BICYCLIC AMINE DERIVATIVES AS GABAA α5 RECEPTOR MODULATORS

THE FIELD OF THE INVENTION

The present invention provides compounds of formula (I) having affinity and selectivity for the gamma-aminobutyric acid A receptor subunit alpha 5 ($GABA_A$ α5) and act as $GABA_A$ α5 positive allosteric modulators ($GABA_A$ α5 PAMs), thereby useful in the treatment or prevention of diseases related to the $GABA_A$ α5 receptor, process for the preparation and intermediates of the preparation process thereof, pharmaceutical compositions comprising them and their use as medicaments.

THE BACKGROUND OF THE INVENTION

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. Receptors sensitive for GABA are divided into two main families, the ligand gated $GABA_A$ receptors and the G-protein coupled $GABA_B$ receptors.

The ligand gated $GABA_A$ receptor mediates the majority of inhibitory neurotransmission in the adult mammalian brain. The receptor is composed by the pentameric assembly of multiple subunits (α1-6, β1-3, γ1-3, δ, ε, π, θ, ρ1-3) (Olsen and Sieghart, *Pharmacol Rev* 2008, 60:243-260) forming a ligand-gated chloride-channel. Subunit distribution varies developmentally and regionally in the brain. This high variability leads to broad variation in inhibitory and in certain conditions excitatory neural mechanisms and provides the possibility for specific therapeutic interventions (Fritschy and Möhler, *J Comp Neurol* 1995, 359:154-194; Jacob, *Front Mol Neurosci* 2019, 12: Art 179). Physiological roles and pharmacological profiles of $GABA_A$ receptors are strongly dependent on the subunit constitution. Studies on genetically modified mice have demonstrated that receptor subunit composition, especially regarding the α subtypes, considerably determines pharmacology of compounds acting on the benzodiazepine-sensitive allosteric modulatory site (BDZ-site) (Rudolph and Knoflach, *Nat Rev Drug Discov* 2011, 10:685-697). The widely distributed α1-containing receptors mediate the sedative and amnesic effects, whereas the α2- and α3-containing receptors account for the anxiolytic, anticonvulsant and myorelaxant effects (Sieghart and Sperk, *Curr Top Med Chem* 2002, 2:795-816; Whiting et al, *Drug Discov Today* 2003, 8:445-450). α5 subunit containing receptors ($\alpha5GABA_ARs$) are preferentially expressed in the hippocampus, prefrontal cortex, amygdala and nucleus accumbens (Olsen and Sieghart, *Neuropharmacology* 2009, 56:141-148; Sur et al., *Brain Res* 1999, 822:265-270;

Martin et al., *Biochem Soc Trans* 2009, 37:1334-1337) and thought to be involved in a variety of CNS disorders.

α5-containing receptors are predominantly extrasynaptic and mediate tonic inhibition (Caraiscos et al., *Proc Natl Acad Sci USA* 2004, 101:3662-3667). In contrast to their inhibitory role in the mature nervous system, α5GABA$_A$Rs can provoke excitation in early hippocampal circuit development (Marchionni et al., *J Physiol.* 2007, 581:515-528). Their modulatory effect on the excitability of hippocampal and cortical principal neurons can explain the significant effect of α5GABA$_A$Rs in neuronal development, cognition, learning and memory and their potential therapeutic usefulness in various disorders including stroke, mild cognitive impairment, schizophrenia, depression, dementia-related conditions or diseases related to impaired social cognition or neurodevelopmental disorders such as Down syndrome or autism spectrum disorder (ASD) (Jacob, *Front Mol Neurosci* 2019, 12: Art 179; Mohamad and Tarmizi Che Has, *J Mol Neurosci* 2019, 67:343-351; Soh and Lynch, *Curr Drug Targets* 2015, 16:735-746).

Genetic and pharmacological reduction in α5-mediated tonic inhibition may improve learning and memory (Möhler and Rudolph, *F1000Res* 2017 Feb 3;6. pii: F1000 Faculty Rev-101) through enhanced neuronal plasticity (Martin et al., *J Neurosci* 2010, 30:5269-5282) and network oscillatory activity (Towers et al, *J Physiol* 2004, 559:721-728; Glykis and Mody, *Neurophysiol* 2008, 95:2796-2807). However, hippocampal and cortical hyperactivity arising from reduced α5GABA$_A$R function might also result hyperlocomotion and impaired sensorimotor gating (Hauser at al., *Mol Psychiatry* 2005, 10:201-207), impaired social behaviour (Zurek et al., *Ann Clin Transl Neurol* 2016, 3:392-398) and cognitive deficit in rodents (Engin et al., *J Neurosci* 2015, 35:13698-13712; Martin et al., *J Neurosci* 2010, 30:5269-5282; Prut et al., *Genes Brain Behav* 2010, 9:478-488), those behavioural changes characteristic in a variety of CNS disorders. In such a pathological condition facilitation rather than blockade of α5GABA$_A$R function may be a promising treatment for positive, negative and cognitive symptoms associated with such diseases. In support of this idea, virally-induced overexpression of the α5 subunit of the GABA$_A$ receptor in the ventral hippocampus normalized physiological and behavioural deficits in a rat model of schizophrenia (Donegan et al., *Nature Communications* 2019, 10:2819).

The University of Wisconsin-Milwaukee described certain 4*H*-benzo[f]imidazo[1,5-a][1,4]diazepine derivatives (WO 2017/161370 A1) as α5-preferring PAM compounds, such as SH-053-2'F-R-CH3, MP-III-022 or GL-II-73 (Stamenić et al. *Eur J Pharmacol* 2016, 791:433-433; Savic et al., *Neuropsychopharmacology* 2008, 33:332-339; Prevot et al., *ACS*

Chem. Neurosci. 2019, 10:2088−2090) that showed procognitive, anxiolytic and antidepressant effects in mouse stress models and in aged mice (Prevot et al., *Mol Neuropsychiatry* 2019, 5:84–97). MP-III-022 and the 6,7-dihydro-2-benzothiophen-4(5*H*)-one α5 PAM Compound 44 (Chambers et al., *J Med Chem* 2003, 46:2227-2240) improved cognitive performance of young and aged rats, respectively (Poe, Michael M., *Theses and Dissertations*. 1301 (2016) https://dc.uwm.edu/etd/1301; Koh et al. *Neuropharmacology* 2013, 64:145:152. Acute treatment with GL-II-73 rescued chemogenetically induced behavioural deficits in a mouse model of depression (Fee et al., *Int J Neuropsychopharmacol* 2021, 24:505-518), while chronic treatment with GL-II-73 reversed age-related neuronal atrophy as well as impairment in working memory in adult mice (Sibille et al., *Biol Psychiatry* 2020, 87:Suppl1, page S85). In addition, SH-053-2'F-R-CH3 and MP-III-022 attenuated pathological changes of locomotor activity of rats in developmental models of schizophrenia (Gill et al., *Neuropsychopharmacology* 2011, 36:1903-1911; Batinic et al. *Int J Dev Neurosci* 2017, 61:31-39).

AgeneBio Inc. described imidazo[1,5-*a*][1,2,4]-triazolo[1,5-*d*][1,4]benzodiazepine derivatives (WO 2015/095783 A1) as $GABA_A$ α5 PAMs and found in preclinical proof of biology studies of age-related cognitive impairment that such compounds occupy $GABA_A$ α5 receptors in the hippocampus under conditions of hippocampal overactivity (Press release, AgeneBio, 11 Sep 2019; https://www.agenebio.com/agenebio-announces-additional-funding-to-advance-novel-gaba-a-therapeutic-program-to-address-alzheimers-and-other-cns-conditions/), as their lead series has potent and selective compounds with good in vivo efficacy in age-impaired rats (https://grantome.com/grant/NIH/R44-AG063607-01).

The most preferred indication in accordance with the present invention is autism spectrum disorder (ASD). ASD is a complex, heterogeneous neurodevelopmental disorder characterized by a deterioration of social relationships, a decrease in communication, typical repetitive behaviours, and impairment in executive functions (Anagnostou et al., *CMAJ* 2014, 186:509-519; Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013 - Diagnostic Criteria for 299.00 Autism Spectrum Disorder). There are no medications approved for the treatment of core symptoms of ASD. Current pharmacological treatment is limited to atypical antipsychotics risperidone and aripiprazole which are approved for the treatment of ASD-associated aggression and irritability (Anagnostou et al., *Curr Opin Neurol* 2018, 31:119-125). Antidepressants are used off-label for alleviating obsessive/compulsive symptoms in ASD; the efficacy and the tolerability of these treatments are modest (Carrasco et al., *Pediatrics* 2012, 129:e1301-e1310), so there is

an unmet need for more selective, pathophysiology-based treatment of the aforementioned conditions.

