, 2009, 37(2), 634-641).

[11] Angiogenesis is a critical physiological process for cell survival and is pathologically important for cancer proliferation; several non-neural nicotinic ACh receptors, particularly $\alpha 7$, $\alpha 5$, $\alpha 3$, $\beta 2$, and $\beta 4$, are involved in such processes (Hugo R. Arias et al., *International Journal of Biochemistry and Cell Biology*, 41 (2009), 1441-1451; Christopher Heeschen et al., *The Journal of Clinical Investigation*, 2002, 110(4), 527-536). The role of nicotinic ACh receptors in the development of cervical cancer, lung carcinogenesis and pediatric lung disorders in smoking-exposed population has been studied (Itzel E. Calleja-Macias et al., *Int. J. Cancer.*, 124, 1090-1096 (2009); Hildegard M. Schuller et al., *European Journal of Pharmacology*, 393 (2000), 265-277). Several $\alpha 7$ nAChR agonists and partial agonists have been characterized for their efficacy in clinical and preclinical studies. EVP-6124, an agonist at $\alpha 7$ nAChR, has reportedly demonstrated a significant improvement in sensory processing and cognition biomarkers in Phase Ib study with patients suffering from schizophrenia (EnVivo Pharmaceuticals press

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release 2009, Jan. 12). GTS-21 (DMXB-Anabaseine), an $\alpha 7$ nAChR agonist, in the P II clinical trials, has reportedly shown efficacy in improving cognitive deficits in schizophrenia and the inhibition of endotoxin-induced TNF- α release (Ann Olincy et al., Biol. Psychiatry, 2005, 57(8, Suppl.), Abst 44; Ann Olincy et al., Arch. Gen. Psychiatry, 2006, 63, 630-638; Richard Goldstein et al., Acad. Emerg. Med., 2007, 5 14(5), s185-s186). CP-810123, an $\alpha 7$ nAChR agonist, reportedly exhibits protection against scopolamine-induced dementia and inhibition of amphetamine-induced auditory evoked potentials in preclinical studies (Christopher J. O'Donnell et al., J. Med. Chem., 2010, 53, 1222-1237). SSR-180711A, also an $\alpha 7$ nAChR agonist, 10 reportedly enhances learning and memory, and protects against MK-801/scopolamine-induced memory loss and prepulse inhibition in preclinical studies (John P. Redrobe et al., European Journal of Pharmacology, 602 (2009), 58-65; John Dunlop et al., Journal of Pharmacology and Experimental Therapeutics, 2009, 328, 766-776; Philippe Pichat et al., 15 Neuropsychopharmacology, 2007, 32, 17-34). SEN-12333 reportedly protects against scopolamine-induced amnesia in a passive avoidance test in preclinical studies (Renza Roncarati et al., The Journal of Pharmacology and Experimental Therapeutics, 2009, 329, 459-468). AR-R-17779, an agonist of the $\alpha 7$ nAChR, reportedly exhibits an improvement in the social recognition task performed in rats 20 (Marja Van Kampen et al., Psychopharmacology, 2004, 172, 375-383). ABBF, an agonist of the $\alpha 7$ nAChR, reportedly improves social recognition memory and working memory in the Morris maze task in rats (Frank G. Boess et al., The Journal of Pharmacology and Experimental Therapeutics, 2007, 321, 716-725). TC-5619, a selective $\alpha 7$ nAChR agonist has reportedly demonstrated efficacy in 25 animal models of positive and negative symptoms and cognitive dysfunction in schizophrenia (T. A. Hauser et al., Biochemical Pharmacology, 78 (2009), 803-812).

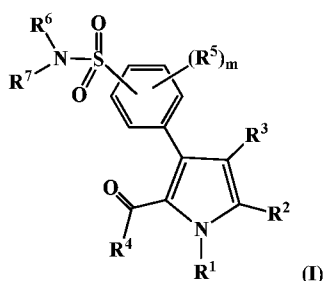
[12] An alternative strategy to reinforce or potentiate the endogenous cholinergic neurotransmission of ACh without directly stimulating the target receptor is the positive allosteric modulation (PAM) of $\alpha 7$ nAChR (E. X. 30 Albuquerque et al., Alzheimer Diseases and Associated Disorder, Vol. 15, Suppl 1,

S19-S25). Several PAMs have been characterized, albeit only in preclinical stages of discovery. A-86774, an $\alpha 7$ nAChR PAM, reportedly improves sensory gating in DBA/2 mice by significantly reducing the T: C ratio in a preclinical model of schizophrenia (Ramin Faghieh et al., *Journal of Medicinal Chemistry*, 2009, 52, 3377-3384). XY-4083, an $\alpha 7$ nAChR PAM, reportedly normalizes the sensorimotor gating deficits in the DBA/2 mice and memory acquisition in the 8-arm radial maze test without altering the receptor desensitization kinetics (Herman J. Hg et al., *PNAS*, 2007, 104(19), 8059-8064). Yet another PAM, PNU-120596, reportedly alters $\alpha 7$ nAChR desensitization kinetics while simultaneously protecting against the disruption of prepulse inhibition by MK-801. NS-1738, another PAM, reportedly exhibits efficacy in-vivo in the animal models of social recognition and spatial memory acquisition in the Morris maze task (Daniel B. Timmermann et al., *Journal of Pharmacology and Experimental Therapeutics*, 2007, 323, 294-307). In addition, several patents/applications published are listed below - US 2006/0142349, US 2007/0142450, US 2009/0253691, WO 2007/031440, WO 2009/115547, WO 2009/135944, WO 2009/127678, WO 2009/127679, WO 2009/043780, WO 2009/043784, US 7683084, US 7741364, WO 2009/145996, US 2010/0240707, WO 2011/064288, US 2010/0222398, US 2010/0227869, EP 1866314, WO 2010/130768, WO 2011/036167, US 2010/0190819, WO 2012/104782, WO 2012/114285, WO 2012/131576, WO 2013/005153, and WO 2013/132380, which reportedly disclose efficacy of allosteric modulators of nicotinic ACh receptors, underscoring their therapeutic potential.

[13] Despite the foregoing proposals in the art, there exists a need for novel modulators of the nicotinic acetylcholine receptors, particularly the $\alpha 7$ nAChR, pharmaceutical compositions comprising such modulators, and methods of treating diseases, disorders, or conditions that are treatable or preventable by the use of such modulators.

BRIEF SUMMARY OF THE INVENTION

[14] The present invention provides a compound of the general formula (I), its tautomeric forms, its stereoisomers, its pharmaceutically acceptable salts, its combinations with one or more of suitable other medicaments, its pharmaceutical compositions, and its use as nicotinic acetylcholine receptor $\alpha 7$ subunit ($\alpha 7$ nAChR) modulator.



[15] According to one aspect of the present invention, there is provided a compound represented by the general formula (I), its tautomeric forms, its stereoisomers, its pharmaceutically acceptable salts, its combinations with one or more of suitable other medicaments, and its pharmaceutical compositions, wherein R¹ to R⁷ and m are described in details below.

[16] Thus the present invention further provides a pharmaceutical composition containing the compound of the general formula (I), its tautomeric forms, its stereoisomers, and/or its pharmaceutically acceptable salts in combination with pharmaceutically acceptable carriers, diluents, and the like, which is useful for the treatment and/or prophylaxis of diseases, disorders, or conditions 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 decline associated with stroke, poststroke neuroprotection, 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
5 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
10 with organ transplantation, septic shock, toxic shock syndrome, sepsis syndrome, depression, and rheumatoid spondylitis.

[17] The present invention also provides a pharmaceutical composition containing a compound of the general formula (I), its tautomeric forms, its stereoisomers, its pharmaceutically acceptable salts, its polymorphs, its solvates,
15 and/or its optical isomers in combination with pharmaceutically acceptable carriers, diluents, and the like, which is useful for the treatment and/or prophylaxis of diseases, disorders, or conditions classified or diagnosed as major or minor neurocognitive disorders, or disorders arising due to neurodegeneration.

[18] The present invention also provides a method of treatment wherein a
20 compound of formula (I), its tautomeric forms, its stereoisomers, or its pharmaceutically acceptable salts is administered in combination with or as an 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
25 Lewy bodies, or traumatic brain injury.

[19] The present invention also provides a method of treatment wherein a compound of formula (I), its tautomeric forms, its stereoisomers, or its pharmaceutically acceptable salts is administered in combination with or as an adjunct to acetylcholinesterase inhibitors, disease modifying drugs or biologics for

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neurodegenerative disorders, dopaminergic drugs, antidepressants, or a typical or atypical antipsychotic.

[20] The present invention also provides the use of a compound of formula (I), its tautomeric forms, its stereoisomers, or its pharmaceutically acceptable salts, in the preparation of a medicament for treating a disease, disorder, or condition
5 selected from the group of disorders classified or diagnosed as major or minor neurocognitive disorders and disorders arising due to neurodegeneration.

[21] The present invention also provides the use of a compound of formula (I), its tautomeric forms, its stereoisomers, or its pharmaceutically acceptable salts, in
10 the preparation of a medicament for treating a disease, disorder, or condition selected from attention deficit hyperactivity disorders, schizophrenia, cognitive disorders, Alzheimer's disease, Parkinson's dementia, vascular dementia or dementia associated with Lewy bodies, and traumatic brain injury.

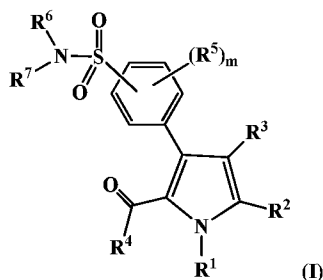
[22] The present invention also provides the use of compound of formula (I),
15 its tautomeric forms, its stereoisomers, or its pharmaceutically acceptable salts, in combination with or as an adjunct to acetylcholinesterase inhibitors, disease modifying drugs or biologics for neurodegenerative disorders, dopaminergic drugs, antidepressants, or a typical or atypical antipsychotic.

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DETAILED DESCRIPTION OF THE INVENTION

[23] The present invention provides a compound of the general formula (I), its tautomeric forms, its stereoisomers, its pharmaceutically acceptable salts, its combinations with suitable other medicaments, and its pharmaceutical compositions,

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wherein,

R¹ is selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, and substituted- or unsubstituted- cycloalkyl;

5 R² is selected from substituted- or unsubstituted- alkyl and substituted- or unsubstituted- cycloalkyl;

R³ is selected from the group consisting of substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl;

10 R⁴ is selected from the group consisting of substituted- or unsubstituted- alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, substituted- or unsubstituted- heterocyclyl, and -NR⁸R⁹;

15 R⁵ is selected independently at each occurrence from the group consisting of halogen, substituted- or unsubstituted- alkyl, perhaloalkyl, substituted- or unsubstituted- cycloalkyl, -OR^{8b}, -NR⁸R⁹, and -C(=O)R^{8a}; or

R⁶ and R⁷ are independently selected from the group consisting of hydrogen and substituted- or unsubstituted- alkyl;

20 R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, and substituted- or unsubstituted- cycloalkyl;

R^{8a} is selected from the group consisting of substituted- or unsubstituted- alkyl, perhaloalkyl, and substituted- or unsubstituted- cycloalkyl;

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R^{8b} is selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, perhaloalkyl, and substituted- or unsubstituted- cycloalkyl;

m is an integer selected from 0, 1, and 2;

when the alkyl group is substituted, it is substituted with 1 to 3 substituents
5 independently selected from oxo, halogen, nitro, cyano, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -SO₂R^{10a}, -C(=O)OR^{10a}, -OC(=O)R^{10a}, -C(=O)N(H)R¹⁰, -C(=O)N(alkyl)R¹⁰, -N(H)C(=O)R^{10a}, -N(H)R¹⁰, -N(alkyl)R¹⁰, -N(H)C(=O)N(H)R¹⁰, and -N(H)C(=O)N(alkyl)R¹⁰;

when the cycloalkyl group is substituted, it is substituted with 1 to 3
10 substituents independently selected from oxo, halogen, nitro, cyano, alkyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -SO₂R^{10c}, -C(=O)R^{10c}, -C(=O)OR^{10c}, -OC(=O)R^{10c}, -C(=O)N(H)R^{10d}, -C(=O)N(alkyl)R^{10d}, -N(H)C(=O)R^{10c}, -N(H)R^{10d}, -N(alkyl)R^{10d}, -N(H)C(=O)N(H)R^{10d}, and -N(H)C(=O)N(alkyl)R^{10d};

when the aryl group is substituted, it is substituted with 1 to 3 substituents
15 independently selected from halogen, nitro, cyano, hydroxy, alkyl, perhaloalkyl, cycloalkyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH₂, -SO₂-alkyl, -SO₂-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH₂, -SO₂N(alkyl)alkyl, -SO₂N(H)alkyl, and -SO₂NH₂;

when the heteroaryl group is substituted, it is substituted with 1 to 3
20 substituents independently selected from halogen, nitro, cyano, hydroxy, alkyl, perhaloalkyl, cycloalkyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH₂, -SO₂-alkyl, -SO₂-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH₂, -SO₂N(alkyl)alkyl, -SO₂N(H)alkyl, and -SO₂NH₂;

when the heterocyclyl group is substituted, it can be substituted either on a ring carbon atom(s) or on a ring hetero atom; when it substituted on a ring carbon atom(s), it is substituted with 1 to 3 substituents independently selected from

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halogen, nitro, cyano, oxo, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -C(=O)OR^{10c}, -OC(=O)R^{10c}, -C(=O)N(H)R^{10d}, -C(=O)N(alkyl)R^{10d}, -N(H)C(=O)R^{10c}, -N(H)R^{10d}, -N(alkyl)R^{10d}, -N(H)C(=O)N(H)R^{10d}, and -N(H)C(=O)N(alkyl)R^{10d}; and when the heterocyclyl group is substituted on a ring
5 nitrogen, it is substituted with a substituent selected from alkyl, cycloalkyl, aryl, heteroaryl, -SO₂R^{10c}, -C(=O)R^{10c}, -C(=O)N(H)R^{10d}, and -C(=O)N(alkyl)R^{10d};

R¹⁰ is selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl;

10 R^{10a} is selected from alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl;

R^{10b} is selected from hydrogen, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl;

R^{10c} is selected from alkyl, perhaloalkyl, and cycloalkyl;

R^{10d} is selected from hydrogen, alkyl, and cycloalkyl.

