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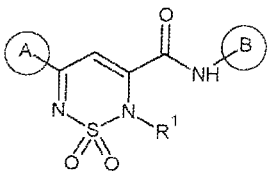
(57) Abstract: The invention relates to thiadiazine derivatives, or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof, as well as to pharmaceutical compositions containing them and to their use as modulators of α7 nicotinic acetylcholine receptor activity in a mammalian subject. Formula (I):



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THIADIAZINE DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to pharmacologically active thiadiazine compounds, or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof, as well as to pharmaceutical compositions containing them and to their use as modulators of α7 nicotinic acetylcholine receptor activity in a mammalian subject.

BACKGROUND OF THE INVENTION

Acetylcholine (ACh) exerts its functions as a neurotransmitter in the mammalian central nervous system (CNS) by binding to cholinergic receptors. The mammalian CNS contains two predominant types of ACh receptors: muscarinic (mAChR) and nicotinic (nAChR) receptors, based on the agonist activities of muscarine and nicotine, respectively. Nicotinic acetylcholine receptors are ligand-gated ion channels made up of five subunits (Purves et al. *Neuroscience 4th ed.* (2008) 122–126). The subunits of the nicotinic receptors belong to a multigene family and have been divided into two groups based on their amino acid sequences; one containing alpha, and another containing beta subunits. Pentameric assemblies of different subunit combinations result in large number of receptor subtypes with various pharmacological properties. Assembly of the most broadly expressed subtypes include muscle-type ($(\alpha1)_2\beta_1\delta\varepsilon$), ganglion-type ($(\alpha3)_2(\beta4)_3$) and CNS-type $(\alpha4)_2(\beta2)_3$ or $(\alpha7)_5$) nAChR subtypes (Le Novère N et al. *Journal of Molecular Evolution 40* (1995) 155-172). α7 subunits have been shown to form functional receptors when expressed alone, and thus are presumed to form homooligomeric pentameric receptors.

Activation of the nAChR ion channel is primarily controlled by binding of ligands at conventional agonist binding sites, but is also regulated by either negative, or positive allosteric modulators (NAMs and PAMs). The allosteric transition state model of the nAChR involves at least a resting state, an activated state and a "desensitized" closed channel state, a process by which receptors become insensitive to the agonist. Different nAChR ligands can

stabilize the conformational state of a receptor, to which they preferentially bind. For example, the agonists ACh and (-)-nicotine respectively stabilize the active and desensitized states. Changes of the activity of nicotinic receptors have been implicated in a number of diseases. Reductions in nicotinic receptors have been hypothesized to mediate cognitive deficits seen in diseases, such as Alzheimer's disease and schizophrenia. The effects of nicotine from tobacco are also mediated by nicotinic receptors, and since the effect of nicotine is to stabilize receptors in a desensitized state, an increased activity of nicotinic receptors may reduce the desire to smoke.

However, treatment with nicotinic receptor agonists, which act at the same site as ACh is problematic, because ACh not only activates, but also blocks receptor activity through processes, which include desensitization and uncompetitive blockade. Furthermore, prolonged activation appears to induce a long-lasting inactivation. Therefore, agonists of ACh can be expected to lose effectiveness upon chronic administration.

While the α7 nAChR is characterized by its fast activation kinetics and high permeability to Ca^{2+} compared to other subtypes (Delbono et al. *J. Pharmacol. Exp. Ther. 280* (1997) 428-438), it also exhibits rapid desensitization following exposure to agonists at the orthosteric site (Castro et al. *Neurosci. Lett. 164* (1993) 137-140; Couturier et al. *Neuron 5* (1990) 847-856). In spite that development of a variety of α7-selective agonists and partial agonists has been carried out in the recent years, their clinical efficacy proved to be suboptimal, due to this receptor blockade (desensitisation) following the agonist activation. This problem may be overcomed by treatment with PAMs, enhancing α7 nAChR activation mediated by the endogenous agonist. The positive modulation of α7 nAChRs has been shown to have cognitive benefits in various preclinical models (Thomsen et al. *Curr Pharm Des 16* (2010) 323-343; Lendvai et al. *Brain Res Bull 93* (2013) 86-96).

The compounds of the present invention may be useful for the treatment of diseases and conditions mediated by, or associated to the positive allosteric modulation of the α7 nAChR, including, but not limited to psychotic disorders, for example schizophrenia (Deutsch SI et al. *Schizophr Res 148* (2013) 138-144), schizophreniform disorder (Rowe AR et al. *J Psychopharmacol 29* (2015) 197-211), schizoaffective disorder (Martin LF et al. *Am J Med Genet B Neuropsychiatr Genet 144B* (2007) 611-614), delusional disorder (Carson R et al. *Neuromolecular Med 10* (2008) 377-384), brief psychotic disorder, psychotic disorder due to

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a general medical condition, substance-induced psychotic disorder, or psychotic disorder not otherwise specified, cognitive impairment including, for example the treatment of impairment of cognitive functions, as well as cognitive impairment as a result of stroke, Alzheimer's disease (Lewis AS et al. *Prog Neuropsychopharmacol Biol Psychiatry 75* (2017) 45-53), Huntington's disease (Foucault-Fruchard L et al. *Neural Regen Res 13* (2018) 737-741), Pick disease (Fehér A et al. *Dement Geriatr Cogn Disord* 28 (2009) 56-62), HIV associated dementia (Capó-Vélez CM et al. *Sci Rep 8* (2018) 1829), frontotemporal dementia (Minami SS et al. *Biochem Pharmacol 97* (2015) 454-462), Lewy body dementia (Perry EK et al. *Neuroscience 64* (1995) 385-395), vascular dementia (Putignano S et al. *Clin Interv Aging 7* (2012) 113-118), cerebrovascular disease (Si ML and Lee TJF *Circ Res* 91 (2002) 62-69) or other dementia states, and dementia associated to other degenerative disorders (amyotrophic lateral sclerosis (Kawamata et al. *Ther Adv Chronic Dis 2* (2011) 197-208), etc.), other acute or sub-acute conditions that may cause cognitive decline such as delirium (Sfera A et al. *Front Med 2* (2015) 56), traumatic brain injury (Shin SS et al. *Neural Regen Res 10* (2015) 1552-1554), senile dementia (Whitehouse PJ et et al. *Science 215* (1982) 1237-1239), mild cognitive impairment (Ikonomovic MD et al. *Arch Neurol 66* (2009) 646-651), Down's syndrome (Deutsch SI et al. *Clin Neuropharmacol 26* (2003) 277-283), depression and cognitive deficit related to other diseases and dyskinetic disorders (Parameswaran N et al. *Soc Neurosci Abstr* (2007)), such as Parkinson's disease (Quik M et al. *Biochem Pharmacol 97* (2015) 399-407), as well as neuroleptic-induced parkinsonism, or tardive dyskinesias (Terry AV and Gearhart DA *Eur J Pharmacol 571* (2007) 29-32), depression and mood disorders, including depressive disorders and episodes (Philip NS et al. *Psychopharmacology 212* (2010) 1-12), bipolar disorders (Leonard S and Freedman R. *Biol Psychiatry 60* (2006) 115-122), cyclothymic disorder (Ancín I et al. *J Affect Disord 133* (2011) 340-345), and bipolar disorder not otherwise specified, other mood disorders (Shytle RD et al. *Depression and Anxiety 16* (2002) 89-92), substance-induced mood disorder, and mood disorder not otherwise specified, anxiety disorders (Picciotto MR et al. *Neuropharmacology 96* (2015) 235-243), panic disorder and panic attacks (Zvolensky MJ et al. Clin Psychol Rev 25 (2005) 761-789), obsessive compulsive disorder (Tizabi Y et al. *Biol Psychiatry 51* (2002) 164-171), posttraumatic stress disorder (Sun R et al. *Neuroscience 344* (2017) 243-254), acute stress disorder (Mineur YS et al. *Neuropsychopharmacology 41* (2015) 1579-1587), generalized anxiety disorder (Cocores JA *Prim Care Companion J Clin Psychiatry* 10 (2008) 253-254), anxiety disorder due to a general medical condition, substance-induced anxiety disorder,

phobias, and anxiety disorder not otherwise specified, substance related disorders for example substance use or substance-induced disorders, e.g., alcohol- (de Fiebre NC and de Fiebre CM *Alcohol* 31 (2003) 149-153; Diaper AM et al. *Br J Clin Pharmacol 77* (2014) 302-314) nicotine- (Leslie FM et al. *Mol Pharmacol 83* (2013) 753-758), amphetamine- (Pubill D et al. *Pharmaceuticals 4* (2011) 822-847), phencyclidine- (Thomsen MS et al. *Neuropharmacology 56* (2009) 1001-1009), opioid- (Zhang W, Int *J Clin Exp Med 8* (2015) 1871-1879), cannabis- (Solinas M et al. *J Neurosci 27* (2007) 5615-5620), cocaine- (Francis MM et al. *Mol Pharmacol 60* (2001) 71-79), caffeine-, hallucinogen-, inhalant-, sedative-, hypnotic-, anxiolytic-, polysubstance- or other substance-related disorders, sleep disorders (McNamara JP et al. *Psychol Health Med 19* (2014) 410-419), such as narcolepsy (Krahn et al *J Clin Sleep Med 5* (2009) 390), dyssomnias, primary hypersomnia, breathing-related sleep disorders, circadian rhythm sleep disorder, and dyssomnia not otherwise specified, parasomnias, sleep terror disorder, sleepwalking disorder, and parasomnia not otherwise specified, sleep disorders related to another mental disorder (including, insomnia related to another mental disorder and hypersomnia related to another mental disorder), sleep disorder due to a general medical condition and substance-induced sleep disorder, metabolic and eating disorders (Somm E *Arch Immunol Ther Exp 62* (2014) 62: 87-101), such as anorexia nervosa (Cuesto G et al. *J Neurogenet 31* (2017) 266-287), bulimia nervosa, obesity (Lakhan SE and Kirchgessner A *J Transl Med 9* (2011) 129-139), compulsive eating disorder, binge eating disorder, and eating disorder not otherwise specified, diabetes mellitus (Marrero MB et al. *J Pharmacol Exp Ther 332* (2010) 173-180), ulcerative colitis (Salaga et al. *JPET 356* (2016) 157-169), Crohn's disease (Bencherif M et al. *Cell Mol Life Sci 68* (2011) 931-949), irritable bowel syndrome (Keszthelyi D et al. *Neurogastroenterol Motil 21* (2009) 1239-1249), autism spectrum disorders (Deutsch et al. *Clin Neuropharmacol* 33 (2010) 114-120), including autistic disorder, Asperger's disorder, Rett's disorder, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified, attention deficit hyperactivity disorder (Wilens TE and Decker MW *Biochem Pharmacol 74* (2007) 1212-1223), disruptive behaviour disorders, oppositional defiant disorder, and disruptive behaviour disorder not otherwise specified, and tic disorders such as Tourette's disorder (Gotti C and Clementi F *Prog Neurobiol 74* (2004) 363-396), personality disorders (Kamens HM et al. *Behav Genet 46* (2016) 693-704), sexual dysfunctions, such as sexual desire disorders, sexual arousal disorders, orgasmic disorders, sexual pain disorder, sexual dysfunction not otherwise specified, paraphilias, gender identity disorders, infertility (Bray C et al. *Biol Reprod 73*

(2005) 807-814), premenstrual syndrome (Gündisch D and Eibl C *Expert Opin Ther Pat 21* (2011) 1867-1896), and sexual disorders not otherwise specified, disorders of the respiratory system like cough (Canning BJ *Am J Respir Crit Care Med 195* (2017) A4498), asthma (Santana FPR et al. *Eur Respir J 48* (2016) PA5066), chronic obstructive pulmonary disease (Maouche K et al. *Proc Natl Acad Sci USA 110* (2013) 4099-4104), lung inflammation (Enioutina EY et al. *PLoS One 10* (2015) e0121128), disorders of the cardiovascular system such as cardiac failure (Mai XK et al. *J Immunol 200* (2018) 108.11), heart arrhythmia (Mazloom R et al. *PLoS One 8* (2013) e82251), and hypertension (Chen JK et al. *BMC Cardiovasc Disord* 12 (2012) 38).

The compounds of the invention are also useful in treating inflammation, inflammatory and neuropathic pain (Alsharari SD et al. *Biochem Pharmacol 86* (2013) 1201-1207), rheumatoid arthritis (van Maanen MA et al. *Arthritis & Rheumatism 60* (2009) 1272-1281), osteoarthritis (Lee SE *Neurosci Lett 548* (2013) 291-295), allergy (Yamamoto T et al. *PLoS One 9* (2014) e85888), sarcoidosis (Nicotine Treatment for Pulmonary Sarcoidosis: A Clinical Trial Pilot Study Elliott Crouser MD, Principal Investigator, Ohio State University ClinicalTrials.gov Identifier: NCT02265874), psoriasis (Westman M et al. *Scand J Immunol 70* (2009) 136-140), ataxia (Taslim N et al. *Behav Brain Res 217* (2011) 282-292), dystonia (Zimmerman CN et al. *Front Syst Neurosci 11* (2017) 43), systemic lupus erythematosus (Fairley AS and Mathis KW *Physiol Rep 5* (2017) e13213), mania (Janowsky DS et al. *Lancet 2* (1972) 632-635), restless legs syndrome (Buchfuhrer MJ *Neurotherapeutics 9* (2012) 776-790), progressive supranuclear palsy (Warren NM et al. *Brain 128* (2005) 239-245), epilepsy (Bertrand D *Epilepsy Curr 2* (2002) 191-193), myoclonus (Leppik IE *Epilepsia 44* (2003) 2-6), migraine (Liu Q et al. *J Pain Res 11* (2018) 1129-1140), amnesia (Bali Zs K et al. *Front Cell Neurosci 11* (2017) 271), chronic fatigue syndrome (Shan ZY et al. *J Magn Reson Imaging 44* (2016) 1301-1311), cataplexy (Ebben MR and Krieger AC *J Clin Sleep Med 8* (2012) 195-196), brain ischemia (Han Z et al. *J Neurochem 131* (2014) 498-508), multiple sclerosis (Di Bari M et al. *Cent Nerv Syst Agents Med Chem 17* (2017) 109-115), encephalomyelitis (Hao J et al. *Exp Neurol 227* (2011): 110–119), jetlag (Shi M et al. *eLife 3* (2014) e01473), cerebral amyloid angiopathy (Clifford PM et al. *Brain Res 1234* (2008) 158-171), sepsis (Ren C et al. *Int J Biol Sci 14* (2018) 748-759), and in general, in treating all types of diseases and disorders connected to the positive allosteric modulation of the α7 nAChR.

Furthermore, these compounds can also be combined with other therapeutic agents including, but not limited to acetylcholinesterase inhibitors (such as galantamine, rivastigmine, donepezil, tacrine, phenserine, ladostigil and ABT-089); NMDA receptor agonists or antagonists (such as memantine, neramexane, EVT101, and AZD4282); anti-amyloid antibodies including anti-amyloid humanized monoclonal antibodies (such as bapineuzumab, ACCOOl, CAD 106, AZD3102, H12A11V1); beta- (such as verubecestat, and AZD3293) or gamma-secretase inhibitors (such as LY450139 and TAK 070) or modulators; tau phosphorylation inhibitors; ApoE4 conformation modulators; p25/CDK5 inhibitors; NK1/NK3 receptor antagonists; COX-2 inhibitors (such as celecoxib, rofecoxib, valdecoxib, 406381 and 644784); LRRK2 inhibitors; HMG-CoA reductase inhibitors; NSAIDs (such as ibuprofen); vitamin E; glycine transport inhibitors; glycine site antagonists (such as lacosamide); LXR β agonists; androgen receptor modulators; blockers of Aβ oligomer formation; NR2B antagonists, anti-inflammatory compounds (such as (R)-flurbiprofen, nitroflurbiprofen, ND-1251, VP-025, HT-0712, and EHT-202); PPAR gamma agonists (such as pioglitazone and rosiglitazone); CB-1 receptor antagonists or inverse agonists (such as AVE1625); CB-2 agonists (such as 842166 and SAB378); VR-1 antagonists (such as AMG517, 705498, 782443, PAC20030, VI 14380 and A425619); bradykinin Bl receptor antagonists (such as SSR240612 and NVPSAA164); sodium channel blockers and antagonists (such as VX409 and SPI860); NOS inhibitors (such as SD6010 and 274150); antibiotics; growth hormone secretagogues (such as ibutamoren, ibutamoren mesylate, and capromorelin); potassium channel openers; AMPA agonists or AMPA modulators (such as CX-717, LY 451395, LY404187 and S-18986); GSK3 inhibitors (such as AZD1080, SAR502250 and CEP16805); neuronal nicotinic agonists; MARK ligands; M_1 or M_4 mAChR agonists or PAMs; mGluR2 antagonists or NAMs or PAMs; mGluR5 antagonists (such as AZD9272); alpha-adrenerg agonists; ADAM-10 ligands; sedatives, hypnotics, anxiolytics, antipsychotics, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents; orexin antagonists and agonists; prokineticin agonists and antagonists; T-type calcium channel antagonists; triazolopyridines benzodiazepines, barbiturates; 5-HT_{1A} antagonists (such as lecozotan); 5-HT_2 antagonists; 5-HT_4 agonists (such as PRX-03140); 5-HT_6 antagonists (such as GSK 742467, SGS-518, FK-962, SL-65.0155, SRA- 333 and xaliproden); histamine H_3 receptor antagonists and inverse agonists (such as S38093, ABT-834, ABT 829, GSK 189254 and CEP16795); PDE_4 inhibitors (such as HT0712); PDE_9 inhibitors (such as BI40936); PDE_{10} inhibitors;

HDAC inhibitors; KCNQ antagonists; $GABA_A$ inverse agonists; GABA signalling enhancers; GABA agonists, $GABA_A$ receptor alpha5 subunit NAMs or PAMs, antipsychotics; MAO-B inhibitors; dopamine transport inhibitors; noradrenaline transport inhibitors; D_2 agonists and partial agonists; anticholinergics (such as biperiden); COMT inhibitors (such as entacapone); A2a adenosine receptor antagonists; cholinergic agonists; compounds from the phenothiazine, thioxanthene (such as chlorprothixene and thiothixene), heterocyclic dibenzazepine (such as clozapine), butyrophenone (such as haloperidol), diphenylbutylpiperidine (such as pimozide) and indolone (such as molindolone) classes of neuroleptic agents; loxapine, sulpiride and risperidone; levodopa; calcium channel blockers (such as ziconotide and NMED160); MMP inhibitors; thrombolytic agents; opioid analgesics (such as codeine, fentanyl, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, propoxyphene); pramipexole; ropinirole; neutrophil inhibitory factor; SSRIs or SSNRIs; tricyclic antidepressant drugs; norepinephrine modulators; lithium; valproate; gabapentin; pregabalin; rizatriptan; zolmitriptan; naratriptan and sumatriptan or other drugs that affect receptors or enzymes that either increase the efficacy, safety, convenience, or reduce unwanted side effects or toxicity of the compounds of the present invention.

Known positive allosteric modulators of the α7 nicotinic acetylcholine receptor include 2-aniline-4-aryl thiazole derivatives (WO 2007/031440 A2, JANSSEN PHARMACEUTICA NV), amide derivatives (WO 2009/100294 A2, ABBOT LAB.), trisubstituted 1,2,4-triazoles (WO 2009/115547 A1, JANSSEN PHARMACEUTICA NV), indole derivatives (WO 2009/127678 A1, GLAXO GROUP LTD. and WO 2009/127679 A1, GLAXO GROUP LTD.), tetrazole-substituted aryl amide derivatives (WO 2009/043780 A1, HOFFMANN LA ROCHE), cyclopropyl aryl amide derivatives (WO 2009/043784 A1, HOFFMANN LA ROCHE), trisubstiuted pyrazoles (WO 2009/135944 A1, JANSSEN PHARMACEUTICA NV), pyrrole derivatives (WO 2014/141091 A1, LUPIN LTD), cyclopropylbenzene derivatives (WO 2017/165256 A1, MERCK SHARP & DOHME CORP.), and substituted bicyclic heteroaryl derivatives (WO 2018/085171 A1, MERCK SHARP & DOHME CORP.).

The present invention is directed to a novel class of compounds that exhibit positive allosteric modulation of the α7 nicotinic acetylcholine receptor.

A reference herein to a patent document or any other matter identified as prior art, is not to be taken as an admission that the document or other matter was known or that the information it contains was part of the common general knowledge as at the priority date of any of the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

An exemplary embodiment of the present invention is illustrated by way of example in the accompanying drawings in which like reference numbers indicate the same or similar elements and in which:

Figure 1 illustrates the results of place recognition test of compound Example 1. Exploration times spent in the novel [N] vs. familiar [O] arms of the Y maze are depicted). Scop: scopolamine (1 mg/kg, ip.). $^{+}p<0.05$; $^{++}p<0.01$; $^{+++}p<0.001$.

Figure 2 illustrates the results of place recognition test of compound Example 21. Exploration times spent in the novel [N] vs. familiar [O] arms of the Y maze are depicted). Scop: scopolamine (1 mg/kg, ip.). $^{+}p<0.05$; $^{++}p<0.01$; $^{+++}p<0.001$.

Figure 3 illustrates the results of place recognition test of compound Example 29. Exploration times spent in the novel [N] vs. familiar [O] arms of the Y maze are depicted). Scop: scopolamine (1 mg/kg, ip.). $^{+}p<0.05$; $+^{+}p<0.01$; $^{+++}p<0.001$.

Figure 4 illustrates the results of place recognition test of compound Example 33. Exploration times spent in the novel [N] vs. familiar [O] arms of the Y maze are depicted). Scop: scopolamine (1 mg/kg, ip.). $^{+}p<0.05$; $^{++}p<0.01$; $^{+++}p<0.001$.

Figure 5 illustrates the results of place recognition test of compound Example 37. Exploration times spent in the novel [N] vs. familiar [O] arms of the Y maze are depicted). Scop: scopolamine (1 mg/kg, ip.). $^{+}p<0.05$; $^{++}p<0.01$; $^{+++}p<0.001$.

Figure 6 illustrates the results of place recognition test of compound Example 86. Exploration times spent in the novel [N] vs. familiar [O] arms of the Y maze are depicted). Scop: scopolamine (1 mg/kg, ip.). $^{+}p<0.05$; $^{++}p<0.01$; $^{+++}p<0.001$.

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Figure 7 illustrates the results of place recognition test of compound Example 89. Exploration times spent in the novel [N] vs. familiar [O] arms of the Y maze are depicted). Scop: scopolamine (1 mg/kg, ip.). $^{+}p<0.05$; $^{++}p<0.01$; $^{+++}p<0.001$.

SUMMARY OF THE INVENTION

Unless the context requires otherwise, where the terms “comprise”, “comprises”, “comprised” or “comprising” are used in this specification (including the claims) they are to be interpreted as specifying the presence of the stated features, integers, steps or components, but not precluding the presence of one or more other features, integers, steps or components, or group thereof.

According to a first aspect of the present invention, there is provided a compound, selected from the group of:

5-(3,4-dimethoxyphenyl)-2-methyl-N-(3-methylphenyl)-1,1-dioxo-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-(1,3-dimethyl-1H-indazol-5-yl)-2-methyl-N-(3-methylphenyl)-1,1-dioxo-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-2-ethyl-N-(3-methylphenyl)-1,1-dioxo-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-2-ethyl-1,1-dioxo-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

2-ethyl-5-[4-methoxy-3-(trifluoromethyl)phenyl]-N-(3-methoxyphenyl)-1,1-dioxo-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

2-ethyl-5-[4-methoxy-3-(trifluoromethyl)phenyl]-N-(4-methoxyphenyl)-1,1-dioxo-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

2-ethyl-1,1-dioxo-5-[(1r,4r)-4-(trifluoromethyl)cyclohexyl]-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

N-(6-cyanopyridin-2-yl)-2-ethyl-1,1-dioxo-5-[(1r,4r)-4-(trifluoromethyl)cyclohexyl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-(propan-2-yl)-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

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5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-propyl-N-[3-(trifluoromethyl)phenyl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-propyl-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-[4-methoxy-3-(trifluoromethyl)phenyl]-1,1-dioxo-2-propyl-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-(4-methoxy-3-methylphenyl)-1,1-dioxo-2-propyl-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-(3-chloro-4-methoxyphenyl)-1,1-dioxo-2-propyl-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

2-(cyclopropylmethyl)-1,1-dioxo-5-[(1r,4r)-4-(trifluoromethyl)cyclohexyl]-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-(prop-2-en-1-yl)-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-N-(4-methoxyphenyl)-1,1-dioxo-2-propyl-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-N-(3-methylphenyl)-1,1-dioxo-2-propyl-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-[4-methoxy-3-(trifluoromethyl)phenyl]-1,1-dioxo-2-propyl-N-[3-(trifluoromethyl)phenyl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-N-(6-fluoropyridin-2-yl)-1,1-dioxo-2-(propan-2-yl)-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

N-(6-fluoropyridin-2-yl)-1,1-dioxo-2-(propan-2-yl)-5-[(1r,4r)-4-(trifluoromethyl)cyclohexyl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

2-(cyclopropylmethyl)-N-(6-fluoropyrazin-2-yl)-1,1-dioxo-5-[(1r,4r)-4-(trifluoromethyl)cyclohexyl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

2-[(2R)-butan-2-yl]-5-(3,4-dimethoxyphenyl)-1,1-dioxo-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

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2-ethyl-5-[4-methoxy-3-(trifluoromethyl)phenyl]-1,1-dioxo-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

1,1-dioxo-2-(propan-2-yl)-5-[(1r,4r)-4-(trifluoromethyl)cyclohexyl]-N-[6-(trifluoromethyl)pyrazin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

2-(cyclopropylmethyl)-5-(4,4-difluorocyclohexyl)-1,1-dioxo-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

2-(cyclopropylmethyl)-1,1-dioxo-5-[(1r,4r)-4-(trifluoromethyl)cyclohexyl]-N-[2-(trifluoromethyl)pyrimidin-4-yl]-2H-1λ⁶,2,6-thiadiazine-3-carboxamide;

or a pharmaceutically acceptable salt, a racemate, an enantiomer, a diastereomer, a solvate or a hydrate thereof.