ASD can be associated with genomic alterations coupled with $GABA_AR$ subunits. Chromosomal abnormalities, namely duplication of copy number variations in the q11.2-13 region on chromosome 15 were reported in ASD patients. In humans, this region contains genes that encode the $\alpha5$, $\beta3$ and $\gamma3$ subunits of the $GABA_A$ receptor (Coghlan et al., *Neurosci Biobehav Rev* 2012, 36:2044-2055). An autism patient exome study identified missense mutations in $Gabra5^{-/-}$ and RDX, the genes for the $\alpha5GABA_AR$ and its anchoring protein radixin, further supporting a $\alpha5GABA_AR$ deficiency in ASD (Zurek et al., *Ann Clin Transl Neurol* 2016, 3:392-398). There is increasing evidence for excitatory/inhibitory (E/I) imbalance arising from deteriorated GABAergic function in ASD. Reduced expression of the GABA synthesizing enzymes GAD65 and GAD67 and the reduction of $GABA_A$ receptor density have been reported in post-mortem ASD brain (Fatemi et al., *Biol Psychiatry* 2002 52:805-810; Oblak et al, *Autism Res* 2009, 2:205-219). In imaging studies using positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) reductions in GABA concentration and $GABA_A$ receptor availability have been reported in patients with ASD (Mori et al., *Brain Dev* 2011, 34:648-654; Puts et al., *Autism Res* 2016, 10:608-619; Robertson et al., *Curr Biol* 2016, 26:80-85). A pilot PET study showed reduced binding of an $\alpha5GABA_AR$ selective tracer [^{11}C]Ro154513 across multiple brain regions suggesting reduced level of $\alpha5GABA_AR$ in ASD (Mendez at al., *Neuropharmacology* 2013, 68:195-201). Another study showed changes in a GABA-sensitive perceptual task in ASD patients (Horder et al., *Sci Transl Med* 2018, pii: eaam8434). In line with these observations, postmortem analyses revealed reduced expression of $\alpha5GABA_AR$ (Blatt et al., *J Autism Dev Disord* 2001, 31:537-54; Fatemi et al. *J Autism Dev Disord*, 2010, 40:743-750). Impaired GABAergic function in ASD patients can be considered, thus facilitating cortical inhibition and restoring E/I balance by $\alpha5$ PAMs can be a feasible therapeutic strategy in the treatment of the disease.

Increased neuronal excitability in the cortex may lead to autism-like behavioural deficits in rodents (Yizhar et al., *Nature* 2011, 477:171-178). Supporting the clinical findings genetic reduction of $\alpha5GABA_AR$ exhibited a reduced tonic currents and increased excitability of principal hippocampal neurons in $Gabra5^{-/-}$mice (Bonin et al., *J Neurophysiol* 2007, 98:2244-2254). Besides the impairment in the executive function, robust autism-like behaviours and pathologies were observed in $Gabra5^{-/-}$ mice (Zurek et al., *Ann Clin Transl Neurol* 2016, 3:392-398; Mesbah-Oskui et al., *Neurotoxicol Teratol* 2017, 61:115-122). Similarly, Fragile X syndrome model ($Fmr1^{-/-}$) mice showed downregulation of $\alpha5GABA_AR$ and a deficit in tonic inhibition (Curia et al., *Cereb Cortex* 2009, 19:1515-1520) which accompanied

with behavioural hallmarks of ASD (Bakker and Oostra, *Cytogenet Genome Res* 2003, 100:111-123).

The prenatal valproate model has excellent construct and face validity, therefore it is a widely accepted disease model of ASD (Christensen et al., *JAMA* 2013, 309:1696-1703; Roullet et al., *Neurotox Teratol.* 2013, 36:45-56). In this method, time-mated female Wistar rats are administered a single dose of valproic acid on gestational day 12.5. After investigational drug treatment, offspring are examined behaviorally in the social preference assay at postnatal day 59. The social preference test is a highly accepted assay to assess autistic behavior in rodents (Nadler et al., *Genes Brain Behav* 2007, 3:303-314; Bambini-Junior et al., *Brain Res* 2011, 1408:8-16). Briefly, in this assay a test animal is allowed to investigate a conspecific separated by a dividing perforated wall or a similar area however, without a target conspecific. An autistic animal (such as a prenatally valproate-exposed rat) spends little time with social investigation during a test session. It is believed that the reduced social behaviour of VPA-treated animals can be reversed to the normal level by the restoration of α5GABA$_A$ receptor mediated inhibitory synaptic transmission (Wang et al., *Front Neurol* 2018, 9:Article 1052). Thus, examples of the present invention may be of great behavioral benefit in this preclinical disease model that recapitulates the core symptoms of ASD. Therefore, it can be presented that the compounds of the invention, specifically GABA$_A$ α5 PAMs, may have therapeutic potential for the core symptoms of autism spectrum disorder in humans.

GABA-A receptor positive modulators, such as the non-selective clonazepam in low dose, have also proven to ameliorate symptoms in preclinical models of ASD (Han et al., *Nature* 2012, 489:385-390; Okamoto et al., *J Neuroimmunol* 2018, 321:92-96) increasing the expectations that clinically used benzodiazepines could be used in extremely low doses for the treatment of the disease. Besides this strategy subunit selective compounds, such as α2/3 modulators (AZD7325; https://www.clinicaltrials.gov/ct2/show/NCT03678129) or α5 positive allosteric modulators may offer an alternative approach for the treatment of ASD possibly with an improved therapeutic window. Accordingly, the α5 selective PAM compound RG7816 (RO7017773) is in Phase II clinical development for the treatment of ASD (https://www.clinicaltrials.gov/ct2/show/NCT04299464).

Therefore, compounds having high affinity and selectivity for the α5GABA$_A$Rs, GABA$_A$ α5 PAMs respectively, can be used, alone or in combination with one or more other active ingredients, for the treatment or prevention of disorders of the central nervous system where one of the symptoms and/or syndromes of the disease may be related to the GABA$_A$ α5

receptor. These include, but not limited to neurodevelopmental disorders such as autism spectrum disorder (ASD) (Mendez et al., *Neuropharmacology* 2013, 68:195-201), Fragile X disorder (Curia et al, *Cereb. Cortex* 2009, 19:1515-1520), Prader-Willi syndrome (Bittel et al., *J Med Genet* 2003, 40:568-574), or Down syndrome (Braudeau et al., *J Psychopharmacology* 2011, 25:1030-1042; Martinez-Cue et al., *J Neurosci* 2013, 33: 953-966), neurocognitive disorders (Collinson et al., *J Neurosci* 2002, 22:5572-5580) such as Alzheimer's disease (AD) (Kwakowsky et al., *J Neurochem* 2018, 145:374-392; Solas et al., *Curr Pharm Des* 2015; 21:4960-4971; Wu et al., *Nat Commun* 2014, 4159), prodromal AD and mild cognitive impairment (Maubach, *Curr Drug Targets CNS Neurol Disord* 2003, 2:233-239), vascular cognitive impairment and vascular dementia (Gacsályi et al., *Eur J Pharmacol* 2018, 834:118-125), frontotemporal lobar degeneration including frontotemporal dementia, progressive supranuclear palsy and corticobasal syndrome (Murley and Rowe, *Brain* 2018, 5:1263-1285), Lewy body dementia (Khundakar et al., *Acta Neuropathol Commun* 2016, 4:66), age-associated memory impairment and cognitive decline (Koh et al., *Neuropharmacology* 2013, 64:142-152), cognitive impairment associated with brain cancers including, but not limited to medulloblastomas (Sengupta et al., *CNS Oncol* 2014, 3:245-247), post-operative dementia (Cheng et al., *J Neurosci* 2006, 26:3713-3720), inflammation-induced dementia (Wang et al., *Cell Rep* 2012, 2: 488-496), HIV-Associated neurocognitive disorder (Green and Thayer, *Neuropharmacology* 2019, 149:161-168), cognitive impairments associated with the diseases including, but not limited to migraine and tension headache (Russo et al., *Am J Hum Genet* 2005, 76:327-333), multiple sclerosis (Kammel et al., *Neuroscience* 2018, 395:89-100), Parkinson's disease (Blaszczyk, *Front Neurosci* 2016, 10:269-277), epilepsy (McGinnity et al., *Brain Commun* 2021, 3(1):fcaa190; Schipper et al., *Mol Neurobiol* 2016, 53:5252-5265), attention deficit hyperactivity disorder and adult attention deficiency (Bollmann et al., *Transl Psychiatry* 2015, 8:e589; Edden et al., *Arch Gen Psychiatry* 2014, 69:750-753) or other CNS diseases including, but not limited to post-traumatic stress disorder (Lu et al., *Neuronal Plast* 2017, 2017:5715816), schizophrenia (Guidotti et al., *Psychopharmacology* 2005, 180:191-205), positive, negative and/or cognitive symptoms associated with schizophrenia (Asai et al., *Schizophrenia Res* 2008, 99:333-340; Donegan et al., *Nature Communications* 2019, 10: Article number 2819; Gill et al., *Neuropsychopharmacology* 2011, 36:1903-1911; Hauser et al., *Mol Psychiatry* 2005, 10:201-207; Marques et al., *Mol Psychiatry* 2021, 26:2616-2625; Redrobe et al., *Psychopharmacology* 2012, 221: 451-468), bipolar disorders (Otani et al., *Neurosci Lett* 2005, 381:108-113), Huntington's disease (Du et al., *Front Mol Neurosci.* 2017, 10:198), neurofibromatosis type I (Ribeiro et al., *Cortex* 2015, 64:194-208), sleep disorders (Mesbah-Oskui et al., *Neurotoxicol Teratol* 2017, 61:115-122), substance-related and addictive disorders including, but not limited to alcohol use disorder or gambling disorder (Mick