15 **[24]** In accordance with an embodiment of the invention, R¹ is selected from substituted- or unsubstituted- alkyl and substituted- or unsubstituted- cycloalkyl.

[25] In certain embodiments, R¹ is selected from methyl and ethyl.

[26] In certain embodiments, R² is selected from methyl, ethyl, and propyl.

20 **[27]** In certain embodiments, R³ is phenyl substituted with 1 to 2 substituents selected from chloro, fluoro, and methyl.

[28] In certain embodiments, R⁴ is selected from ethyl and pyridyl.

[29] In any of the above embodiments, R⁵ is halogen.

[30] In any of the above embodiments, m is selected from 0 and 1.

[31] In any of the above embodiments, R⁶ and R⁷ are hydrogens.

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[32] Whenever a range of the number of atoms in a structure is indicated (e.g., a C₁₋₁₂, C₁₋₈, C₁₋₆, or C₁₋₄ alkyl, alkylamino, etc.), it is specifically contemplated that any sub-range or individual number of carbon atoms falling within the indicated range also can be used. Thus, for instance, the recitation of a range of 1-8 carbon atoms (e.g., C_{1-C8}), 1-6 carbon atoms (e.g., C_{1-C6}), 1-4 carbon atoms (e.g., C_{1-C4}), 1-3 carbon atoms (e.g., C_{1-C3}), or 2-8 carbon atoms (e.g., C_{2-C8}) as used with respect to any chemical group (e.g., alkyl, alkylamino, etc.) referenced herein encompasses and specifically describes 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and/or 12 carbon atoms, as appropriate, as well as any sub-range thereof (e.g., 1-2 carbon atoms, 1-3 carbon atoms, 1-4 carbon atoms, 1-5 carbon atoms, 1-6 carbon atoms, 1-7 carbon atoms, 1-8 carbon atoms, 1-9 carbon atoms, 1-10 carbon atoms, 1-11 carbon atoms, 1-12 carbon atoms, 2-3 carbon atoms, 2-4 carbon atoms, 2-5 carbon atoms, 2-6 carbon atoms, 2-7 carbon atoms, 2-8 carbon atoms, 2-9 carbon atoms, 2-10 carbon atoms, 2-11 carbon atoms, 2-12 carbon atoms, 3-4 carbon atoms, 3-5 carbon atoms, 3-6 carbon atoms, 3-7 carbon atoms, 3-8 carbon atoms, 3-9 carbon atoms, 3-10 carbon atoms, 3-11 carbon atoms, 3-12 carbon atoms, 4-5 carbon atoms, 4-6 carbon atoms, 4-7 carbon atoms, 4-8 carbon atoms, 4-9 carbon atoms, 4-10 carbon atoms, 4-11 carbon atoms, and/or 4-12 carbon atoms, etc., as appropriate).

[33] General terms used in formula can be defined as follows; however, the meaning stated should not be interpreted as limiting the scope of the term *per se*.

[34] The term "alkyl", as used herein, means a straight or branched hydrocarbyl chain containing from 1 to 20 carbon atoms. Preferably, the alkyl group contains 1 to 10 carbon atoms. More preferably, alkyl group contains up to 6 carbon atoms. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, and n-hexyl.

[35] In a substituted alkyl group, the alkyl group is substituted with 1 to 3 substituents independently selected from oxo, halogen, nitro, cyano, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -SO₂R^{10a}, -C(=O)OR^{10a}, -

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OC(=O)R^{10a}, -C(=O)N(H)R⁹, -C(=O)N(alkyl)R¹⁰, -N(H)C(=O)R^{10a}, -N(H)R¹⁰, -N(alkyl)R¹⁰,
-N(H)C(=O)N(H)R¹⁰, and -N(H)C(=O)N(alkyl)R¹⁰; wherein R¹⁰ is selected from
hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl; R^{10a} is selected from
alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl; R^{10b} is selected
5 from hydrogen, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl.

[36] The term “perhaloalkyl” used herein means an alkyl group as defined
hereinabove wherein all the hydrogen atoms of the said alkyl group are substituted
with halogen. The perhaloalkyl group is exemplified by trifluoromethyl,
pentafluoroethyl, and the like.

10 **[37]** The term “cycloalkyl” as used herein, means a monocyclic, bicyclic, or
tricyclic non-aromatic ring system containing from 3 to 14 carbon atoms,
preferably monocyclic cycloalkyl ring containing 3 to 6 carbon atoms. Examples of
monocyclic ring systems include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl,
cycloheptyl, and cyclooctyl. Bicyclic ring systems include monocyclic ring system
15 fused across a bond with another cyclic system which may be an alicyclic ring or
an aromatic ring. Bicyclic rings also include spirocyclic systems wherein the
second ring gets annulated on a single carbon atom. Bicyclic ring systems are also
exemplified by a bridged monocyclic ring system in which two non-adjacent carbon
atoms of the monocyclic ring are linked by an alkylene bridge. Examples of bicyclic
20 ring systems include, but are not limited to, bicyclo[3.1.1]heptane,
bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane,
bicyclo[3.3.1]nonane, bicyclo[4.2.1]nonane, bicyclo[3.3.2]decane,
bicyclo[3.1.0]hexane, bicyclo[4.1.0]heptane, bicyclo[3.2.0]heptanes, octahydro-1*H*-
indene, spiro[2.5]octane, spiro[4.5]decane, spiro[bicyclo[4.1.0]heptane-2,1'-
25 cyclopentane], and hexahydro-2'*H*-spiro[cyclopropane-1,1'-pentalene]. Tricyclic ring
systems are the systems wherein the bicyclic systems as described about are
further annulated with third ring, which may be alicyclic ring or aromatic ring.
Tricyclic ring systems are also exemplified by a bicyclic ring system in which two
non-adjacent carbon atoms of the bicyclic ring are linked by a bond or an alkylene

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bridge. Examples of tricyclic-ring systems include, but are not limited to, tricyclo[3.3.1.0^{3,7}]nonane and tricyclo[3.3.1.1^{3,7}]decane (adamantane).

[38] When the cycloalkyl group is substituted, it is substituted with 1 to 3 substituents independently selected from oxo, halogen, nitro, cyano, alkyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -SO₂R^{10c}, -C(=O)R^{10c}, -C(=O)OR^{10c}, -OC(=O)R^{10c}, -C(=O)N(H)R^{10d}, -C(=O)N(alkyl)R^{10d}, -N(H)C(=O)R^{10c}, -N(H)R^{10d}, -N(alkyl)R^{10d}, -N(H)C(=O)N(H)R^{10d}, and -N(H)C(=O)N(alkyl)R^{10d}; wherein R^{10b} is selected from hydrogen, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl; R^{10c} is selected from alkyl, perhaloalkyl, and cycloalkyl; R^{10d} is selected from hydrogen, alkyl, and cycloalkyl.

[39] The term "aryl" refers to a monocyclic, bicyclic or tricyclic aromatic hydrocarbon ring system. Examples of aryl groups include phenyl, naphthyl, anthracenyl, fluorenyl, indenyl, azulenyl, and the like. Aryl group also includes partially saturated bicyclic and tricyclic aromatic hydrocarbons such as tetrahydro-naphthalene.

[40] When the aryl group is substituted, it is substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, hydroxy, alkyl, perhaloalkyl, cycloalkyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH₂, -SO₂-alkyl, -SO₂-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH₂, -SO₂N(alkyl)alkyl, -SO₂N(H)alkyl, and -SO₂NH₂.

[41] The term "heteroaryl" refers to a 5-14 membered monocyclic, bicyclic, or tricyclic ring system having 1 to 4 ring heteroatoms selected from O, N, or S, and the remainder ring atoms being carbon (with appropriate hydrogen atoms unless otherwise indicated), wherein at least one ring in the ring system is aromatic. Heteroaryl groups may be optionally substituted with one or more substituents. In one embodiment, 0, 1, 2, 3, or 4 atoms of each ring of a heteroaryl group may be substituted by a substituent. Examples of heteroaryl groups include, but not limited to pyridyl, 1-oxo-pyridyl, furanyl, thienyl, pyrrolyl, oxazolyl, oxadiazolyl,

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imidazolyl, thiazolyl, isoxazolyl, quinolinyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, triazolyl, thiadiazolyl, isoquinolinyl, benzoxazolyl, benzofuranyl, indolizinyl, imidazopyridyl, tetrazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl, indolyl, azaindolyl, imidazopyridyl, quinazolinyl, 5 purinyl, pyrrolo[2,3]pyrimidinyl, pyrazolo[3,4]pyrimidinyl, benzo(b)thienyl, 2,3-thiadiazolyl, 1*H*-pyrazolo[5,1-*c*]-1,2,4-triazolyl, pyrrolo[3,4-*d*]-1,2,3-triazolyl, cyclopentatriazolyl, 3*H*-pyrrolo[3,4-*c*]isoxazolyl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, 2,3-dihydro-benzo[1,4]dioxin-5-yl, 2,3-dihydro-benzofuran-5-yl, 2,3-dihydro-benzofuran-4-yl, 2,3-dihydro-benzofuran-6-yl, 2,3-dihydro-benzofuran-6-yl, 2,3-10 dihydro-1*H*-indol-5-yl, 2,3-dihydro-1*H*-indol-4-yl, 2,3-dihydro-1*H*-indol-6-yl, 2,3-dihydro-1*H*-indol-7-yl, benzo[1,3]dioxol-4-yl, benzo[1,3]dioxol-5-yl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 2,3-dihydrobenzothien-4-yl, 2-oxoindolin-5-yl, and the like.

[42] When the heteroaryl group is substituted, it is substituted with 1 to 3 15 substituents independently selected from halogen, nitro, cyano, hydroxy, alkyl, perhaloalkyl, cycloalkyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH₂, -SO₂-alkyl, -SO₂-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH₂, -SO₂N(alkyl)alkyl, -SO₂N(H)alkyl, and -SO₂NH₂.

[43] The term "heterocyclyl" as used herein, means a 'cycloalkyl' group 20 wherein one or more of the carbon atoms replaced by -O-, -S-, -S(O₂)-, -S(O)-, -N(R^m)-, and -Si(R^m)Rⁿ-, wherein, R^m and Rⁿ are independently selected from hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, and heterocyclyl. The heterocycle may be connected to the parent molecular moiety through any carbon atom or any 25 nitrogen atom contained within the heterocycle. Examples of monocyclic heterocycle include, but are not limited to, azetidinyl, azepanyl, aziridinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolinyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, 30 piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl,

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tetrahydrofuranyl, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1.1-dioxidethiomorpholinyl (thiomorpholine sulfone), thiopyranyl, and trithianyl. Examples of bicyclic heterocycle include, but are not limited to 1,3-benzodioxolyl, 1,3-benzodithiolyl, 2,3-dihydro-1,4-benzodioxinyl, 2,3-dihydro-1-benzofuranyl, 2,3-dihydro-1-benzothienyl, 2,3-dihydro-1H-indolyl, and 1,2,3,4-tetrahydroquinolinyl. The term heterocycle also include bridged heterocyclyl systems such as azabicyclo[3.2.1]octane, azabicyclo[3.3.1]nonane, and the like.

[44] The heterocyclyl group, when it is substituted, it may be substituted on ring carbon atom(s) and/or ring nitrogen atom. For example, it is substituted on ring carbons with 1 to 3 substituents independently selected from halogen, nitro, cyano, oxo, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -C(=O)OR^{10c}, -OC(=O)R^{10c}, -C(=O)N(H)R^{10d}, -C(=O)N(alkyl)R^{10d}, -N(H)C(=O)R^{10c}, -N(H)R^{10d}, -N(alkyl)R^{10d}, -N(H)C(=O)N(H)R^{10d}, and -N(H)C(=O)N(alkyl)R^{10d}; wherein R^{10b} is selected from hydrogen, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl; R^{10c} is selected from alkyl, perhaloalkyl, and cycloalkyl; R^{10d} is selected from hydrogen, alkyl, and cycloalkyl.