According to a second aspect of the present invention, there is provided a pharmaceutical composition comprising as active ingredient a compound according to the first aspect above and at least one pharmaceutically acceptable excipient.

According to a third aspect of the presemt invention, there is provided use of compound according to the first aspect above or a pharmaceutical composition according to the second aspect above in the manufacture of a medicament for the treatment or prevention of a disease selected from the group of psychotic disorders, including, but not limited to, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorder or psychotic disorder not otherwise specified, cognitive impairment, including, but not limited to, cognitive impairment as a result of stroke, Alzheimer's disease, Huntington's disease, Pick disease, HIV associated dementia, frontotemporal dementia, Lewy body dementia, vascular dementia, cerebrovascular disease or other dementia states and dementia associated to other degenerative disorders, including, but not limited to, amyotrophic lateral sclerosis, other acute or sub-acute conditions that may cause cognitive decline, including, but not limited to, delirium, traumatic brain injury, senile dementia, mild cognitive impairment, Down’s syndrome, depression and cognitive deficit related to other diseases, and dyskinetic disorders including, but not limited to, Parkinson's disease, neuroleptic-induced parkinsonism, or tardive dyskinesias, depression and mood disorders, including, but not limited to, depressive disorders and episodes, bipolar disorders, cyclothymic disorder, and bipolar disorder not otherwise specified, other mood disorders,

substance-induced mood disorder and mood disorder not otherwise specified, anxiety disorders, panic disorder and panic attacks, obsessive compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, phobias, and anxiety disorder not otherwise specified, substance related disorders, including, but not limited to, substance use or substance-induced disorders, including, but not limited to, alcohol-, nicotine-, amphetamine-, phencyclidine-, opioid-, cannabis-, cocaine-, caffeine-, hallucinogen-, inhalant-, sedative-, hypnotic-, anxiolytic-, polysubstance- or other substance-related disorders, sleep disorders, including, but not limited to, narcolepsy, dyssomnias, primary hypersomnia, breathing-related sleep disorders, circadian rhythm sleep disorder and dyssomnia not otherwise specified, parasomnias, sleep terror disorder, sleepwalking disorder and parasomnia not otherwise specified, sleep disorders related to another mental disorder, sleep disorder due to a general medical condition and substance-induced sleep disorder, metabolic and eating disorders, including, but not limited to, anorexia nervosa, bulimia nervosa, obesity, compulsive eating disorder, binge eating disorder and eating disorder not otherwise specified, diabetes mellitus, ulcerative colitis, Crohn's disease, irritable bowel syndrome, autism spectrum disorders, including, but not limited to, autistic disorder, Asperger's disorder, Rett's disorder, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified, attention deficit hyperactivity disorder, disruptive behaviour disorders, oppositional defiant disorder and disruptive behaviour disorder not otherwise specified, and tic disorders, including, but not limited to, Tourette's disorder, personality disorders, sexual dysfunctions such as sexual desire disorders, sexual arousal disorders, orgasmic disorders, sexual pain disorder, sexual dysfunction not otherwise specified, paraphilias, gender identity disorders, infertility, premenstrual syndrome and sexual disorders not otherwise specified, disorders of the respiratory system like cough, asthma, chronic obstructive pulmonary disease, lung inflammation, disorders of the cardiovascular system such as cardiac failure, heart arrhythmia, hypertension, inflammation, inflammatory and neuropathic pain, rheumatoid arthritis, osteoarthritis, allergy, sarcoidosis, psoriasis, ataxia, dystonia, systemic lupus erythematosus, mania, restless legs syndrome, progressive supranuclear palsy, epilepsy, myoclonus, migraine, amnesia, chronic fatigue syndrome, cataplexy, brain ischemia, multiple sclerosis, encephalomyelitis, jetlag, cerebral amyloid angiopathy, and sepsis.

According to a fourth aspect of the present invention, there is provided a method for the treatment or prevention of a disease associated with α7 nicotinic acetylcholine receptor activity, the method comprising administering to a mammal in need of such treatment or prevention an effective amount of at least one compound according to the first aspect above or a pharmaceutical composition according to the second aspect above, wherein the disease associated with α7 nicotinic acetylcholine receptor activity is selected from the group of psychotic disorders, including, but not limited to, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorder or psychotic disorder not otherwise specified, cognitive impairment, including, but not limited to, cognitive impairment as a result of stroke, Alzheimer's disease, Huntington's disease, Pick disease, HIV associated dementia, frontotemporal dementia, Lewy body dementia, vascular dementia, cerebrovascular disease or other dementia states and dementia associated to other degenerative disorders, including, but not limited to, amyotrophic lateral sclerosis, other acute or sub-acute conditions that may cause cognitive decline, including, but not limited to, delirium, traumatic brain injury, senile dementia, mild cognitive impairment, Down's syndrome, depression and cognitive deficit related to other diseases, and dyskinetic disorders including, but not limited to, Parkinson's disease, neuroleptic-induced parkinsonism, or tardive dyskinesias, depression and mood disorders, including, but not limited to, depressive disorders and episodes, bipolar disorders, cyclothymic disorder, and bipolar disorder not otherwise specified, other mood disorders, substance-induced mood disorder and mood disorder not otherwise specified, anxiety disorders, panic disorder and panic attacks, obsessive compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, phobias, and anxiety disorder not otherwise specified, substance related disorders, including, but not limited to, substance use or substance-induced disorders, including, but not limited to, alcohol-, nicotine-, amphetamine-, phencyclidine-, opioid-, cannabis-, cocaine-, caffeine-, hallucinogen-, inhalant-, sedative-, hypnotic-, anxiolytic-, polysubstance- or other substance-related disorders, sleep disorders, including, but not limited to, narcolepsy, dyssomnias, primary hypersomnia, breathing-related sleep disorders, circadian rhythm sleep disorder and dyssomnia not otherwise specified, parasomnias, sleep terror disorder, sleepwalking disorder and parasomnia not otherwise specified, sleep disorders related to another mental disorder, sleep disorder due to a general medical condition and

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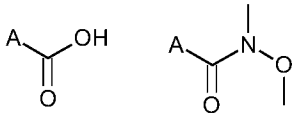
substance-induced sleep disorder, metabolic and eating disorders, including, but not limited to, anorexia nervosa, bulimia nervosa, obesity, compulsive eating disorder, binge eating disorder and eating disorder not otherwise specified, diabetes mellitus, ulcerative colitis, Crohn's disease, irritable bowel syndrome, autism spectrum disorders, including, but not limited to, autistic disorder, Asperger's disorder, Rett's disorder, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified, attention deficit hyperactivity disorder, disruptive behaviour disorders, oppositional defiant disorder and disruptive behaviour disorder not otherwise specified, and tic disorders, including, but not limited to, Tourette's disorder, personality disorders, sexual dysfunctions such as sexual desire disorders, sexual arousal disorders, orgasmic disorders, sexual pain disorder, sexual dysfunction not otherwise specified, paraphilias, gender identity disorders, infertility, premenstrual syndrome and sexual disorders not otherwise specified, disorders of the respiratory system like cough, asthma, chronic obstructive pulmonary disease, lung inflammation, disorders of the cardiovascular system such as cardiac failure, heart arrhythmia, hypertension, inflammation, inflammatory and neuropathic pain, rheumatoid arthritis, osteoarthritis, allergy, sarcoidosis, psoriasis, ataxia, dystonia, systemic lupus erythematosus, mania, restless legs syndrome, progressive supranuclear palsy, epilepsy, myoclonus, migraine, amnesia, chronic fatigue syndrome, cataplexy, brain ischemia, multiple sclerosis, encephalomyelitis, jetlag, cerebral amyloid angiopathy, and sepsis.

According to a fifth aspect of the present invention, there is provided a process for manufacturing a compound of the first aspect above, comprising reacting formula (IIa) or formula (IIb)



(IIa) (IIb)

or

– wherein the meaning of A is a saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl or is saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged heterocyclyl,– with methyl lithium, or reacting compound of formula (IIc)

(IIc)

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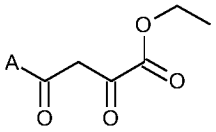
– wherein the meaning of A is an aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl or an aromatic, monocyclic or bycyclic, fused or bridged heterocyclyl, optionally substituted by one or more C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl – with tributyl(1-ethoxyvinyl)tin, or reacting compound of formula (IId)

(IId)

with acetyl chloride – wherein the meaning of A is an aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl or an aromatic, monocyclic or bycyclic, fused or bridged heterocyclyl, optionally substituted by one or more C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, halogen – to obtain the ketone derivative of formula (III)

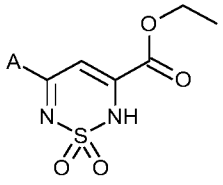
(III)

– wherein the meaning of A is as described above– which is reacted with diethyl oxalate to provide 2,4-dioxo ester derivative of formula (IV)



(IV)

– wherein the meaning of A is as described above– which is reacted with sulfamide, and then the obtained 1,1-dioxo-1,3-thiadiazine carboxylic acid ester derivative of formula (V)



(V)

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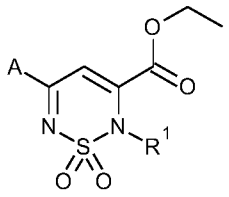
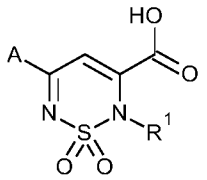
– wherein the meaning of A is as described above– is transformed to the desired end product in different ways:

ROUTE A) the compound of formula (V) is alkylated to furnish *N*-alkyl thiadiazine derivative of formula (VI)



(VI)

– wherein the meaning of A is as described aboveand R^1 is C_{1-6}alkyl, C_{1-6}alkenyl, haloC_{1-6}alkyl, C_{3-8}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, or C_{4-6}heterocyclyl – which is hydrolysed leading to carboxylic acid derivative of formula (VII)



(VII)

– wherein the meaning of A and R^1 is as described above– which is coupled with an appropriate amine (B-NH_2) – wherein the meaning of B is saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl, or a saturated, unsaturated or aromatic monocyclic or bycyclic, fused or bridged heterocyclyl, optionally substituted by one or more halogen atom or halogen atoms, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, CN, C(O)C_{1-6}alkyl, or haloC_{1-6}alkoxy – to provide the desired amide of formula (I)

or

ROUTE B) the ester derivative of formula (V) is hydrolysed to furnish the carboxylic acid derivative of formula (VIII)

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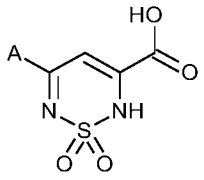
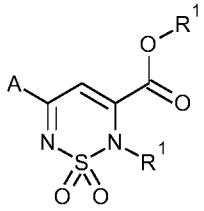


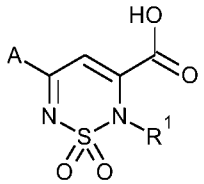
(VIII)

– wherein the meaning of A is as described above– which is then *N,O*-dialkylated in one step resulting the corresponding ester compound of formula (X)



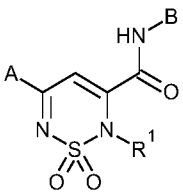
(X)

– wherein the meaning of A and R^1 is as described above– which is either hydrolysed to derivative of formula (VII)



(VII)

– wherein the meaning of A and R^1 is as described above– and then reacted with the appropriate amine (B-NH_2) resulting in the targeted amide derivative of formula (I),



(I)

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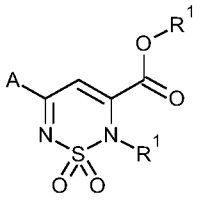
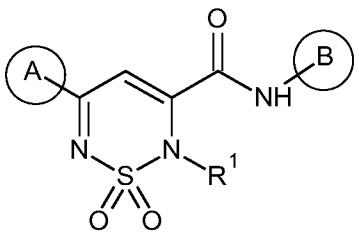
or compound of formula (X)



(X)

– wherein the meaning of A and R^1 is as described above– is transformed directly to the amide derivative of the formula (I) by reaction with the appropriate amine (B-NH_2).

Disclosed herein are compounds of formula (I),



(I)

wherein

A is saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl, or a saturated, unsaturated or aromatic monocyclic or bycyclic, fused or bridged heterocyclyl, optionally substituted by one or more halogen atom or halogen atoms, C_{1-6}alkyl, C_{1-6}alkoxy, or haloC_{1-6}alkyl;

B is saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl, or a saturated, unsaturated or aromatic monocyclic or bycyclic, fused or bridged heterocyclyl, optionally substituted by one or more halogen atom or halogen atoms, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, CN, C(O)C_{1-6}alkyl, or haloC_{1-6}alkoxy;

R^1 is C_{1-6}alkyl, C_{1-6}alkenyl, haloC_{1-6}alkyl, C_{3-8}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, or C_{4-6}heterocyclyl;

or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

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In a further aspect, the present invention provides a compound of formula (I), as defined above for use in the treatment or prevention of a disease associated with α7 nicotinic acetylcholine receptor activity.

In a further aspect, the present invention provides the use of a compound of formula (I), as defined above, for the manufacture of a medicament for the treatment or prevention of a disease associated with α7 nicotinic acetylcholine receptor activity.

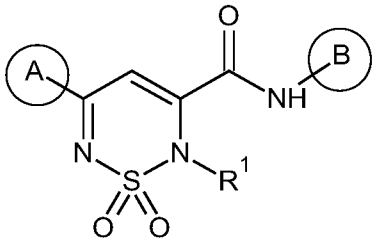
In a further aspect, the present invention provides a method for the treatment or prevention of a disease associated with α7 nicotinic acetylcholine receptor activity comprising administering to a mammal in need of such treatment or prevention an effective amount of at least one compound of formula (I), as defined above.

In a further aspect, the compounds of formula (I) as defined above, can be administered in combination with other compounds used for the treatment or prevention of a disease associated with α7 nicotinic acetylcholine receptor activity.

In a further aspect, the present invention provides a process for the manufacture of the compounds of formula (I).

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of formula (I),



(I)

wherein

A is saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl, or a saturated, unsaturated or aromatic monocyclic or bycyclic, fused or bridged heterocyclyl, optionally substituted by one or more halogen atom or halogen atoms, C_{1-6}alkyl, C_{1-6}alkoxy, or haloC_{1-6}alkyl;

B is saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl, or a saturated, unsaturated or aromatic monocyclic or bycyclic, fused or bridged heterocyclyl, optionally substituted by one or more halogen atom or halogen atoms, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, CN, C(O)C_{1-6}alkyl, or haloC_{1-6}alkoxy;

R^1 is C_{1-6}alkyl, C_{1-6}alkenyl, haloC_{1-6}alkyl, C_{3-8}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, or C_{4-6}heterocyclyl;

or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

The term "saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl" refers alone or in combination with other groups to a monovalent monocyclic or bicyclic, fused or bridged, saturated, mono-, or bi-unsaturated, or aromatic ring system comprising 3 to 10 carbon ring atoms. Saturated carbocycles include monovalent monocyclic or bicyclic, fused or bridged, saturated carbocyclic groups comprising 3 to 10 carbon ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[3.1.0]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl or adamantanyl and the like. Unsaturated carbocycles include monovalent monocyclic or bicyclic, fused or bridged, mono-, or bi-unsaturated carbocyclic groups comprising 4 to 10 carbon ring atoms. Examples include cyclobutenyl, cyclopentenyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl and the like. Aromatic carbocycles include monovalent, mono- or bicyclic aromatic carbocyclic groups comprising 6 to 10 carbon ring atoms. Examples include phenyl and naphthyl.

The term "saturated, unsaturated or aromatic monocyclic or bycyclic, fused or bridged heterocyclyl" refers alone or in combination with other groups to a monovalent monocyclic or bicyclic, fused or bridged, saturated, mono-, or bi-unsaturated, or aromatic ring system comprising 3 to 12 ring atoms, having at least one ring comprising one, two, or three or four ring heteroatoms, chosen from nitrogen, oxygen or sulphur, preferably nitrogen and oxygen. Saturated heterocycles include monovalent monocyclic or bicyclic, fused or bridged, saturated heterocyclic groups comprising 3 to 12 ring atoms, having at least one ring comprising one, two, or three or four ring heteroatoms, chosen from nitrogen, oxygen or sulphur, preferably nitrogen and oxygen. Examples include, azetidinyl, oxetanyl, pyrrolidinyl, pirazolidinyl, izoxasolidinyl, tetrahydrofuryl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, decahydroquinolinyl, decahydroisoquinolinyl,

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azaadamantanyl. Unsaturated heterocycles include monovalent monocyclic or bicyclic, fused or bridged, mono-, or bi-unsaturated heterocyclic groups comprising 5 to 12 ring atoms, having at least one ring comprising one, two, or three or four ring heteroatoms, chosen from nitrogen, oxygen or sulphur, preferably nitrogen and oxygen. Examples include, pyrrolinyl, pyrazolinyl, benzoxazolyl, benzthiazolyl, indolyl, isoindolyl, azaindolyl, benzodioxolyl, pyrazolo[1,5-a]pyrimidinyl, pyrazolo[1,5-a]pyridinyl, 1,2,3,4-tetrahydro-isoquinolinyl. Aromatic heterocycles include monovalent, mono- or bicyclic aromatic heterocyclic groups comprising 5 to 12 ring atoms, having at least one ring comprising one, two, or three or four ring heteroatoms, chosen from nitrogen, oxygen or sulphur, preferably nitrogen and oxygen. Examples include, pyrrolyl, pyrazolyl, imidazolyl, furyl, thiophenyl, oxazolyl, isoxazolyl, thiazolyl, pyridyl, pyridazyl, pyrimidinyl, pyrazinyl, benzimidazolyl, quinolinyl, isoquinolinyl.

The term "halo" or "halogen", as used herein as such or as part of another group, refers to fluoro, chloro, bromo or iodo.

The term "C_{1-6}alkyl", as used herein as such or as part of another group, refers to a branched or straight chain saturated hydrocarbon group having one, two, three, four, five or six carbon atoms including, but not limited to, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *sec*-butyl, and *tert*-butyl.

The term "haloC_{1-6}alkyl", as used herein, refers to at least one halogen, as defined above, bonded to the parent molecular moiety through an "C_{1-6}alkyl" group, as defined above. When there are several halogens, the halogens can be identical or different and the halogens can be attached to different carbon atoms or several halogens can be attached to the same carbon atom. HaloC_{1-6}alkyl groups include, but are not limited to, difluoromethyl, trifluoromethyl, trifluoroethyl and 2-chloroethyl.

The term "C_{1-6}alkoxy", as used herein refers to an C_{1-6}alkyl group, as defined above, bonded to the parent molecular moiety through an oxygen atom including, but not limited to, methoxy, ethoxy, *n*-propoxy, *i*-propoxy and *tert*-butoxy.

The term "haloC_{1-6}alkoxy", as used herein refers to at least one halogen, as defined above, bonded to the parent molecular moiety through a "C_{1-6}alkoxy" group, as defined above. When there are several halogens, the halogens can be identical or different and the halogens

can be attached to different carbon atoms or several halogens can be attached to the same carbon atom. HaloC_{1-6}alkoxy groups include, but are not limited to, trifluoromethoxyl, difluoromethoxyl, trifluoroethoxyl.

The term "C_{1-6}alkenyl", as used herein refers to linear or branched-chain monovalent hydrocarbon radical of two to six carbon atoms with at least one site of unsaturation, i.e., a carbon-carbon, sp double bond, wherein the alkenyl radical includes radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations. Examples include, but are not limited to, ethylenyl or vinyl (—CH=CH_2), allyl (—CH_2CH=CH_2), and the like.

The term "C_{3-8}cycloalkyl", as used herein as such or as part of another group, refers to cyclopropyl, cyclobutyl or cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl.

The term "C_{3-8}cycloalkylC_{1-6} alkyl", as used herein refers to refers to a C_{3-8}cycloalkyl group, as defined above, bonded to the parent molecular moiety through a "C_{1-6}alkyl" group, as defined above, including, but not limited to, cyclopropylmethyl and cyclobutylmethyl.

The term "C_{1-6}alkoxyC_{1-6}alkyl"as used herein refers to refers to a C_{1-6}alkoxy group, as defined above, bonded to the parent molecular moiety through a "C_{1-6}alkyl" group, as defined above, including, but not limited to, -C_2H_5-O-CH_3, -CH_3-O-C_2H_5, -CH_3-O-CH_3, -C_2H_5-O-C_2H_5, -C_3H_7-O-CH_3, -CH_3-O-C_3H_7, -C_3H_7-O-C_2H_5, -C_2H_5-O-C_3H_7.

The term "C_{4-6}heterocyclyl", as used herein refers to an optionally substituted moiety, consisting of 4-6 atoms forming one to two rings, incorporating one, two, or three or four heteroatoms, chosen from nitrogen, oxygen or sulfur. Examples of heterocyclyl moieties include, but are not limited to, optionally substituted piperidinyl, piperazinyl, homopiperazinyl, azepinyl, pyrrolidinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, pyridinyl, pyridazinyl, pyrimidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiazolidinyl, isothiazolidinyl, thiadiazolylidinyl, dihydrofuryl, tetrahydrofuryl, dihydropyranyl, tetrahydropyranyl, thiamorpholinyl.

The term "pharmaceutically acceptable" describes an ingredient that is useful in preparing a pharmaceutical composition, is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes those acceptable for veterinary use as well as human pharmaceutical use.

The term "hydrate" means non-covalent combinations between water and solute.

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The term “solvate” means non-covalent combinations between solvent and solute. Solvents include, but are not limited to, ethanol, 2-propanol, acetonitrile and tetrahydrofuran.

"Optional" or "optionally" means that the subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

"Optionally substituted" means unsubstituted or substituted with one or more of the substituents as described herein. Here, "one or more" means from one to the highest possible number of substitution, that is, from replacing one hydrogen to replacing all hydrogens. One, two or three substituents on a given atom are preferred.

"Treating" or "treatment" of a disease state includes:

a) preventing the disease state, i.e. causing the clinical symptoms of the disease state not to develop in a subject that may be exposed to or predisposed to the disease state, but does not yet experience or display symptoms of the disease state,

b) inhibiting the disease state, i.e., arresting the development of the disease state or its clinical symptoms, or

c) relieving the disease state, i.e., causing temporary or permanent regression of the disease state or its clinical symptoms.

The term "pharmaceutically acceptable salt" refers to a conventional acid addition salt or a base addition salt, which preserves the biological efficacy and properties of the compounds of formula (I) and which can be formed with suitable non-toxic organic or inorganic acids or organic or inorganic bases. Examples of acid addition salts include salts derived from inorganic acids, such as, but not limited to, hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulphamic acid, phosphoric acid, nitric acid and perchloric acid and derived from various organic acids, such as, but not limited to, acetic acid, propionic acid, benzoic acid, glycolic acid, phenylacetic acid, salicylic acid, malonic acid, maleic acid, oleic acid, pamoic acid, palmitic acid, benzenesulfonic acid, toluenesulfonic acid, methanesulfonic acid, oxalic acid, tartaric acid, succinic acid, citric acid, malic acid, lactic acid, glutamic acid, fumaric acid and the like. Examples of base addition salts are salts derived from

ammonium-, potassium-, sodium- and quaternary ammonium hydroxides such as tetramethylammonium hydroxide.

The term "pro-drug" refers to derivatives of compounds of formula (I) according to the invention which themselves have no therapeutic effect but containing such groups which, after *in vivo* chemical or metabolic degradation (biotransformation) become "biologically active metabolite" which is responsible for the therapeutic effect. Such decomposing groups associated with the compounds of formula (I) of the present invention, in particular those suitable for prodrugs, are known in the art and may also be applied for the compounds of the present invention (Rautio et al., *Nature Reviews - Drug Discovery* 2008, 7:255-270).