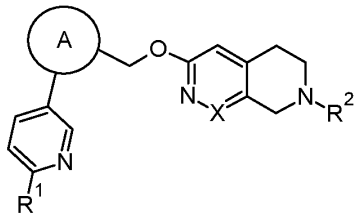
et al., *Addict Biol* 2017, 22:1601-1609; Stephens et al., *Eur J Pharmacol* 2005, 526:240-250), fetal alcohol spectrum disorder (Toso et al., *Am J Obstet Gynecol* 2006, 195:522-527), mood disorders (Bugay et al., *Neuropsychopharmacology* 2020, 45:2289-2298; Carreno et al., *Int J Neuropsychopharmacology* 2017, 20:504-509; Choudary et al., *Proc Natl Acad Sci USA* 2005, 102:15653-15658; Fischell et al., *Neuropsychopharmacology* 2015; 40:2499-2509), psychotic disorders (Wearne et al., *Neuropharmacology* 2016, 111:107-118), substance-induced psychotic disorder (Neugebauer et al., *Behav Brain Res* 2018, 342:11-18), anxiety disorders (Behlke et al., *Neuropsychopharmacology* 2016, 41:2492-2501; Botta et al., *Nat Neuroscience* 2015, 18:1493-1500), fear related disorders (Botta et al., *Nat Neuroscience* 2015, 18:1493-1500; Crestani et al., *Proc Natl Acad Sci USA 2002*, 99:8980-8985), stress disorder (Fischell et al., *Neuropsychopharmacology* 2015; 40:2499-2509), Alzheimer's disease related neuropsychiatric symptoms (Xu et al., *Psychopharmacology* 2018, 235:1151-1161), stroke (Clarkson et al., *Nature* 2010, 468:305-309; Lake et al., *J Cereb Blood Flow Metab* 2015, 35:1601-1609), traumatic brain injury (Khodaei et al., *Crit Care Med* 2020, 48:533-544), neuropathic pain (Hérnandez-Reyes et al., *Pain* 2019, 160:1448-1458) and inflammatory pain (Bravo-Hernández et al., *Eur J Pharmacol.* 2014, 734:91-97; Munro et al., *Neuropharmacology* 2011, 61:121-132). Modulating α5GABA$_A$Rs may also be beneficial in treating diseases and conditions including, but not limited to bronchoconstrictive diseases such as, but not limited to asthma, chronic obstructive pulmonary disease, and bronchopulmonary dysplasia (Gallos et al., *Am J Physiol Lung Cell Mol Physiol* 2015, 308:L931-942; Mizuta et al., *Am J Physiol Lung Cell Mol Physiol* 2008, 294:L1206-1216) and obesity (Xia et al., *Mol Psychiatry* 2021, doi: 10.1038/s41380-021-01053-w). Compounds capable of modulating α5GABA$_A$Rs are in particular expected to be useful candidates for the treatment of neurodevelopmental disorders, neurocognitive disorders, mood disorders and schizophrenia.

Many structurally different compounds active on the α5 subunit of the GABA$_A$ receptor are known in the art (Guerrini et al., *Expert Opin Ther Patents* 2013, 23(7):843-866), including isoxazole (e.g., WO 2009/071477 A1, WO 2018/104419 A1, WO 2019/238633 A1) and triazole derivatives (e.g., WO 2012/062687 A1, WO 2014/001278 A1, WO 2014/001279 A1, WO 2014/001282 A1, WO 2020/016443 A1).

Despite the numerous studies and modulators of the GABA$_A$ α5 receptor, unmet need still persists to provide compounds that can be useful in the treatment or prevention of diseases related to the GABA$_A$ α5 receptor.

SUMMARY OF THE INVENTION

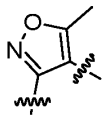
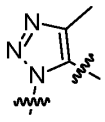
The present invention relates to compounds of formula (I)



(I)

wherein

A is represented by

 group, or  group;

R^1 is an alkyl, an alkoxy, or a haloalkyl group;

R^2 is hydrogen; an alkyl group optionally substituted with -$S(O)_2$-alkyl, a cycloalkyl or a heterocycle; a cycloalkyl group; a heterocycle group optionally substituted with an alkyl; or a heteroaryl group;

X is CH or N;

and/or salts thereof and/or stereoisomers thereof and/or enantiomers thereof and/or racemates thereof or diastereomers thereof and/or biologically active metabolites thereof or prodrugs thereof or solvates thereof or hydrates thereof and/or polymorphs thereof.

The present invention provides a compound of formula (I), as defined above for use as medicament.

The present invention provides a compound of formula (I), as defined above for use in the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

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 diseases related to the $GABA_A$ α5 receptor.

The present invention provides a method of treating or preventing a disease related to the $GABA_A$ α5 receptor comprising administering to a subject, including humans, in need of

such treatment or prevention an effective amount of at least one compound of formula (I), as defined above.

The present invention provides the combinational use of compounds of formula (I) as defined above, with one or more other active ingredients for the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

The present invention provides pharmaceutical compositions containing the compound of formula (I), as defined above as active ingredients.

The present invention provides medicaments (combinational pharmaceutical compositions) comprising a combination of the compound of formula (I), as defined above with one or more other active ingredients.

The present invention provides pharmaceutical compositions containing the compound of formula (I), as defined above as active ingredients alone or in combination with one or more other active ingredients for use in the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

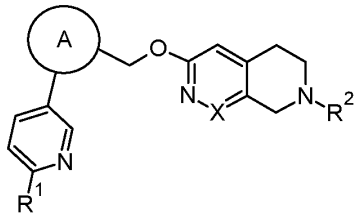
The present invention provides a process for the manufacture of the compounds of formula (I), as defined above and intemediates of the preparation process as well.

The present invention also provides preparation of pharmaceutical compositions containing the compounds of formula (I), as defined above alone, or in combination with one or more other active ingredients.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds of formula (I) having affinity and selectivity for the alpha 5 subunit-containing gamma-aminobutyric acid A receptor ($GABA_A$ α5 receptor) and act as $GABA_A$ α5 receptor positive allosteric modulators, thereby useful in the treatment or prevention of diseases related to the $GABA_A$ α5 receptor, process for the preparation thereof, pharmaceutical compositions comprising them alone or in combination with one or more other active ingredients and their use as medicaments.

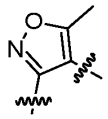
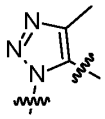
The present invention relates to compounds of formula (I)



(I)

wherein

A is represented by

 group, or  group;

R^1 is an alkyl, an alkoxy, or a haloalkyl group;

R^2 is hydrogen; an alkyl group optionally substituted with -$S(O)_2$-alkyl, cycloalkyl or heterocycle; a cycloalkyl group; a heterocycle group optionally substituted with an alkyl; or a heteroaryl group;

X is CH or N;

and/or salts thereof and/or stereoisomers thereof and/or enantiomers thereof and/or racemates thereof or diastereomers thereof and/or biologically active metabolites thereof or prodrugs thereof or solvates thereof or hydrates thereof and/or polymorphs thereof.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, suitable methods and materials are described below.

The nomenclature used is based on IUPAC systematic nomenclature, unless indicated otherwise.

Any open valency appearing on a carbon, oxygen, sulfur or nitrogen atom in the structures herein indicates the presence of a hydrogen, unless indicated otherwise.

Definition of the general terms used herein, whether or not the terms in question are presented individually or in combination with other groups are described below.

"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.

The term "substituent" denotes an atom or a group of atoms replacing a hydrogen atom on the parent molecule.

The term "substituted" denotes that a specified group bears one or more substituents.

Where any group may carry multiple substituents and a variety of possible substituents is provided, the substituents are independently selected and need not to be the same.

The term "unsubstituted" means that the specified group bears no substituents.

The term "optionally substituted" means that any atom of the specified group is unsubstituted or substituted by one or more substituents, independently chosen from the group of possible substituents. When indicating the number of substituents, the term "one or more" means from one substituent to the highest possible number of substitutions, i.e., replacement of one hydrogen up to replacement of all hydrogens by substituents. The possible substituents include, but are not limited to C_{1-4}alkyl, oxo and the like.

The term "alkyl" refers alone or in combination with other groups to a straight or branched, single or multiple branched, hydrocarbon radical and consists of 1 to 6 carbon atoms. Preferably, an alkyl group consists of 1 to 4 carbon atoms. Examples include, but are not limited to methyl, ethyl, propyl, *i*-propyl (isopropyl), *n*-butyl, 2-butyl (*sec*-butyl) or *t*-butyl (*tert*-butyl) group. C_{1-2}alkyl groups are more preferred. Methyl group is most preferred.

The term "alkoxy" refers alone or in combination with other groups to -O-alkyl group, wherein the alkyl is as defined above. Preferably, an alkoxy group is a -O-alkyl group wherein the alkyl group consists of 1 to 4 carbon atoms. Examples include, but are not limited to methoxy, ethoxy, *i*-propoxy, *n*-propoxy or *t*-butoxy. C_{1-2}alkoxy groups are more preferred. Methoxy group is most preferred.

The term "halogen", "halo" or "halide" refers alone or in combination with other groups to fluoro (fluorine), chloro (chlorine), bromo (bromine) or iodo (iodine). Preferably, the halogen is fluorine.

The term "haloalkyl" refers alone or in combination with other groups to an alkyl as defined above substituted with one or more identical or different halogens on any carbon atoms of said alkyl, including vicinal and/or germinal halo-substitutions as well, such as perhaloalkyl groups. The term "perhaloalkyl" refers to an alkyl where all hydrogen atoms have been replaced by the same or different halogen atoms. Examples include, but are not

limited to trihalo, dihalo-, or monohaloalkyl groups, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, difluoromethyl or trifluoromethyl. Preferably, the haloalkyl group is a halo-C_{1-2}alkyl group, more preferably difluoromethyl or trifluoromethyl, most preferably trifluoromethyl.

The term "cycloalkyl" refers to monovalent monocyclic saturated carbocyclic groups comprising 3 to 7 carbon ring atoms. Examples include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane. Preferably, the cycloalkyl group comprises 4 to 6 carbon ring atoms. Most preferably the cycloalkyl is cyclobutane or cyclopentane.