[45] When the heterocyclyl group is substituted on ring nitrogen, it is substituted with a substituent selected from alkyl, cycloalkyl, aryl, heteroaryl, -SO₂R^{10c}, -C(=O)R^{10c}, -C(=O)N(H)R^{10d}, and -C(=O)N(alkyl)R^{10d}; wherein R^{10c} is selected from alkyl, perhaloalkyl, and cycloalkyl; R^{10d} is selected from hydrogen, alkyl, and cycloalkyl.

[46] When a parent group is substituted with an "oxo" group, it means a divalent oxygen (=O) becomes attached to a carbon atom of the parent group. For example, when a CH₂ group is substituted with an oxo substituent, the parent CH₂ group becomes a carbonyl (C=O) group; thus, oxo substituted on cyclohexane forms a cyclohexanone, for example.

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[47] The term “annulated” means the ring system under consideration is either annulated with another ring at a carbon atom of the cyclic system or across a bond of the cyclic system as in the case of fused or spiro ring systems.

[48] The term “bridged” means the ring system under consideration contain
5 an alkylene bridge having 1 to 4 methylene units joining two non-adjacent ring atoms.

[49] A compound, its stereoisomers, its racemates, and its pharmaceutically acceptable salt thereof as described hereinabove, wherein, the compound of general formula (I) is selected from:

10 **[50]** 4-(4-(4-chlorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 1);

[51] 4-(4-(4-fluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 2);

15 **[52]** 4-(4-(4-chloro-3-methylphenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 3);

[53] 4-(4-(4-chlorophenyl)-5-ethyl-1-methyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 4);

[54] 4-(4-(4-chlorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)-2-fluorobenzenesulfonamide (Compound 5);

20 **[55]** 4-(4-(4-chlorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)-3-fluorobenzenesulfonamide (Compound 6);

[56] 4-(4-(4-chlorophenyl)-1-ethyl-5-methyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 7);

25 **[57]** 4-(4-(3,4-difluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 8);

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[58] 4-(4-(2,4-difluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 9);

[59] 4-(4-(3-fluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 10);

5 **[60]** 4-(4-(4-fluoro-3-methylphenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 11);

[61] 4-(1,5-dimethyl-2-propionyl-4-(p-tolyl)-1H-pyrrol-3-yl)benzenesulfonamide (Compound 12);

10 **[62]** 4-(4-(4-chloro-2-fluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 13);

[63] 4-(4-(4-chloro-3-fluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 14);

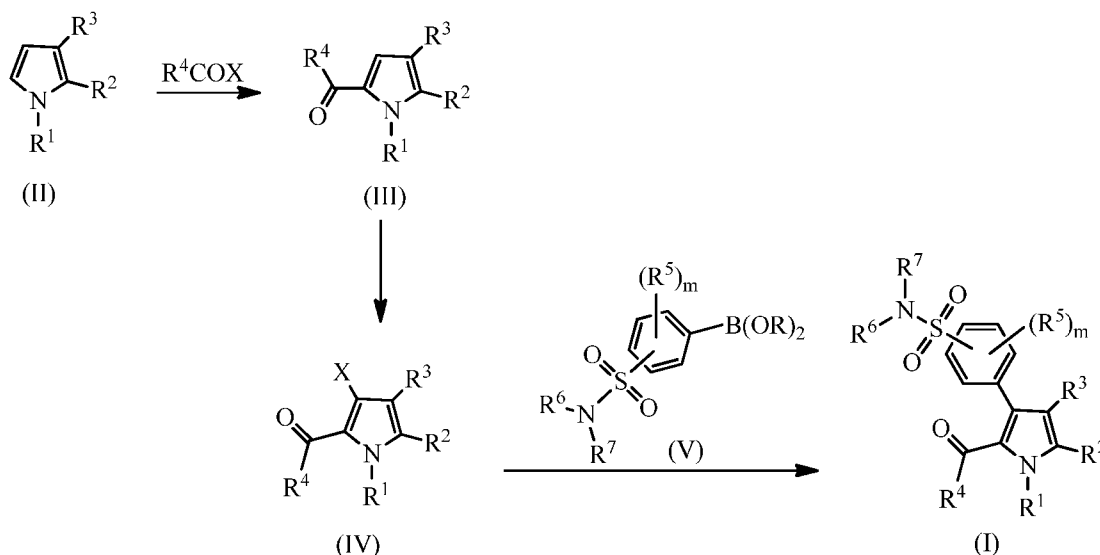
[64] 4-(4-(4-chlorophenyl)-1-methyl-2-propionyl-5-propyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 15); and

15 **[65]** 4-(4-(4-chlorophenyl)-1,5-dimethyl-2-nicotinoyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 16);

20 **[66]** According to another aspect of the present invention, the compound of general formula (I) where all the symbols are as defined earlier was prepared by methods described below. However, the synthetic methods should not be construed limiting the invention, which lies in the whole genus described by compound of formula (I) above.

25 **[67]** Scheme 1 below shows a method of preparation of the compound of the formula (I) (where R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and m are as described under compound of generic formula (I)) from compound represented by general formula (II) (where R¹, R², and R³ are same as defined under general formula (I)). The compound of formula (II) was prepared according to the procedure described in Tetrahedron Letters, 46 (2005), 4539-4542.

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Scheme-1

[68] The compound of the formula (II) is reacted with R^4COX (where X is a halogen and R^4 is as defined earlier), in the presence of acid or zinc under Friedel-Crafts reaction conditions as described in Tetrahedron Letters, 43 (2002), 8133-8135, to obtain the compound of formula (III). Preferably, the reaction is carried out in toluene in presence of zinc.

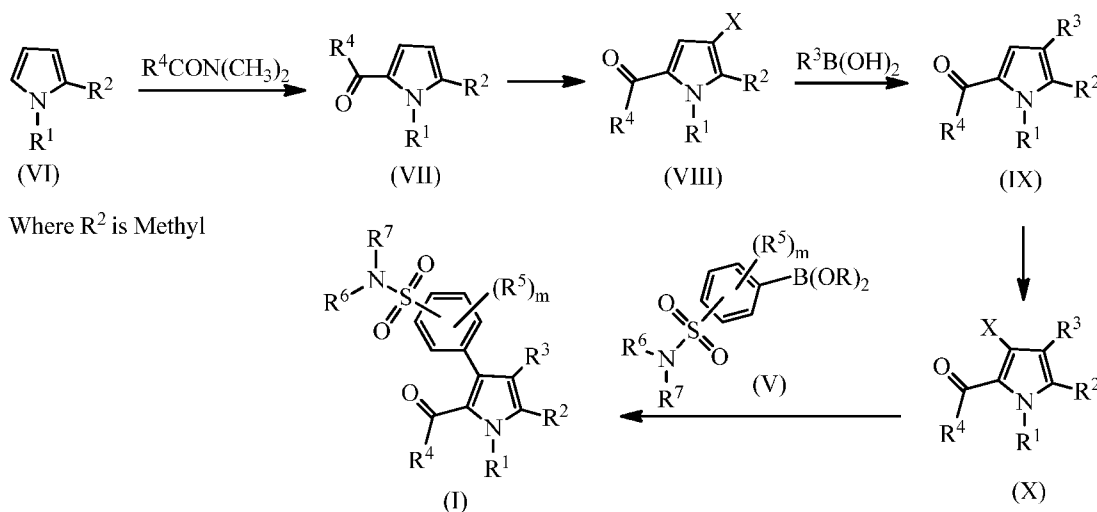
[69] The compound of the formula (III) so obtained is reacted with halogenating reagents such as bromine, N-bromosuccinimide, N-chlorosuccinimide, and phosphorous tribromide (as provided in Synlett., 2002, No. 7, 1152-1154) to obtain compound of formula (IV). Preferably, the halogenation reaction is carried out in presence of N-bromosuccinimide in THF.

[70] The compound of formula (IV) as obtained in the previous step was subjected to Suzuki coupling with boronic acids or esters represented by formula (V) (where R^5 , R^6 , R^7 , and m are as defined earlier) to obtain compound of formula (I) (where R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and m are as defined earlier). Suzuki coupling with boronic acid and esters can be carried out following the procedures well known in the art. Preferably, the Suzuki coupling is carried out in a mixture of ethanol and toluene or dioxane and water, in presence of base such as potassium

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phosphate, potassium carbonate, or the like, and tetrakis(triphenylphosphine)palladium(0) at a temperature of about 50°C or higher. Boronic acid used in this reaction can be prepared by the methods well known in the art by hydrolyzing the corresponding boronate. Boronates are generally commercially available. Besides, such boronates can also be prepared by reacting an appropriate iodo- or bromo compound with an alkyl lithium such as butyl lithium and then reacting with a borate ester or by methods well known in the art (EP 1 012 142; Review article by N. Miyaura and A. Suzuki, Chem. Rev. 1995, 95, 2457-2483).

- 10 **[71]** Scheme 2 below shows a method of preparation of the compound of the formula (I) (where R² is methyl, R¹, R³, R⁴, R⁵, R⁶, R⁷, and m are as described under compound of generic formula (I)) from compound represented by general formula (VI) (where R² is methyl and R¹ is same as defined under general formula (I)). The compound of formula (VI) was prepared according to the procedure described in US
- 15 6,884,801.



Scheme-2

- [72]** The compound of the formula (VI) is reacted with R⁴CON(CH₃)₂, (where R⁴ is as defined earlier) in the presence of POCl₃ under Vilsmeier-Haack reaction

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conditions as described in Tetrahedron, 2007, 63, 8124-8134, to obtain the compound of the formula (VII) (where R² is methyl, R¹ and R⁴ are as defined earlier).

[73] The compound of the formula (VII) so obtained is reacted with halogenating reagent such as bromine, N-bromosuccinimide, N-chlorosuccinimide, and phosphorous tribromide (as provided in Synlett., 2002, No. 7, 1152-1154) to obtain compound of formula (VIII). Preferably, the halogenation reaction is carried out in presence of N-bromosuccinimide in THF.

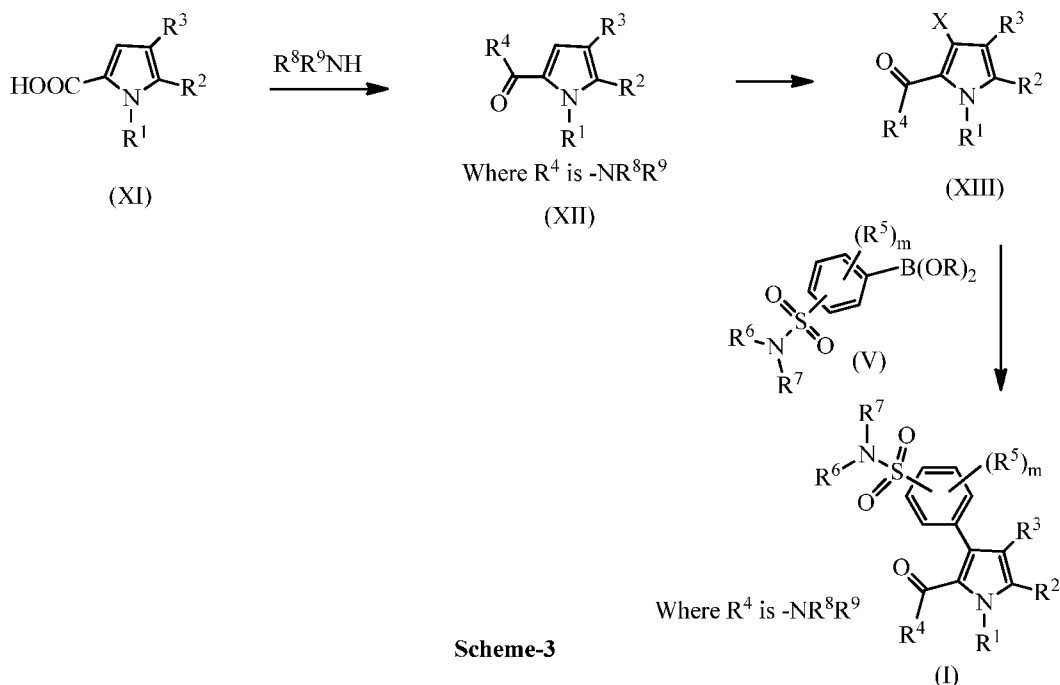
[74] The compound of formula (VIII) as obtained in the previous step was subjected to Suzuki coupling with boronic acid represented by formula R³B(OH)₂, (where R³ is as defined earlier) to obtain compound of formula (IX) (where R² is methyl, R¹, R³, and R⁴ are as defined earlier).

[75] The compound of the formula (IX) so obtained is reacted with halogenating reagent such as bromine, N-bromosuccinimide, N-chlorosuccinimide, and phosphorous tribromide (as provided in Synlett., 2002, No. 7, 1152-1154) to obtain compound of formula (X) (where X is halogen, R² is methyl, R¹, R³, and R⁴ are as defined earlier). Preferably, the halogenation reaction is carried out in presence of N-bromosuccinimide in THF.