In one embodiment, the present invention relates to compounds of formula (I), wherein
A is saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl, or a saturated, unsaturated or aromatic monocyclic or bycyclic, fused or bridged heterocyclyl, containing 1-3 heteroatoms selected from the group nitrogen, oxygen and sulphur, optionally substituted by one or more halogen atom or halogen atoms, C_{1-3}alkyl, C_{1-3}alkoxy, or haloC_{1-3}alkyl;
B is saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl, or a saturated, unsaturated or aromatic monocyclic or bycyclic, fused or bridged heterocyclyl, containing 1-3 heteroatoms selected from the group nitrogen, oxygen and sulphur, optionally substituted by one or more halogen atom or halogen atoms, C_{1-3}alkyl, C_{1-3}alkoxy, haloC_{1-3}alkyl, CN, C(O)C_{1-3}alkyl, or haloC_{1-3}alkoxy;
$\mathbf{R^1}$ is C_{1-4}alkyl, C_{1-3}alkenyl, haloC_{1-3}alkyl, C_{3-5}cycloalkylC_{1-3} alkyl, C_{1-3}alkoxyC_{1-3}alkyl, or C_{4-6}heterocyclyl;
or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

In one embodiment, the present invention relates to compounds of formula (I), wherein
A is saturated, unsaturated or aromatic, 4-9 membered, monocyclic or bycyclic, fused or bridged carbocyclyl, or a saturated, unsaturated or aromatic 4-9 membered, monocyclic or bycyclic, fused or bridged heterocyclyl containing 1-3 heteroatoms selected from the group nitrogen and oxygen, optionally substituted by one or more halogen atom or halogen atoms, C_{1-6}alkyl, C_{1-6}alkoxy, or haloC_{1-6}alkyl;

B is saturated, unsaturated or aromatic, 4-9 membered, monocyclic or bycyclic, fused or bridged carbocyclyl, or a saturated, unsaturated or aromatic 4-9 membered, monocyclic or bycyclic, fused or bridged heterocyclyl containing 1-3 heteroatoms selected from the group of nitrogen and oxygen, optionally substituted by one or more halogen atom or halogen atoms, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, CN, C(O)C_{1-6}alkyl, or haloC_{1-6}alkoxy;

R^1 is C_{1-6}alkyl, C_{1-6}alkenyl, haloC_{1-6}alkyl, C_{3-8}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, or C_{4-6}heterocyclyl;

or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

In one embodiment, the present invention relates to compounds of formula (I), wherein **A** is saturated, unsaturated or aromatic, 4-9 membered, monocyclic or bycyclic, fused or bridged carbocyclyl, or a saturated, unsaturated or aromatic 4-9 membered, monocyclic or bycyclic, fused or bridged heterocyclyl containing 1-3 heteroatoms selected from the group of nitrogen, and oxygen optionally substituted by one or more halogen atom or halogen atoms, C_{1-3}alkyl, C_{1-3}alkoxy, or haloC_{1-3}alkyl;

B is saturated, unsaturated or aromatic, 4-9 membered, monocyclic or bycyclic, fused or bridged carbocyclyl, or a saturated, unsaturated or aromatic 4-9 membered, monocyclic or bycyclic, fused or bridged heterocyclyl containing 1-3 heteroatoms selected from the group nitrogen, and oxygen, optionally substituted by one or more halogen atom or halogen atoms, C_{1-3}alkyl, C_{1-3}alkoxy, haloC_{1-3}alkyl, CN, C(O)C_{1-3}alkyl, or haloC_{1-3}alkoxy;

R^1 is C_{1-4}alkyl, C_{1-3}alkenyl, haloC_{1-3}alkyl, C_{3-5}cycloalkylC_{1-3}alkyl, C_{1-3} alkoxyC_{1-3}alkyl, or C_{4-6}heterocyclyl;

or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

In one embodiment, the present invention relates to compounds of formula (I), **A** is a cyclopentenyl, cyclohexyl, phenyl, cycloheptyl, bicyclo[3.1.0]hexanyl or indazolyl, optionally substituted by one or more halogen atom or halogen atoms, C_{1-3}alkyl, C_{1-3}alkoxy, or haloC_{1-3}alkyl;

B is a phenyl, pyridyl, pyrazyl, pyrazinyl, pyrimidinyl, benzodioxolyl, 1,2,3,4-tetrahydro-isoquinolinyl, or pyrazolo[1,5-a]pyridinyl, optionally substituted by one or more halogen atom or halogen atoms, C_{1-3}alkyl, C_{1-3}alkoxy, haloC_{1-3}alkyl, CN, C(O)C_{1-3}alkyl, or haloC_{1-3}alkoxy;

R[1] is CH_3, C_2H_5, *n*Pr, *i*Pr, *n*Bu, *sec*Bu, allyl, -CH_2-CF_3, -CH_2-cBu, -CH_2-cPr, -C_2H_5-O-CH_3, or tetrahydrofuryl;
or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

In one embodiment, the present invention relates to compounds of formula (I) selected from the group of:

5-(3,4-dimethoxyphenyl)-2-methyl-*N*-(3-methylphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(1,3-dimethyl-1*H*-indazol-5-yl)-2-methyl-*N*-(3-methylphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-2-ethyl-*N*-(3-methylphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-2-ethyl-1,1-dioxo-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

2-ethyl-5-[4-methoxy-3-(trifluoromethyl)phenyl]-*N*-(3-methoxyphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

2-ethyl-5-[4-methoxy-3-(trifluoromethyl)phenyl]-*N*-(4-methoxyphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

2-ethyl-1,1-dioxo-5-[(1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl]-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

N-(6-cyanopyridin-2-yl)-2-ethyl-1,1-dioxo-5-[(1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-(propan-2-yl)-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-propyl-*N*-[3-(trifluoromethyl)phenyl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-propyl-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-[4-methoxy-3-(trifluoromethyl)phenyl]-1,1-dioxo-2-propyl-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(4-methoxy-3-methylphenyl)-1,1-dioxo-2-propyl-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3-chloro-4-methoxyphenyl)-1,1-dioxo-2-propyl-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

2-(cyclopropylmethyl)-1,1-dioxo-5-[(1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl]-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-(prop-2-en-1-yl)-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-*N*-(4-methoxyphenyl)-1,1-dioxo-2-propyl-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-*N*-(3-methylphenyl)-1,1-dioxo-2-propyl-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-[4-methoxy-3-(trifluoromethyl)phenyl]-1,1-dioxo-2-propyl-*N*-[3-(trifluoromethyl)phenyl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-*N*-(6-fluoropyridin-2-yl)-1,1-dioxo-2-(propan-2-yl)-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

N-(6-fluoropyridin-2-yl)-1,1-dioxo-2-(propan-2-yl)-5-[(1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

2-(cyclopropylmethyl)-*N*-(6-fluoropyrazin-2-yl)-1,1-dioxo-5-[(1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

2-[(2R)-butan-2-yl]-5-(3,4-dimethoxyphenyl)-1,1-dioxo-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ^6,2,6-thiadiazine-3-carboxamide;

2-ethyl-5-[4-methoxy-3-(trifluoromethyl)phenyl]-1,1-dioxo-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ^6,2,6-thiadiazine-3-carboxamide;

1,1-dioxo-2-(propan-2-yl)-5-[(1r,4r)-4-(trifluoromethyl)cyclohexyl]-N-[6-(trifluoromethyl)pyrazin-2-yl]-2H-1λ^6,2,6-thiadiazine-3-carboxamide;

2-(cyclopropylmethyl)-5-(4,4-difluorocyclohexyl)-1,1-dioxo-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ^6,2,6-thiadiazine-3-carboxamide;

2-(cyclopropylmethyl)-1,1-dioxo-5-[(1r,4r)-4-(trifluoromethyl)cyclohexyl]-N-[2-(trifluoromethyl)pyrimidin-4-yl]-2H-1λ^6,2,6-thiadiazine-3-carboxamide;

or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

In a further aspect, the present invention provides a compound of formula (I), as defined above for use in the treatment or prevention of a disease associated with α7 nicotinic acetylcholine receptor activity.

In a further aspect, the present invention provides the use of a compound of formula (I), as defined above, for the manufacture of a medicament for the treatment or prevention of a disease associated with α7 nicotinic acetylcholine receptor activity.

In a further aspect, the present invention provides a method for the treatment or prevention of a disease associated with α7 nicotinic acetylcholine receptor activity comprising administering to a mammal in need of such treatment or prevention an effective amount of at least one compound of formula (I), as defined above.

In one embodiment, the disease associated with α7 nicotinic acetylcholine receptor activity is selected from the group of psychotic disorders, including, but not limited to, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorder or psychotic disorder not otherwise specified; cognitive impairment, including, but not limited to, cognitive impairment as a result of stroke, Alzheimer's disease, Huntington's disease, Pick disease, HIV associated dementia, frontotemporal dementia, Lewy body dementia, vascular dementia, cerebrovascular disease or other dementia states and dementia associated to other degenerative disorders, including, but not limited to, amyotrophic lateral sclerosis, other acute or sub-acute conditions that may cause cognitive decline, including, but not limited to, delirium, traumatic brain injury, senile dementia, mild cognitive impairment, Down’s syndrome, depression and cognitive deficit related to other diseases, and dyskinetic disorders including, but not limited to, Parkinson's disease, neuroleptic-induced parkinsonism, or tardive dyskinesias, depression and mood disorders,

including, but not limited to, depressive disorders and episodes, bipolar disorders, cyclothymic disorder, and bipolar disorder not otherwise specified, other mood disorders, substance-induced mood disorder and mood disorder not otherwise specified; anxiety disorders, panic disorder and panic attacks, obsessive compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, phobias, and anxiety disorder not otherwise specified; substance related disorders, including, but not limited to, substance use or substance-induced disorders, including, but not limited to, alcohol-, nicotine-, amphetamine-, phencyclidine-, opioid-, cannabis-, cocaine-, caffeine-, hallucinogen-, inhalant-, sedative-, hypnotic-, anxiolytic-, polysubstance- or other substance-related disorders; sleep disorders, including, but not limited to, narcolepsy, dyssomnias, primary hypersomnia, breathing-related sleep disorders, circadian rhythm sleep disorder and dyssomnia not otherwise specified; parasomnias, sleep terror disorder, sleepwalking disorder and parasomnia not otherwise specified; sleep disorders related to another mental disorder; sleep disorder due to a general medical condition and substance-induced sleep disorder; metabolic and eating disorders, including, but not limited to, anorexia nervosa, bulimia nervosa, obesity, compulsive eating disorder, binge eating disorder and eating disorder not otherwise specified; diabetes mellitus, ulcerative colitis, Crohn’s disease, irritable bowel syndrome; autism spectrum disorders, including, but not limited to, autistic disorder, Asperger's disorder, Rett's disorder, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified; attention deficit hyperactivity disorder, disruptive behaviour disorders, oppositional defiant disorder and disruptive behaviour disorder not otherwise specified; and tic disorders, including, but not limited to, Tourette's disorder; personality disorders; sexual dysfunctions such as sexual desire disorders, sexual arousal disorders, orgasmic disorders, sexual pain disorder, sexual dysfunction not otherwise specified, paraphilias, gender identity disorders, infertility, premenstrual syndrome and sexual disorders not otherwise specified; disorders of the respiratory system like cough, asthma, chronic obstructive pulmonary disease, lung inflammation, disorders of the cardiovascular system such as cardiac failure, heart arrhythmia, hypertension; inflammation, inflammatory and neuropathic pain, rheumatoid arthritis, osteoarthritis, allergy, sarcoidosis, psoriasis, ataxia, dystonia, systemic lupus erythematosus, mania, restless legs syndrome, progressive supranuclear palsy, epilepsy, myoclonus, migraine, amnesia, chronic fatigue syndrome,

cataplexy, brain ischemia, multiple sclerosis, encephalomyelitis, jetlag, cerebral amyloid angiopathy, and sepsis.

In one embodiment, the disease associated with α7 nicotinic acetylcholine receptor activity is selected from the group of cognitive impairment, schizophrenia and autism.

The invention, further relates to combination therapies wherein a compound of the invention or a pharmaceutical composition or formulation comprising a compound of the invention is administered with another therapeutic agent or agents, for the treatment of one or more of the conditions previously indicated. Such therapeutic agents may be selected from: acetylcholinesterase inhibitors, NMDA receptor agonists or antagonists, anti-amyloid antibodies including anti-amyloid humanized monoclonal antibodies, beta- or gamma-secretase inhibitors or modulators, tau phosphorylation inhibitors, ApoE4 conformation modulators, p25/CDK5 inhibitors, NK1/NK3 receptor antagonists, COX-2 inhibitors, LRRK2 inhibitors, HMG-CoA reductase inhibitors, NSAIDs, vitamin E, glycine transport inhibitors, glycine site antagonists, LXR β agonists, androgen receptor modulators, blockers of Aβ oligomer formation, NR2B antagonists, anti-inflammatory compounds, PPAR gamma agonists, CB-1 receptor antagonists or inverse agonists, CB-2 agonists, VR-1 antagonists, bradykinin Bl receptor antagonists, sodium channel blockers and antagonists, NOS inhibitors, antibiotics, growth hormone secretagogues, potassium channel openers, AMPA agonists or AMPA modulators, GSK3 inhibitors, neuronal nicotinic agonists, MARK ligands, M_1 or M_4 mAChR agonists or PAMs, mGluR2 antagonists or NAMs or PAMs, mGluR5 antagonists, alpha-adrenerg agonists, ADAM-10 ligands, sedatives, hypnotics, anxiolytics, antipsychotics, cyclopyrrolones, imidazopyridines, pyrazolopyrimidines, minor tranquilizers, melatonin agonists and antagonists, melatonergic agents, orexin antagonists and agonists, prokineticin agonists and antagonists, T-type calcium channel antagonists, triazolopyridines benzodiazepines, barbiturates, 5-HT_{1A} antagonists, 5-HT_2 antagonists, 5-HT_4 agonists, 5-HT_6 receptor antagonists, histamine H_3 receptor antagonists and inverse agonists, PDE_4 inhibitors, PDE_9 inhibitors, PDE_{10} inhibitors, HDAC inhibitors, KCNQ antagonists, $GABA_A$ inverse agonists, GABA signalling enhancers, GABA agonists, $GABA_A$ receptor alpha5 subunit NAMs or PAMs, antipsychotics, MAO-B inhibitors, dopamine transport inhibitors, noradrenaline transport inhibitors, D_2 agonists and partial agonists, anticholinergics, COMT inhibitors, A2a adenosine receptor antagonists, cholinergic agonists, neuroleptic agents, loxapine, sulpiride and risperidone, levodopa, calcium channel blockers, MMP inhibitors,

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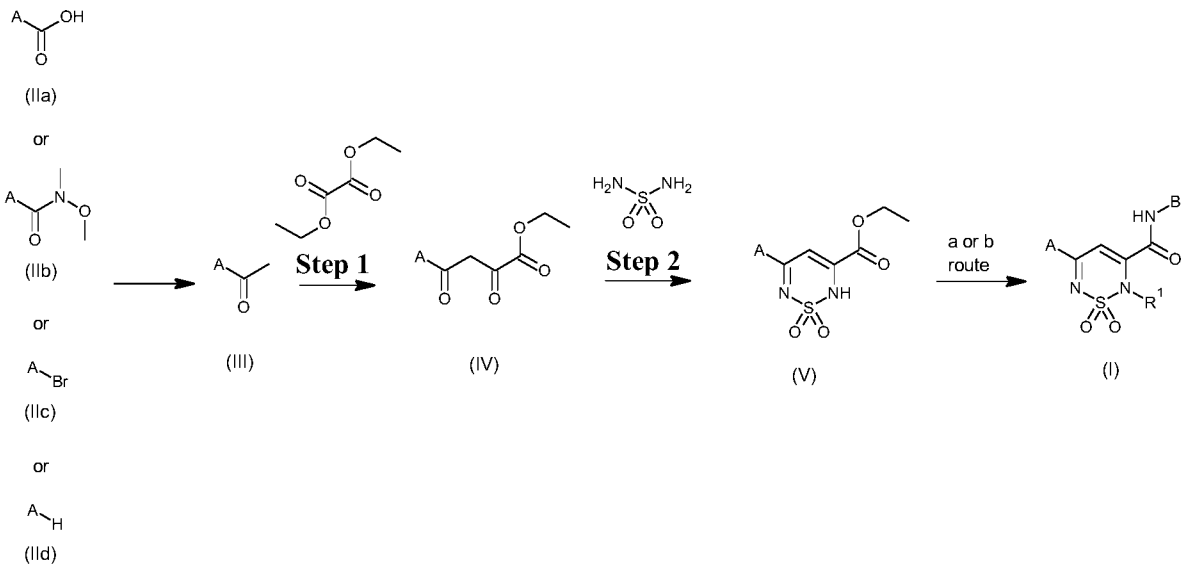
thrombolytic agents, opioid analgesics, pramipexole, ropinirole, neutrophil inhibitory factor, SSRIs or SSNRIs, tricyclic antidepressant drugs, norepinephrine modulators, lithium, valproate, gabapentin, pregabalin, rizatriptan, zolmitriptan, naratriptan, and sumatriptan.

In one embodiment, the therapeutic agents are selected from the goup of: acetylcholinesterase inhibitors, NMDA receptor antagonists, beta- secretase inhibitors, antipsychotics, $GABA_A$ receptor alpha5 subunit NAMs or PAMs, histamine H_3 receptor antagonists, 5-HT_6 receptor antagonists, M1 or M4 mAChR agonists or PAMs, mGluR2 antagonists or NAMs or PAMs, and levodopa.

In a further aspect the present invention provides a process for the manufacture of the compounds of formula (I) according to the following reaction route:

Throughout the specification, general formulae are designated by Roman numerals (I), (II), (III) etc.



ROUTE A)

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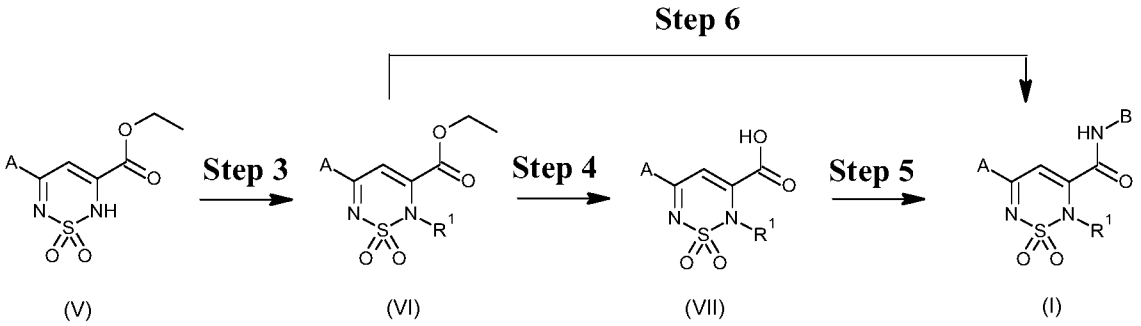
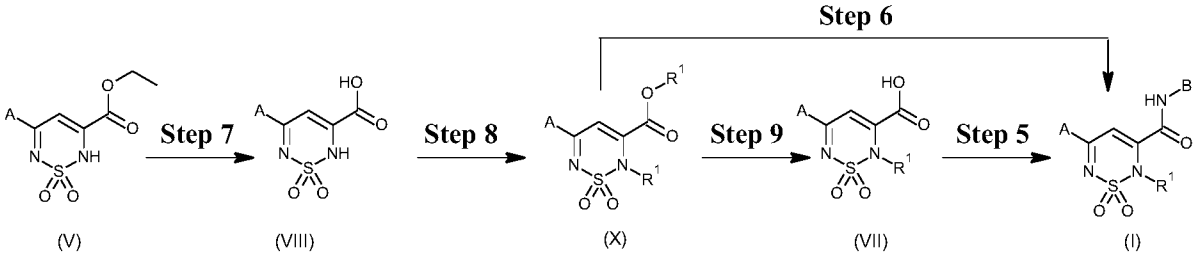


ROUTE B)

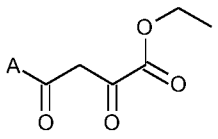


Reacting a carboxylic acid of formula (IIa) or a carboxylic acid derivative of formula (IIb) – wherein the meaning of A is described above for compound of formula (I) – with methyl lithium, or reacting compound of formula (IIc) – wherein the meaning of A is an aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl or a saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged heterocyclyl, optionally substituted by one or more of C_{1-6}alkyl, C_{1-6}alkoxy, or haloC_{1-6}alkyl – with tributyl(1-ethoxyvinyl)tin, or reacting compound of formula (IId) with acetyl chloride – wherein the meaning of A is an aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl or a saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged heterocyclyl, optionally substituted by one or more of C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, or halogen – ketone derivative of formula (III) was obtained

(III)

– wherein the meaning of A is as described above for formula (I) – and

compound of formula (III) is reacted with diethyl oxalate to provide 2,4-dioxo ester derivative of formula (IV)



(IV)

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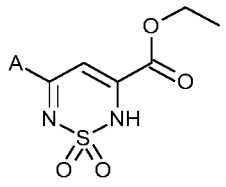
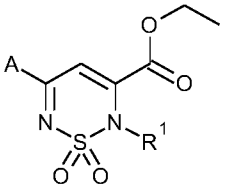
– wherein the meaning of A is as described above for formula (I) – which is reacted with sulfamide, then the obtained 1,1-dioxo-1,3-thiadiazine carboxylic acid ester derivative of formula (V)



(V)

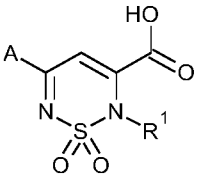
– wherein the meaning of A is as described above for formula (I) – can be transformed to the desired end product of the formula (I) in different ways:

ROUTE A) compound of formula (V) is alkylated to furnish *N*-alkyl thiadiazine derivative of formula (VI)



(VI)

– wherein the meaning of A and R^1 is as described above for formula (I) – which is hydrolysed leading to carboxylic acid derivative of formula (VII)



(VII)

– wherein the meaning of A and R^1 is as described above for formula (I) – which is coupled with an appropriate amine ($B\text{-}NH_2$) – wherein the meaning of B is as described above for formula (I) – to provide the desired amide of formula (I);

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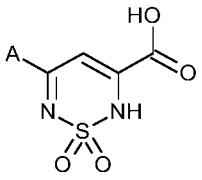
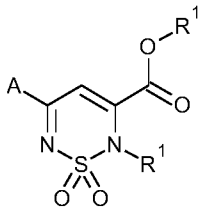
or

ROUTE B) the ester derivative of formula (V) is hydrolysed to furnish the carboxylic acid derivative of formula (VIII)



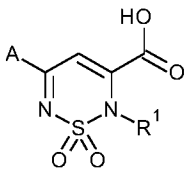
(VIII)

– wherein the meaning of A is as described above for formula (I) – which is then *N,O*-dialkylated in one step resulting the corresponding ester compound of formula (X)



(X)

– wherein the meaning of A and R^1 is as described above for formula (I) – which is then either hydrolysed to derivative of formula (VII)



(VII)

– wherein the meaning of A and R^1 is as described above for formula (I) – and then reacted with the appropriate amine (B-NH_2) resulting in the targeted amide derivative of formula (I),

or compound of formula (X) is transformed directly to the amide derivative of the formula (I) by reaction with the appropriate amine (B-NH_2).

The ketone derivative of formula (III) can be purchased or synthesized in the following ways:

i. The reaction of a carboxylic acid derivative of formula (IIa) with methyl lithium is preferably carried out in a suitable solvent, e.g., diethyl ether. The reaction is preferably carried out at –15 °C. The necessary reaction time is 2-4 hours. The reactions are followed by thin layer chromatography. The reaction mixture is preferably quenched by addition of saturated ammonium chloride solution. The product is isolated by extraction with a suitable organic solvent, e.g., diethyl ether.

ii. The reaction of Weinreb amide of formula (IIb) with methyl lithium is preferably carried out in a suitable solvent, e.g., diethyl ether. The reaction is preferably carried out at – 78 °C. The necessary reaction time is 2-4 hours. The reactions are followed by thin layer chromatography. The reaction mixture is preferably quenched by addition of aqueous hydrogen chloride solution. The product is isolated by extraction with a suitable organic solvent, e.g., diethyl ether.

iii. The reaction of the corresponding halogenide of formula (IIc) with tributyl(1-ethoxyvinyl)tin in the presence of a suitable palladium catalyst, e.g., tetrakis(triphenylphosphine)palladium(0) and a base, preferably tripotassium phosphate in a suitable solvent, e.g., toluene or *N*-methyl-2-pyrrolidone. The reaction is preferably carried out at 80-90 °C. The necessary reaction time is 6-7 hours. The reactions are followed by thin layer chromatography. The reaction mixture is diluted with water and extracted with an appropriate organic solvent, e.g., ethyl acetate. The organic phase is treated with 1 M hydrochloric acid solution at room temperature by vigorously stirring for 30 minutes. The pH of the mixture is adjusted to 7-8 by the addition of 25 % aqueous ammonia solution and extracted with a suitable organic solvent, e.g., ethyl acetate and purified by column chromathography.

iv. The Friedel-Crafts reaction of the corresponding aromatic compound of formula (IId) with acetyl chloride in the presence of a suitable base, preferably aluminium chloride in a suitable solvent, preferably dichloromethane is carried out at 40 °C. The necessary reaction time is 2 hours. The reaction mixture is poured onto 3 M HCl solution and extracted with diethyl ether. The combined organic layer is washed with saturated $NaHCO_3$ solution and brine, dried and evaporated to dryness.

The synthesis of compounds of formula (I) is described in more detail below:

Step 1

The Claisen condensation reaction of the acetyl derivative of formula (III) with diethyl oxalate to dioxoester derivative of formula (IV) is preferably carried out in the presence of a strong base, preferably sodium ethylate in a suitable solvent, e.g., ethanol. The reaction is preferably carried out at room temperature. The necessary reaction time is 6-15 hours. The reaction is followed by thin layer chromatography. The reaction mixture is quenched by pouring onto diluted aqueous hydrochloric acid solution (pH=1-3), and the product is isolated by filtration or by extraction with a suitable organic solvent, e.g., ethyl acetate.

Step 2

Cyclisation of the dioxoester of formula (IV) with sulfamide providing 1,1-dioxo-1,3-thiadiazine carboxylic acid ester derivative of formula (V) is performed in the presence of anhydrous ethanol saturated with hydrochloric acid in ethanol, as the solvent. The reaction is preferably carried out at 60-80 °C. The necessary reaction time is 2-15 hours. The reactions are followed by thin layer chromatography. The product is isolated either by filtration, or by extraction.

The 1,1-dioxo-1,3-thiadiazine carboxylic acid ester derivative of formula (V) can be transformed to the desired end product of formula (I) in different ways:

ROUTE A)

N-alkylation of 1,1-dioxo-1,3-thiadiazine carboxylic acid ester derivative of formula (V) is executed in different methods:

Step 3

Thiadiazine derivative of formula (V) is reacted with a suitable alkyl halogenide in a suitable solvent, preferably acetone, acetonitrile or *N,N*-dimethylformamide in the presence of a suitable amine, e.g., triethyl amine, diisopropyl ethylamine at 65-80 °C. The necessary reaction time is 2-24 hours. The reaction mixture is diluted with water and acidified with aqueous hydrochloric acid solution. The product is isolated by extraction with a suitable organic solvent, preferably ethyl acetate and the isomers of product are separated by column chromatography. The structures of the products are determined by NMR spectroscopy and mass spectrometry.