The term "heterocycle" refers alone or in combination with other groups to a monovalent saturated or partly unsaturated monocyclic, bicyclic, fused, bridged or spiro ring system of 3 to 10 ring atoms comprising 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon. Examples for monocyclic heterocycles are aziridine, 2*H*-azirine, oxirane, thiirane, azetidine, oxetane, thietane, azetidine-2-one, pyrrolidine, pyrrolidinone, pyrroline, pyrazolidine, imidazoline, pyrazoline, tetrahydrofuran, dihydrofuran, dioxolane, tetrahydrothiophene, oxazolidine, dihydro-oxazole, isoxazolidine, oxathiolane, sulfolane, thiazolidine, thiazolidinedione, succinimid, oxazolidone, hydantoin, piperidine, piperidinone, piperazine, tetrahydropyran, tetrahydrothiopyrane, dihydropyrane, tetrahydropyridine, dioxane, thiane, dithiane, 1,1-dioxo-thiane, morpholine, thiomorpholine, 1,1-dioxo-thiomorpholin, azepane, diazepane, homopiperazine, oxazepnayl and the like. Preferably, the heterocycle refers alone or in combination with other groups to a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising 1, or 2 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon. More preferably, the heterocycle refers alone or in combination with other groups to a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising one ring heteroatom selected from O and S, the remaining ring atoms being carbon. Most preferably, the heterocycle refers alone or in combination with other groups to a monovalent saturated monocyclic ring of 3 to 6 ring atoms comprising one ring heteroatom selected from O and S, the remaining ring atoms being carbon such as oxetane, tetrahydrofuran, tetrahydrothiophene, tetrahydropyran.

The term "heteroaryl" refers alone or in combination with other groups to a monovalent, heterocyclic aromatic, mono- or bicyclic ring system of 5 to 10 ring atoms, comprising 1, 2 or 3 heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon. Examples for heteroaryl are pyrrole, furan, thiophene, imidazole, oxazole, isoxazole, thiazole, isothiazole, triazole, tetrazole, oxadiazole, thiadiazole, tetrazole, pyridine, pyrazine, pyrazole, pyridazine, pyrimidine, triazine, azepine, diazepine, benzofuran, benzothiophene, indole, isoindole, isobenzofuran, benzimidazole, benzoxazole, benzoisoxazole,

benzothiazole, benzoisothiazole, benzooxadiazole, benzothiadiazole, benzotriazole, purine, quinoline, isoquinoline, quinazoline, quinoxaline, carbazole, or acridine. Preferably, the heteroaryl refers alone or in combination with other groups to a monovalent, heterocyclic aromatic, monocyclic ring system of 5 to 6 ring atoms, comprising 1, or 2 heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon. More preferably, the heteroaryl refers alone or in combination with other groups to a monovalent, heterocyclic aromatic, monocyclic ring system of 6 ring atoms, comprising 1, or 2 heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon. Most preferably, the heteroaryl refers alone or in combination with other groups to a monovalent, heterocyclic aromatic, monocyclic ring system of 6 ring atoms, comprising 1, or 2 heteroatoms being N, the remaining ring atoms being carbon, such as pyridine, pyridazine, pyrimidine, pyrazine.

The terms “compound(s) of this invention”, “compound(s) of the present invention”, “compounds of formula (I), as defined above” refers to compounds of formula (I) and/or salts thereof and/or stereoisomers thereof and/or enantiomers thereof and/or racemates thereof or diastereomers thereof and/or biologically active metabolites thereof or prodrugs thereof or solvates thereof or hydrates thereof and/or polymorphs thereof.

The term “salt” refers to pharmaceutically acceptable or to pharmaceutically non-acceptable salts.

The term “pharmaceutically acceptable salt” refers to a conventional acid addition or 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, naphthalenedisulfonic 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 “pharmaceutically non-acceptable salts” may be preferred for the purification or isolation of the compounds of formula (I) and are therefore also within the scope of the invention.

The term “prodrug” 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.

Optical isomers can be prepared by resolving the racemic mixtures by known methods, for example, by using an optically active acid or base to form diastereoisomeric salts or by forming covalent diastereomers. Suitable acids include, for example, tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, ditoluoyltartaric acid and camphorsulfonic acid. Diastereoisomeric mixtures can be separated into individual diastereomers based on their physical and/or chemical differences, by methods known to those skilled in the art, such as chromatography or fractional crystallization. Subsequently, the optically active bases or acids are liberated from the separated diastereoisomeric salts. Various methods of separating optical isomers include chiral chromatography (e.g., chiral HPLC columns) optionally used by derivatization with the aim to maximize the separation of enantiomers. Appropriate chiral HPLC columns can be routinely chosen as desired. Where applicable, enzymatic separations carried out by derivatization may also be used. The optically active compounds of general formula (I) can also be prepared using optically active starting materials using chiral synthesis without racemization reaction conditions.

The absolute configuration of the chiral compounds can be determined e.g., by optical rotation, VCD (vibrational circular dichroism spectroscopy) and/or single crystal X-ray diffraction analysis, or ^{1}H NMR spectroscopic assays of the diastereomeric pair of compounds synthesized from chiral compounds.

The compounds of formula (I) may exist in various polymorphic forms. As is known in the art, polymorphism is the ability of a compound to crystallize in more than one crystalline form, i.e., in polymorphic form. Polymorphic forms of a particular compound can be defined by identical chemical formula or composition and differ in their chemical structure as crystalline structures of two different chemical compounds.

The compounds of formula (I) and salts thereof may also be present as solvates or hydrates, which are also within the scope of the invention. The term "solvate" refers to non-covalent stoichiometric or nonstoichiometric combinations of solvent and solute. The term

"hydrate" refers to non-covalent stoichiometric or nonstoichiometric combinations of water and solute.

The present invention provides pharmaceutical compositions comprising at least one compound of formula (I), as defined above as active ingredient.

The present invention provides pharmaceutical compositions comprising a combination of the compound of formula (I), as defined above with one or more other active ingredients. The pharmaceutical composition may comprise at least one compound of the invention together with one or more other active ingredients in a single dosage form or separately. The combinational composition may be administered simultaneously, separately or sequentially.

The term “pharmaceutical composition” (or “composition”) refers to a mixture or solution comprising a therapeutically effective amount of an active ingredient together with pharmaceutically acceptable excipients to be administered to a subject, e.g., a human in need thereof.

The present invention also relates to the preparation of pharmaceutical compositions.

The pharmaceutical compositions of the present invention may be formulated in various pharmaceutical formulations, such as, but not limited to, solid oral dosage forms such as tablets (e.g., buccal, sublingual, effervescent, chewable, orally dispersible), capsules, pills, orally dispersible films, granules, powders; liquid formulations such as solutions, emulsions, suspensions, syrups, elixirs, drops; parenteral dosage forms such as intravenous injections, intramuscular injections, subcutaneous injections; other forms of medicine such as eye drops, semi-solid ophthalmic preparations, semi-solid dermal preparations (such as ointments, creams, pastes), transdermal therapeutic systems, suppositories, rectal capsules, rectal solutions, emulsions and suspensions, etc..

The pharmaceutical compositions of the present invention may be administered in various ways, such as, but not limited to oral, rectal, mucous, transdermal or intestinal administration; parenteral administration including intramuscular, subcutaneous, intravenous, intramedullary injections as well as intraarticular, intrathecal, direct intraventricular, intraperitoneal, intranasal or intraocular injections and eye drops.

Alternatively, the compounds may be administered locally and not systemically, for example by direct injection of the compound to the kidney or the heart, often in a modified release formulation. In addition, the drug may be administered in a targeted carrier system, for example in a tissue-specific antibody encapsulated liposome.

The pharmaceutical composition may be administered in various ways and in various pharmaceutical forms. The compound of the invention may be administered alone or in combination with pharmaceutically acceptable excipients, in single or multiple doses.

For simple administration, it is preferred that the pharmaceutical compositions consist of dosage units that contain the amount of active ingredient(s) to be administered once, or a small number of multiple, or half, one third, a quarter. Such dosage units are, for example, tablets that can be provided with a half or quarter groove to facilitate half or quarter-splitting of the tablet in order to weigh the required amount of active ingredient(s).

Pharmaceutical compositions containing the active ingredient(s) according to the invention generally contain from 0.001 to 500 mg of active ingredient(s) per dosage unit. It is of course also possible that the amount of active ingredient(s) in each formulation exceeds the above limit either up or down.

The present invention relates also to pharmaceutical compositions for use in pediatric use such as, but not limited to, solutions, syrups, elixirs, suspensions, powders for the preparation of suspensions, dispersible or effervescent tablets, chewable tablets, orally disintegrating tablets or granules, tablets or coated tablets, sparkling powders or granules, capsules.

The pharmaceutical compositions of the present invention may be prepared by methods known per se such as conventional mixing, dissolution, emulsification, suspending, microencapsulation, freeze drying, extrusion and spheronization, lamination, film coating, granulation, encapsulation, pelletization or pressing.

The pharmaceutical compositions of the present invention may be formulated in the usual way using one or more physiologically or pharmaceutically acceptable excipients which promote the incorporation of the active ingredient into pharmaceutically acceptable pharmaceutical forms. The term “physiologically or pharmaceutically acceptable excipient” denotes any ingredient used in formulating pharmaceutical products which have no therapeutic activity and non-toxic. The proper formulation depends on the mode of administration chosen. Any of the techniques and excipients well known in the art can be used.

The excipients applicable in the preparation may be selected from the following categories, such as, but not limited to fillers of tablets and capsules, binders of tablets and capsules, drug release modifying agents, disintegrants, glidants, lubricants, sweeteners, taste-masking agents, flavorants, coating materials, surfactants, stabilizers, preservatives or antioxidants, buffering agents, complexing agents, wetting or emulsifying agents, salts for adjusting the osmotic pressure, lyophilization excipients, microencapsulating agents, ointment

materials, penetration enhancers, solubilizers, solvents, suppository materials, suspending agents.