[76] The compound of formula (X) as obtained in the previous step was subjected to Suzuki coupling with boronic acid or ester represented by formula (V) (where R⁵, R⁶, R⁷, and m are as defined earlier) to obtain compound of formula (I) (where R² is methyl, R¹, R³, R⁴, R⁵, R⁶, R⁷, and m are as defined earlier). Suzuki coupling with boronic acid and ester can be carried out by following the procedures described in Scheme 1.

Scheme 3 below shows a method of preparation of the compound of the formula (I) (where R⁴ is -NR⁸R⁹, R¹, R², R³, R⁵, R⁶, R⁷, and m are as described under compound of generic formula (I)) from compound represented by general formula (XI) (R¹, R² and R³, are same as defined under general formula (I)). The compound of formula (XI) can be prepared according to the procedure described in WO 2007/029364.

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[77] The compound of formula (XI) can be reacted with R^7R^8NH to obtain the compound of the formula (XII) (where R^4 is $-NR^8R^9$, R^1 , R^2 and R^3 are as described under compound of generic formula (I)). The said coupling reaction can be carried out according to the conditions known for converting carboxylic acids to amides to a person skilled in the art. The reaction can be carried out in the presence of an organic solvent, for example, DMF, THF, a halogenated hydrocarbon such as chloroform and dichloromethane, an aromatic hydrocarbon such as xylene, benzene, toluene, or mixtures thereof or the like in the presence of suitable base such as triethylamine, diisopropylethylamine, pyridine or the like at a temperature between 0-50°C using reagents such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 1,3-dicyclohexylcarbodiimide (DCC), and auxiliary reagents such as 1-hydroxy-7-azabenzotriazole (HOAT), hydroxybenzotriazole hydrate (HOBT) or the like.

[78] The compound of the formula (XII) so obtained can be reacted with halogenating reagent such as bromine, N-bromosuccinimide, N-chlorosuccinimide,

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and phosphorous tribromide (as provided in Synlett., 2002, No. 7, 1152-1154) to obtain compound of formula (XIII).

[79] The compound of formula (XIII) as obtained in the previous step can be subjected to Suzuki coupling with boronic acid or ester represented by formula (V) (where R⁵, R⁶, R⁷, and m are as defined earlier) to obtain compound of formula (I) (where R⁴ is -NR⁸R⁹, R¹, R², R³, R⁵, R⁶, R⁷ and m are as described under compound of generic formula (I)). Suzuki coupling with boronic acid and ester can be carried out by following the procedures described in Scheme 1.

[80] The intermediates and the compounds of the present invention may be obtained in pure form in a manner known *per se*, for example, by distilling off the solvent in vacuum and re-crystallizing the residue obtained from a suitable solvent, such as pentane, diethyl ether, isopropyl ether, chloroform, dichloromethane, ethyl acetate, acetone or their combinations or subjecting them to one of the purification methods, such as column chromatography (e.g., flash chromatography) on a suitable support material such as alumina or silica gel using an eluent such as dichloromethane, ethyl acetate, hexane, methanol, acetone and their combinations. Preparative LC-MS method is also used for the purification of the molecules described herein.

[81] Salts of the compound of formula (I) can be obtained by dissolving the compounds in a suitable solvent, for example in a chlorinated hydrocarbon, such as methylene chloride or chloroform or a low molecular weight aliphatic alcohol, for example, ethanol or isopropanol, which is then treated with the desired acid or base as described by Stephen M. Berge, et al., "Pharmaceutical Salts," a review article in Journal of Pharmaceutical sciences, 1977, 66(1), 1-19, and in the Handbook of Pharmaceutical Salts, Properties, Selection, and Use, by P. Heinrich Stahl and Camille G. Wermuth, Wiley-VCH (2002). Lists of suitable salts can also be found in Remington's Pharmaceutical Sciences, 18th ed., Mack Publishing Company, Easton, PA, 1990, p. 1445, and Stephen M. Berge et al., Journal of Pharmaceutical Science, 1977, 66(1), 1-19. For example, they can be a salt of an

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alkali metal (e.g., sodium or potassium), alkaline earth metal (e.g., calcium), or an ammonium salt.

[82] The compound of the invention or a composition thereof can potentially be administered as a pharmaceutically acceptable acid-addition, base neutralized or addition salt, formed by reaction with inorganic acids, such as hydrochloric acid, hydrobromic acid, perchloric acid, nitric acid, thiocyanic acid, sulfuric acid, and phosphoric acid, and organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, and fumaric acid, or by reaction with an inorganic base, such as sodium hydroxide and potassium hydroxide. The conversion to a salt is accomplished by treatment of the base compound with at least a stoichiometric amount of an appropriate acid. Typically, the free base is dissolved in an inert organic solvent such as diethyl ether, ethyl acetate, chloroform, ethanol, methanol, and the like, and the acid is added in a similar solvent. The mixture is maintained at a suitable temperature (e.g., between 0°C and 50°C). The resulting salt precipitates spontaneously or can be brought out of solution with a less polar solvent.

[83] The stereoisomers of the compound 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.

[84] The prodrugs can be prepared in situ during the isolation and purification of the compounds, or by separately reacting purified compound with a suitable derivatizing agent. For example, the hydroxy groups can be converted into esters via treatment with a carboxylic acid in the presence of a catalyst. Examples of cleavable alcohol prodrug moieties include substituted- or unsubstituted-, branched or unbranched lower alkyl ester moieties, e.g., ethyl esters, lower alkenyl esters, di-lower alkylamino lower-alkyl esters, e.g., dimethylaminoethyl ester, acylamino lower alkyl esters, acyloxy lower alkyl esters (e.g., pivaloyloxymethyl

ester), aryl esters, e.g., phenyl ester, aryl-lower alkyl esters, e.g., benzyl ester, optionally substituted, e.g., with methyl, halo, or methoxy substituents aryl and aryl-lower alkyl esters, amides, lower-alkyl amides, di-lower alkyl amides, and hydroxy amides.

5 **[85]** The present invention further provides a pharmaceutical composition comprising a compound as described above and a pharmaceutically acceptable carrier. The present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount, e.g., a therapeutically effective amount, including a prophylactically effective amount, of one or more of
10 the aforesaid compounds, or salts thereof, of the present invention.

[86] The pharmaceutically acceptable carrier can be any of those conventionally used and is limited only by chemico-physical considerations, such as solubility and lack of reactivity with the compound, and by the route of administration. It will be appreciated by one of skill in the art that, in addition to
15 the following described pharmaceutical compositions; the compounds of the present invention can be formulated as inclusion complexes, such as cyclodextrin inclusion complexes, or liposomes.

[87] The pharmaceutically acceptable carriers described herein, for example, vehicles, adjuvants, excipients, or diluents, are well known to those who are skilled
20 in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier be one which is chemically inert to the active compounds and one which has no detrimental side effects or toxicity under the conditions of use.

[88] The choice of carrier will be determined in part by the particular active
25 agent, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical composition of the present invention. The following formulations for oral, aerosol, parenteral, subcutaneous, intravenous, intraarterial, intramuscular,

interperitoneal, intrathecal, rectal, and vaginal administration are merely exemplary and are in no way limiting.

[89] Formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the compound dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and cornstarch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible carriers. Lozenge forms can comprise the active ingredient in a flavour, usually sucrose and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerine, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such carriers as are known in the art.

[90] The compounds of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer.

[91] Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions
5 that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The compound can be administered in a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol, isopropanol, or hexadecyl alcohol, glycols, such as
10 propylene glycol, or polyethylene glycol, or glycerol, ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, such as poly(ethyleneglycol) 400, an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, carbomers, methylcellulose,
15 hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

[92] Oils, which can be used in parenteral formulations, include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty
20 acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters. Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as for example, dimethyl dialkyl ammonium halides, and
25 alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylene-polypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl-beta-aminopropionates, and 2-
30 alkyl-imidazoline quaternary ammonium salts, and (3) mixtures thereof.

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[93] The parenteral formulations will typically contain from about 0.5 to about 25% by weight of the active ingredient in solution. Suitable preservatives and buffers can be used in such formulations. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more
5 nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations ranges from about 5 to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene
10 oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile
15 powders, granules, and tablets of the kind previously described.

[94] The compounds of the present invention may be made into injectable formulations. The requirements for effective pharmaceutical carriers for injectable compositions are well known to those of ordinary skill in the art. See *Pharmaceutics and Pharmacy Practice*, J. B. Lippincott Co., Philadelphia, Pa., Banker and
20 Chalmers, eds., pages 238-250 (1982), and *ASHP Handbook on Injectable Drugs*, Toissel, 4th ed., pages 622-630 (1986).

[95] Additionally, the compounds of the present invention may be made into suppositories by mixing with a variety of bases, such as emulsifying bases or water-soluble bases. Formulations suitable for vaginal administration may be
25 presented as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

[96] In accordance with the invention, modulation of the nicotinic cholinergic receptors, particularly $\alpha 7$, provides for efficacy in a range of cognitive states, right
30 from pre-attention to attention and subsequently working, reference and

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recognition memory. Accordingly, the present invention finds application in the treatment and prophylaxis of a multitude of diseases or conditions including, either one or combinations of, schizophrenia, schizophreniform disorder, cognitive deficits in schizophrenia, brief psychotic disorder, delusional disorder, schizoaffective disorder, shared psychotic disorder, paranoid personality disorder, schizoid personality disorder, schizotypal personality disorder, attention deficit disorder, attention deficit hyperactivity disorder, depression, maniac depression, major depressive disorder, posttraumatic stress disorder, generalized anxiety disorder, tourette's syndrome, cyclothymic disorder, dysthymic disorder, agoraphobia, panic disorder (with or without agoraphobia), phobias (including social phobia) and bipolar disorders (Morten S. Thomsen, et al., *Current Pharmaceutical Design*, 2010, 16, 323-343; Peng Zhi-Zhen et al., *Zhonghua Yi Xue Yi Chuan Xue Za Zhi*, 2008, 25, 154-158; Jared W. Young, et al., *European Neuropsychopharmacology*, (2007), 17, 145-155; Laura F. Martin, et al., *American Journal of Medical Genetics, Part B (Neuropsychiatric Genetics)*, 2007, 144B, 611-614; Laura F. Martin, et al., *Psychopharmacology*, (2004), 174, 54-64; Agnes Feher, et al., *Dement. Geriatr. Cogn. Disord.*, 2009, 28, 56-62; Timothy E. Wilens, et al., *Biochem. Pharmacol.*, 2007, 74 (8), 1212-1223; S. L. Verbois, et al., *Neuropharmacology*, 44 (2003), 224-233; Paul R. Sanberg, et al., *Pharmacol. Ther.*, 1997, 74(1), 21-25). The cholinergic system, particularly through $\alpha 7$ nAChR, also has implications in traumatic brain injury-induced psychosis. Accordingly, the present invention also finds application in the treatment of deficits in cholinergic $\alpha 7$ nAChR following traumatic brain injury.

[97] Modulation of nicotinic ACh receptors, particularly the $\alpha 7$ subtype also helps to supplement the down-regulated cholinergic receptor expression and transmission as in dementia(s), and also in slowing disease progression by reduction of the $\alpha 7$ - $\alpha \beta_{1-42}$ complexation and internalization in AD and Down's syndrome (Agneta Nordberg, et al., *Neurotoxicity Research*, 2000, 2, 157-165; Simon N. Haydar et al., *Bioorganic & Medicinal Chemistry*, 17 (2009), 5247-5258; Stephen I. Deutsch et al., *Clinical Neuropharmacology*, 2003, 26(5), 277-283).

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[98] The compounds of the invention also finds application in the treatment and prophylaxis of a number of diseases or conditions including, either one or combinations of, dementia(s) due to Alzheimer's disease, dementia with Lewy bodies, or dementia due to Down's syndrome, head trauma, stroke, hypoperfusion, Parkinson's disease, Huntington's disease, Prion diseases, progressive supranuclear palsy, radiation therapy, brain tumors, normal-pressure hydrocephalus, subdural hematoma, human immunodeficiency virus (HIV) infection, vitamin deficiency, hypothyroidism, chronic medication, drugs abuse, drug addiction, alcohol abuse, alcohol addiction, metal poisoning such as aluminium, lead, mercury, and heavy metals, syphilis, Lyme disease, viral encephalitis, fungal infection and cryptococcosis (Xilong Zhao et al., *Annals New York Academic Science*, 2001, 939, 179-186; Elaine Perry et al., *European Journal of Pharmacology*, 393 (2000), 215-222; C. R. Harrington et al., *Dementia*, 1994, 5, 215-228; Juan Wang et al., *Journal of Neuroscience Research*, 88, 807-815 (2010); Kamil Duris et al., *Stroke*, 2011, 42(12), 3530-3536). The compounds of the present invention also find application in the prophylaxis and preventive measures immediately after early-stage identification of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.