Thiadiazine derivative of formula (V) is reacted with a secondary alcohol in the presence of triphenyl phosphine and diisopropyl azodicarboxylate in a suitable solvent, preferably tetrahydrofuran at 25-67 °C. The necessary reaction time is 20-72 hours. The solvent is evaporated *in vacuo* and the procuct is isolated by column chromatography.

Step 4

Hydrolysis of *N*-alkylated ester of formula (VI) is carried out with base, e.g., 1-5 M NaOH or LiOH solution in a suitable solvent, e.g., tetrahydrofuran, or preferably ethanol at room temperature. The necessary reaction time is 1-3 hours. The reaction mixture is neutralised with aqueous hydrochloric acid solution. The organic solvent is evaporated *in vacuo*, the aqueous residue is acidified to pH=1-2, and the product is isolated by filtration or extraction with a suitable organic solvent, preferably ethyl acetate.

Step 5

The carboxylic acid of formula (VII) is coupled with the corresponding amine using a suitable coupling agent, such as HATU (1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate) or EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide) in the presence of a suitable base, e.g., triethylamine, diisopropylethylamine, in a suitable solvent, preferably *N,N*-dimethylformamide. The reaction is preferably carried out at room temperature. The necessary reaction time is 6-48 hours. The reaction mixture is worked up either by evaporation of the solvent, or poured onto aqueous hydrochloric acid solution and extracted with a suitable organic solvent, preferably ethyl acetate. The product is isolated by column chromatography. The structures of the products are determined by NMR and mass spectrometry.

The amidation of carboxylic acid of formula (VII) can be performed via the corresponding carboxylic acid chloride as follows:

Carboxylic acid of formula (VII) is treated with oxalyl chloride using a catalytic amount of *N,N*-dimethylformamide in a suitable organic solvent, preferably dichloromethane. After evaporation of the volatile components, the acyl chloride is reacted with the corresponding amine in the presence of a suitable base, e.g., triethylamine, diisopropylethylamine or tripotassium phosphate in a suitable solvent, e.g., dichloromethane, 1,2-dichloroethane or tetrahydrofuran. The reaction is carried out at 25-80 °C. The necessary reaction time is 3-16 hours. The reaction mixture is worked up either by evaporation of the solvent, or poured onto aqueous hydrochloric acid solution, and extracted with a suitable organic solvent, e.g., ethyl acetate or dichloromethane. The product is isolated by column chromatography. The structures of the products are determined by NMR and mass spectrometry.

Step 6

The reaction of *N*-alkylated ester of formula (VI) with the corresponding amine is carried out in the presence of a strong base, preferably triethyl aluminium, in a suitable solvent, e.g., 1,2-dichloroethane or toluene at 50-110 °C. The necessary reaction time is 6-48 hours. The reaction mixture is vigorously stirred with aqueous hydrochloric acid solution at 25-40 °C. The product is isolated by extraction with a suitable organic solvent, e.g., ethyl

acetate or dichloromethane and by subsequent column chromatography. The structures of the products are determined by NMR and mass spectrometry.

ROUTE B)

Step 7

Hydrolysis of 1,1-dioxo-1,3-thiadiazine carboxylic acid ester derivative of formula (V) is carried out with a base, e.g., 5 M aqueous NaOH solution in a suitable solvent, e.g., tetrahydrofuran, or preferably ethanol at room temperature. The necessary reaction time is 1-3 hours. The product is isolated in two different ways.

i) The reaction mixture is neutralised with aqueous hydrochloric acid solution, and evaporated to dryness *in vacuo,* the product –which contains sodium chloride–, obtained in this way was used in the next step without further purification.

ii) The reaction mixture is neutralised with aqueous hydrochloric acid solution. The organic solvent is evaporated *in vacuo*, the aqueous residue is acidified to pH=1-2 and the product is isolated by filtration.

Step 8

N,O-dialkylation of 1,1-dioxo-1,3-thiadiazine carboxylic acid derivative of formula (VIII) with a suitable primary alkyl halogenide or pseudohalogenide, such as propyl bromide, butyl bromide or 2-bromoethyl methylether is carried out in a suitable solvent, preferably acetonitrile or *N,N*-dimethyl formamide, in the presence of a suitable amine, e.g., triethyl amine, diisopropyl ethylamine or sodium hydride at 65-80 °C. The necessary reaction time is 2-24 hours. The reaction mixture is diluted with water and acidified with aqueous hydrochloric acid solution. The product is isolated by extraction with a suitable organic solvent, preferably ethyl acetate, and the isomers of product are separated by column chromatography. The structures of the products are determined by NMR spectroscopy and mass spectrometry.

Step 9

Hydrolysis of *N*-alkylated ester of formula (X) is carried out with a base, e.g., 1-2 M NaOH or LiOH solution in a suitable solvent, e.g., tetrahydrofuran, or preferably ethanol at room temperature. The necessary reaction time is 1-3 hours. The reaction mixture is neutralised with aqueous hydrochloric acid solution. The organic solvent is evaporated *in vacuo*, the aqueous residue is acidified to pH=1-2, and the product is isolated by filtration or extraction with a suitable organic solvent, preferably ethyl acetate.

Amidation of *N*-alkylated carboxylic acid of formula (VII) to provide amide of formula (I) is performed as described in Step 5 above.

The reaction of *N*-alkylated ester of formula (X) with the corresponding amine is carried out as described in Step 6 above.

The present disclosure includes within its scope all the possible isotopically labelled forms of the compounds.

The compounds of the present invention can be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, intraarticular, intrathecal, intraperitoneal, direct intraventricular, intracerebroventicular, intramedullary injection, intracisternal injection or infusion, subcutaneous injection or implant), ophtalmic, nasal, vaginal, rectal, sublingual and topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations comprising pharmaceutically acceptable excipients suitable for each route of administration.

Alternatively, one may administer the compounds in a local rather than systemic manner, for example, via injection of the compound directly in the renal or cardiac area, often in a modified release formulation. Furthermore, one may administer the drug in a targeted drug delivery system, for example, in a liposome coated with a tissue-specific antibody. The liposomes are taken up selectively by the targeted organ.

The pharmaceutical compositions of the present invention usually contain 0.01 to 500 mg of the active ingredient in a single dosage unit. However, it is possible that the amount of the active ingredient in some compositions exceeds the upper or lower limits defined above.

The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

This dosage level and regimen can be adjusted to provide the optimal therapeutic response. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition and the host undergoing therapy.

As a further aspect of the invention, there is provided the pharmaceutical manufacture of medicaments containing the compounds of formula (I) or pharmaceutically acceptable salts, biologically active metabolites, pro-drugs, racemates, enantiomers, diastereomers, solvates and hydrates thereof.

The pharmaceutical compositions of the present invention may be formulated as different pharmaceutical dosage forms, including, but not limited to, solid oral dosage forms like tablets (e.g., buccal, sublingual, effervescents, chewable, orodispersible, freeze dried), capsules, lozenges, pastilles, pills, orodispersible films, granules, powders; liquid oral dosage forms, including, but not limited to, solutions, emulsions, suspensions, syrups, elixirs, oral drops; parenteral dosage forms, including, but not limited to, intravenous injections, intramuscular injections, subcutaneous injections; other dosage forms, including, but not limited to, eye drops, semi-solid eye preparations, nasal drops or sprays, transdermal dosage forms, suppositories, rectal capsules, rectal solutions, emulsions and suspensions, etc.

The pharmaceutical compositions of the present invention can be manufactured in any conventional manner, e.g., by mixing, dissolving, emulsifying, suspending, entrapping, freeze-drying, extruding, laminating, film-casting, granulating, grinding, encapsulating, dragee-making or tabletting processes.

Pharmaceutical compositions for use in accordance with the present invention thus can be formulated in any conventional manner using one or more physiologically acceptable excipients. Any of the well-known techniques and excipients may be used as suitable and as understood in the art.

Suitable excipients for the preparation of the dosage forms may be selected from the following categories, including, but not limited to, tablet and capsule fillers, tablet and capsule binders, release modifying agents, disintegrants, glidants, lubricants, sweetening agents, taste-masking agents, flavoring agents, coating agents, surfactants, antioxidants, buffering agents, complexing agents, emulsifying agents, lyophilization aids, microencapsulating agents, ointment bases, penetration enhancers, solubilizing agents, solvents, suppository bases, and suspending agents.

In one embodiment, the invention relates to the use of specific excipients which are capable of improving the solubility, dissolution, penetration, absorption and/or bioavailability of the active ingredient(s), including, but not limited to, hydrophilic polymers, hot melt extrusion excipients, surfactants, buffering agents, complexing agents, emulsifying agents, lyophilization aids, superdisintegrants, microencapsulating agents, penetration enhancers, solubilizing agents, co-solvents, and suspending agents.

The above described ingredients and different routes of manufacture are merely representative. Other materials as well as processing techniques and the like well known in the art can also be used.

EXAMPLES

The invention is further defined in the following Examples. It should be understood that the Examples are given by way of illustration only. From the above discussion and the Examples, one skilled in the art can ascertain the essential characteristics of the invention, and without departing from the spirit and scope thereof, can make various changes and modifications to adapt the invention to various uses and conditions. As a result, the invention is not limited by the illustrative examples set forth herein below, but rather defined by the claims appended hereto.

In general, the compounds of formula (I) can be prepared in accordance with the general knowledge of one skilled in the art and/or using methods set forth in the Example and/or Intermediate sections that follow. Solvents, temperatures, pressures, and other reaction conditions can readily be selected by one of ordinary skill in the art. Starting materials are commercially available and/or readily prepared by one skilled in the art.

The present invention will be now illustrated by the following not limiting examples.

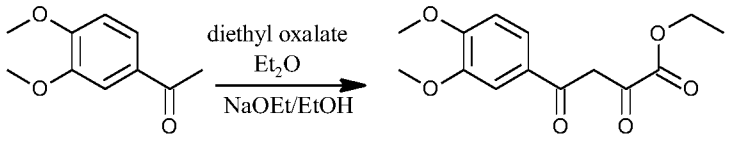
In the following examples “room temperature” denotes a temperature in the range from 20 °C to 25 °C.

The abbreviations used in the specific examples have the following meanings:

$AlEt_3$	triethylaluminium
conc.	concentrated
DMSO	dimethyl sulfoxide
EDC	(1-ethyl-3-(3-dimethylaminopropyl)carbodiimide)
ESI	electronspray ionisation
HATU	(1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate)
HEPES	(4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid)
LC-MS	liquid chromatography coupled with mass spectroscopy
THF	tetrahydrofuran

Step 1

Intermediate 1



intermediate 1

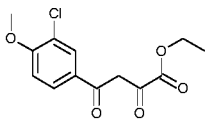
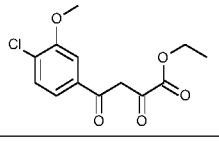
Ethyl 4-(3,4-dimethoxyphenyl)-2,4-dioxobutanoate

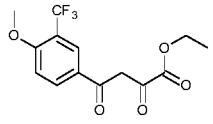
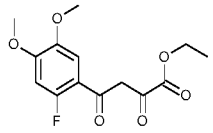
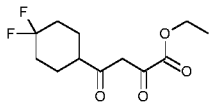
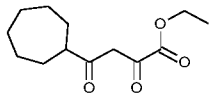
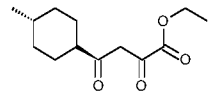
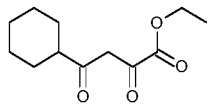
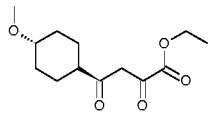
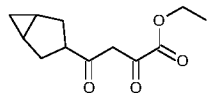
In an inert atmosphere, diethyl oxalate (20 ml, 0.15 mol) was added to a sodium ethylate solution freshly prepared from sodium (3.5 g, 0.15 mol) and ethanol (300 mL). A solution of 1-(3,4-dimethoxyphenyl)ethanone (9,20 g, 0.05 mol) in diethyl ether (150 mL) was added dropwise, and the mixture was stirred for 2 hours at room temperature.

The reaction mixture was poured onto ice-water (500 mL) and acidified to pH=1-2 by the addition of 6 M HCl solution during cooling with ice. The yellow precipitate was collected by filtration, washed with water, and dried under vacuum at room temperature. Yield: 13.5 g (94 %) yellow solid, m/z $(M+H)^+$: 281.2

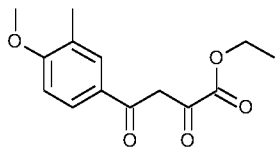
The intermediates in Table 1 were synthesized according to the procedure described for Intermediate 1. All necessary starting materials were purchased from different vendors.

Table 1

Intermediate	Structure
2	
3	

4	
5	
6	
7	
8	
9	
10	
11	

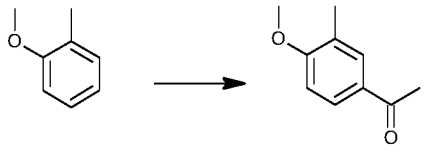
Intermediate 12



Ethyl 4-(4-methoxy-3-methylphenyl)-2,4-dioxobutanoate

The title compound was prepared from 1-(4-methoxy-3-methylphenyl)ethanone according to the method described for Intermediate 1.

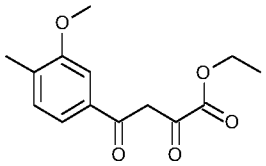
1-(4-methoxy-3-methylphenyl)ethanone was synthesized according to the following method:



Under an inert atmosphere, to a solution of 2-methylanisol (7.92 g, 64.8 mmol) in dichloromethane (40 mL), aluminium chloride (9.45 g, 70.9 mmol) was added. To the obtained mixture (5.1 mL, 71.5 mmol) acetyl chloride was added dropwise, and the mixture was heated under reflux for 2 hours.

The reaction mixture was poured slowly onto 3 M HCl solution and extracted with diethyl ether. The combined organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4 and evaporated to dryness. Yield: 10.33 g (97 %) light yellow oil.

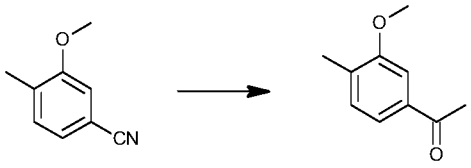
Intermediate 13



Ethyl 4-(3-methoxy-4-methylphenyl)-2,4-dioxobutanoate

The title compound was prepared from 1-(3-methoxy-4-methylphenyl)ethanone according to the method described for Intermediate 1.

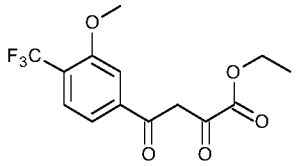
1-(3-methoxy-4-methylphenyl)ethanone was synthesized according to the following method:



Under an inert atmosphere, to a solution of 3-methoxy-4-methylbenzonitrile (2.00 g, 13.6 mmol) in tetrahydrofuran (50 mL), a methylmagnesium chloride solution (5 mL, 3M in tetrahydrofuran) was added dropwise during cooling with ice at 0-2 °C, and the mixture was stirred at 40 °C for 12 hours.

The reaction mixture was quenched by dropwise addition of 6 M HCl solution (3.4 mL), and was stirred stirred at 40 °C for another hour. The mixture was extracted with ethyl acetate, the combined organic layer was washed with brine, dried over Na_2SO_4, evaporated, and the crude residue was purified with column chromatography on silica gel with gradient elution, using a mixture of dichloromethane and cyclohexane as eluent. Yield: 356 mg (16 %).

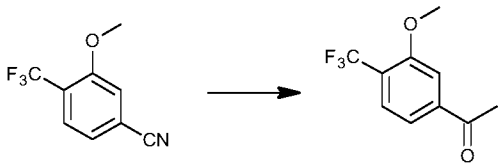
Intermediate 14



Ethyl 4-[3-methoxy-4-(trifluoromethyl)phenyl]-2,4-dioxobutanoate

The title compound was prepared from 1-(3-methoxy-4-trifluoromethylphenyl)ethanone according to the method described for Intermediate 1.

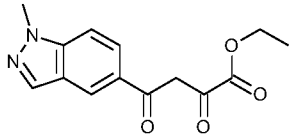
1-[3-methoxy-4-(trifluoromethyl)phenyl]ethanone was synthesized according to the following method:



Under an inert atmosphere, to a solution of 3-methoxy-4-(trifluoromethyl)benzonitrile (4.11 g, 20.4 mmol) in diethyl ether (100 mL), a methylmagnesium chloride solution (7.5 mL, 3M in tetrahydrofuran) was added dropwise during cooling with ice at 0-2 °C, and the mixture was stirred at room temperature further for 2 hours.

The reaction mixture was quenched by dropwise addition of 6 M HCl solution (100 mL), and was stirred at room temperature for another hour. The mixture was extracted with ethyl acetate, the combined organic layer was washed with brine, dried over Na_2SO_4, evaporated, and the crude residue was purified with column chromatography on silica gel, using a 1:9 mixture of ethyl acetate and cyclohexane as eluent. Yield: 600 mg (13 %) yellow solid.

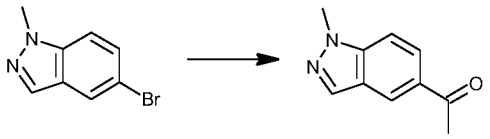
Intermediate 15



Ethyl 4-(1-methyl-1*H*-indazol-5-yl)-2,4-dioxobutanoate

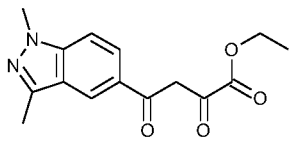
The title compound was prepared from 1-(1-methyl-1*H*-indazol-5-yl)ethanone according to the method described for Intermediate 1.

1-(1-methyl-1*H*-indazol-5-yl)ethanone was synthesized according to the following method:



A solution of 5-bromo-1-methyl-1*H*-indazole (2.91 g, 13.8 mmol) in *N*-methyl-2-pyrrolidone (55 mL) was purged with argon gas for 15 minutes. Tripotassium phosphate (5.85 g, 27.6 mmol), tributyl(1-ethoxyvinyl)tin (4.7 mL, 13.9 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.80 g, 0.69 mmol) were added, and the mixture was stirred at 80-90 °C for 6 hours under argon atmosphere. The reaction mixture was diluted with water, and extracted with ethyl acetate. The organic phase was treated with 1 M hydrochloric acid solution at room temperature by vigorously stirring for 30 minutes. The pH of the mixture was adjusted to 7-8 by the addition of 25 % w/w aqueous ammonia solution, and extracted with ethyl acetate. The organic phase was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by column chromathography on silica gel using a mixture of ethyl acetate and cyclohexane (3:1) as eluent. Yield: 1.64 g (68 %).

Intermediate 16

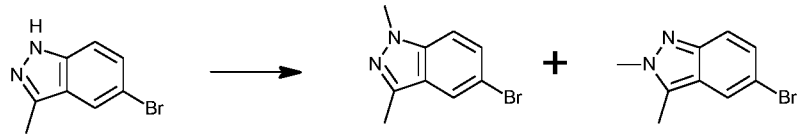


Ethyl 4-(1,3-dimethyl-1*H*-indazol-5-yl)-2,4-dioxobutanoate

The title compound was prepared from 1-(1,3-dimethyl-1*H*-indazol-5-yl)ethanone according to the method described for Intermediate 1.

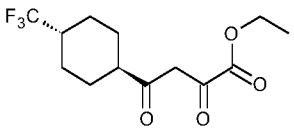
1-(1,3-dimethyl-1*H*-indazol-5-yl)ethanone was prepared from 5-bromo-1,3-dimethyl-1*H*-indazol according to the method described for Intermediate 15.

5-bromo-1,3-dimethyl-1*H*-indazol was synthesized according to the following method:



To a suspension of sodium hydride (0.98 g, 24.5 mmol, 60 % in mineral oil) in *N,N*-dimethylformamide (70 mL), 5-bromo-3-methyl-1*H*-indazol (4.30 g, 20.4 mmol) was added in portions under an inert atmosphere at room temperature, and the obtained suspension was stirred further for 15 minutes. Iodomethane (1.7 ml, 27.5 mmol) was added, and the mixture was stirred further for 3 hours at room temperature. Water was added, and the mixture was extracted with ethyl acetate. The organic phase was washed with 2 M $Na_2S_2O_3$ solution and water, dried over Na_2SO_4, and evaporated to dryness. The regioisomeric products were separated by column chromathography on silica gel, using a mixture of ethyl acetate and cyclohexane (2:1) as eluent. Yield: 3.16 g (69 %) for the desired product 5-bromo-1,3-dimethyl-1*H*-indazol and 1.26 g (27 %) for 5-bromo-2,3-dimethyl-1*H*-indazol.

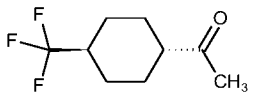
Intermediate 17



Ethyl 2,4-dioxo-4-[(1r,4r)-4-(trifluoromethyl)cyclohexyl]butanoate

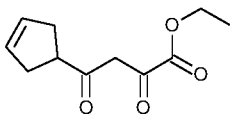
The title compound was prepared from 1-[*trans*-4-(trifluoromethyl)cyclohexyl]ethanone according to the method described for Intermediate 1.

1-[*trans*-4-(trifluoromethyl)cyclohexyl]ethanone was synthesized according to the following method:



Under argon, atmosphere to a solution of *trans*-4-(trifluoromethyl)cyclohexanecarboxylic acid (3.14 g, 16 mmol) in dry diethyl ether (75 mL), a methyl lithium solution in diethyl ether (1.6 M, 25 mL, 40 mmol) was added dropwise at -20 ºC to 15 ºC for 45-60 minutes, and the mixture was stirred further at -15 ºC for 1 hour. The reaction mixture was quenched by addition of saturated NH_4Cl solution (25 mL) (pH ~8) and water (25 mL) at 0 °C, and extracted with diethyl ether. The combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* (at 350-400 mbar at room temperature). Yield: 3.075 g (99 %) colourless oil.

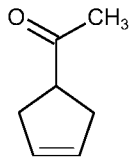
Intermediate 18



Ethyl 4-(cyclopent-3-en-1-yl)-2,4-dioxobutanoate

The title compound was prepared from 1-(cyclopent-3-en-1-yl)ethanone according to the method described for Intermediate 1.

1-(cyclopent-3-en-1-yl)ethanone was synthesized according to the following method:

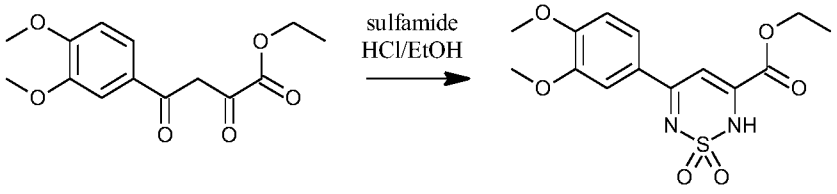


To a solution of cyclopent-3-ene-1-carboxylic acid (1.346 g, 12 mmol) and a few drops of *N,N*-dimethylformamide in dry dichloromethane (30 mL), oxalyl chloride (2.03 mL, 24 mmol) in dichloromethane (5 mL) was added dropwise at 25 ºC under argon atmosphere. The reaction mixture was stirred for 30 minutes and the volatile components were removed *in vacuo*. The obtained cyclopent-3-ene-1-carbonyl chloride was dissolved in dichloromethane (25 mL), and the solution was added dropwise to a mixture of *N,O*-dimethylhydroxylamine hydrochloride (1.117 g, 12 mmol) and triethylamine (3.68 mL, 26.41 mmol) in dry dichloromethane (25 mL) at 25 °C. The reaction mixture was concentrated *in vacuo* and suspended in ethyl acetate (30 mL). The suspension was filtered, and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel, eluting with a mixture of cyclohexane and ethyl acetate (7:3) to yield 1.043 g (78 %) of the Weinreb amide.

To a solution of Weinreb amide (1.043 g, 6.1 mmol) in diethyl ether (50 mL), a methyl lithium solution in diethyl ether (1.6 M, 4.54 mL, 7.26 mmol) was added dropwise at -65 ºC to -78 ºC, and the mixture was stirred further at -78 ºC for 2 hours. The reaction mixture was allowed to warm to 0 °C, and quenched by the addition of 1 M HCl solution (10 mL) and water (10 mL) during ice cooling. The reaction mixture was extracted with diethyl ether, the combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* (at 350-400 mbar at room temperature). The title compound was obtained (0.663 g, 99 %) as an oil.

Step 2

Intermediate 19



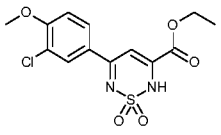
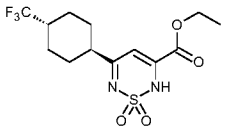
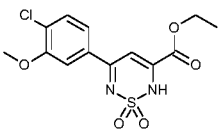
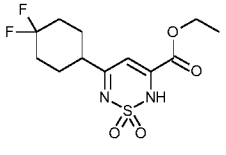
intermediate 1 intermediate 19

Ethyl 5-(3,4-dimethoxyphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxylate

To a suspension of Intermediate 1 (ethyl 4-(3,4-dimethoxyphenyl)-2,4-dioxobutanoate, 13.5 g, 48,2 mmol) in ethanol (280 mL), sulfamide (9.4 g, 98 mmol) and ethanol saturated with hydrogen chloride (30 %, 35 mL) was added, and the mixture was stirred at 60 °C (inner) overnight. The obtained suspension was cooled in an ice-water bath, and the yellow precipitate was collected by filtration, washed with cold ethanol, and dried *in vacuo* at 40 °C. Yield: 15,79 g (96 %) yellow solid, m/z $(M+H)^+$: 341.1

The following intermediates in Table 2 were synthesized from the corresponding intermediates (1-18) according to the procedure described for Intermediate 19.