The excipients described above and the various methods of preparation are only representative examples. Other materials and process techniques known in the art may also be used.

The term “other active ingredient” refers to therapeutic agents including, but not limited to 5-HT_{1A} antagonists or agonists (such as lecozotan, NLX 101, sarizotan); 5-HT_{1B} and 5-HT_{1D} agonists (such as rizatriptan, zolmitriptan, naratriptan and sumatriptan); 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); A2a adenosine receptor antagonists; acetylcholinesterase inhibitors (such as galantamine, rivastigmine, donepezil, tacrine, phenserine, ladostigil and ABT-089); ADAM-10 ligands; alpha adrenoceptor agonists; AMPA agonists or modulators (such as CX-717, LY 451395, LY404187 and S-18986); androgen receptor modulators (such as SFX 01); anti-amyloid antibodies including anti-amyloid humanized monoclonal antibodies (such as bapineuzumab, ACCOOI, CAD 106, AZD3102, H12A11V1); anticholinergics (such as biperiden); anticonvulsants (such as acetazolamide, carbamazepine, eslicarbazepine acetate, ethosuximide, lacosamide, nitrazepam, oxcarbazepine, perampanel, phenobarbital, phenytoin, primidone, rufinamide, stiripentol, topiramate, valproate); anti-inflammatory compounds (such as (R)-flurbiprofen, nitroflurbiprofen, ND-1251, VP-025, HT-0712, and EHT-202); ApoE4 conformation modulators; atypical antipsychotics (such as aripiprazole, asenapine, brexpiprazole, brilaroxazine, cariprazine, iloperidone, loxapine, lumateperone tosylate, lurasidone hydrochloride, molindone, olanzapine, paliperidone, quetiapine, risperidone, sulpiride and ziprasidone); barbiturates; beta- (such as verubecestat, and AZD3293) and gamma-secretase inhibitors (such as LY450139 and TAK 070) or modulators; blockers of Aβ oligomer formation; bradykinin B1 receptor antagonists (such as SSR240612, NVPSAA164 or any of those compounds described in WO 2007/072092 A2, WO 2008/068540 A1, WO 2008/050167 A1, WO 2008/050168 A1); butyrophenone (such as haloperidol); calcium channel blockers (such as ziconotide and NMED160); CB-1 receptor antagonists or inverse agonists (such as drinabant, cannabidiol); CB-2 agonists (such as GW-842166X and SAB378) or CB modulators (cannabidivarin, T1/C20, tetrahydrocannabinol conjugate, ZYN-002); cholinergic agonist; phenothiazines (such as chlorpromazine, fluphenazine, mesoridazine, perphenazine, thioridazine, trifluoperazine); thioxanthenes (such as chlorprothixene and thiothixene); COMT inhibitors (such as entacapone); cyclopyrrolones; diphenylbutylpiperidine (such as pimozide) and indolone (such as molindolone) classes of neuroleptic agents; DNA-directed DNA

polymerase inhibitors (such as suramin sodium); dopamine agonists and partial agonists (such as pramipexole, ropinirole); dopamine precursors (such as carbidopa, levodopa); dopamine transport inhibitors; enzyme modulators or replacements (such as CM-AT, CM-4612 and CM-182); fatty acid amide hydrolase inhibitors (such as JNJ 42165279); fatty acid or triglyceride replacements (such as triheptanoin); fenamate compounds (such as ASD-002); $GABA_A$ blockers (such as S44819, NGD 97-1, α5IA, α5IA-II, MRK-016, basmisanil or any those compounds described in PCT/IB2019/058208); $GABA_A$ receptor agonists (such as acamprosate); $GABA_A$ signaling enhancers (such as AZD-7325, PF-06372865, L-838,417, TPA-023, brexanolone, zuranolone, alphaxalone, ganaxolone, gaboxadol, tiagabine, vigabatrine, bumetanide); $GABA_B$ receptor agonists (such as arbaclofen or any of those compounds described in WO 2018/167629 A1 or WO 2018/167630 A1); gabapentinoids (such as pregabalin, gabapentin); glutamate modulators (such as AMO 04); glycine transport inhibitors; glycogen synthase kinase 3 beta inhibitors (such as tideglusib, AZD1080, SAR502250 and CEP16805); growth hormone secretagogues (such as ibutamoren, ibutamoren mesylate, and capromorelin); HDAC inhibitors; heterocyclic dibenzazepines (such as clozapine); histamine H3 receptor antagonists and inverse agonists (such as S38093, ABT-834, ABT 829, GSK 189254, CEP16795 or any of those compounds described in WO 2014/136075 A1); HMG-CoA reductase inhibitors; imidazopyridines (such as zolpidem); immunomodulators (such as IMM-124E); KCNQ antagonists; lithium; LRRK2 inhibitors; LXR β agonists; lysine specific demethylase 1 inhibitors (such as vafidemstat); M1 or M4 mAChR agonists or PAMs; MARK ligands; melatonergic agents; melatonin agonists and antagonists; methyl-CpG binding protein 2 (MECP2) gene replacement therapy (such as AVXS 201); mGluR2 antagonists or modulators; mGluR4 positive allosteric modulators (such as ADX-88178, foliglurax); mGluR5 antagonists (such as HTL-14242, AZD9272, mavoglurant); microbiome modulators (such as AB-2004, CP-101, SB-121); minor tranquilizers; MMP inhibitors; α7 nAChR agonists or positive allosteric modulators (such as ABT-126, AZD0328, EVP-6124, AVL-3288, PNU-120596 or any of those compounds described in WO 2020/012422 A1, WO 2020/012423 A1 or WO 2020/012424 A1) or antagonist (such as mecamylamine hydrochloride); neuropeptide receptor modulators (such as trofinetide, davunetide, NNZ-2591); neutrophil inhibitory factor; NK1/NK3 receptor antagonists; NMDA receptor agonists or antagonists (such as memantine, neramexane, EVT101, AZD4282, BHV 5000); noradrenaline transport inhibitors; norepinephrine modulators; NOS inhibitors (such as SD6010 and 274150); NQO1 modulators (such as vatiquinone); NR2B antagonists (such as radiprodil); NSAIDs (such as ibuprofen); opioid analgesics (such as codeine, fentanyl, hydromorphone, levorphanol, meperidine, methadone, morphine, oxycodone, oxymorphone, pentazocine, propoxyphene); orexin antagonists and agonists; oxytocin; p25/CDK5 inhibitors;

PDE10 inhibitors; PDE4 inhibitors (such as HT0712); PDE9 inhibitors (such as BI40936); PI3KB inhibitors (such as BBP-472); potassium channel openers; PPAR gamma agonists (such as pioglitazone and rosiglitazone); prokineticin agonists and antagonists; pyrazolopyrimidines; pyrrolidone compounds modulating cholinergic/metabotropic glutamate receptors (such as fasoracetam, levetiracetam, brivaracetam, piracetam); sigma-1 receptor agonists (such as blarcamesine); sodium channel blockers and antagonists (such as lamotrigine, VX409 and SPI860); sphingosine 1 phosphate receptor modulators (such as fingolimod, ozanimod, siponimod, ponesimod); SSRIs or SNRIs (such as fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, sertraline; or desvenlafaxine, duloxetine, venlafaxine); sulfonamides (such as zonisamide); tau phosphorylation inhibitors; thrombolytic agents; triazolopyridines; benzodiazepines; tricyclic antidepressant drugs; T-type calcium channel antagonists; tyrosine hydroxylase inhibitors (such as L1-79); vasopressin; V1a receptor antagonists (such as balovaptan, BTRX-323511 or any of those compounds described in WO 2019/116324 A1 or WO 2019/116325 A1); vitamin E; VR-1 antagonists (such as AMG517, 705498, 782443, PAC20030, VI 14380 and A425619) 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.

In one embodiment, the other active ingredient refers to 5-HT_{1A} antagonists or agonists (such as lecozotan, NLX 101, sarizotan); atypical antipsychotics (such as aripiprazole, asenapine, brexpiprazole, brilaroxazine, cariprazine, iloperidone, loxapine, lumateperone tosylate, lurasidone hydrochloride, molindone, olanzapine, paliperidone, quetiapine, risperidone, sulpiride and ziprasidone); CB-1 receptor antagonists or inverse agonists (such as drinabant, cannabidiol); CB-2 agonists (such as GW-842166X and SAB378) or CB modulators (cannabidivarin, T1/C20, tetrahydrocannabinol conjugate, ZYN-002); DNA-directed DNA polymerase inhibitors (such as Suramin sodium); fatty acid amide hydrolase inhibitors (such as JNJ 42165279); fatty acid or triglyceride replacements (such as triheptanoin); $GABA_A$ receptor agonists (such as acamprosate); $GABA_A$ signaling enhancers (such as AZD-7325, PF-06372865, L-838,417, TPA-023, brexanolone, zuranolone, alphaxalone, ganaxolone, gaboxadol, tiagabine, vigabatrine, bumetanide); $GABA_B$ receptor agonists (such as arbaclofen or any of those compounds described in WO 2018/167629 A1 or WO 2018/167630 A1); glutamate modulators (such as AMO 04); glycogen synthase kinase 3 beta inhibitors (such as tideglusib, AZD1080, SAR502250 and CEP16805); lysine specific demethylase 1 inhibitors (such as vafidemstat); methyl-CpG binding protein 2 (MECP2) gene replacement therapy (such as AVXS 201); microbiome modulators (such as AB-2004, CP-101, SB-121); neuropeptide receptor modulators (such as trofinetide, davunetide, NNZ-2591);

NMDA receptor agonists or antagonists (such as memantine, neramexane, EVT101, AZD4282, BHV 5000); NQO1 modulators (such as vatiquinone); oxytocin; pyrrolidone compounds modulating cholinergic/metabotropic glutamate receptors (such as fasoracetam, levetiracetam, brivaracetam, piracetam); sigma-1 receptor agonists (such as blarcamesine); sphingosine 1 phosphate receptor modulators (such as fingolimod, ozanimod, siponimod, ponesimod); SSRIs or SNRIs (such as fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, sertraline; or desvenlafaxine, duloxetine, venlafaxine); tyrosine hydroxylase inhibitors (such as L1-79) vasopressin; or V1a receptor antagonists (such as balovaptan, BTRX-323511 or any of those compounds described in WO 2019/116324 A1 or WO 2019/116325 A1).