[99] Modulation of the nicotinic ACh receptors, particularly the $\alpha 4\beta 2$, $\alpha 3\beta 4$ and $\alpha 7$ receptors, also has implications in the development of therapies for nicotine or cannabis addiction and relapse prevention. Accordingly, the compounds of the invention find application in the prophylaxis or therapy of nicotine addiction, cannabis addiction, and relapse prevention of nicotine or cannabis addiction. Additionally, the invention further provides an alternative therapy for non-responding addiction patients, patients having intolerable side-effects with de-addiction therapies or those requiring long-term maintenance therapies. (Alexander Kuzmin et al., *Psychopharmacology*, (2009), 203, 99-108; Robert B. Weiss et al., *PLoS Genetics*, 2008, 4(7), e1000125; Marcello Solinas et al., *The Journal of Neuroscience*, 2007, 27(21), 5615-5620; Jon O Ebbert et al., *Patient Preference and Adherence*, 2010, 4, 355-362).

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[100] The compounds of the invention also find application in the treatment and prophylaxis of a multitude of pain conditions including, either one or combinations of, pain arising from, peripheral nervous system (PNS), post-diabetic neuralgia (PDN), post-herpetic neuralgia (PHN), multiple sclerosis, Parkinson's disease, low-back pain, fibromyalgia, post-operative pain, acute pain, chronic pain, 5 mononeuropathy, primary lateral sclerosis, pseudobulbar palsy, progressive muscular palsy, progressive bulbar palsy, postpolio syndrome, diabetes induced polyneuropathy, acute demyelinating polyneuropathy (Guillain-Barre syndrome), acute spinal muscular atrophy (Werdnig-Hoffman disease) and secondary 10 neurodegeneration (Diana L. Donnelly-Roberts et al., *Journal of Pharmacology and Experimental Therapeutics*, 1998, 285, 777-786; T. J. Rowley et al., *British Journal of Anaesthesia*, 105(2), 201-207, (2010); A. Bruchfeld et al., *Journal of Internal Medicine*, 2010, 268, 94-101).

[101] The compounds of the invention also find application in the treatment 15 and prophylaxis of a number of inflammation and pain related states involving TNF- α and providing symptomatic relief in either any one or combination of, rheumatoid arthritis, bone resorption diseases, atherosclerosis, inflammatory bowel disease, Crohn's disease, inflammation, cancer pain, muscle degeneration, osteoarthritis, osteoporosis, ulcerative colitis, rhinitis, pancreatitis, spondylitis, 20 acute respiratory distress syndrome (ARDS), joint inflammation, anaphylaxis, ischemia reperfusion injury, multiple sclerosis, cerebral malaria, septic shock, tissue rejection of graft, brain trauma, toxic shock syndrome, herpes virus infection (HSV-1 & HSV-2), herpes zoster infection, sepsis, fever, myalgias, asthma, uveitis, contact dermatitis, obesity-related diseases, and endotoxemia (Ida A. J. Giebelen et 25 al., *Shock*, 2007, 27(4), 443-447; Pena Geber et al., *Eur. J. Immunol.*, 2010, 40, 2580-2589).

[102] The invention also provides a method of 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 30 or susceptible to said disease or its symptoms or disorder with a therapeutically

effective amount of a compound of formula (I), its tautomeric forms, its stereoisomers, or its pharmaceutically acceptable salts.

[103] The disorder, condition, and disease as described above are selected from 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 decline associated with stroke, poststroke neuroprotection, 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, 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.

[104] The disease, disorder and condition as described above are particularly selected from the group classified or diagnosed as major or minor neurocognitive disorders, or disorders arising due to neurodegeneration.

[105] The invention further provides a method comprising administering a compound of formula (I) in combination with or as adjunct to medications utilized in the treatment of attention deficit hyperactivity disorders, schizophrenia, cognitive disorders such as Alzheimer's disease, Parkinson's dementia, vascular dementia, dementia associated with Lewy bodies, or traumatic brain injury. The medications can be administered simultaneously, sequentially, or cyclically with a compound of formula (I).

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[106] The invention further provides a method comprising administering a compound of formula (I) in combination with or as an adjunct to other medications, for example, acetylcholinesterase inhibitors, disease modifying drugs or biologics for neurodegenerative disorders, dopaminergic drugs, antidepressants, or a typical or atypical antipsychotic. The other medications can be administered simultaneously, sequentially, or cyclically with a compound of formula (I).

[107] The invention also provides for the use of a compound of formula (I), its tautomeric forms, its stereoisomers, and its pharmaceutically acceptable salts in the preparation of a medicament for preventing or treating a disease or its symptoms or a disorder mediated partially or completely by nicotinic acetylcholine receptors.

[108] In the use described above, 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.

[109] The use described above is in combination with or as adjunct to medications utilized in the treatment of attention deficit hyperactivity disorders, schizophrenia, cognitive disorders, Alzheimer's disease, Parkinson's dementia, vascular dementia or dementia associated with Lewy bodies, and traumatic brain injury.

[110] The use described above is in combination with or as an adjunct to acetylcholinesterase inhibitors, disease modifying drugs or biologics for neurodegenerative disorders, dopaminergic drugs, antidepressants, or a typical or atypical antipsychotic.

[111] It would be useful to list here some of the known medications that are used to treat attention deficit hyperactivity disorders, schizophrenia, cognitive disorders, Alzheimer's disease, Parkinson's dementia, vascular dementia or dementia associated with Lewy bodies, and traumatic brain injury and acetylcholinesterase inhibitors, disease modifying drugs or biologics for

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neurodegenerative disorders, dopaminergic drugs, antidepressants, or a typical or atypical antipsychotic.

[112] The terms “treat” or “prevent,” as well as words stemming therefrom, as used herein, do not necessarily imply 100% or complete treatment or prevention.

5 Rather, there are varying degrees of treatment and prevention of which one of ordinary skill in the art recognizes as having a potential benefit or therapeutic effect. In this respect, the inventive methods can provide any amount of any level of treatment or prevention of the disorder in a mammal. For example, a disorder, including symptoms or conditions thereof, may be reduced by, for example, 100%,
10 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, or 10%. Furthermore, the treatment or prevention provided by the inventive method can include treatment or prevention of one or more conditions or symptoms of the disorder. Also, for purposes herein, “treatment” or “prevention,” can encompass delaying the onset of the disorder, or a symptom or condition thereof.

15 **[113]** Following are the abbreviations used and meaning thereof in the specification:

[114] AIDS: Acquired Immunodeficiency Syndrome.

[115] HBSS: Hank's Balanced Salt Solution.

[116] HEPES: 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid.

20 **[117]** THF: Tetrahydrofuran.

[118] TLC: Thin Layer Chromatography.

[119] NMR: Nuclear Magnetic Resonance.

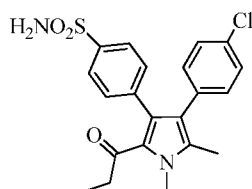
[120] $\alpha 7$ nAChR: nicotinic acetylcholine receptor $\alpha 7$ subunit.

[121] The following examples further illustrate the present invention and
25 should not be construed in any way to limit the scope of the present invention.

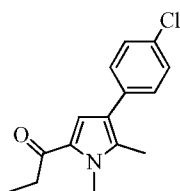
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[122] All ^1H NMR spectra were determined in the solvents indicated and chemical shifts are reported in δ units downfield from the internal standard tetramethylsilane (TMS) and interproton coupling constants are reported in Hertz (Hz).

5 [123] **Example 1: Preparation of 4-(4-(4-chlorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 1)**



[124] **Step 1:** 1-(4-(4-chlorophenyl)-1,5-dimethyl-1H-pyrrol-2-yl)propan-1-one (Compound 1a)



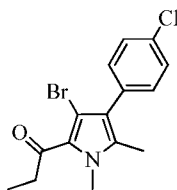
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[125] Propionyl chloride (0.64 g, 6.95 mmol) was added to the stirred solution of 3-(4-chlorophenyl)-1,2-dimethyl-1H-pyrrole (prepared according to the procedure given in Tetrahedron Letters, 2005, 46, 4539-4542) (0.65 g, 3.16 mmol) and Zinc (0.62 g, 9.48 mmol) in toluene (20 ml) at 25°C. The reaction mixture is stirred at 15 25°C for 1 h and at 60°C for 3 h. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with saturated solution of sodium bicarbonate (20 ml) and layers were separated. Aqueous layer was extracted with ethyl acetate (3×25 ml). The combined organic layer was washed with water (1×20 ml) and dried over anhydrous Na_2SO_4 . The solvent was evaporated from organic 20 layer under reduced pressure to obtain a crude product. This crude product was purified by column chromatography using 5-10% ethyl acetate in hexanes as an eluent to obtain title compound 1a (0.26 g, 31.0%). MS: m/z 262 (M+1).

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[126] ^1H NMR (CDCl_3 , 400 MHz): δ 7.35 - 7.39 (m, 2H), 7.29 - 7.30 (m, 2H), 7.02 (s, 1H), 3.95 (s, 3H), 2.83 (q, $J = 7.2$ Hz, 2H), 2.33 (s, 3H), 1.21 (t, $J = 7.2$ Hz, 3H).

[127] Step 2: 1-(3-bromo-4-(4-chlorophenyl)-1,5-dimethyl-1H-pyrrol-2-yl)propan-1-one (Compound 1b)

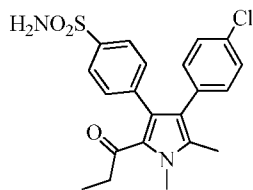


[128] To a stirred solution of 1-(4-(4-chlorophenyl)-1,5-dimethyl-1H-pyrrol-2-yl)propan-1-one (Compound 1a, 0.25 g, 0.95 mmol) in THF (10 ml) at -78°C was added a solution of N-bromosuccinimide (0.20 g, 1.15 mmol) in THF (10.0 ml) in a drop wise manner. The resulting mixture was stirred at -78°C for 10 min. The progress of reaction was monitored by TLC. The reaction mixture was quenched by addition of saturated sodium bicarbonate solution (5 ml) and evaporated under reduced pressure to obtain a residue which was dissolved in ethyl acetate (30 ml). Organic layer was washed with saturated sodium bicarbonate solution (1×10 ml) followed by water (1×10 ml). Combined organic layer was dried over anhydrous Na_2SO_4 . The solvent was evaporated from the organic layer under reduced pressure to obtain a crude product, which was purified by flash column chromatography using 10% ethyl acetate in hexanes to obtain the title compound 1b (0.085 g, 25.8%). MS: m/z 341 ($\text{M}+1$).

[129] ^1H NMR (CDCl_3 , 400 MHz): δ 7.38 - 7.42 (m, 2H), 7.21 - 7.24 (m, 2H), 3.86 (s, 3H), 2.78 (q, $J = 7.2$ Hz, 2H), 2.20 (s, 3H), 1.23 (t, $J = 7.2$ Hz, 3H).

[130] Step 3: 4-(4-(4-chlorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzene sulfonamide (Compound 1)

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[131] 4-aminosulfonylbenzene boronic acid (0.07 g, 0.35 mmol) and potassium carbonate (0.067 g, 0.48 mmol) were added to the solution of (1-(3-bromo-4-(4-chlorophenyl)-1,5-dimethyl-1H-pyrrol-2-yl)propan-1-one (Compound 1b, 0.11 g, 0.32 mmol) in a mixture of toluene: ethanol (1:3 ml) in a tube at 25°C. The nitrogen gas was bubbled through resulting mixture for 15 minutes. Tetrakis(triphenylphosphine) palladium(0) (0.019 g, 0.016 mmol) was added to the reaction mixture under nitrogen atmosphere and tube was sealed. The reaction mixture was heated at 90-95°C for 5 hr under stirring. The progress of reaction was monitored by TLC. The reaction mixture was cooled to 25°C and filtered through celite. The residue thus obtained was washed with mixture of 10% methanol in dichloromethane. The resulting filtrate was concentrated under reduced pressure to obtain a crude product, which was purified by flash column chromatography using 30% ethyl acetate in hexanes as an eluent to obtain the title compound 1 (0.037 g, 27.5%). MS: m/z 417 (M+1).

[132] ^1H NMR (CDCl_3 , 400 MHz): δ 7.81 (d, $J = 8.4$ Hz, 2H), 7.25 - 7.27 (m, 2H), 7.16 (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 4.82 (bs-exchanges with D_2O , 2H), 3.86 (s, 3H), 2.22 (s, 3H), 2.01 (q, $J = 7.2$ Hz, 2H), 0.91 (t, $J = 7.2$ Hz, 3H).

[133] The following compounds were prepared according to the procedure described above for compound 1, with appropriate changes to the reactants.

[134] 4-(4-(4-chlorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)-2-fluorobenzenesulfonamide (Compound 5) [MS: m/z 435 (M+1)],

[135] ^1H NMR (CDCl_3 , 400 MHz) δ 7.82 (t, $J = 7.8$ Hz, 1H), 7.22 (d, $J = 8.0$ Hz, 2H), 7.04 - 7.08 (m, 1H), 6.96 - 7.02 (m, 1H), 6.88 (d, $J = 8.0$ Hz, 2H), 5.11 (bs-

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exchanges with D₂O, 2H), 3.88 (s, 3H), 2.23 (s, 3H), 2.16 (q, *J* = 7.2 Hz, 2H), 0.97 (t, *J* = 7.2 Hz, 3H).