Table 2

Inter-mediate	Structure	Starting inter-mediate	Inter-mediate	Structure	Starting inter-mediate
20		2	**29**		17
21		3	**30**		6

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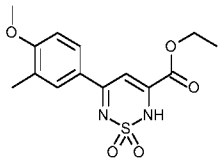
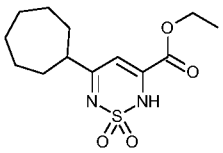
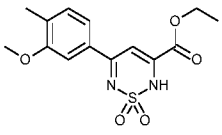
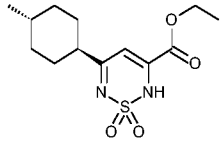
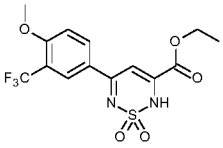
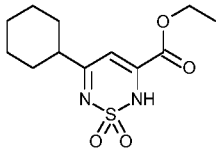
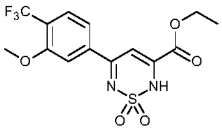
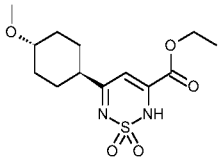
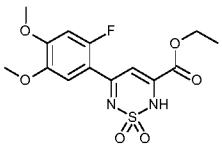
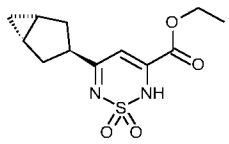
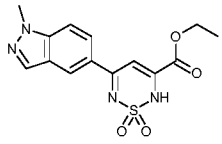
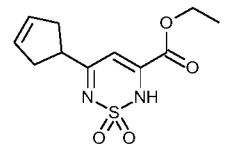
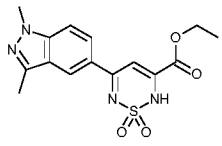
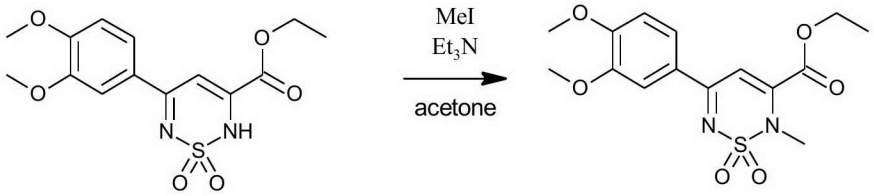
22		12	**31**		7
23		13	**32**		8
24		4	**33**		9
25		14	**34**		10
26		5	**35**		11
27		15	**36**		18
28		16			

Step 3

Intermediate 37



intermediate 19 intermediate 37

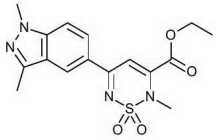
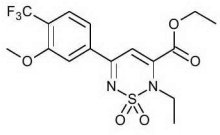
Ethyl 5-(3,4-dimethoxyphenyl)-2-methyl-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxylate

A mixture of Intermediate 19 (8.26 g, 24.27 mmol), triethylamine (3.7 mL, 26.7 mmol) and iodomethane (17 mL, 273 mmol) in acetone (430 mL) was stirred at 56 °C for 4.5 hours.

The solvent was removed under reduced pressure, to the residue 5 % HCl solution (120 mL) was added, and the mixture was extracted with dichloromethane. The organic phase was washed with water, 5 % $Na_2S_2O_3$ solution and water again. The combined organic layer was dried over Na_2SO_4, filtered, concentrated *in vacuo* and the residue was purified by column chromatography on silica gel, using a stepwise gradient of a mixture of cyclohexane and diisopropyl ether (40:1 to 10:1) as the eluent, to give 5.60 g (65 %) of the product as yellow crystals.

The following intermediates in Table 3 were synthesized from the corresponding intermediates (see them in step 2) according to the procedure described for Intermediate 37.

Table 3

Inter-mediate	Structure	Starting inter-mediate	Inter-mediate	Structure	Starting inter-mediate
38		28	**48**		25

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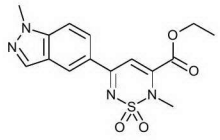
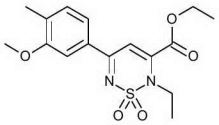
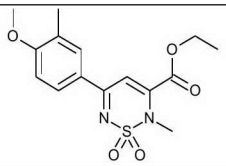
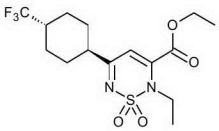
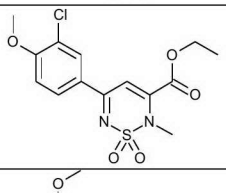
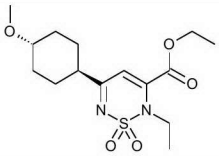
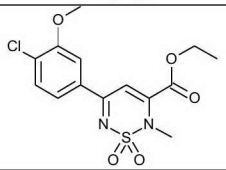
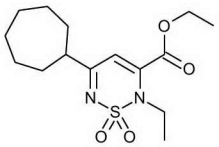
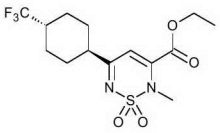
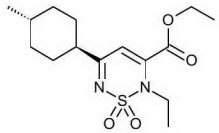
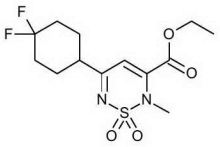
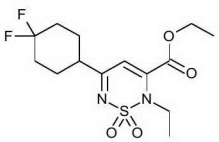
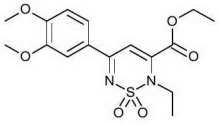
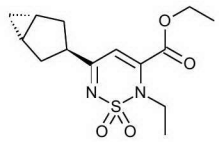
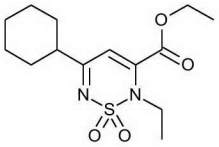
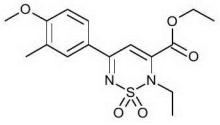
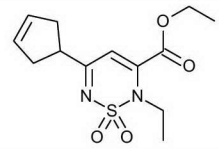
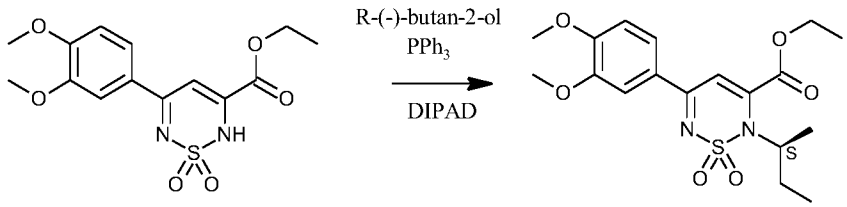
39		27	**49**		23
40		22	**50***		29
41		20	**51***		34
42		21	**52***		31
43*		29	**53***		32
44*		30	**54***		30
45		19	**55***		35
46		24	**56***		33
47		22	**57***		36

* *N,N*-dimethylformamide was applied as solvent instead of acetone

Intermediate 58



intermediate 19 intermediate 58

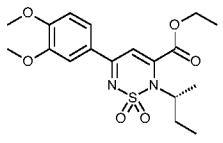
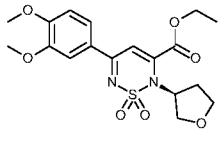
Ethyl 2-[(2*S*)-butan-2-yl]-5-(3,4-dimethoxyphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxylate

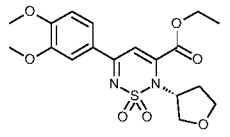
To a suspension of Intermediate 19 (ethyl 5-(3,4-dimethoxyphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxylate, 3.74 g, 11 mmol), triphenyl phosphine (2.88 g, 11 mmol) and *R*-(-)-butan-2-ol (0.92 mL, 10 mmol) in a mixture of tetrahydrofuran (50 mL) and *N,N*-dimethylformamide (10 mL) diisopropyl azodicarboxylate (2.2 mL, 11 mmol) was added dropwise during cooling with ice under an inert atmosphere. The obtained solution was heated under reflux for 7 hours, evaporated to dryness and the residue was purified by flash column chromatography on silica gel in two stages. At first, dichloromethane was used as the eluent, and in the second stage a slow gradient of a mixture of ethyl acetate and dichloromethane was applied. Yield: 460 mg (12 %) yellow oil.

The optical purity was not determined in this stage, the product was used in the next step without separating the enantiomers.

The following intermediates in Table 4 were synthesized in Mitsunobu reaction from the Intermediate 19 according to the procedure described for Intermediate 58.

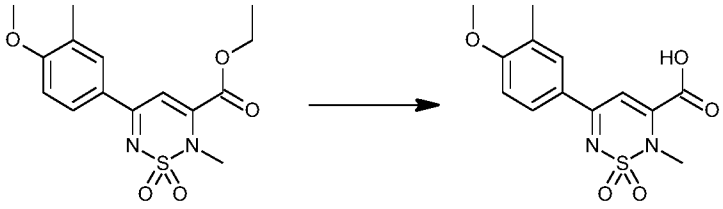
Table 4

Intermediate	Structure
59	
60	

61	

Step 4

Intermediate 62



Intermediate 40 Intermediate 62

5-(4-methoxy-3-methylphenyl)-2-methyl-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxylic acid

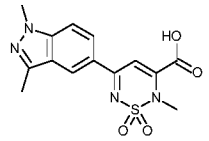
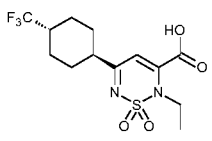
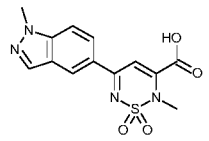
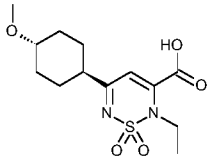
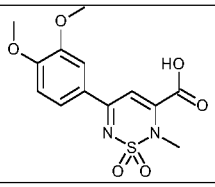
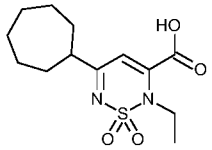
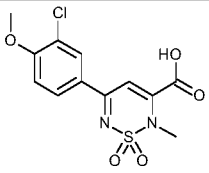
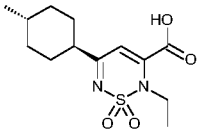
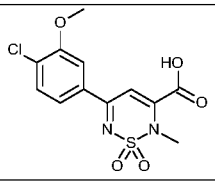
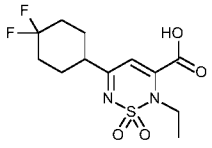
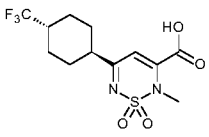
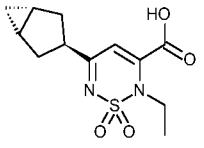
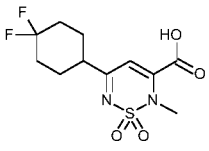
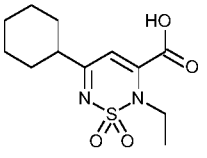
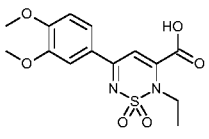
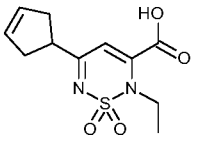
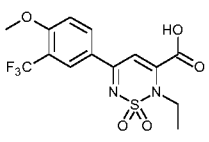
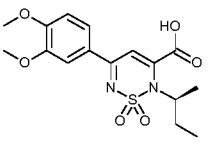
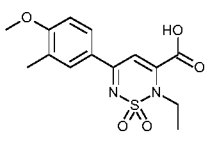
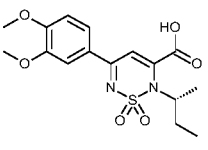
To a suspension of intermediate 40 (ethyl 5-(4-methoxy-3-methylphenyl)-2-methyl-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxylate, 520 mg, 1.54 mmol) in ethanol (35 mL), 1 M aqueous NaOH solution (3 mL) was added, and the mixture was stirred at room temperature for 1 hour. The pH of the mixture was adjusted to 4-5 by the addition of 1 % HCl solution during cooling with ice. Ethanol was removed under reduced pressure, water was added, and the mixture was acidified further by the addition of 10 % HCl to pH=1-2. The mixture was extracted with ethyl acetate, the combined organic layer was washed with brine, dried over Na_2SO_4, filtered and evaporated to dryness to give the product in a quantitative yield.

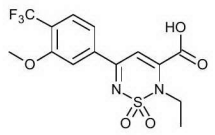
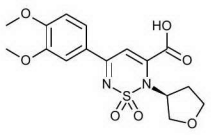
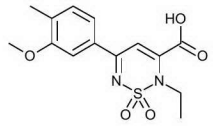
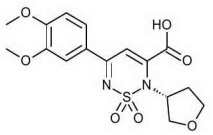
The following intermediates in Table 5 were synthesized via the hydrolysis of the corresponding ester intermediates according to the procedure described for Intermediate 62.

Table 5

Inter-mediate	Structure	Starting inter-mediate	Inter-mediate	Structure	Starting inter-mediate

2019300515 17 Dec 2024

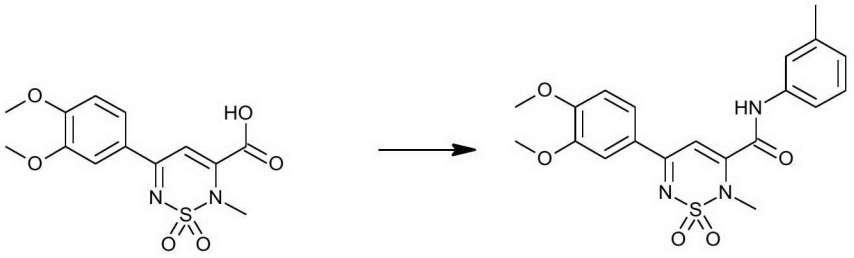
63*		38	**75**		50
64*		39	**76**		51
65		37	**77**		52
66		41	**78**		53
67		42	**79**		54
68		43	**80**		55
69		44	**81**		56
70		45	**82**		57
71*		46	**83**		58
72*		47	**84**		59

73*		48	**85**		60
74		49	**86**		61

*5 mol equivalents 5 M conc. aqueous NaOH solution

Step 5

Example 1



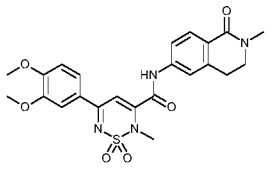
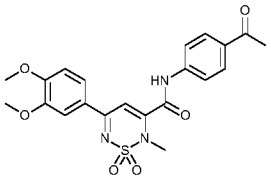
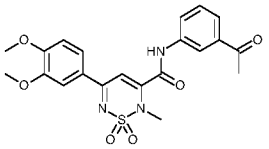
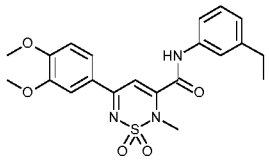
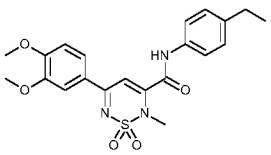
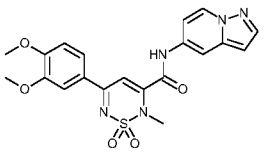
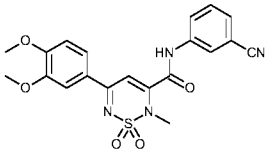
intermediate 65 Example 1

5-(3,4-dimethoxyphenyl)-2-methyl-*N*-(3-methylphenyl)-1,1-dioxo-2*H*-1λ⁶,2,6-thiadiazine-3-carboxamide

Under an inert atmosphere, to a suspension of Intermediate 65 (5-(3,4-dimethoxyphenyl)-2-methyl-1,1-dioxo-2*H*-1λ⁶,2,6-thiadiazine-3-carboxylic acid, 700 mg, 2.15 mmol) and 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 1.06 g, 2.79 mmol) in *N,N*-dimethylformamide (20 mL) *m*-toluidine (0.46 mL, 4.3 mmol) and *N,N*-diisopropylethylamine (1.48 mL, 8.50 mmol) was added during cooling with ice, and the obtained solution was stirred at room temperature for 2 days. 10 % HCl solution (100 mL) was added, and the mixture was extracted with ethyl acetate, the combined organic layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by flash column chromatography on silica gel, applying gradient elution with a 0 to 2.5 % V/V ethyl acetate - dichloromethane mixture as eluent, and a subsequent crystallization from a mixture of dichloromethane and diethyl ether. Yield: 460 mg (52 %) yellow crystals, m/z $(M+H)^+$: 416.1.

The following examples in Table 6 were synthesized according to the procedure (via HATU coupling) described for Example 1.

Table 6

Example	Structure	LC-MS (ESI) m/z $(M+H)^+$	Starting intermediate
2		485.1	65
3*		purchased library compound*	-
4		444.1	65
5		430.2	65
6		430.1	65
7		442.1	65
8		427.1	65

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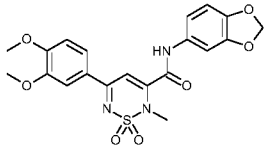
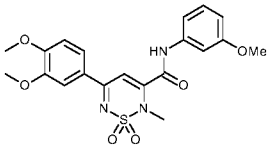
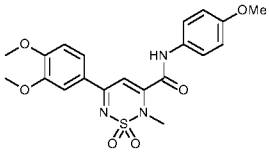
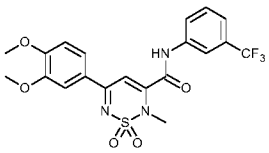
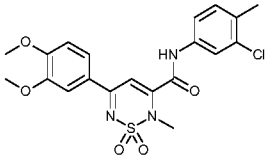
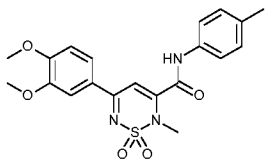
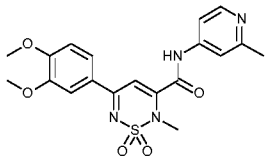
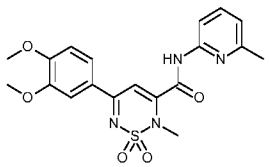
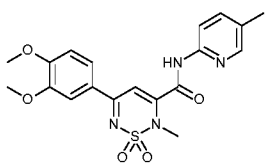
9		446.0	65
10		432.1	65
11		432.1	65
12		470.2	65
13		450.1	65
14		416.1	65
15		417.1	65
16		417.1	65
17		417.1	65

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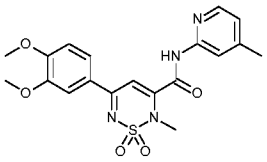
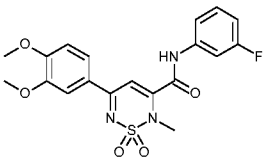
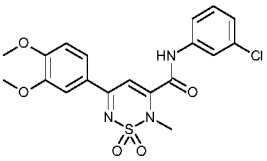
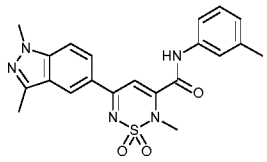
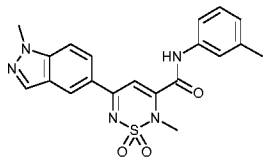
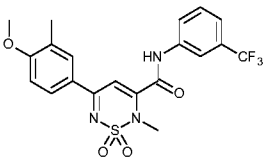
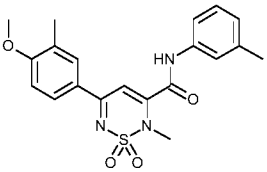
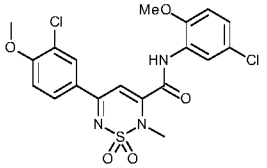
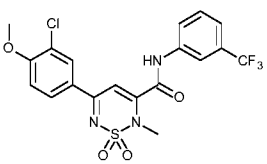
18		417.1	65
19		420.1	65
20		436.1	65
21		424.1	63
22		410.1	64
23		454.1	62
24		400.2	62
25		470.0	66
26		474.0	66

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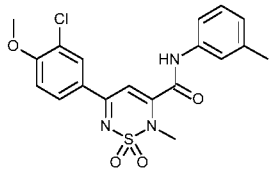
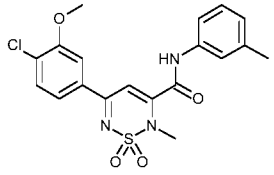
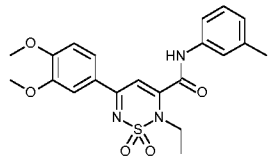
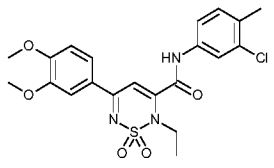
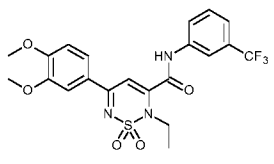
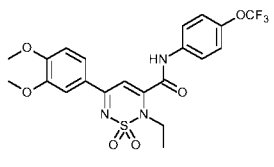
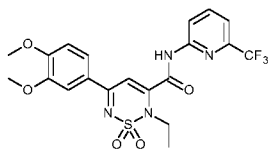
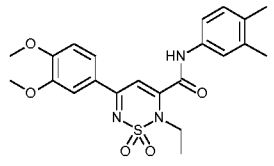
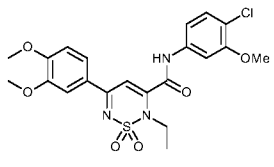
27		420.0	66
28		420.2	67
29		430.1	70
30		464.1	70
31		484.2	70
32		500.2	70
33		485.2	70
34		444.2	70
35		480.2	70

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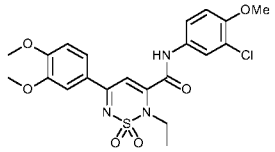
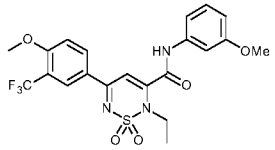
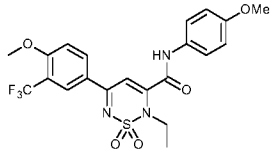
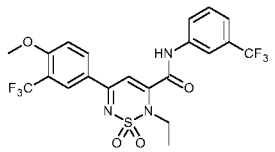
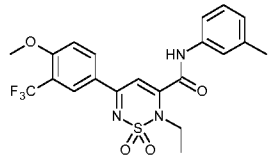
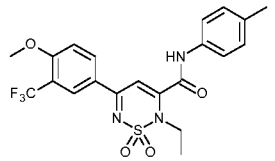
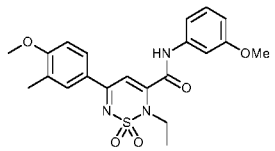
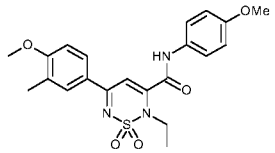
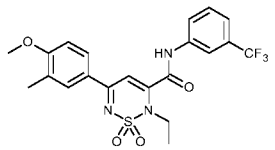
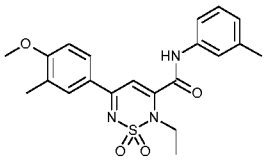
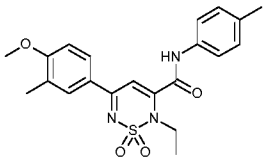
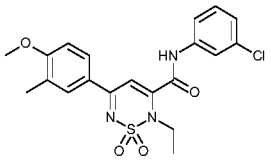
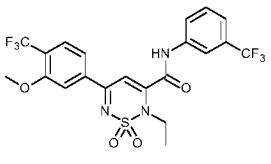
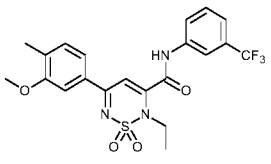
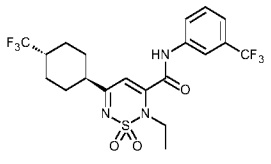
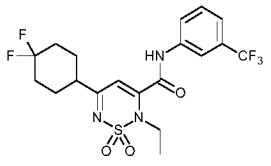
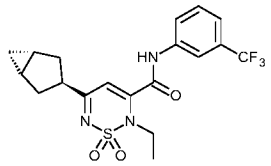
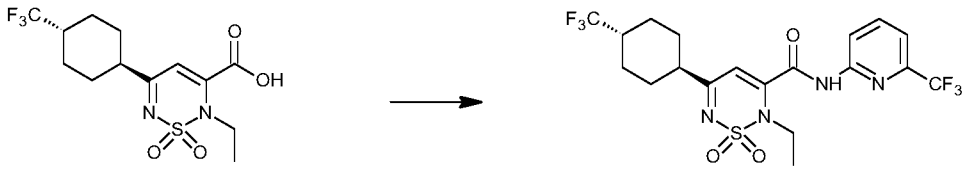
36		480.1	70
37		484.2	71
38		484.2	71
39		522.2	71
40		468.2	71
41		468.2	71
42		430.2	72
43		430.2	72
44		468.2	72

45		414.2	72
46		414.2	72
47		434.2	72
48		522.1	73
49		468.1	74
50		498.2	75
51		466.1	79
52		428.1	80

*Purchased library compound from ChemDiv (compound ID: E135-0764)

Example 53



intermediate 75 Example 53

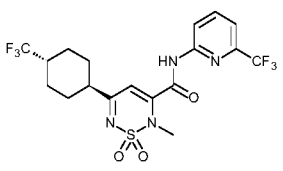
2-ethyl-1,1-dioxo-5-[(1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl]-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ⁶,2,6-thiadiazine-3-carboxamide

In an inert atmosphere, to a solution of Intermediate 75 (2-ethyl-1,1-dioxo-5-[(1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl]-2*H*-1λ⁶,2,6-thiadiazine-3-carboxylic acid; 500 mg, 1.41 mmol) and *N,N*-dimethylformamide (3 drops) in dichloromethane (20 mL), a solution of oxalyl chloride (0.24 mL, 2.82 mmol) in dichloromethane (10 mL) was added dropwise at room temperature. After 15 minutes of stirring at room temperature, the reaction mixture was evaporated to dryness, dichloromethane (20 mL) was added, and it was evaporated to dryness again. The residue (carbonyl chloride) was dissolved in tetrahydrofuran under an inert atmosphere, cooled to 0 °C, tripotassium phosphate (375 mg, 1.76 mmol) and 2-amino-6-(trifluormethyl)pyridine (229 mg, 1.41 mmol) was added, and the mixture was stirred at room temperature for 3 hours.