The term “modulators” refers to molecules interacting with the target receptor, wherein the interaction can be e.g., agonistic, antagonistic or inverse agonistic.

The term “inhibitors” referes to molecules competing with, reducing or preventing the binding of a particular ligand to a particular receptor or reducing or preventing the inhibition of the function of a particular protein.

The term “agonists” refers to compounds having affinity to a receptor binding site and enhancing the activity of the receptor-mediated response. “Full-agonists” effect a full response, “partial agonists” effects less than full activation even when occupying the total receptor population.

The term “inverse agonists” refers to compounds producing an effect opposite to that of an agonist by binding to the same agonist binding site, or reducing the effect of an agonist by binding at a different allosteric binding site.

The term “antagonists” refers to compounds diminishing or preventing the action of another compound or receptor site, or attenuating the effect of an agonist. “Competitive antagonists” bind to the same site as the agonist but does not activate it, thus blocks the agonists’ action. “Non-competitive antagonists” binds to an allosteric site on the receptor to prevent activation of the receptor. Binding of “reversible antagonists” to a receptor is non-covalent (can be washed out), while binding of “irreversible antagonists” is covalent (cannot be washed out).

The term “allosteric modulators” refers to compounds binding to a receptor at a site distinct from the agonist binding site, i.e., to the allosteric site, wherein by inducing conformational change in the receptor, alter the affinity and/or activity of the receptor for the endogenous ligand or agonist. “Positive allosteric modulators” or “PAMs” increase the affinity and/or activity, whilst “negative allosteric modulators” or “NAMs” decrease the affinity and/or

activity of a receptor. The compounds of formula (I), as defined above are positive allosteric modulators.

The term “inhibition constant” (K_i) refers to the absolute binding affinity of a particular inhibitor to a receptor. It is measured using competition binding assays and is calculated from the concentration where the particular inhibitor would occupy half of the receptors (IC_{50}) if no competing ligand was present using the Cheng Prusoff relationship: $K_i = IC_{50}/[1+([L]/K_D)]$, where [L] is the radioligand concentration and K_D the affinity of the labeled ligand for the receptor binding site. K_i values can be converted logarithmically to pK_i values ($-\log K_i$) in which higher values indicate exponentially greater potency.

The term “submaximal effective concentration” refers to the concentration of a particular compound required for obtaining 10% of the maximum of a particular effect.

The terms “condition”, “defect”, “deficit”, “disability”, “disorder", “disease” or “disease state” are used interchangeably to denote any disease, condition, symptom, syndrome, disorder or indication.

The term ”disease related to the $GABA_A$ α5 receptor” refers to a disease, condition or disorder of the central nervous system where one of the symptoms and/or syndromes of the disease may be related to the $GABA_A$ α5 receptor. Such a disease includes, but not limited to a neurodevelopmental disorder, a neurodegenerative disorder, a neurocognitive disorder, schizophrenia, a mood disorder, a pain disorder, a substance-related and addictive disorder or other diseases.

The diseases related to the $GABA_A$ α5 receptor may show comorbidity with each other. Comorbidity indicates a medical condition existing simultaneously but independently with another condition in a patient, or a medical condition in a patient that causes, is caused by, or is otherwise related to another condition in the same patient. However, in psychiatric, psychologic, or mental health diseases comorbidity does not necessarily imply the presence of multiple diseases, but instead can reflect our current inability to supply a single diagnosis that accounts for all symptoms.

The term “neurodevelopmental disorder” includes, but not limited to autism spectrum disorder (ASD), Angelman syndrome, Fragile X disorder, Prader-Willi syndrome, Rett syndrome or Down syndrome.

The term “neurodegenerative disorder” includes, but not limited to Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), or amyotrophic lateral sclerosis (ALS).

The term “neurocognitive disorder” includes, but not limited to cognition deficiency disorders, memory deficits, age-associated memory impairment or cognitive decline, dementia (or different forms thereof such as dementia in Alzheimer’s disease, Niemann Pick-disease, Parkinson’s disease, or Huntington’s disease, dementia with Lewy bodies (DLB), frontotemporal dementia, vascular dementia (VaD), subcortical dementia, mixed vascular and subcortical dementia, multi-infarct dementia, post-operative dementia, or inflammation-induced dementia), Alzheimer’s disease related neuropsychiatric symptoms, mild cognitive impairment (MCI), vascular cognitive impairment (VCI), CNS conditions occurring after stroke, cognitive impairment associated with brain cancers (including, but not limited to medulloblastomas), cognitive decline in Down Syndrome (DS), cognitive dysfunction in major depressive disorder (MDD) or HIV-Associated neurocognitive disorder. The term “schizophrenia” includes, but not limited to, different forms of schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, schizotypal and delusional disorders.

The term “pain disorder” includes, but not limited to nociceptive, neuropathic or inflammatory pain.

The term “mood disorder” includes, but not limited to depression-related disorders (such as major depressive disorder (MDD), dysthymia, cyclothymic disorder, seasonal affective disorder/seasonal depression, depression after traumatic brain injury (TBI), postpartum depression, premenstrual dysphoric disorder, depressive symptoms associated with menopause, depression following substance abuse/withdrawal, bipolar disorders (bipolar disorder in remission, or depressive episodes of bipolar disorder), substance (alcohol or drug) induced, or not otherwise specified mood disorders (MD-NOS).

The term “other disease” includes, but not limited to attention deficit hyperactivity disorder and adult attention deficiency, other stress related conditions, stroke, neurofibromatosis type I, multiple sclerosis, acute meningitis, alcohol use disorder, fetal alcohol spectrum disorder, bronchoconstrictive diseases (such as asthma, chronic obstructive pulmonary disease, and bronchopulmonary dysplasia) or obesity.

In one embodiment, the disease related to the $GABA_A$ α5 receptor refers to autism spectrum disorder (ASD); Angelman syndrome, Fragile X disorder, Prader-Willi syndrome, Rett syndrome, Down syndrome, Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease, amyotrophic lateral sclerosis (ALS), cognition deficiency disorders, memory deficits, age-associated memory impairment or cognitive decline, dementia or different forms thereof such as dementia in Alzheimer’s disease, Niemann Pick-disease,

Parkinson's disease, or Huntington's disease, dementia with Lewy bodies (DLB), frontotemporal dementia, vascular dementia (VaD), subcortical dementia, mixed vascular and subcortical dementia, multi-infarct dementia, post-operative dementia, or inflammation-induced dementia), Alzheimer's disease related neuropsychiatric symptoms, mild cognitive impairment (MCI), vascular cognitive impairment (VCI), CNS conditions occurring after stroke, cognitive impairment associated with brain cancers (including but not limited to medulloblastomas), cognitive decline in Down Syndrome (DS), cognitive dysfunction in major depressive disorder (MDD), HIV-Associated neurocognitive disorder; different forms of schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, schizotypal and delusional disorders; nociceptive, neuropathic or inflammatory pain; depression-related disorders (such as major depressive disorder (MDD), dysthymia, cyclothymic disorder, seasonal affective disorder/seasonal depression, depression after traumatic brain injury (TBI), postpartum depression, premenstrual dysphoric disorder, depressive symptoms associated with menopause, depression following substance abuse/withdrawal, bipolar disorders (bipolar disorder in remission, or depressive episodes of bipolar disorder), substance (alcohol or drug) induced, not otherwise specified mood disorders (MD-NOS); attention deficit hyperactivity disorder and adult attention deficiency, other stress related conditions, stroke, neurofibromatosis type I, multiple sclerosis, acute meningitis, alcohol use disorder, fetal alcohol spectrum disorder, bronchoconstrictive diseases (such as asthma, chronic obstructive pulmonary disease, and bronchopulmonary dysplasia) or obesity.

In a preferred embodiment, the disease related to the $GABA_A$ α5 receptor refers to autism spectrum disorder (ASD), Angelman syndrome, Fragile X disorder, Prader-Willi syndrome, Rett syndrome, Alzheimer's disease (AD), cognition deficiency disorders, memory deficits, age-associated memory impairment or cognitive decline, dementia, mild cognitive impairment (MCI), bipolar disorders, negative and/or cognitive symptoms associated with schizophrenia, epilepsy, post-traumatic stress disorder, amyotrophic lateral sclerosis.

The present invention provides a method of treating or preventing a disease related to the $GABA_A$ α5 receptor comprising administering to a subject, preferably a mammal, more preferably a human being, in need of such treatment or prevention, therapeutically effective amount of a compound of formula (I), as defined above alone or with at least one pharmaceutically acceptable excipient in the form of a pharmaceutical formulation.

The present invention provides a method of treating or preventing a disease related to the $GABA_A$ α5 receptor comprising administering to a subject, preferably a mammal, more preferably a human being, in need of such treatment or prevention, therapeutically effective

amount of a compound of formula (I), as defined above in combination with one or more other active ingredients.