[136] 4-(4-(4-chlorophenyl)-1-ethyl-5-methyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 7) [MS: *m/z* 432 (M+1)],

5 **[137]** ¹H NMR (CDCl₃, 400 MHz): δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.85 (bs-exchanges with D₂O, 2H), 4.37 (q, *J* = 6.8 Hz, 2H), 2.26 (s, 3H), 2.11 (q, *J* = 6.8 Hz, 2H), 1.43 (t, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 6.8 Hz, 3H).

10 **[138]** 4-(4-(4-chlorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)-3-fluorobenzenesulfonamide (Compound 6) [MS: *m/z* 435 (M+1)],

[139] ¹H NMR (DMSO-d₆, 400 MHz) δ 7.56 – 7.60 (m, 2H), 7.54 (bs-exchanges with D₂O, 2H), 7.38 – 7.47 (m, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 2.21 (s, 3H), 2.10 (q, *J* = 7.2 Hz, 2H), 0.83 (t, *J* = 7.2 Hz, 3H).

15 **[140]** 4-(4-(4-fluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 2) [MS: *m/z* 401 (M+1)],

[141] ¹H NMR (CDCl₃, 400 MHz): δ 7.81-7.86 (m, 2H), 7.28 - 7.30 (m, 2H), 6.88-6.92 (m, 4H), 4.82 (bs-exchanges with D₂O, 2H), 3.89 (s, 3H), 2.24 (s, 3H), 2.13 (q, *J* = 7.2 Hz, 2H), 0.94 (t, *J* = 7.2 Hz, 3H).

20 **[142]** 4-(4-(4-chloro-3-methylphenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 3) [MS: *m/z* 431 (M+1)],

[143] ¹H NMR (CDCl₃, 400 MHz): δ 7.85 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.67 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.84 (bs-exchanges with D₂O, 2H), 3.89 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 2.13 (q, *J* = 6.8 Hz, 2H), 0.93 (t, *J* = 6.8 Hz, 3H).

25 **[144]** 4-(4-(4-chlorophenyl)-5-ethyl-1-methyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 4) [MS: *m/z* 431 (M+1)],

41

[145] ^1H NMR (CDCl_3 , 400 MHz): δ 7.84 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.17 (d, $J = 8.4$ Hz, 2H), 6.90 (d, $J = 8.4$ Hz, 2H), 4.85 (bs-exchanges with D_2O , 2H), 3.91 (s, 3H), 2.62 (q, $J = 6.8$ Hz, 2H), 2.15 (q, $J = 6.8$ Hz, 2H), 1.18 (t, $J = 6.8$ Hz, 3H), 0.93 (t, $J = 6.8$ Hz, 3H).

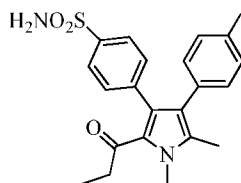
5 **[146]** 4-(4-(4-chlorophenyl)-1-methyl-2-propionyl-5-propyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 15) [MS: m/z 445 (M+1)],

[147] ^1H NMR (CDCl_3 , 400 MHz): δ 7.83 (d, $J = 8.0$ Hz, 2H), 7.28 (d, $J = 8.0$ Hz, 2H), 7.18 (d, $J = 8.4$ Hz, 2H), 6.90 (d, $J = 8.4$ Hz, 2H), 4.89 (bs-exchanges with D_2O , 2H), 3.89 (s, 3H), 2.55-2.57 (m, 2H), 2.12 (q, $J = 6.8$ Hz, 2H), 1.54-1.56 (m, 2H),
10 0.90-0.92 (m, 6H).

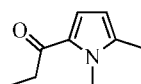
[148] 4-(4-(4-chlorophenyl)-1,5-dimethyl-2-nicotinoyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 16) [MS: m/z 466 (M+1)],

[149] ^1H NMR (CDCl_3 , 400 MHz) δ 8.47 (s, 1H), 8.38 (d, $J = 4.8$ Hz, 1H), 7.80 – 7.88 (m, 1H), 7.44 (d, $J = 8.4$ Hz, 2H), 7.23 (d, $J = 8.4$ Hz, 2H), 7.11 (dd, $J = 8.0$,
15 4.8 Hz, 1H), 6.84 – 6.96 (m, 4H), 5.11 (bs-exchanges with D_2O , 2H), 3.98 (s, 3H), 2.36 (s, 3H).

[150] Example 2: Preparation of 4-(1,5-dimethyl-2-propionyl-4-(p-tolyl)-1H-pyrrol-3-yl)benzenesulfonamide (Compound 12)



20 **[151] Step 1: 1-(1,5-dimethyl-1H-pyrrol-2-yl)propan-1-one (Compound 12a)**



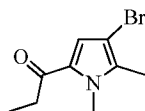
[152] POCl_3 (15.07 g, 9.16 ml, 98.00 mmol) was added to N,N-dimethylpropionamide (9.94 g, 10.8 ml, 98.00 mmol) at 0°C and under stirring.

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The reaction was continued at 0°C for 15 min. The reaction mixture was allowed to come at room temperature, stirred for 20 min and diluted with 1,2-dichloroethane (25 ml). 1,2-dimethyl-1H-pyrrole (prepared according to the procedure described in US 6,884,801) (8.50 g, 89.0 mmol) was dissolved in 1,2 dichloroethane (25 ml) and was added to the reaction mixture at 0°C. The reaction mixture was heated to reflux temperature (95°C) for 30 min. The progress of reaction was monitored by TLC. The reaction mixture was cooled to room temperature. Sodium acetate (66.90 g, 491.00 mmol) was dissolved in water (150 ml) and added to the reaction mixture. The reaction mixture was stirred at 100°C for 1 hr. The progress of reaction was monitored by TLC. Reaction mixture was cooled to room temperature, diluted with DCM (150 ml) and water (50 ml) was added to it. The resulting organic layer was separated, dried over anhydrous sodium sulfate and concentrated to get a crude product. This crude product was purified by column chromatography using 5-10% ethyl acetate in hexanes as an eluent to obtain the title compound 12a (8.60 g, 63.7%). MS: m/z 152 (M+1).

[153] ^1H NMR (CDCl_3 , 400 MHz): δ 6.93 (d, $J = 4.0$ Hz, 1H), 5.94 (d, $J = 4.0$ Hz, 1H), 3.87 (s, 3H), 2.79 (q, $J = 7.2$ Hz, 2H), 2.26 (s, 3H), 1.19 (t, $J = 7.2$ Hz, 3H).

[154] Step 2: 1-(4-bromo-1,5-dimethyl-1H-pyrrol-2-yl)propan-1-one (Compound 12b)



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[155] To a stirred solution of 1-(1,5-dimethyl-1H-pyrrol-2-yl)propan-1-one (Compound 12a, 4.00 g, 26.50 mmol) in THF (30 ml) at -78°C was added a solution of N-bromosuccinimide (5.18 g, 29.10 mmol) in THF (10.0 ml) in a drop-wise manner. The resulting mixture was stirred at -78°C for 10 min. The progress of reaction was monitored by TLC. The reaction mixture was quenched by addition of saturated sodium bicarbonate solution (5 ml) and then evaporated under reduced pressure to obtain a residue which was dissolved in ethyl acetate (75 ml). The resulting organic layer was washed with saturated sodium bicarbonate solution

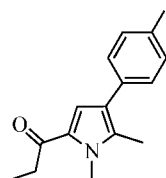
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(1×20 ml) followed by water (1×20 ml). The combined organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to obtain a crude product, which was purified by flash column chromatography using 10% ethyl acetate in hexanes to obtain the title compound 12b (4.02 g, 66.0%). MS: *m/z* 231 (M+1).

[156] ¹H NMR (CDCl₃, 400 MHz): δ 6.94 (s, 1H), 3.89 (s, 3H), 2.75 (q, *J* = 7.2 Hz, 2H), 2.24 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H).

[157] Step 3: 1-(1,5-dimethyl-4-(*p*-tolyl)-1H-pyrrol-2-yl)propan-1-one (Compound 12c)



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[158] *p*-tolylboronic acid (0.84 g, 6.21 mmol) and potassium carbonate (1.95 g, 14.12 mmol) were added to the solution of 1-(4-bromo-1,5-dimethyl-1H-pyrrol-2-yl)propan-1-one (Compound 12b, 1.30 g, 5.65 mmol) in a mixture of toluene: ethanol (4:12 ml) in a tube at 25°C. The nitrogen gas was bubbled through resulting mixture for 15 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.32 g, 0.28 mmol) was added to the reaction mixture under nitrogen atmosphere and tube was sealed. The reaction mixture was heated at 90-95°C for 5 hr under stirring. The progress of reaction was monitored by TLC. The reaction mixture was cooled to 25°C and filtered through celite. The residue thus obtained was washed with mixture of 10% methanol in dichloromethane. The resulting filtrate was concentrated under reduced pressure to obtain a crude product, which was purified by flash column chromatography using 30% ethyl acetate in hexanes as an eluent to obtain the title compound 12c (1.20 g, 88.0%). MS: *m/z* 242 (M+1).

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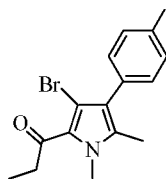
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[159] ¹H NMR (CDCl₃, 400 MHz): δ 7.21-7.29 (m, 4H), 7.05 (s, 1H), 3.96 (s, 3H), 2.84 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 2.35 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H).

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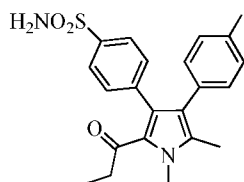
[160] Step 4: 1-(3-bromo-1,5-dimethyl-4-(p-tolyl)-1H-pyrrol-2-yl)propan-1-one (Compound 12d)



[161] To a stirred solution of 1-(1,5-dimethyl-4-(p-tolyl)-1H-pyrrol-2-yl)propan-1-one (Compound 12c, 1.18 g, 4.89 mmol) in THF (10 ml) at -78°C was added a solution of N-bromosuccinimide (0.95 g, 5.38 mmol) in THF (10.0 ml) in a drop wise manner. The resulting mixture was stirred at -78°C for 10 min. The progress of reaction was monitored by TLC. The reaction mixture was then quenched by addition of saturated sodium bicarbonate solution (10 ml) evaporated under reduced pressure to obtain a residue which was dissolved in ethyl acetate (50 ml). The resulting organic layer was washed with saturated sodium bicarbonate solution (1×10 ml) followed by water (1×10 ml). The combined organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to obtain a crude product, which was purified by flash column chromatography using 10% ethyl acetate in hexanes to obtain the title compound 12d (0.51 g, 32.6%). MS: *m/z* 321 (M+1).

[162] ¹H NMR (CDCl₃, 400 MHz): δ 7.24-7.32 (m, 4H), 3.87 (s, 3H), 3.12 (q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 2.21 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H).

[163] Step 5: 4-(1,5-dimethyl-2-propionyl-4-(p-tolyl)-1H-pyrrol-3-yl)benzenesulfonamide (Compound 12)



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[164] 4-aminosulfonylbenzene boronic acid (0.34 g, 1.72 mmol) and potassium carbonate (0.54 g, 3.90 mmol) were added to the solution of 1-(3-bromo-1,5-dimethyl-4-(p-tolyl)-1H-pyrrol-2-yl)propan-1-one (Compound 12d, 0.50 g, 1.56 mmol) in a mixture of 1,4-dioxane: water (4:1 ml) in a tube at 25°C. The nitrogen gas was bubbled through resulting mixture for 15 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.09 g, 0.078 mmol) was added to the reaction mixture under nitrogen atmosphere and tube was sealed. The reaction mixture was heated at 90-95°C for 5 hr under stirring. The progress of reaction was monitored by TLC. The reaction mixture was cooled to 25°C and filtered through celite. The residue thus obtained was washed with mixture of 10% methanol in dichloromethane. The resulting filtrate was concentrated under reduced pressure to obtain a crude product, which was purified by flash column chromatography using 30% ethyl acetate in hexanes as an eluent to obtain the title compound 12 (0.10 g, 17.1%). MS: m/z 397 (M+1).

[165] ^1H NMR (DMSO- d_6 , 400 MHz): δ 7.71 (d, $J = 8.0$ Hz, 2H), 7.39 (bs-exchanges with D_2O , 2H), 7.31 (d, $J = 8.0$ Hz, 2H), 7.04 (d, $J = 8.0$ Hz, 2H), 6.87 (d, $J = 8.0$ Hz, 2H), 3.79 (s, 3H), 2.23 (s, 3H), 2.18 (s, 3H), 2.03 (q, $J = 7.2$ Hz, 2H), 0.80 (t, $J = 7.2$ Hz, 3H).

[166] The following compounds were prepared according to the procedure described above for compound 12, with appropriate changes to the reactants.

[167] 4-(4-(3,4-difluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 8) [MS: m/z 419 (M+1)],

[168] ^1H NMR (CDCl_3 , 400 MHz): δ 7.85 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.4$ Hz, 2H), 7.00-7.02 (m, 1H), 6.75-6.78 (m, 1H), 6.64-6.67 (m, 1H), 4.83 (bs-exchanges with D_2O , 2H), 3.89 (s, 3H), 2.24 (s, 3H), 2.12 (q, $J = 6.8$ Hz, 2H), 0.94 (t, $J = 6.8$ Hz, 3H).