The inorganic salts were filtered off, the filtrate was concentrated, and the residue was purified by column chromatography on silica gel with a terner mixture of cyclohexane, ethyl acetate and diisopropyl ether (40:10:1), as eluent. Yield: 440 mg (63 %), m/z $(M+H)^+$: 499.1.

The following examples in Table 7 were synthesized according to the procedure (via acid chloride coupling) described for Example 53.

Table 7

Example	Structure	LC-MS (ESI) m/z $(M+H)^+$	Starting intermediate
54		485.1	68

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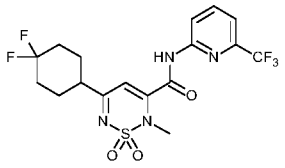
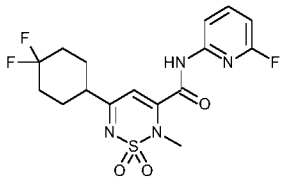
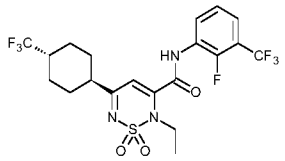
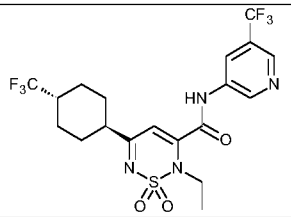
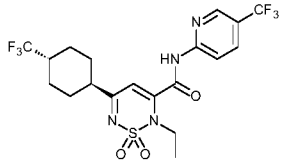
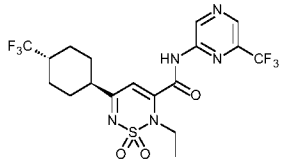
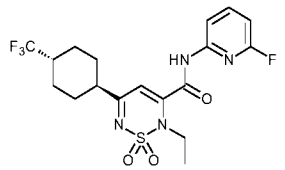
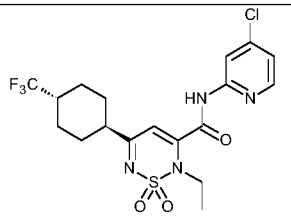
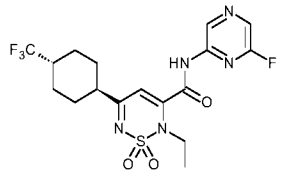
55		453.1	69
56		$M+Na^+$ = 425.1	69
57		516.2	75
58		499.1	75
59		499.1	75
60*		500.1	75
61		449.2	75
62		465.1	75
63*		450.0	75

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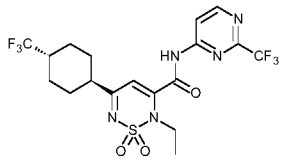
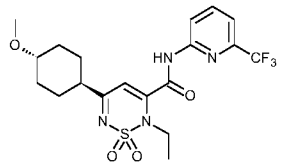
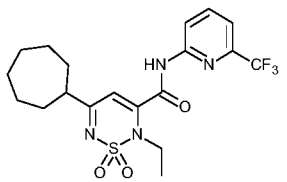
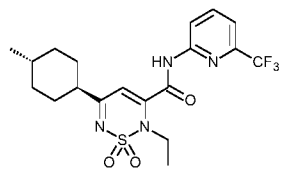
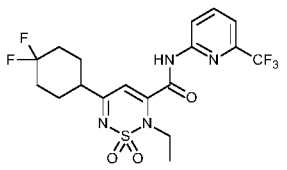
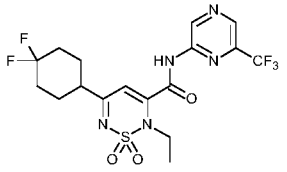
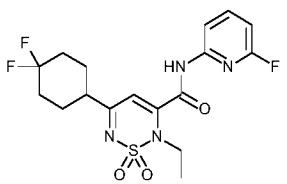
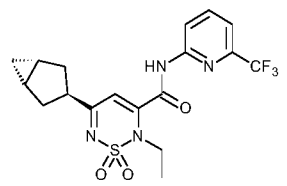
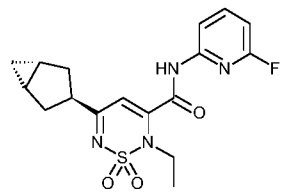
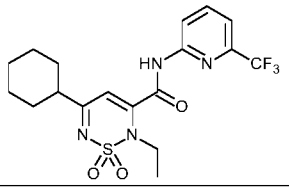
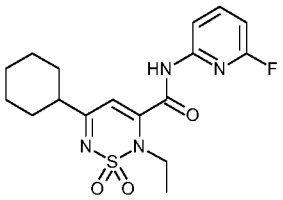
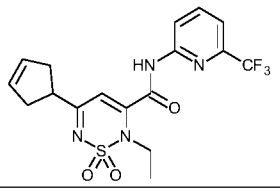
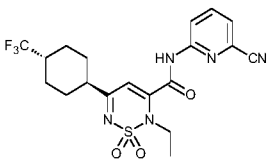
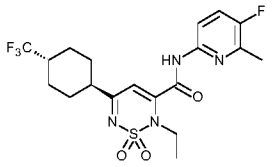
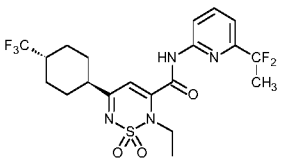
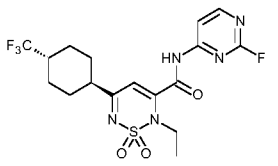
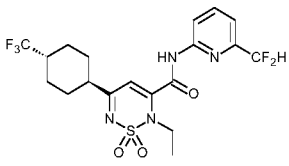
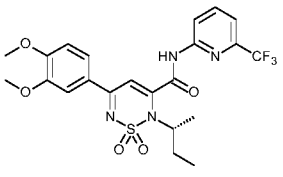
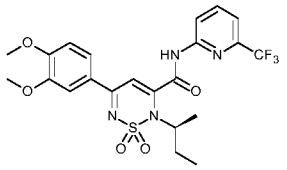
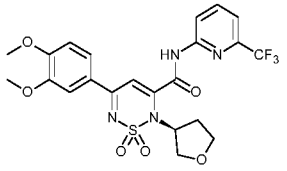
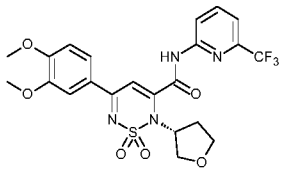
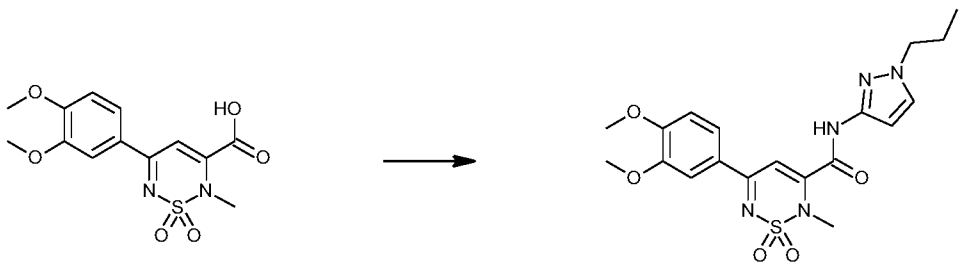
64*		500.1	75
65		461.2	76
66		445.2	77
67		445.2	78
68		467.1	79
69*		468.2	79
70		417.1	79
71		429.1	80
72		379.2	80

73		431.1	81
74		381.1	81
75		415.1	82
76*		456.1	75
77		463.1	75
78		495.1	75
79*		450.1	75
80		481.3	75
81		513.1	84

82		513.1	83
83		527.1	85
84		527.1	86

*Triethylamine was applied (replacement of K_3PO_4) in dichloroethane, at 75 °C

Example 85



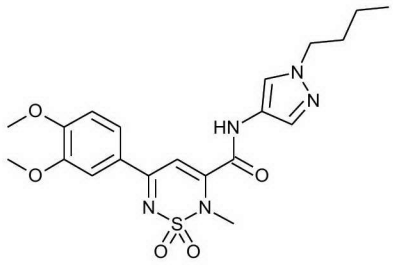
intermediate 65 Example 85

5-(3,4-dimethoxyphenyl)-2-methyl-1,1-dioxo-*N*-(1-propyl-1*H*-pyrazol-3-yl)-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide

Under an inert atmosphere, to a mixture of Intermediate 65 (5-(3,4-dimethoxyphenyl)-2-methyl-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxylic acid; 210 mg, 0.64 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC, 248 mg, 1.29 mmol) in *N,N*-dimethylformamide (9 mL), 1-propyl-1*H*-pyrazol-3-amine (99 mg, 0.79 mmol) and 4-(dimethylamino)pyridine (209 mg, 1.71 mmol) was added, and the mixture was stirred at room temperature for 4 days. Another portion of 1-propyl-1*H*-pyrazol-3-amine (85 mg, 0.68 mmol) in *N,N*-dimethylformamide (2mL) was added, and the mixture was stirred further for 2 days. 10 % HCl solution was added, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with water, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by column chromatography on silica gel with a mixture of

ethyl acetate and cyclohexane (1:1), as eluent. Yield: 5 mg (2 %) yellow crystals, m/z $(M+H)^+$: 434.1.

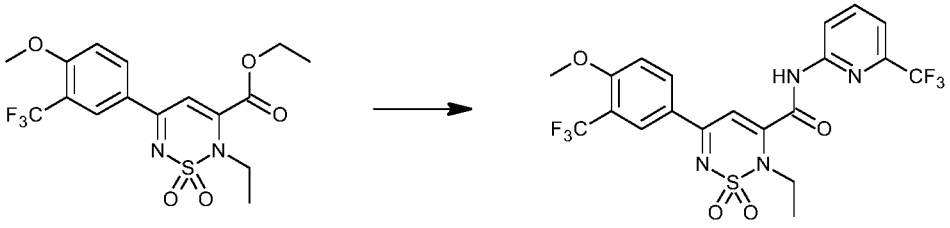
Example 86



***N*-(1-butyl-1*H*-pyrazol-4-yl)-5-(3,4-dimethoxyphenyl)-2-methyl-1,1-dioxo-2*H*-1λ⁶,2,6-thiadiazine-3-carboxamide** (purchased library compound, Chemdiv (catalog no.: E135-0831)).

Step 6

Example 87



Intermediate 46 Example 87

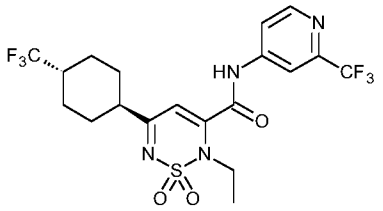
2-ethyl-5-[4-methoxy-3-(trifluoromethyl)phenyl]-1,1-dioxo-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide

To a solution of 2-amino-6-(trifluoromethyl)pyridine (389 mg, 2.4 mmol) in 1,2-dichloroethane (3 mL), a solution of triethyl aluminium (1.9M, 1.25 mL) in toluene was added dropwise at 20-25 °C during slight cooling under argon atmosphere, and the solution was stirred at room temperature for another hour. A solution of Intermediate 46 (ethyl 2-ethyl-5-[4-methoxy-3-(trifluoromethyl)phenyl]-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxylate, 203 mg, 0.5 mmol) in 1,2-dichloroethane (3 mL) was added, and the mixture was heated at 65 °C overnight.

After cooling to room temperature, 1 M HCl solution (10 mL) was added dropwise, and the mixture was stirred at 35-40 °C for an hour. The phases were separated, and the aqueous phase was extracted with dichloromethane. The combined organic layer was washed with water, dried over Na_2SO_4, filtered, concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel, with a gradient of a mixture of diisopropyl ether and dichloromethane. Yield: 206 mg (79 %), m/z $(M+H)^+$: 523.1.

Example 88 was synthesized from Intermediate 50 according to the procedure described for Example 82.

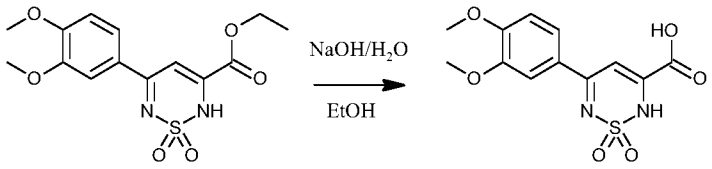
Example 88



2-ethyl-*N*-(2-methylpyridin-4-yl)-1,1-dioxo-5-[(1*r*,4*r*)-4-methylcyclohexyl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide, m/z (M+H)$^+$: 499.1.

Step 7

Intermediate 87



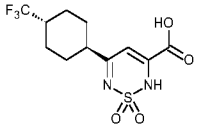
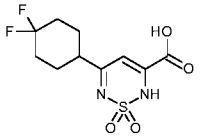
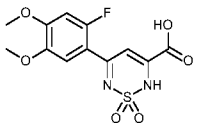
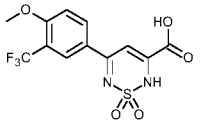
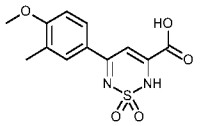
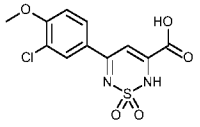
intermediate 19 intermediate 87

5-(3,4-dimethoxyphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazin-3-carboxylic acid

To a suspension of Intermediate 19 (ethyl 5-(3,4-dimethoxyphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxylate, 8.00 g, 23.5 mmol) in ethanol (400 mL), an aqueous 5 M NaOH solution (19 mL) was added, and the mixture was stirred at room temperature for 2.5 hours. The pH of the mixture was adjusted to 5-6 by the addition of 3 M HCl solution during cooling with ice. The solvent was removed *in vacuo*, and dried at 40 °C in a drying oven until permanent mass had been achieved. The obtained product (containing significant amount of NaCl) was used in the next step without further purification (m/z (M+H)$^+$: 313.1).

The following intermediates in Table 8 were synthesized according to the procedure described for Intermediate 87.

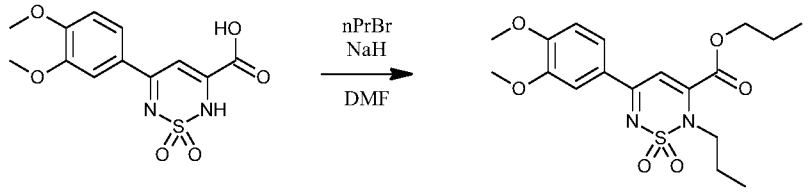
Table 8

Intermediate	Structure	Starting intermediate
88		29
89		30
90*		26
91		24
92		22
93*		20

*2M conc. aqueous NaOH solution, 2-3 mol equivalents

Step 8

Intermediate 94



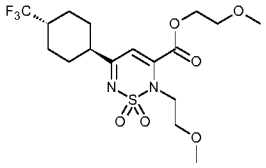
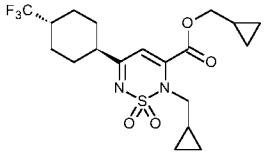
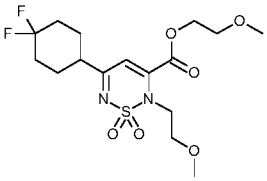
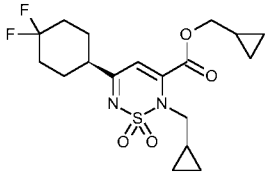
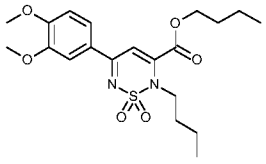
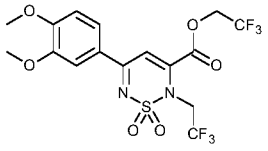
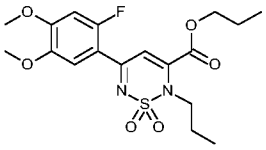
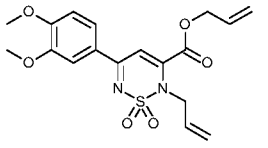
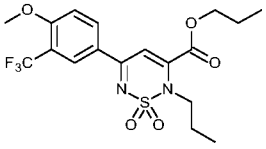
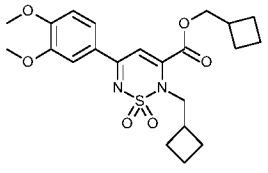
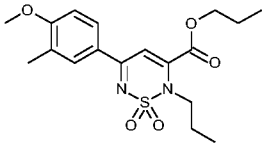
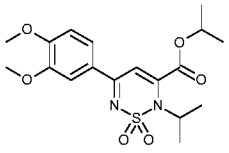
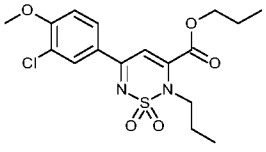
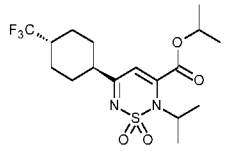
intermediate 87 intermediate 94

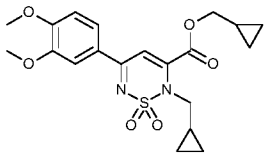
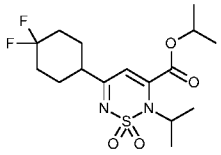
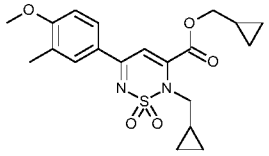
Propyl 5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-propyl-2*H*-1λ^6,2,6-thiadiazine-3-carboxylate

To a suspension of Intermediate 87 (5-(3,4-dimethoxyphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxylic acid; 11.8 mmol) in *N,N*-dimethylformamide (80 mL), sodium hydride (1.88 g, 47.0 mmol, 60 % in mineral oil) was added under an inert atmosphere. 1-bromopropane (21.3 mL, 235 mmol) was added, and the mixture was stirred at 80 °C overnight. The reaction mixture was allowed to cool to room temperature, water (20 mL) and 10 % HCl solution (20 mL) was added, and it was extracted with ethyl acetate. The combined organic layer was washed with water, 1 M $Na_2S_2O_3$ solution and brine, dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel, using a mixture of dichloromethane and diisopropyl ether (60:1) as eluent. Yield: 3.14 g (67 %) yellow crystals.

The following intermediates in Table 9 were synthesized according to the procedure described for Intermediate 94.

Table 9

Inter-mediate	Structure	Starting inter-mediate	Inter-mediate	Structure	Starting inter-mediate
95*		88	**104**		88
96*		89	**105**		89
97		87	**106**		87
98		90	**107**		87
99		91	**108**		87
100		92	**109**		87
101		93	**110**		88

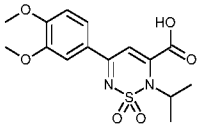
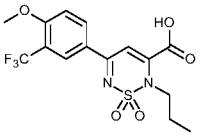
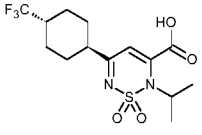
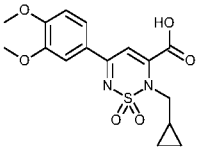
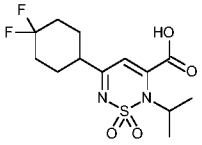
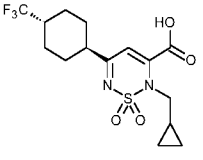
102		87	**111**		89
103		92			

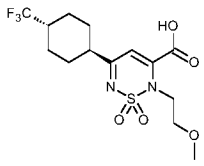
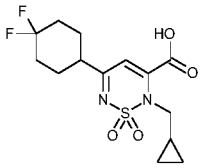
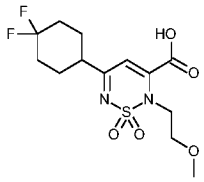
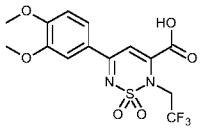
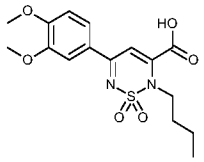
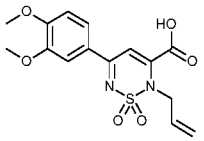
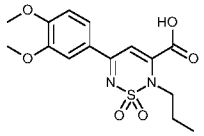
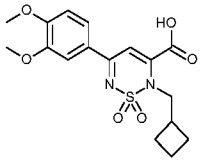
*DIPEA was applied as the replacement of NaH

Step 9

The following intermediates in Table 10 were synthesized according to the procedure described for Intermediate 62, except that 1.2-1.5 mol eqvivalent, 1-2 M NaOH or LiOH solution was used.

Table 10

Inter-mediate	**Structure**	**Starting inter-mediate**	**Inter-mediate**	**Structure**	**Starting inter-mediate**
112		109	**119****		99
113		110	**120**		102
114		111	**121**		104

115		95	**122**		105
116		96	**123***		106
117		97	**124***		107
118*		94	**125**		108

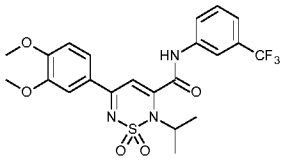
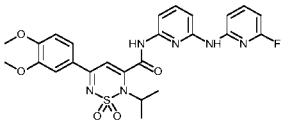
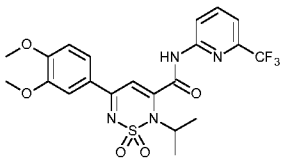
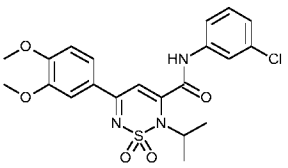
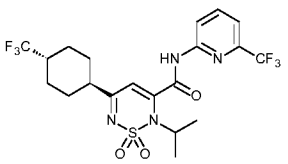
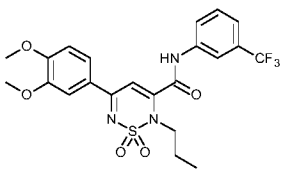
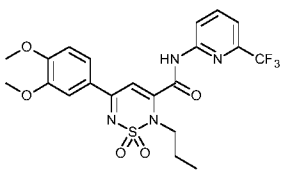
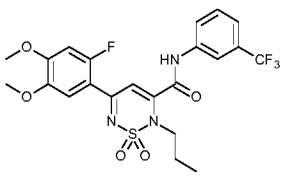
*LiOH, 1 M conc., 1.3-2 mol equivalents, in THF

**NaOH, 5 M conc., 4 mol equivalents

Step 5

The following examples in Table 11 were synthesized according to the procedure (via ester amidation in the presence of $AlEt_3$) described for Example 87.

Table 11

Example	Structure	LC-MS (ESI) m/z $(M+H)^+$	Starting intermediate
89		498.1	109
90*		541.2	109
91*		499.1	109
92		464.1	109
93*		513.1	110
94		498.2	94
95		499.1	94
96		516.1	98

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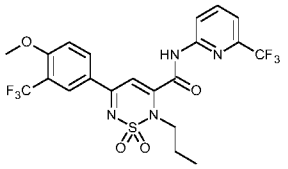
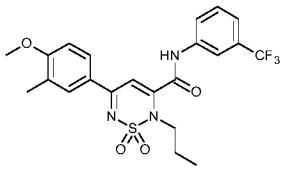
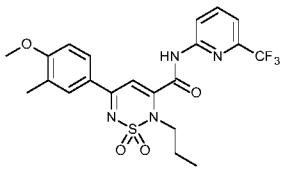
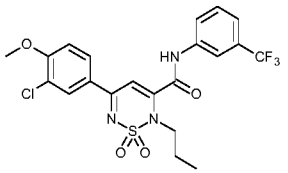
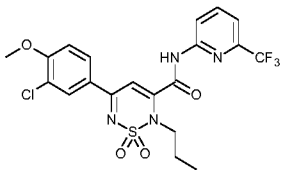
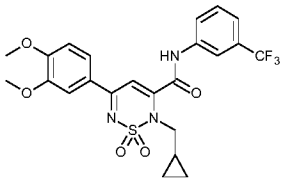
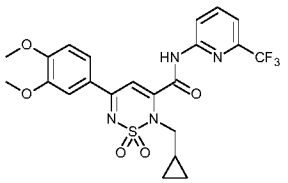
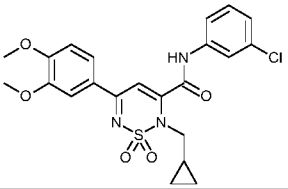
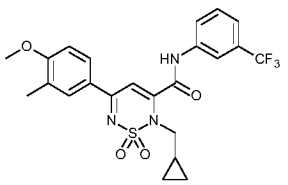
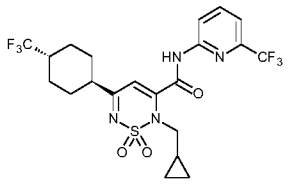
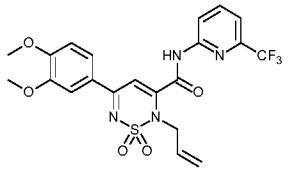
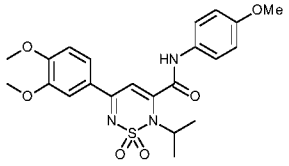
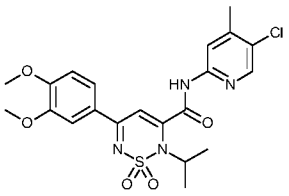
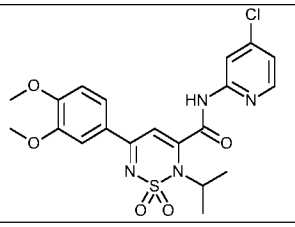
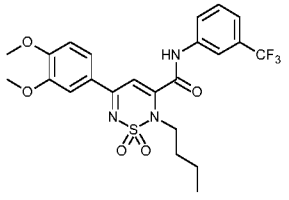
97		537.1	99
98		482.1	100
99		483.1	100
100		502.1	101
101		503.1	101
102*		510.2	102
103		511.1	102
104		476.1	102
105		494.1	103

106*		525.1	104
107		497.1	107

*Toluene was applied as solvent at 80-110 °C

The following examples in Table 12 were synthesized according to the procedure described for Example 1 (amide coupling with HATU reagent).