The present invention provides a method of treating or preventing of a neurodevelopmental disorder, neurodegenerative disorder, neurocognitive disorder, schizophrenia, a mood disorder, a pain disorder, a substance-related and addictive disorder or other disease, or at least one of the symptoms and/or syndromes thereof, where one of the symptoms and/or syndromes of the disease may be related to the $GABA_A$ α5 receptor, in a subject, preferably a mammal, more preferably a human being, suffering therefrom. This method of treatment comprises administering to a subject, preferably a mammal, more preferably a human being, in need of such treatment or prevention, therapeutically effective amount of the compound of formula (I), as defined above. The method of treatment may include administering to a subject preferably a mammal, more preferably a human being, in need of such treatment therapeutically effective amount of a pharmaceutical composition comprising the compound of formula (I), as defined above.

The present invention provides a method of treating or preventing autism spectrum disorder (ASD), Angelman syndrome, Fragile X disorder, Prader-Willi syndrome, Rett syndrome, Alzheimer's disease (AD), cognition deficiency disorders, memory deficits, age-associated memory impairment or cognitive decline, dementia, mild cognitive impairment (MCI), bipolar disorders, negative and/or cognitive symptoms associated with schizophrenia, epilepsy, post-traumatic stress disorder, amyotrophic lateral sclerosis, or at least one of the symptoms and/or syndromes thereof, in a subject, preferably a mammal, more preferably a human being, suffering therefrom comprising administering a therapeutically effective amount of the compound of formula (I), as defined above.

The present invention provides the compound of formula (I), as defined above for use in the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

The present invention provides the compound of formula (I), as defined above in combination with one or more other active ingredients for use in the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

The present invention provides the compound of formula (I), as defined above for use in the treatment or prevention of a neurodevelopmental disorder, a neurodegenerative disorder, a neurocognitive disorder, schizophrenia, a mood disorder, a pain disorder, a substance-related and addictive disorder or other disease, or at least one of the symptoms and/or syndromes thereof.

The present invention provides the compound of formula (I), as defined above for use in the treatment or prevention of autism spectrum disorder (ASD), Angelman syndrome, Fragile X disorder, Prader-Willi syndrome, Rett syndrome, Alzheimer's disease (AD), cognition deficiency disorders, memory deficits, age-associated memory impairment or cognitive decline, dementia, mild cognitive impairment (MCI), bipolar disorders, negative and/or cognitive symptoms associated with schizophrenia, epilepsy, post-traumatic stress disorder, amyotrophic lateral sclerosis, or at least one of the symptoms and/or syndromes thereof.

The present invention provides the use of the compound of formula (I), as defined above for the manufacture of a medicament for the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

The present invention provides the use of the compound of formula (I), as defined above in combination with one or more other active ingredients, for the manufacture of a medicament for the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

The present invention provides the use of the compound of formula (I), as defined above for the manufacture of a medicament for the treatment or prevention of a neurodevelopmental disorder, a neurodegenerative disorder, a neurocognitive disorder, schizophrenia, a mood disorder, a pain disorder, a substance-related and addictive disorders or other disease, or at least one of the symptoms and/or syndromes thereof.

The present invention provides the use of the compound of formula (I), as defined above for the manufacture of a medicament for the treatment or prevention of autism spectrum disorder (ASD), Angelman syndrome, Fragile X disorder, Prader-Willi syndrome, Rett syndrome, Alzheimer's disease (AD), cognition deficiency disorders, memory deficits, age-associated memory impairment or cognitive decline, dementia, mild cognitive impairment (MCI), bipolar disorders, negative and/or cognitive symptoms associated with schizophrenia, epilepsy, post-traumatic stress disorder, amyotrophic lateral sclerosis, or at least one of the symptoms and/or syndromes thereof.

The present invention also relates to pharmaceutical composition comprising the compound of formula (I), as defined above for use in the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

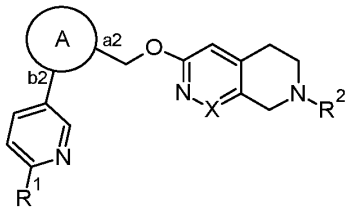
The present invention also relates to pharmaceutical composition comprising the compound of formula (I), as defined above with one or more other active ingredients for use in the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

The term “treatment” refers to the alleviation of a specific pathological condition, the elimination or reduction of one or more of the symptoms of the condition, the slowing or elimination of the progression of the disease state, and the prevention or delay of recurrency of the pathological condition of a patient or subject already suffering from or diagnosed with the disease. The “prevention” (or prophylaxis or delay of action of the disease) is typically performed by administering the drug in the same or similar way as if it were given to a patient with a disease or condition already developed.

The term “therapeutically effective amount” refers to the amount of active ingredient - in comparison with the corresponding subject who did not receive such amount - which results in the treatment, cure, prevention or improvement of the disease or disease state or side effect, and reduces the progression of the disease or pathological condition. The term also includes effective amounts to enhance normal physiological function. For use in therapy the compound of formula (I), as defined above as well as any salts thereof and/or salts thereof and/or stereoisomers thereof and/or enantiomers thereof and/or racemates thereof or diastereomers thereof and/or biologically active metabolites thereof or prodrugs thereof or solvates thereof or hydrates thereof and/or polymorphs thereof may be administered in a therapeutically effective amount as a raw chemical. In addition, the active ingredient is available as a pharmaceutical formulation.

The term “subject” refers to a vertebrate. In certain embodiments, the vertebrate is a mammal. Mammals include humans, non-human primates such as chimpanzees and other apes and monkey species, farm animals such as cattle, horses, sheep, goats, and swine, domestic animals such as rabbits, dogs, and cats, laboratory animals including rodents, such as rats, mice, and guinea pigs. In certain embodiments, a mammal is a human. The term subject does not denote a particular age or sex.

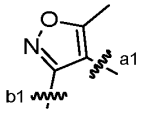
In one embodiment, the present invention relates to compounds of formula (I’)



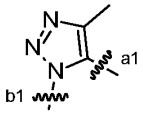
(I’)

wherein

A is represented by



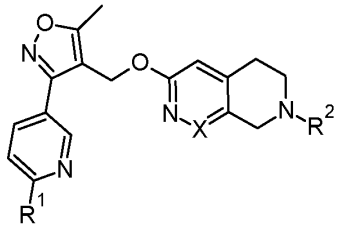
group, or



group;

wherein site "a1" of any ring A is attached to site "a2" and wherein site "b1" of any ring A is attached to site "b2"; R^1, R^2 and X are as defined above for the compounds of formula (I) and/or salts thereof and/or stereoisomers thereof and/or enantiomers thereof and/or racemates thereof or diastereomers thereof and/or biologically active metabolites thereof or prodrugs thereof or solvates thereof or hydrates thereof and/or polymorphs thereof.

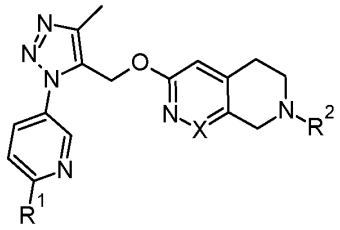
In one embodiment, the present invention relates to compounds of formula (I-a)



(I-a)

wherein R^1, R^2 and X are as defined above for the compounds of formula (I) and/or salts thereof and/or stereoisomers thereof and/or enantiomers thereof and/or racemates thereof or diastereomers thereof and/or biologically active metabolites thereof or prodrugs thereof or solvates thereof or hydrates thereof and/or polymorphs thereof.

In one embodiment, the present invention relates to compounds of formula (I-b)



(I-b)

wherein R^1, R^2 and X are as defined above for the compounds of formula (I) and/or salts thereof and/or stereoisomers thereof and/or enantiomers thereof and/or racemates thereof or

diastereomers thereof and/or biologically active metabolites thereof or prodrugs thereof or solvates thereof or hydrates thereof and/or polymorphs thereof.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^1 is a C_{1-6}alkyl, a C_{1-6}alkoxy, or a halo-C_{1-6}alkyl group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is hydrogen; a C_{1-6}alkyl group optionally substituted with -$S(O)_2$-C_{1-6}alkyl, C_{3-7}cycloalkyl or a monovalent saturated or partly unsaturated monocyclic, bicyclic, fused, bridged or spiro ring system of 3 to 10 ring atoms comprising 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon; a C_{3-7}cycloalkyl group; a monovalent saturated or partly unsaturated monocyclic, bicyclic, fused, bridged or spiro ring system of 3 to 10 ring atoms comprising 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon optionally substituted with a C_{1-6}alkyl; or a monovalent, heterocyclic aromatic, mono- or bicyclic ring system of 5 to 10 ring atoms, comprising 1, 2 or 3 heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^1 is a C_{1-6}alkyl, a C_{1-6}alkoxy, or a halo-C_{1-6}alkyl group;

R^2 is hydrogen; a C_{1-6}alkyl group optionally substituted with -$S(O)_2$-C_{1-6}alkyl, C_{3-7}cycloalkyl or a monovalent saturated or partly unsaturated monocyclic, bicyclic, fused, bridged or spiro ring system of 3 to 10 ring atoms comprising 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon; a C_{3-7}cycloalkyl group; a monovalent saturated or partly unsaturated monocyclic, bicyclic, fused, bridged or spiro ring system of 3 to 10 ring atoms comprising 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon optionally substituted with a C_{1-6}alkyl; or a monovalent, heterocyclic aromatic, mono- or bicyclic ring system of 5 to 10 ring atoms, comprising 1, 2 or 3 heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^1 is a C_{1-4}alkyl, a C_{1-4}alkoxy, or a halo-C_{1-4}alkyl group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is hydrogen; a C_{1-4}alkyl group optionally substituted with -$S(O)_2$-C_{1-4}alkyl, a C_{4-6}cycloalkyl or a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising 1, or 2 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon; a C_{4-6}cycloalkyl group; a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising 1, or 2 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon optionally substituted with a C_{1-4}alkyl; or a monovalent, heterocyclic aromatic, monocyclic ring system of 5 to 6 ring atoms, comprising 1, or 2 heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^1 is a C_{1-4}alkyl, a C_{1-4}alkoxy, or a halo-C_{1-4}alkyl group;