[169] 4-(4-(2,4-difluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 9) [MS: m/z 419 (M+1)],

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[170] ^1H NMR (CDCl_3 , 400 MHz): δ 7.83 (d, $J = 8.4$ Hz, 2H), 7.29 (d, $J = 8.4$ Hz, 2H), 6.84-6.86 (m, 1H), 6.74-6.76 (m, 2H), 4.80 (bs-exchanges with D_2O , 2H), 3.90 (s, 3H), 2.13-2.16 (m, 5H), 0.94 (t, $J = 6.8$ Hz, 3H).

[171] 4-(4-(3-fluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 10) [MS: m/z 401 (M+1)],

[172] ^1H NMR (CDCl_3 , 400 MHz): δ 7.84 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.15-7.18 (m, 1H), 6.86-6.88 (m, 1H), 6.67-6.69 (m, 2H), 4.83 (bs-exchanges with D_2O , 2H), 3.89 (s, 3H), 2.26 (s, 3H), 2.13 (q, $J = 6.8$ Hz, 2H), 0.94 (t, $J = 6.8$ Hz, 3H).

[173] 4-(4-(4-fluoro-3-methylphenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 11) [MS: m/z 415 (M+1)],

[174] ^1H NMR (DMSO-d_6 , 400 MHz): δ 7.72 (d, $J = 8.4$ Hz, 2H), 7.38 (bs-exchanges with D_2O , 2H), 7.32 (d, $J = 8.4$ Hz, 2H), 6.92-6.96 (m, 2H), 6.75-6.77 (m, 1H), 3.79 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H), 2.04 (q, $J = 6.8$ Hz, 2H), 0.80 (t, $J = 6.8$ Hz, 3H).

[175] 4-(4-(4-chloro-2-fluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 13) [MS: m/z 435 (M+1)],

[176] ^1H NMR (CDCl_3 , 400 MHz): δ 7.84 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H), 6.98-7.00 (m, 2H), 6.82 (t, $J = 8.0$ Hz, 1H), 4.85 (bs-exchanges with D_2O , 2H), 3.89 (s, 3H), 2.13-2.16 (m, 5H), 0.94 (t, $J = 6.8$ Hz, 3H).

[177] 4-(4-(4-chloro-3-fluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide (Compound 14) [MS: m/z 435 (M+1)],

[178] ^1H NMR (CDCl_3 , 400 MHz): δ 7.86 (d, $J = 8.4$ Hz, 2H), 7.30 (d, $J = 8.4$ Hz, 2H), 7.23 (t, $J = 8.0$ Hz, 1H), 6.75 (dd, $J = 8.0, 2.0$ Hz, 1H), 6.66 (dd, $J = 8.0, 2.0$ Hz, 1H), 4.81 (bs-exchanges with D_2O , 2H), 3.89 (s, 3H), 2.26 (s, 3H), 2.12 (q, $J = 6.8$ Hz, 2H), 0.94 (t, $J = 6.8$ Hz, 3H).

[179] Example 3: Pharmacological screening

[180] The compounds were tested in a cell-based real-time kinetic assay in human IMR-32 cells with native expression of $\alpha 7$ nAChR. The increase in intracellular Ca^{2+} levels was measured in a Fluorometric Imaging Plate Reader (FLIPR). Test compound solutions and agonist solutions were made in assay buffer (HBSS, pH 7.4, 20 mM HEPES, and 10 mM CaCl_2). Briefly, cells were plated into Poly-D-Lysine coated back-walled clear-bottom 96-well microplates at a density of 80,000 to 100,000 cells/well and incubated at 37°C/5% CO_2 for 40-48 h prior to the experiment. For the evaluation of compound mediated potentiation of agonist response, growth media was removed from the wells and 200 μl of FLIPR calcium 4 dye (Molecular Devices), reconstituted in assay buffer, and added to the wells. After dye loading, the microplates were incubated for 30 min at 37°C and 30 min at room temperature and then directly transferred to the FLIPR. Baseline fluorescence was monitored for the first 10 to 30 s followed by the addition of 25 μl of the test compound solution and subsequent monitoring of fluorescence changes for up to 10 min. This was followed by addition of 25 μl of agonist solution (PNU-282987, 10 μM) and measurement of fluorescence for 4 min. (Ramin Faghieh et al. Journal of Medicinal Chemistry, 2009, 52, 3377-3384).

[181] The compound-induced fold increase in agonist response (fold PAM activity) was computed by dividing the maximum effect (Max-Min fluorescence) obtained with the test compound in presence of agonist with the agonist-alone effect. EC_{50} of the compound was calculated using GraphPad Prism software version 5.0, by plotting compound concentrations against fold PAM activity.

[182] Fold activity at 1 μM concentration: the compounds with activity between 2 to 15 folds are grouped as **A**, and the compounds with activity above 15 folds are grouped as **B**.

[183] Table 1 provides the fold activity of the compounds of the present invention.

Table 1

Sr.No.	Fold activation at 1 μ M conc. (Group)	Compound No.
1	A	1, 5, 6, 7, 15, 16
2	B	2, 3, 4, 8, 9, 10, 11, 12, 13, 14

[184] All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

[185] The use of the terms “a” and “an” and “the” and “at least one” and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The use of the term “at least one” followed by a list of one or more items (for example, “at least one of A and B”) is to be construed to mean one item selected from the listed items (A or B) or any combination of two or more of the listed items (A and B), unless otherwise indicated herein or clearly contradicted by context. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to,”) unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the

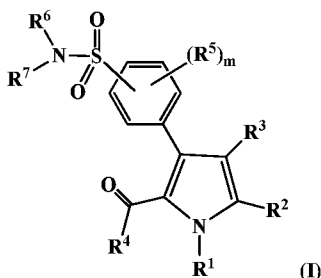
invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

[186] Preferred embodiments of this invention are described herein, including
5 the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this
10 invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

50

CLAIMS

1. A compound of formula (I), a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,



5 wherein,

R¹ is selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, and substituted- or unsubstituted- cycloalkyl;

R² is selected from substituted- or unsubstituted- alkyl and substituted- or unsubstituted- cycloalkyl;

10 R³ is selected from the group consisting of substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl;

R⁴ is selected from the group consisting of substituted- or unsubstituted- alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, substituted- or unsubstituted- heterocyclyl, and -NR⁸R⁹;

15

R⁵ is selected independently at each occurrence from the group consisting of halogen, substituted- or unsubstituted- alkyl, perhaloalkyl, substituted- or unsubstituted- cycloalkyl, -OR^{8b}, -NR⁸R⁹, and -C(=O)R^{8a}; or

R⁶ and R⁷ are independently selected from the group consisting of hydrogen and substituted- or unsubstituted- alkyl;

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R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, and substituted- or unsubstituted- cycloalkyl;

5 R^{8a} is selected from the group consisting of substituted- or unsubstituted- alkyl, perhaloalkyl, and substituted- or unsubstituted- cycloalkyl;

R^{8b} is selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, perhaloalkyl, and substituted- or unsubstituted- cycloalkyl;

m is an integer selected from 0, 1, and 2;

10 when the alkyl group is substituted, it is substituted with 1 to 3 substituents independently selected from oxo, halogen, nitro, cyano, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -SO₂R^{10a}, -C(=O)OR^{10a}, -OC(=O)R^{10a}, -C(=O)N(H)R¹⁰, -C(=O)N(alkyl)R¹⁰, -N(H)C(=O)R^{10a}, -N(H)R¹⁰, -N(alkyl)R¹⁰, -N(H)C(=O)N(H)R¹⁰, and -N(H)C(=O)N(alkyl)R¹⁰;

15 when the cycloalkyl group is substituted, it is substituted with 1 to 3 substituents independently selected from oxo, halogen, nitro, cyano, alkyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -SO₂R^{10c}, -C(=O)R^{10c}, -C(=O)OR^{10c}, -OC(=O)R^{10c}, -C(=O)N(H)R^{10d}, -C(=O)N(alkyl)R^{10d}, -N(H)C(=O)R^{10c}, -N(H)R^{10d}, -N(alkyl)R^{10d}, -N(H)C(=O)N(H)R^{10d}, and -N(H)C(=O)N(alkyl)R^{10d};

20 when the aryl group is substituted, it is substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, hydroxy, alkyl, perhaloalkyl, cycloalkyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH₂, -SO₂-alkyl, -SO₂-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH₂, -SO₂N(alkyl)alkyl, -SO₂N(H)alkyl, and -SO₂NH₂;

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when the heteroaryl group is substituted, it is substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, hydroxy, alkyl, perhaloalkyl, cycloalkyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -

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N(H)alkyl, -NH₂, -SO₂-alkyl, -SO₂-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH₂, -SO₂N(alkyl)alkyl, -SO₂N(H)alkyl, and -SO₂NH₂;

when the heterocyclyl group is substituted, it can be substituted either on a ring carbon atom(s) or on a ring hetero atom; when it substituted on a ring carbon atom(s), it is substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, oxo, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -C(=O)OR^{10c}, -OC(=O)R^{10c}, -C(=O)N(H)R^{10d}, -C(=O)N(alkyl)R^{10d}, -N(H)C(=O)R^{10c}, -N(H)R^{10d}, -N(alkyl)R^{10d}, -N(H)C(=O)N(H)R^{10d}, and -N(H)C(=O)N(alkyl)R^{10d}; and when the heterocyclyl group is substituted on a ring nitrogen, it is substituted with a substituent selected from alkyl, cycloalkyl, aryl, heteroaryl, -SO₂R^{10c}, -C(=O)R^{10c}, -C(=O)N(H)R^{10d}, and -C(=O)N(alkyl)R^{10d};

R¹⁰ is selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl;

R^{10a} is selected from alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl;

R^{10b} is selected from hydrogen, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl;

R^{10c} is selected from alkyl, perhaloalkyl, and cycloalkyl;

R^{10d} is selected from hydrogen, alkyl, and cycloalkyl.

2. The compound of formula (I), a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, as claimed in claim 1, wherein R¹ is selected from substituted- or unsubstituted- alkyl and substituted- or unsubstituted- cycloalkyl.
3. The compound of formula (I), a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, as claimed in claim 1 or 2, wherein R¹ is selected from methyl and ethyl.

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4. The compound of formula (I), a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, as claimed in any one of claim 1 to 3, wherein R² is selected from methyl, ethyl, and propyl.
5. The compound of formula (I), a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, as claimed in any one of claim 1 to 4, wherein R³ is phenyl substituted with 1 to 2 substituents selected from chloro, fluoro, and methyl.
6. The compound of formula (I), a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, as claimed in any one of claim 1 to 5, wherein R⁴ is selected from ethyl and pyridyl.
7. The compound of formula (I), a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, as claimed in any one of claim 1 to 6, wherein R⁵ is halogen.
8. The compound of formula (I), a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, as claimed in any one of claim 1 to 7, wherein m is selected from 0 and 1.
9. The compound of formula (I), a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, as claimed in any one of claim 1 to 8, wherein the compounds is selected from:
- 4-(4-(4-chlorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide;
- 4-(4-(4-fluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide;
- 4-(4-(4-chloro-3-methylphenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide;
- 4-(4-(4-chlorophenyl)-5-ethyl-1-methyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide;

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4-(4-(4-chlorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)-2-fluorobenzenesulfonamide;

4-(4-(4-chlorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)-3-fluorobenzenesulfonamide;

5 4-(4-(4-chlorophenyl)-1-ethyl-5-methyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide;

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

10 4-(4-(2,4-difluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide;

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

4-(4-(4-fluoro-3-methylphenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide;

15 4-(1,5-dimethyl-2-propionyl-4-(p-tolyl)-1H-pyrrol-3-yl)benzenesulfonamide;

4-(4-(4-chloro-2-fluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide;

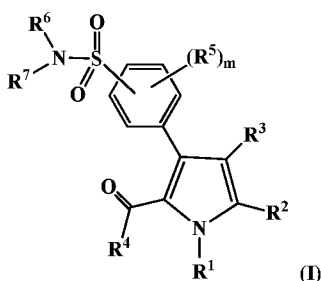
4-(4-(4-chloro-3-fluorophenyl)-1,5-dimethyl-2-propionyl-1H-pyrrol-3-yl)benzenesulfonamide;

20 4-(4-(4-chlorophenyl)-1-methyl-2-propionyl-5-propyl-1H-pyrrol-3-yl)benzenesulfonamide; and

4-(4-(4-chlorophenyl)-1,5-dimethyl-2-nicotinoyl-1H-pyrrol-3-yl)benzenesulfonamide;

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10. A pharmaceutical composition comprising a compound of any one of claims 1 to 9, a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
11. A method of preventing or treating a disease, a symptom, or a disorder mediated partially or completely by nicotinic acetylcholine receptors, said method comprising administering to a subject having or susceptible to said disease, symptom, or disorder a therapeutically effective amount of a compound of any one of claims 1 to 9, a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof.
12. A method of treating a disease, disorder, or condition mediated partially or completely by nicotinic acetylcholine receptors in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of formula (I), a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof,