Table 12

Example	**Structure**	**LC-MS (ESI) m/z $(M+H)^+$**	**Starting intermediate**
108		460.2	112
109		497.1	112
110		465.2	112
111		512.1	117

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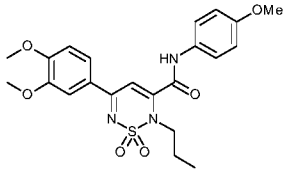
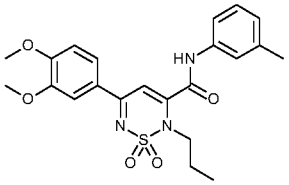
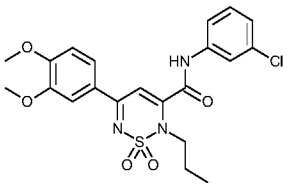
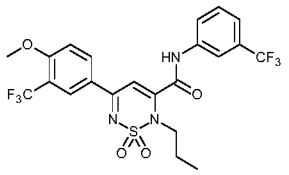
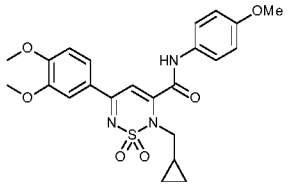
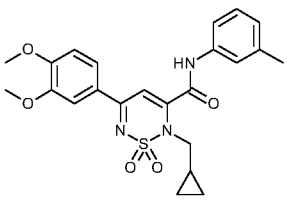
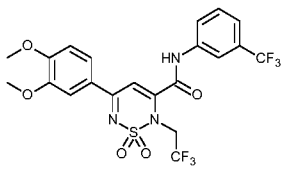
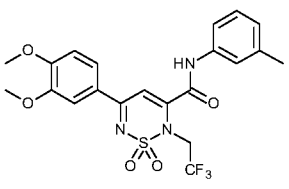
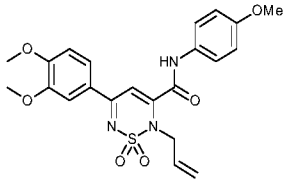
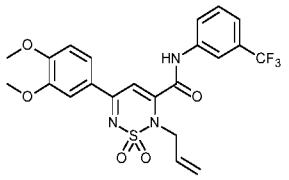
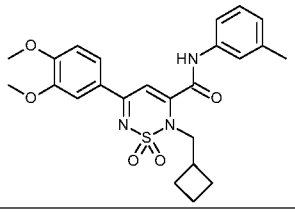
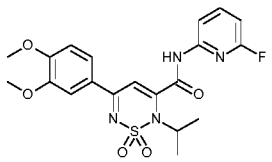
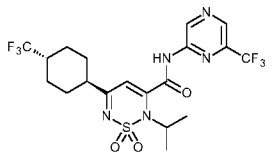
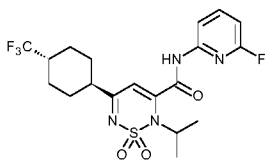
112		460.1	118
113		444.1	118
114		464.2	118
115		536.2	119
116		472.1	120
117		456.1	120
118		538.0	123
119		484.2	123

120		458.1	124
121		496.2	124
122		409.2	125

The following examples in Table 13 were synthesized according to the procedure described for Example 53 (amide formation via acid chloride derivatives).

Table 13

Example	**Structure**	**LC-MS (ESI) m/z $(M+H)^+$**	**Starting intermediate**
123		449.1	112
124*		514.2	113
125		$M+Na^+ = 485.1$	113

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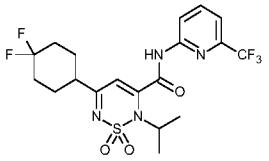
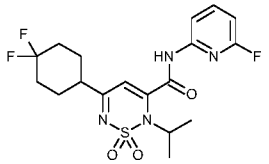
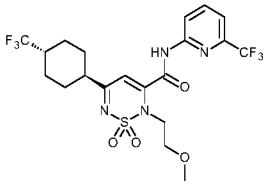
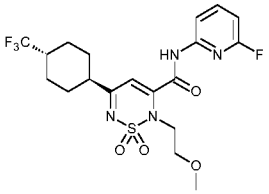
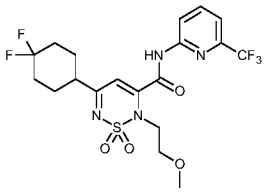
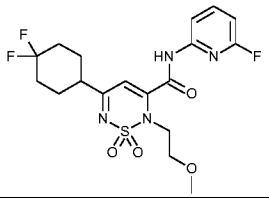
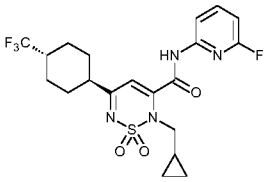
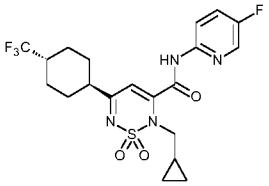
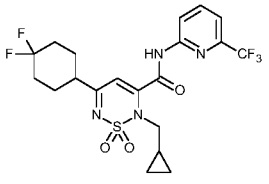
126		481.2	114
127		M+Na$^+$ = 453.1	114
128		529.1	115
129		M+Na$^+$ = 479.1	115
130		497.1	116
131		447.1	116
132		M+Na$^+$ = 497.2	121
133		475.1	121
134		493.2	122

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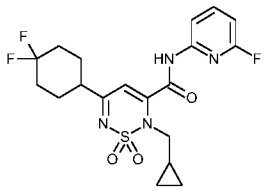
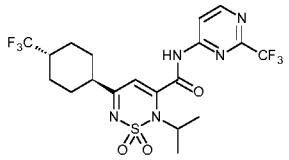
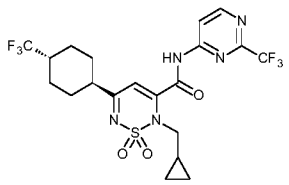
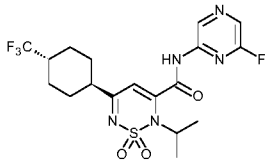
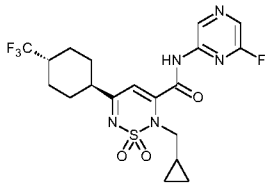
135		$M+Na^+ = 465.1$	122
136*		514.3	113
137*		526.3	121
138*		464.3	113
139*		476.3	121

*Triethylamine was applied (replacement of K_3PO_4) in dichloroethane, at 75 °C

Preparation of pharmaceutical compositions

The following formulation examples illustrate representative pharmaceutical compositions of this invention. The present invention, however, is not limited to the following pharmaceutical compositions.

A) Solid oral dosage forms

I., Tablets

Active ingredient(s)	0.01 – 90 %
Filler	1 – 99.9 %
Binder	0 – 20 %
Disintegrant	0 – 20 %
Lubricant	0 – 10 %
Other specific excipient(s)	0 – 50 %

II., Orodispersible films

Active ingredient(s)	0.01 – 90 %
Film forming agent	1 – 99.9 %
Plasticizer	0 – 40 %
Other specific excipient(s)	0 – 50 %

B) Liquid oral dosage forms

III., Oral suspensions

Active ingredient(s)	0.01 – 50 %
Liquid vehicle	10 – 99.9 %
Wetting agent	0 – 50 %
Thickener	0 – 50 %
Buffering agent	quantum satis
Osmotic agent	0 – 50 %
Preservatives	quantum satis

IV., Syrups

Active ingredient(s)	0.01 – 50 %

Solvent	10 – 99.9 %
Sugar component	1 – 20 %
Flavouring agents	0 – 10 %

C) Parenteral dosage forms

V., Intravenous injections

Active ingredient(s)	0.01 – 50 %
Solvent	10 – 99.9 %
Co-solvent	0 – 99.9 %
Osmotic agent	0 – 50 %
Buffering agent	quantum satis

D) Other dosage forms

VI., Suppositories

Active ingredient(s)	0.01 – 50 %
Suppository base	1 – 99.9 %
Surface-active agents	0 – 20 %
Lubricants	0 – 20 %
Preservatives	quantum satis

VII., Nasal drops or nasal sprays

Active ingredient(s)	0.01 – 50 %
Water	0 – 99.9 %
Solvent	0 – 99.9 %
Co-solvent	0 – 99.9 %
Osmotic agent	0 – 20 %
Viscosity enhancer	0 – 20 %
Buffering agent	quantum satis
Preservatives	quantum satis

BIOLOGICAL ACTIVITY

Human α7 nicotinic acetylcholine receptor $[Ca^{2+}]_i$ assay

Cells: Flp-In 293 cells stably expressing human α7 nAchR and human RIC-3 (α7 cells, generated in house.)

Materials: 96-well plates coated with PDL (Falcon), culture medium, assay buffer, DMSO, FLIPR Calcium 5 kit (Molecular Devices), probenecid, agonist and PAM test compounds.

Culture medium:

– DMEM (Dulbecco's Modified Eagle Medium, Gibco)
– 10 % FBS (Fetal Bovine Serum, Gibco)
– 1 % glutamine (Sigma G)
– 50 μg/ml Hygromycin B
– 800 μg/ml G418
– 1 % penicillin-streptomycin-antimycotic sol. (PSA, Sigma)

Assay buffer:

– 140 mM NaCl
– 5 mM KCl
– 10 mM HEPES
– 2 mM $MgCl_2$
– 2 mM $CaCl_2$
– 10 mM glucose
– 2 mM probenecid,
pH=7.4

Brief description of the method (Ca^{2+} fluorometry)

α7 cells cells stably expressing human α7 nAchR were cultured in the medium detailed above, and were split twice a week. For the fluorometric measurements of cytosolic Ca^{2+} ion concentration ($[Ca^{2+}]_i$) cells were seeded in 96-well microplates at a density of 60000 cells/well and maintained overnight in a tissue culture incubator at 37 °C under an atmosphere of 95 % air/5 % CO_2. The plating medium was identical with the culture medium. 50 μl of the growth medium was aspirated with a cell washer (BioTek Elx405UCVWS). Then 50 μl/well Calcium 5 kit diluted 2-fold in assay buffer was added manually using an 8-channel pipette. After an incubation period (20 minutes, 37 °C) 50 μl/well assay buffer containing vehicle (DMSO, 4 % added) or reference α7 PAMs (4 × of the final concentration) were added manually and the cells were incubated for an additional 10 minutes at 37 °C. Baseline and agonist-evoked [Ca2+]i-changes were monitored with FlexStation II (Molecular Devices,

Sunnyvale, CA), a plate reader fluorometer with integrated 8-channel fluid addition capability. Fluorescence measurements were carried out at 37 °C. The dye was excited at 485 nm, emission was sampled at 525 nm at 1.4-s intervals. Baseline was recorded for 20 seconds followed by agonist stimulation. 50 µl 4 × concentrated agonist solution was added to the cells using the pipettor of FlexStation II and fluorescence was monitored for an additional 40 seconds. Final DMSO concentration was 1 % for all treatments. To achieve this, a series of DMSO stock solutions were prepared from all test compounds. These stocks were stored under 0 °C and were further diluted in assay buffer to obtain the desired final concentration immediately before the measurement. Agonist and PAM concentration-response studies were conducted in the presence of saturating concentrations of PAMs (mostly PNU-120596, 5 µM) and agonists (mostly PNU-282987, 1 µM), respectively. Results were expressed as ΔF/F values using SoftMax Pro software (Molecular Devices), where F was the resting fluorescence preceding agonist application and ΔF was the increase in fluorescence at a given time (ΔF = maximum fluorescence intensity values after stimulation minus average fluorescence intensity values before stimulation). In all experiments, all treatments were measured in multiple wells in parallel, and the mean ΔF/F values were used for analysis.

Table 14 shows the PAM EC_{50} values in the $[Ca^{2+}]_i$ assay:

Table 14

Example	**EC_{50} (nM)**	**Example**	**EC_{50} (nM)**	**Example**	**EC_{50} (nM)**
1	430	**48**	330	**95**	45
2	1400	**49**	490	**96**	330
3	690	**50**	1100	**97**	30
4	980	**51**	810	**98**	100
5	210	**52**	1600	**99**	40
6	1300	**53**	90	**100**	150
7	2000	**54**	480	**101**	65
8	1800	**55**	470	**102**	320
9	1600	**56**	2500	**103**	110

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10	670	**57**	2000	**104**	370
11	440	**58**	1200	**105**	120
12	230	**59**	1300	**106**	70
13	340	**60**	300	**107**	55
14	1400	**61**	100	**108**	1300
15	3000	**62**	2800	**109**	240
16	1400	**63**	190	**110**	640
17	2800	**64**	330	**111**	200
18	2900	**65**	1100	**112**	75
19	1600	**66**	430	**113**	80
20	940	**67**	220	**114**	380
21	230	**68**	140	**115**	85
22	370	**69**	1100	**116**	100
23	400	**70**	620	**117**	110
24	210	**71**	140	**118**	530
25	1400	**72**	430	**119**	380
26	360	**73**	390	**120**	120
27	110	**74**	1100	**121**	220
28	1200	**75**	960	**122**	320
29	340	**76**	85	**123**	55
30	440	**77**	1500	**124**	110
31	440	**78**	790	**125**	45
32	720	**79**	320	**126**	220
33	50	**80**	350	**127**	580
34	130	**81**	120	**128**	310
35	150	**82**	120	**129**	190

36	310	**83**	310	**130**	960
37	45	**84**	130	**131**	1800
38	45	**85**	2000	**132**	35
39	150	**86**	2900	**133**	230
40	60	**87**	10	**134**	80
41	100	**88**	1400	**135**	120
42	120	**89**	290	**136**	150
43	110	**90**	1200	**137**	130
44	360	**91**	35	**138**	140
45	210	**92**	290	**139**	150
46	170	**93**	120		
47	500	**94**	340		

***In vivo* pharmacology (place recognition test)**

Animals: Male NMRI mice (Toxicoop, Hungary)

Substances: Scopolamine was dissolved in saline and administered at 1 mg/kg dose i.p. Test compounds were administered 30 minutes before the acquisition trial (T1) and scopolamine after the acquisition trial at a volume of 0.1 ml/10 g.

Procedure: The task was carried out in a transparent plexiglass Y-maze (each arm has a length of 40 cm, an inner width of 11 cm and a height of 30 cm). Numerous visual cues were placed around the arms and were kept constant during the experiment. The test consisted of two trials (T1 and T2) separated by an intertrial interval of 30 minutes. Mice were placed in the starting arm of the maze at the beginning of each trial. In T1, one of the symmetric arms of the maze was closed (it will be novel in T2) and the animals were allowed to explore the maze for 5 minutes (acquisition phase). In T2, mice had free access to all three arms for 2 minutes (retrieval phase). The time spent with exploration in the novel and familiar arms during T2 was measured. Differences between the exploration times spent in the familiar vs.

novel arms of the maze for each group were evaluated by MANOVA, followed by Duncan post hoc test.

Table 15 shows the reversal of the scopolamine-induced amnesia in the place recognition assay in mice:

Table 15

	Dose (i.p.)		
	1 mg/kg	**3 mg/kg**	**10 mg/kg**
Example 1	++	+++	+++
Example 21	++	+++	++
Example 29	+++	++	+++
Example 33	+++	++	++
Example 37	+++	++	+++
Example 91	+++	+	+++
Example 94	+++	+++	+++

$^{+}p<0.05$; $^{++}p<0.01$; $^{+++}p<0.001$

Significant differences ($^{+}p<0.05$; $^{++}p<0.01$; $^{+++}p<0.001$) were observed between the exploration times spent in the novel vs. familiar arms of the maze.

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CLAIMS

1. A compound selected from the group consisting of:

5-(3,4-dimethoxyphenyl)-2-methyl-*N*-(3-methylphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(1,3-dimethyl-1*H*-indazol-5-yl)-2-methyl-*N*-(3-methylphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-2-ethyl-*N*-(3-methylphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-2-ethyl-1,1-dioxo-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

2-ethyl-5-[4-methoxy-3-(trifluoromethyl)phenyl]-*N*-(3-methoxyphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

2-ethyl-5-[4-methoxy-3-(trifluoromethyl)phenyl]-*N*-(4-methoxyphenyl)-1,1-dioxo-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

2-ethyl-1,1-dioxo-5-[(1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl]-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

N-(6-cyanopyridin-2-yl)-2-ethyl-1,1-dioxo-5-[(1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-(propan-2-yl)-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-propyl-*N*-[3-(trifluoromethyl)phenyl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-propyl-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-[4-methoxy-3-(trifluoromethyl)phenyl]-1,1-dioxo-2-propyl-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(4-methoxy-3-methylphenyl)-1,1-dioxo-2-propyl-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3-chloro-4-methoxyphenyl)-1,1-dioxo-2-propyl-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

2-(cyclopropylmethyl)-1,1-dioxo-5-[(1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl]-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-1,1-dioxo-2-(prop-2-en-1-yl)-*N*-[6-(trifluoromethyl)pyridin-2-yl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-*N*-(4-methoxyphenyl)-1,1-dioxo-2-propyl-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-*N*-(3-methylphenyl)-1,1-dioxo-2-propyl-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-[4-methoxy-3-(trifluoromethyl)phenyl]-1,1-dioxo-2-propyl-*N*-[3-(trifluoromethyl)phenyl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

5-(3,4-dimethoxyphenyl)-*N*-(6-fluoropyridin-2-yl)-1,1-dioxo-2-(propan-2-yl)-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

N-(6-fluoropyridin-2-yl)-1,1-dioxo-2-(propan-2-yl)-5-[(1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

2-(cyclopropylmethyl)-*N*-(6-fluoropyrazin-2-yl)-1,1-dioxo-5-[(1*r*,4*r*)-4-(trifluoromethyl)cyclohexyl]-2*H*-1λ^6,2,6-thiadiazine-3-carboxamide;

2-[(2R)-butan-2-yl]-5-(3,4-dimethoxyphenyl)-1,1-dioxo-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ^6,2,6-thiadiazine-3-carboxamide;

2-ethyl-5-[4-methoxy-3-(trifluoromethyl)phenyl]-1,1-dioxo-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ^6,2,6-thiadiazine-3-carboxamide;

1,1-dioxo-2-(propan-2-yl)-5-[(1r,4r)-4-(trifluoromethyl)cyclohexyl]-N-[6-(trifluoromethyl)pyrazin-2-yl]-2H-1λ^6,2,6-thiadiazine-3-carboxamide;

2-(cyclopropylmethyl)-5-(4,4-difluorocyclohexyl)-1,1-dioxo-N-[6-(trifluoromethyl)pyridin-2-yl]-2H-1λ^6,2,6-thiadiazine-3-carboxamide; and

2-(cyclopropylmethyl)-1,1-dioxo-5-[(1r,4r)-4-(trifluoromethyl)cyclohexyl]-N-[2-(trifluoromethyl)pyrimidin-4-yl]-2H-1λ^6,2,6-thiadiazine-3-carboxamide;

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or a pharmaceutically acceptable salt, a racemate, an enantiomer, a diastereomer, a solvate or a hydrate thereof.

2. A pharmaceutical composition comprising as active ingredient a compound according to claim 1 and at least one pharmaceutically acceptable excipient.

3. Use of compound according to claim 1 or a pharmaceutical composition according to claim 2 in the manufacture of a medicament for the treatment or prevention of a disease selected from the group of: psychotic disorders, including, but not limited to, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorder or psychotic disorder not otherwise specified, cognitive impairment, including, but not limited to, cognitive impairment as a result of stroke, Alzheimer's disease, Huntington's disease, Pick disease, HIV associated dementia, frontotemporal dementia, Lewy body dementia, vascular dementia, cerebrovascular disease or other dementia states and dementia associated to other degenerative disorders, including, but not limited to, amyotrophic lateral sclerosis, other acute or sub-acute conditions that may cause cognitive decline, including, but not limited to, delirium, traumatic brain injury, senile dementia, mild cognitive impairment, Down's syndrome, depression and cognitive deficit related to other diseases, and dyskinetic disorders including, but not limited to, Parkinson's disease, neuroleptic-induced parkinsonism, or tardive dyskinesias, depression and mood disorders, including, but not limited to, depressive disorders and episodes, bipolar disorders, cyclothymic disorder, and bipolar disorder not otherwise specified, other mood disorders, substance-induced mood disorder and mood disorder not otherwise specified, anxiety disorders, panic disorder and panic attacks, obsessive compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, phobias, and anxiety disorder not otherwise specified, substance related disorders, including, but not limited to, substance use or substance-induced disorders, including, but not limited to, alcohol-, nicotine-, amphetamine-, phencyclidine-, opioid-, cannabis-, cocaine-, caffeine-, hallucinogen-, inhalant-, sedative-, hypnotic-, anxiolytic-, polysubstance- or other substance-related disorders, sleep disorders, including, but not limited to, narcolepsy, dyssomnias, primary hypersomnia, breathing-related sleep disorders, circadian rhythm sleep disorder and dyssomnia not otherwise specified, parasomnias, sleep terror disorder, sleepwalking disorder and parasomnia not otherwise

specified, sleep disorders related to another mental disorder, sleep disorder due to a general medical condition and substance-induced sleep disorder, metabolic and eating disorders, including, but not limited to, anorexia nervosa, bulimia nervosa, obesity, compulsive eating disorder, binge eating disorder and eating disorder not otherwise specified, diabetes mellitus, ulcerative colitis, Crohn's disease, irritable bowel syndrome, autism spectrum disorders, including, but not limited to, autistic disorder, Asperger's disorder, Rett's disorder, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified, attention deficit hyperactivity disorder, disruptive behaviour disorders, oppositional defiant disorder and disruptive behaviour disorder not otherwise specified, and tic disorders, including, but not limited to, Tourette's disorder, personality disorders, sexual dysfunctions such as sexual desire disorders, sexual arousal disorders, orgasmic disorders, sexual pain disorder, sexual dysfunction not otherwise specified, paraphilias, gender identity disorders, infertility, premenstrual syndrome and sexual disorders not otherwise specified, disorders of the respiratory system like cough, asthma, chronic obstructive pulmonary disease, lung inflammation, disorders of the cardiovascular system such as cardiac failure, heart arrhythmia, hypertension, inflammation, inflammatory and neuropathic pain, rheumatoid arthritis, osteoarthritis, allergy, sarcoidosis, psoriasis, ataxia, dystonia, systemic lupus erythematosus, mania, restless legs syndrome, progressive supranuclear palsy, epilepsy, myoclonus, migraine, amnesia, chronic fatigue syndrome, cataplexy, brain ischemia, multiple sclerosis, encephalomyelitis, jetlag, cerebral amyloid angiopathy, and sepsis.

4. The use according to claim 3, wherein the disease is selected from the group consisting of: cognitive impairment, schizophrenia, and autism.

5. A method for the treatment or prevention of a disease associated with α7 nicotinic acetylcholine receptor activity, the method comprising administering to a mammal in need of such treatment or prevention an effective amount of at least one compound according to claim 1 or a pharmaceutical composition according to claim 2, wherein the disease associated with α7 nicotinic acetylcholine receptor activity is selected from the group of: psychotic disorders, including, but not limited to, schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychotic disorder or psychotic disorder not otherwise specified, cognitive impairment, including, but not limited to, cognitive impairment as a result of stroke, Alzheimer's disease, Huntington's disease, Pick disease, HIV associated dementia,

frontotemporal dementia, Lewy body dementia, vascular dementia, cerebrovascular disease or other dementia states and dementia associated to other degenerative disorders, including, but not limited to, amyotrophic lateral sclerosis, other acute or sub-acute conditions that may cause cognitive decline, including, but not limited to, delirium, traumatic brain injury, senile dementia, mild cognitive impairment, Down's syndrome, depression and cognitive deficit related to other diseases, and dyskinetic disorders including, but not limited to, Parkinson's disease, neuroleptic-induced parkinsonism, or tardive dyskinesias, depression and mood disorders, including, but not limited to, depressive disorders and episodes, bipolar disorders, cyclothymic disorder, and bipolar disorder not otherwise specified, other mood disorders, substance-induced mood disorder and mood disorder not otherwise specified, anxiety disorders, panic disorder and panic attacks, obsessive compulsive disorder, posttraumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder, phobias, and anxiety disorder not otherwise specified, substance related disorders, including, but not limited to, substance use or substance-induced disorders, including, but not limited to, alcohol-, nicotine-, amphetamine-, phencyclidine-, opioid-, cannabis-, cocaine-, caffeine-, hallucinogen-, inhalant-, sedative-, hypnotic-, anxiolytic-, polysubstance- or other substance-related disorders, sleep disorders, including, but not limited to, narcolepsy, dyssomnias, primary hypersomnia, breathing-related sleep disorders, circadian rhythm sleep disorder and dyssomnia not otherwise specified, parasomnias, sleep terror disorder, sleepwalking disorder and parasomnia not otherwise specified, sleep disorders related to another mental disorder, sleep disorder due to a general medical condition and substance-induced sleep disorder, metabolic and eating disorders, including, but not limited to, anorexia nervosa, bulimia nervosa, obesity, compulsive eating disorder, binge eating disorder and eating disorder not otherwise specified, diabetes mellitus, ulcerative colitis, Crohn's disease, irritable bowel syndrome, autism spectrum disorders, including, but not limited to, autistic disorder, Asperger's disorder, Rett's disorder, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified, attention deficit hyperactivity disorder, disruptive behaviour disorders, oppositional defiant disorder and disruptive behaviour disorder not otherwise specified, and tic disorders, including, but not limited to, Tourette's disorder, personality disorders, sexual dysfunctions such as sexual desire disorders, sexual arousal disorders, orgasmic disorders, sexual pain disorder, sexual dysfunction not otherwise specified, paraphilias, gender identity disorders, infertility, premenstrual syndrome and sexual

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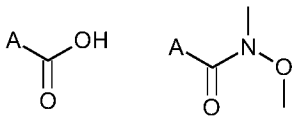
disorders not otherwise specified, disorders of the respiratory system like cough, asthma, chronic obstructive pulmonary disease, lung inflammation, disorders of the cardiovascular system such as cardiac failure, heart arrhythmia, hypertension, inflammation, inflammatory and neuropathic pain, rheumatoid arthritis, osteoarthritis, allergy, sarcoidosis, psoriasis, ataxia, dystonia, systemic lupus erythematosus, mania, restless legs syndrome, progressive supranuclear palsy, epilepsy, myoclonus, migraine, amnesia, chronic fatigue syndrome, cataplexy, brain ischemia, multiple sclerosis, encephalomyelitis, jetlag, cerebral amyloid angiopathy, and sepsis.