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wherein,

R¹ is selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, and substituted- or unsubstituted- cycloalkyl;

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R² is selected from substituted- or unsubstituted- alkyl and substituted- or unsubstituted- cycloalkyl;

R³ is selected from the group consisting of substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl;

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R⁴ is selected from the group consisting of substituted- or unsubstituted-alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, substituted- or unsubstituted- heterocyclyl, and -NR⁸R⁹;

5 R⁵ is selected independently at each occurrence from the group consisting of halogen, substituted- or unsubstituted- alkyl, perhaloalkyl, substituted- or unsubstituted- cycloalkyl, -OR^{8b}, -NR⁸R⁹, and -C(=O)R^{8a}; or

R⁶ and R⁷ are independently selected from the group consisting of hydrogen and substituted- or unsubstituted- alkyl;

10 R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, and substituted- or unsubstituted- cycloalkyl;

R^{8a} is selected from the group consisting of substituted- or unsubstituted-alkyl, perhaloalkyl, and substituted- or unsubstituted- cycloalkyl;

15 R^{8b} is selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, perhaloalkyl, and substituted- or unsubstituted- cycloalkyl;

m is an integer selected from 0, 1, and 2;

20 when the alkyl group is substituted, it is substituted with 1 to 3 substituents independently selected from oxo, halogen, nitro, cyano, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -SO₂R^{10a}, -C(=O)OR^{10a}, -OC(=O)R^{10a}, -C(=O)N(H)R¹⁰, -C(=O)N(alkyl)R¹⁰, -N(H)C(=O)R^{10a}, -N(H)R¹⁰, -N(alkyl)R¹⁰, -N(H)C(=O)N(H)R¹⁰, and -N(H)C(=O)N(alkyl)R¹⁰;

25 when the cycloalkyl group is substituted, it is substituted with 1 to 3 substituents independently selected from oxo, halogen, nitro, cyano, alkyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -SO₂R^{10c}, -C(=O)R^{10c}, -

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C(=O)OR^{10c}, -OC(=O)R^{10c}, -C(=O)N(H)R^{10d}, -C(=O)N(alkyl)R^{10d}, -N(H)C(=O)R^{10c}, -N(H)R^{10d}, -N(alkyl)R^{10d}, -N(H)C(=O)N(H)R^{10d}, and -N(H)C(=O)N(alkyl)R^{10d};

when the aryl group is substituted, it is substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, hydroxy, alkyl, perhaloalkyl, cycloalkyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH₂, -SO₂-alkyl, -SO₂-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH₂, -SO₂N(alkyl)alkyl, -SO₂N(H)alkyl, and -SO₂NH₂;

when the heteroaryl group is substituted, it is substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, hydroxy, alkyl, perhaloalkyl, cycloalkyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH₂, -SO₂-alkyl, -SO₂-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH₂, -SO₂N(alkyl)alkyl, -SO₂N(H)alkyl, and -SO₂NH₂;

when the heterocyclyl group is substituted, it can be substituted either on a ring carbon atom(s) or on a ring hetero atom; when it substituted on a ring carbon atom(s), it is substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, oxo, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -C(=O)OR^{10c}, -OC(=O)R^{10c}, -C(=O)N(H)R^{10d}, -C(=O)N(alkyl)R^{10d}, -N(H)C(=O)R^{10c}, -N(H)R^{10d}, -N(alkyl)R^{10d}, -N(H)C(=O)N(H)R^{10d}, and -N(H)C(=O)N(alkyl)R^{10d}; and when the heterocyclyl group is substituted on a ring nitrogen, it is substituted with a substituent selected from alkyl, cycloalkyl, aryl, heteroaryl, -SO₂R^{10c}, -C(=O)R^{10c}, -C(=O)N(H)R^{10d}, and -C(=O)N(alkyl)R^{10d};

R¹⁰ is selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl;

R^{10a} is selected from alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl;

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R^{10b} is selected from hydrogen, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl;

R^{10c} is selected from alkyl, perhaloalkyl, and cycloalkyl;

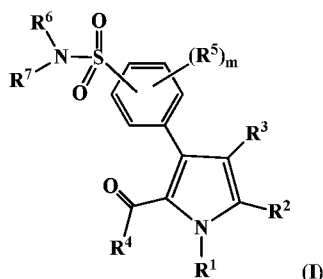
R^{10d} is selected from hydrogen, alkyl, and cycloalkyl.

- 5 **13.** The method of claim 11 or 12, wherein the disorder, condition, or disease is selected from 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
10 syndrome, Huntington's disease, cognitive deficits associated with traumatic brain injury, cognitive decline associated with stroke, poststroke neuroprotection, 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-
15 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 or lack of circulation, arthritis, rheumatoid arthritis, psoriasis, Crohn's disease, ulcerative colitis, pouchitis, inflammatory
20 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.
- 25 **14.** The method of claim 11 or 12, wherein the disease, disorder, or condition is selected from the group classified or diagnosed as major or minor neurocognitive disorders, and disorders arising due to neurodegeneration.
- 15.** The method of claim 11 or 12, further comprising administering another medication effective to treat attention deficit hyperactivity disorders,

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schizophrenia, cognitive disorders, Alzheimer's disease, Parkinson's dementia, vascular dementia or dementia associated with Lewy bodies, or traumatic brain injury.

- 5 **16.** The method of claim 11 or 12, further comprising administering an acetylcholinesterase inhibitor, a disease modifying drug or biologic for neurodegenerative disorders, a dopaminergic drug, an antidepressant, or a typical or atypical antipsychotic.
- 10 **17.** Use of a compound of any one of claims 1 to 9, a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for preventing or treating a disease, symptom, or disorder mediated partially or completely by nicotinic acetylcholine receptors.
- 18.** Use of a compound of formula (I), a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for treating a disease, disorder, or condition,



wherein,

R¹ is selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, and substituted- or unsubstituted- cycloalkyl;

20 R² is selected from substituted- or unsubstituted- alkyl and substituted- or unsubstituted- cycloalkyl;

R³ is selected from the group consisting of substituted- or unsubstituted- aryl and substituted- or unsubstituted- heteroaryl;

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R⁴ is selected from the group consisting of substituted- or unsubstituted-alkyl, substituted- or unsubstituted- cycloalkyl, substituted- or unsubstituted- aryl, substituted- or unsubstituted- heteroaryl, substituted- or unsubstituted- heterocyclyl, and -NR⁸R⁹;

5 R⁵ is selected independently at each occurrence from the group consisting of halogen, substituted- or unsubstituted- alkyl, perhaloalkyl, substituted- or unsubstituted- cycloalkyl, -OR^{8b}, -NR⁸R⁹, and -C(=O)R^{8a}; or

R⁶ and R⁷ are independently selected from the group consisting of hydrogen and substituted- or unsubstituted- alkyl;

10 R⁸ and R⁹ are each independently selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, and substituted- or unsubstituted- cycloalkyl;

R^{8a} is selected from the group consisting of substituted- or unsubstituted-alkyl, perhaloalkyl, and substituted- or unsubstituted- cycloalkyl;

15 R^{8b} is selected from the group consisting of hydrogen, substituted- or unsubstituted- alkyl, perhaloalkyl, and substituted- or unsubstituted- cycloalkyl;

m is an integer selected from 0, 1, and 2;

20 when the alkyl group is substituted, it is substituted with 1 to 3 substituents independently selected from oxo, halogen, nitro, cyano, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -SO₂R^{10a}, -C(=O)OR^{10a}, -OC(=O)R^{10a}, -C(=O)N(H)R¹⁰, -C(=O)N(alkyl)R¹⁰, -N(H)C(=O)R^{10a}, -N(H)R¹⁰, -N(alkyl)R¹⁰, -N(H)C(=O)N(H)R¹⁰, and -N(H)C(=O)N(alkyl)R¹⁰;

25 when the cycloalkyl group is substituted, it is substituted with 1 to 3 substituents independently selected from oxo, halogen, nitro, cyano, alkyl, perhaloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -SO₂R^{10c}, -C(=O)R^{10c}, -

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C(=O)OR^{10c}, -OC(=O)R^{10c}, -C(=O)N(H)R^{10d}, -C(=O)N(alkyl)R^{10d}, -N(H)C(=O)R^{10c}, -N(H)R^{10d}, -N(alkyl)R^{10d}, -N(H)C(=O)N(H)R^{10d}, and -N(H)C(=O)N(alkyl)R^{10d};

when the aryl group is substituted, it is substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, hydroxy, alkyl, perhaloalkyl, cycloalkyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH₂, -SO₂-alkyl, -SO₂-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH₂, -SO₂N(alkyl)alkyl, -SO₂N(H)alkyl, and -SO₂NH₂;

when the heteroaryl group is substituted, it is substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, hydroxy, alkyl, perhaloalkyl, cycloalkyl, heterocyclyl, -O-alkyl, -O-perhaloalkyl, -N(alkyl)alkyl, -N(H)alkyl, -NH₂, -SO₂-alkyl, -SO₂-perhaloalkyl, -N(alkyl)C(=O)alkyl, -N(H)C(=O)alkyl, -C(=O)N(alkyl)alkyl, -C(=O)N(H)alkyl, -C(=O)NH₂, -SO₂N(alkyl)alkyl, -SO₂N(H)alkyl, and -SO₂NH₂;

when the heterocyclyl group is substituted, it can be substituted either on a ring carbon atom(s) or on a ring hetero atom; when it substituted on a ring carbon atom(s), it is substituted with 1 to 3 substituents independently selected from halogen, nitro, cyano, oxo, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, -OR^{10b}, -C(=O)OR^{10c}, -OC(=O)R^{10c}, -C(=O)N(H)R^{10d}, -C(=O)N(alkyl)R^{10d}, -N(H)C(=O)R^{10c}, -N(H)R^{10d}, -N(alkyl)R^{10d}, -N(H)C(=O)N(H)R^{10d}, and -N(H)C(=O)N(alkyl)R^{10d}; and when the heterocyclyl group is substituted on a ring nitrogen, it is substituted with a substituent selected from alkyl, cycloalkyl, aryl, heteroaryl, -SO₂R^{10c}, -C(=O)R^{10c}, -C(=O)N(H)R^{10d}, and -C(=O)N(alkyl)R^{10d};

R¹⁰ is selected from hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl;

R^{10a} is selected from alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl;

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R^{10b} is selected from hydrogen, alkyl, perhaloalkyl, cycloalkyl, aryl, heteroaryl, and heterocyclyl;

R^{10c} is selected from alkyl, perhaloalkyl, and cycloalkyl;

R^{10d} is selected from hydrogen, alkyl, and cycloalkyl.

- 5 **19.** The use as claimed in claim 17 or 18, wherein the disease, disorder, or condition is selected from the group classified or diagnosed as major or minor neurocognitive disorders and disorders arising due to neurodegeneration.
- 10 **20.** The use as claimed in claim 17 or 18, which is in combination with or as adjunct to medications utilized in the treatment of attention deficit hyperactivity disorders, schizophrenia, cognitive disorders, Alzheimer's disease, Parkinson's dementia, vascular dementia or dementia associated with Lewy bodies, and traumatic brain injury.
- 15 **21.** The use as claimed in claim 17 or 18, which is in combination with or as an adjunct to acetylcholinesterase inhibitors, disease modifying drugs or biologics for neurodegenerative disorders, dopaminergic drugs, antidepressants, or a typical or atypical antipsychotic.
- 20 **22.** A compound of formula (I), a tautomer thereof, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 9 or a pharmaceutical composition as claimed in claim 10, for use in treating or preventing a disease, disorder, or condition selected from 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, 25 Huntington's disease, cognitive deficits associated with traumatic brain injury, cognitive decline associated with stroke, poststroke neuroprotection, cognitive and sensorimotor gating deficits associated with schizophrenia, cognitive deficits associated with bipolar disorder, cognitive impairments associated

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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 or lack of
5 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
10 syndrome, sepsis syndrome, depression, and rheumatoid spondylitis.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/062268

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D401/04 C07D207/333 A61K31/3140 A61K31/4439 A61P25/00
 A61P1/00 A61P17/00 A61P31/00 A61P37/00 A61P19/00
 ADD.
 According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
 Minimum documentation searched (classification system followed by classification symbols)
 C07D A61K A61P
 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
 EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/114285 A1 (LUPIN LTD [IN]; SINHA NEELIMA [IN]; JANA GOURHARI [IN]; SACHCHIDANAND) 30 August 2012 (2012-08-30) cited in the application claims 1-28 -----	1-22
A	WO 2012/131576 A1 (LUPIN LTD [IN]; SINHA NEELIMA [IN]; JANA GOURHARI [IN]; TILEKAR AJAY R) 4 October 2012 (2012-10-04) cited in the application claims 1-20 -----	1-22
A	WO 2012/104782 A1 (LUPIN LTD [IN]; SINHA NEELIMA [IN]; JANA GOURHARI [IN]; KARCHE NAVNATH) 9 August 2012 (2012-08-09) cited in the application claims 1-22 -----	1-22

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 14 August 2014	Date of mailing of the international search report 21/08/2014
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Marzi, Elena
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2014/062268

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