6. The method according to claim 5, wherein the disease is selected from the group consiting of: cognitive impairment, schizophrenia, and autism.

7. A process for manufacturing a compound of claim 1, comprising reacting formula (IIa) or formula (IIb)



(IIa) (IIb)

or

– wherein the meaning of A is a saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl or is saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged heterocyclyl,– with methyl lithium, or reacting compound of formula (IIc)

(IIc)

– wherein the meaning of A is an aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl or an aromatic, monocyclic or bycyclic, fused or bridged heterocyclyl, optionally substituted by one or more $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, halo$C_{1\text{-}6}$alkyl – with tributyl(1-ethoxyvinyl)tin, or reacting compound of formula (IId)

(IId)

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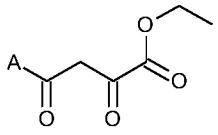
with acetyl chloride – wherein the meaning of A is an aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl or an aromatic, monocyclic or bycyclic, fused or bridged heterocyclyl, optionally substituted by one or more C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, halogen – to obtain the ketone derivative of formula (III)

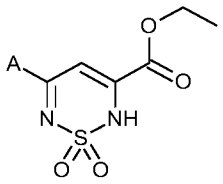
(III)

– wherein the meaning of A is as described above– which is reacted with diethyl oxalate to provide 2,4-dioxo ester derivative of formula (IV)



(IV)

– wherein the meaning of A is as described above– which is reacted with sulfamide, and then the obtained 1,1-dioxo-1,3-thiadiazine carboxylic acid ester derivative of formula (V)



(V)

– wherein the meaning of A is as described above– is transformed to the desired end product in different ways:

ROUTE A) the compound of formula (V) is alkylated to furnish *N*-alkyl thiadiazine derivative of formula (VI)

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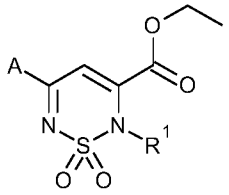
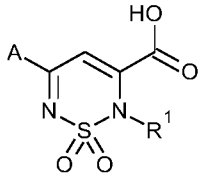


(VI)

– wherein the meaning of A is as described aboveand R^1 is C_{1-6}alkyl, C_{1-6}alkenyl, haloC_{1-6}alkyl, C_{3-8}cycloalkylC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, or C_{4-6}heterocyclyl – which is hydrolysed leading to carboxylic acid derivative of formula (VII)

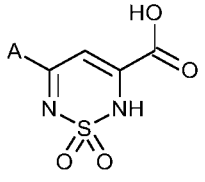


(VII)

– wherein the meaning of A and R^1 is as described above– which is coupled with an appropriate amine (B-NH_2) – wherein the meaning of B is saturated, unsaturated or aromatic, monocyclic or bycyclic, fused or bridged carbocyclyl, or a saturated, unsaturated or aromatic monocyclic or bycyclic, fused or bridged heterocyclyl, optionally substituted by one or more halogen atom or halogen atoms, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, CN, C(O)C_{1-6}alkyl, or haloC_{1-6}alkoxy – to provide the desired amide of formula (I)

or

ROUTE B) the ester derivative of formula (V) is hydrolysed to furnish the carboxylic acid derivative of formula (VIII)



(VIII)

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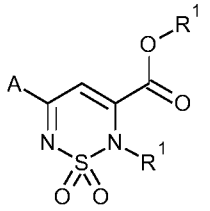
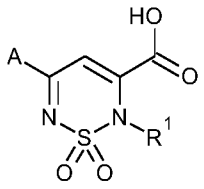
–wherein the meaning of A is as described above– which is then *N,O*-dialkylated in one step resulting the corresponding ester compound of formula (X)



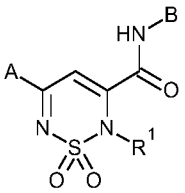
(X)

–wherein the meaning of A and R^1 is as described above– which is either hydrolysed to derivative of formula (VII)



(VII)

–wherein the meaning of A and R^1 is as described above– and then reacted with the appropriate amine (B-NH_2) resulting in the targeted amide derivative of formula (I),



(I)

or compound of formula (X)

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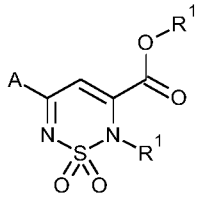

(X)

–wherein the meaning of A and R^1 is as described above– is transformed directly to the amide derivative of the formula (I) by reaction with the appropriate amine (B-NH_2).

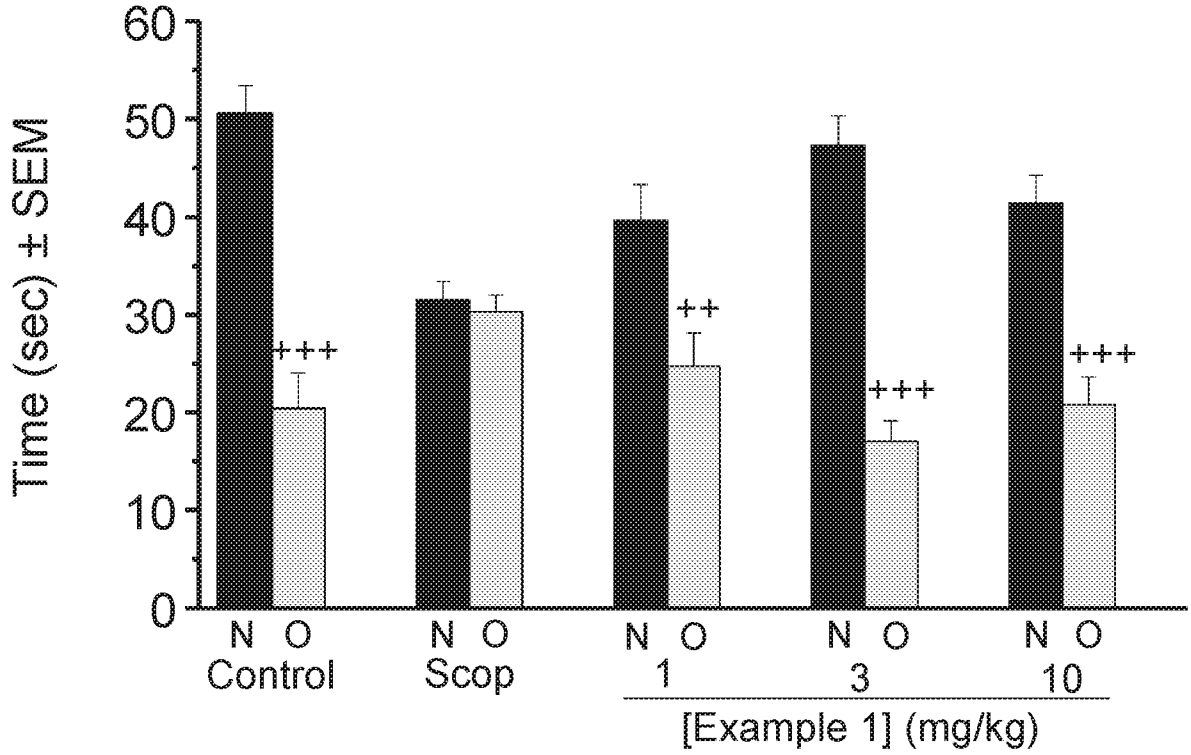

Figure 1

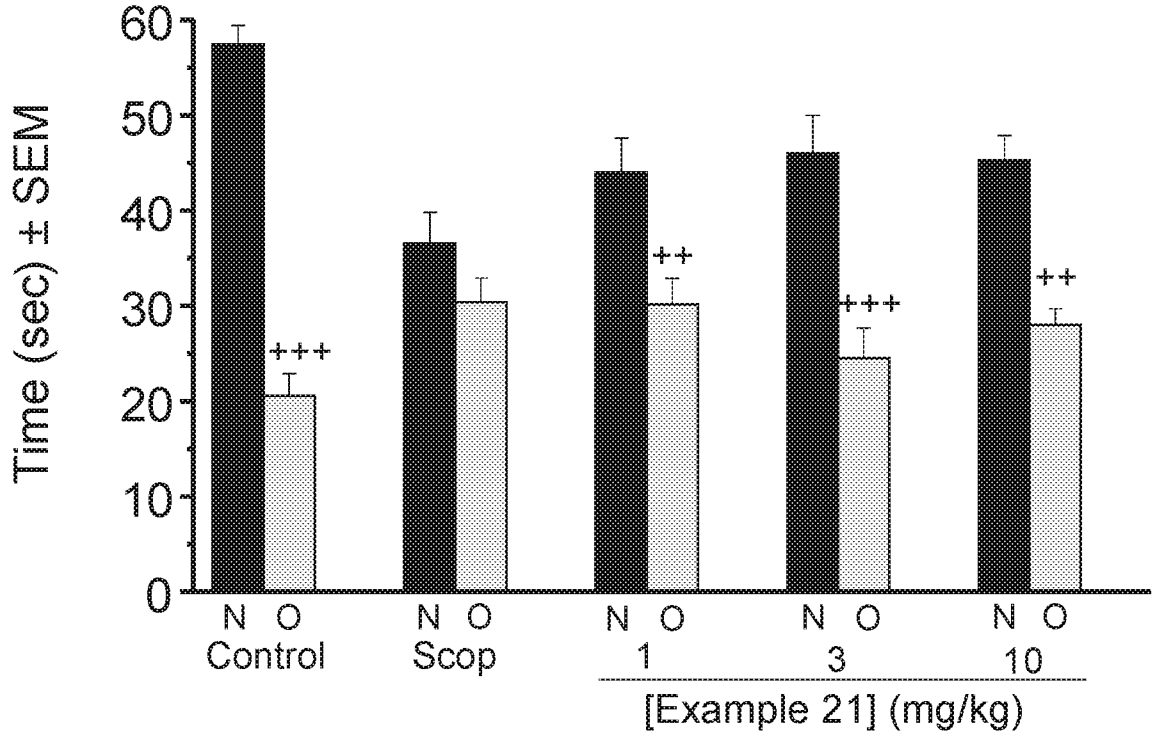

Figure 2

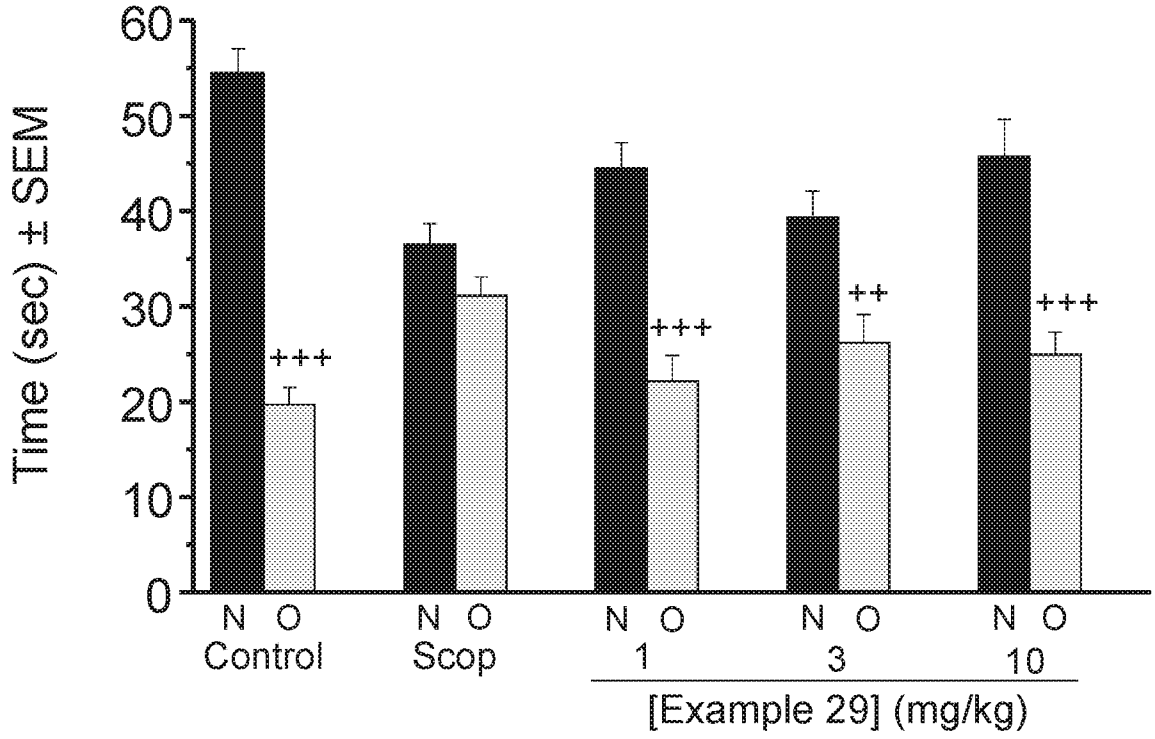

Figure 3

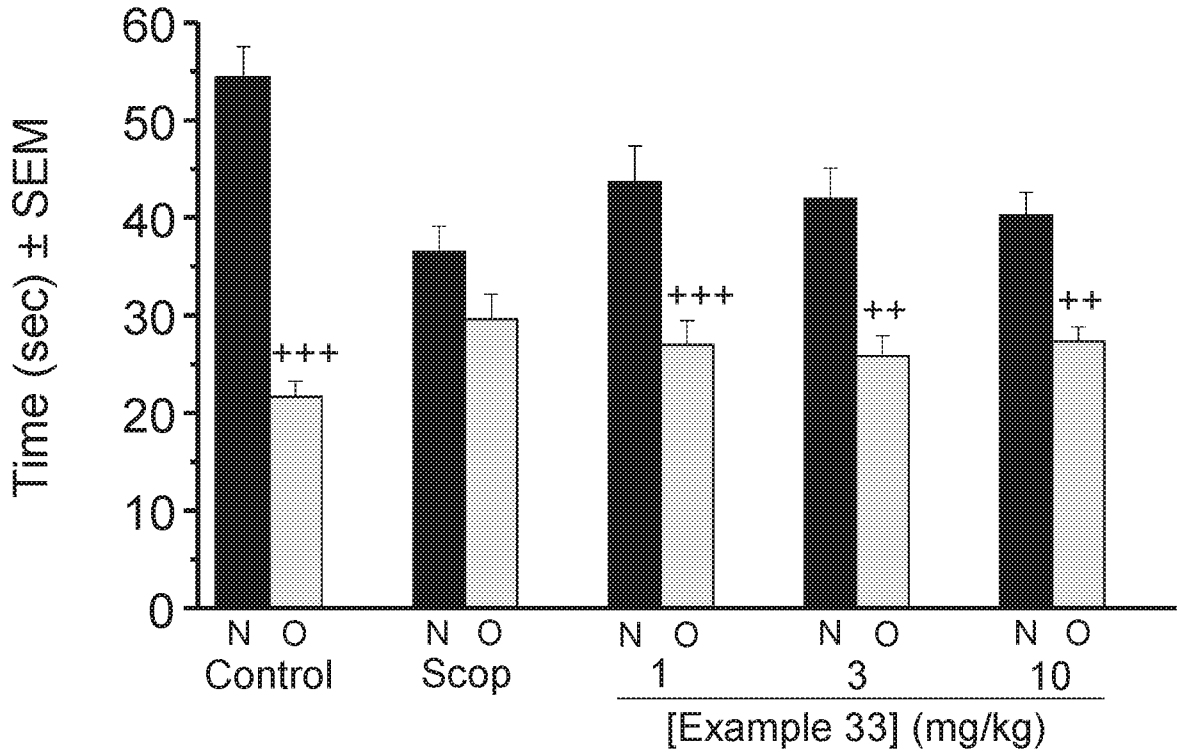

Figure 4

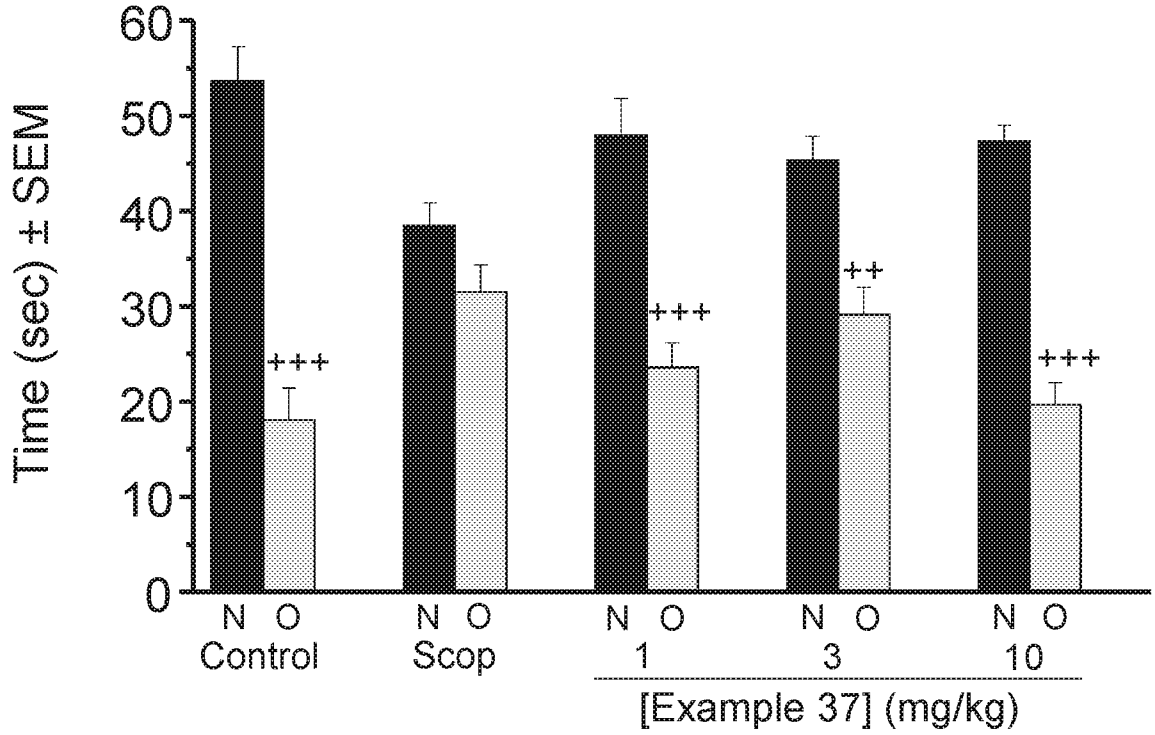

Figure 5

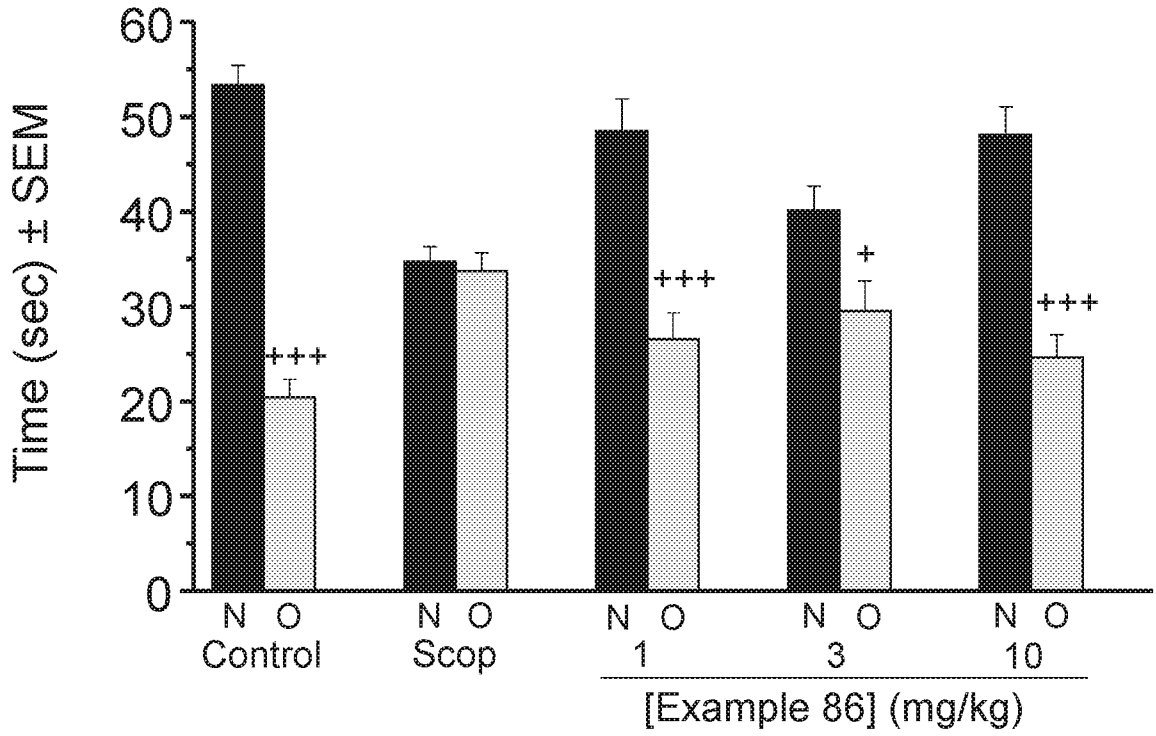

Figure 6

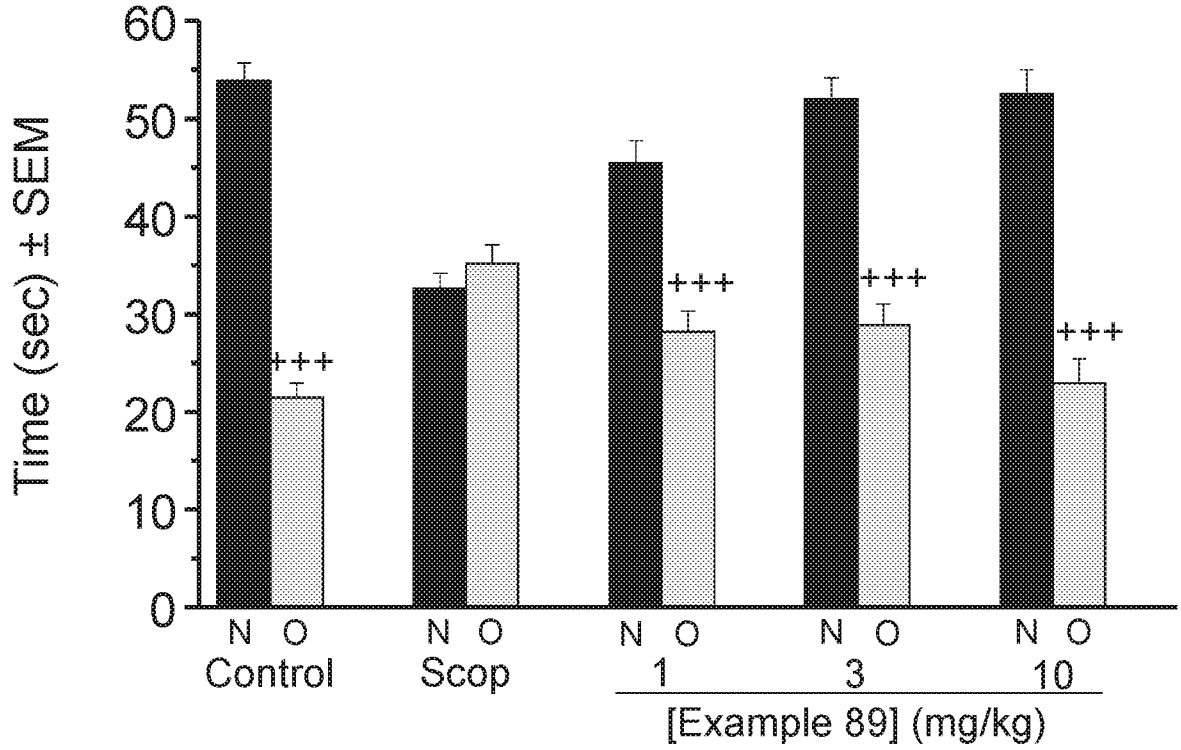
Time (sec) ± SEM
60
50
40
30
20
10
0
+++
+++
+++
+++
N O
Control
N O
Scop
N O
1
N O
3
N O
10
[Example 89] (mg/kg)

Figure 7