R^2 is hydrogen; a C_{1-4}alkyl group optionally substituted with -$S(O)_2$-C_{1-4}alkyl, a C_{4-6}cycloalkyl or a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising 1, or 2 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon; a C_{4-6}cycloalkyl group; a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising 1, or 2 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon optionally substituted with a C_{1-4}alkyl; or a monovalent, heterocyclic aromatic, monocyclic ring system of 5 to 6 ring atoms, comprising 1, or 2 heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^1 is a C_{1-2}alkyl, a C_{1-2}alkoxy, or a halo-C_{1-2}alkyl group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is hydrogen; a C_{1-4}alkyl group optionally substituted with -$S(O)_2$-C_{1-2}alkyl, C_{4-6}cycloalkyl or a a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising one ring heteroatom selected from O and S, the remaining ring atoms being carbon; a C_{4-6}cycloalkyl group; a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising one ring heteroatom selected from O and S, the remaining ring atoms being carbon optionally substituted with a C_{1-4}alkyl; or a monovalent, heterocyclic aromatic, monocyclic ring system of 6 ring atoms,

comprising 1, or 2 heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^1 is a C_{1-2}alkyl, a C_{1-2}alkoxy, or a halo-C_{1-2}alkyl group;

R^2 is hydrogen; a C_{1-4}alkyl group optionally substituted with -$S(O)_2$-C_{1-2}alkyl, C_{4-6}cycloalkyl or a a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising one ring heteroatom selected from O and S, the remaining ring atoms being carbon; a C_{4-6}cycloalkyl group; a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising one ring heteroatom selected from O and S, the remaining ring atoms being carbon optionally substituted with a C_{1-4}alkyl; or a monovalent, heterocyclic aromatic, monocyclic ring system of 6 ring atoms, comprising 1, or 2 heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon.

In one embodiment, the present invention relates to compounds of formula (I) wherein X is CH.

In one embodiment, the present invention relates to compounds of formula (I) wherein X is N.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is hydrogen.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^1 is an alkyl, an alkoxy, or a haloalkyl group; R^2 is hydrogen; and X is CH or N.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^1 is a C_{1-4}alkyl, a C_{1-4}alkoxy, or a halo-C_{1-4}alkyl group; R^2 is hydrogen; and X is CH or N.

In one embodiment, the present invention relates to compounds of formula (I-a) wherein R^1 is a C_{1-2}alkyl, or a halo-C_{1-2}alkyl group; R^2 is hydrogen; and X is CH or N.

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

6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-methyl-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-cyclobutyl-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-(cyclobutylmethyl)-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-cyclopentyl-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxetan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-(1-methanesulfonylpropan-2-yl)-6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(pyridin-2-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-methyl-5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]pyridine,

5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine,

2-methyl-5-{5-methyl-4-[({7-methyl-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl}oxy)methyl]-1,2-oxazol-3-yl}pyridine,

5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine,

5-[5-methyl-4-({[7-(oxolan-3-yl)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl]oxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine,

3-{[3-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl]methyl}-1lambda6-thiolane-1,1-dione,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-methyl-6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(propan-2-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-2-methyl-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(propan-2-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-methyl-6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-2-(propan-2-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxetan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[1-(6-methoxypyridin-3-yl)-4-methyl-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

3-{[6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl]methyl}-1lambda6-thiolane-1,1-dione,

6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(pyridin-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-[(3S)-oxolan-3-yl]-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-[(3R)-oxolan-3-yl]-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[1-(6-methoxypyridin-3-yl)-4-methyl-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(2-methylpropyl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-[3-(propan-2-yl)oxetan-3-yl]-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-(3-ethyloxetan-3-yl)-6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-methyl-5-[4-methyl-5-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1H-1,2,3-triazol-1-yl]pyridine,

5-[5-({[7-(cyclobutylmethyl)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl]oxy}methyl)-4-methyl-1H-1,2,3-triazol-1-yl]-2-methylpyridine, and

5-{5-[({7-cyclobutyl-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl}oxy)methyl]-4-methyl-1H-1,2,3-triazol-1-yl}-2-methylpyridine

and/or salts thereof and/or stereoisomers thereof and/or enantiomers thereof and/or racemates thereof or diastereomers thereof and/or biologically active metabolites thereof or prodrugs thereof or solvates thereof or hydrates thereof and/or polymorphs thereof.

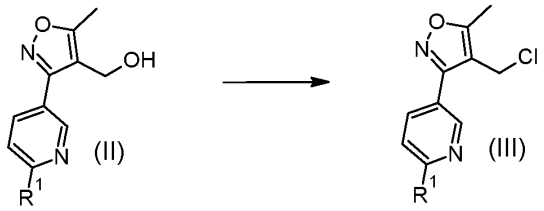
In describing the general synthesis of the compounds of formula (I), the biological assays, Intermediates and Examples, the following abbreviations have been used:

Cs_2CO_3 = cesium carbonate	Na_2SO_4 = sodium sulfate
DCM = dichloromethane	$Pd(OAc)_2$ = palladium(II) acetate
DIBAL-H = diisobutylaluminium hydride	$POCl_3$ = phosphorus oxychloride
DMSO = dimethyl sulfoxide	TBHP = *tert*-butyl hydroperoxide
EtOAc = ethyl acetate	TFA = trifluoroacetic acid
K_2CO_3 = potassium carbonate	THF = tetrahydrofuran
MeOH = methanol	TLC = thin layer chromatography
$MgSO_4$ = magnesium sulfate	brine = high-concentration solution of salt
Na_2CO_3 = sodium carbonate	(usually sodium chloride)
$NaHCO_3$ = sodium bicarbonate	rt = room temperature, 25°C

Process for the preparation of the compounds of formula (I)

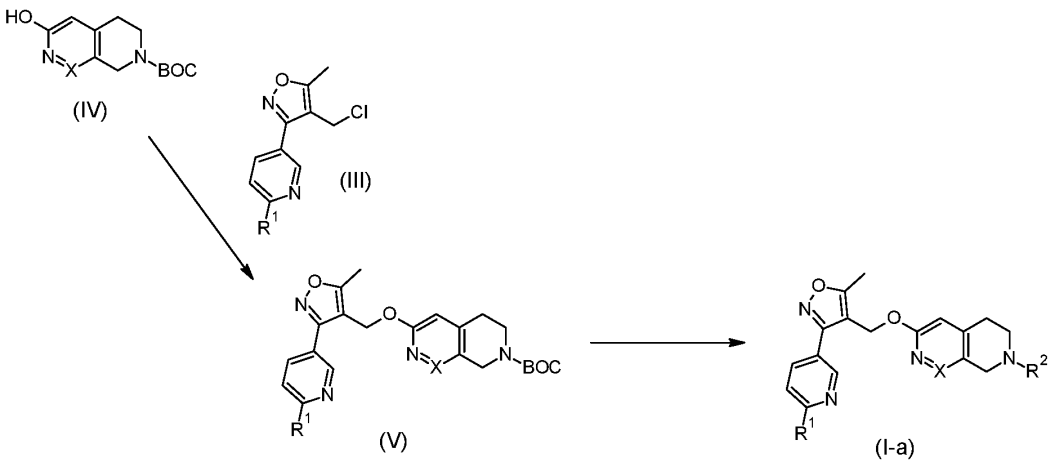
The compounds of formula (I) of the present invention can be synthesized according to the reaction sequence depicted in **Scheme 1, 2, 3, 4 and 5**.

The compounds of formula (I-a) wherein X=CH, and R^1 and R^2 are as defined in any of the embodiments described above can be prepared according to **Scheme 1 and 2**.



Scheme 1

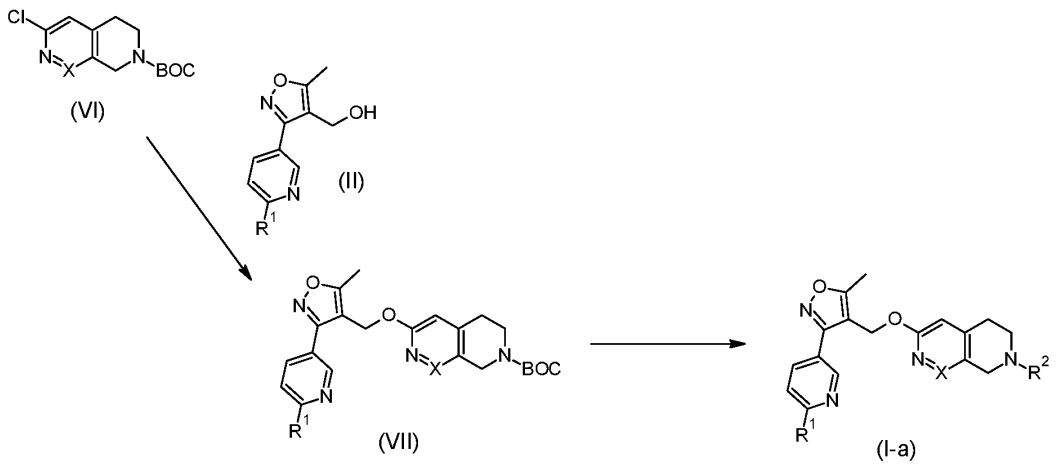
According to **Scheme 1**, reacting a compound of formula (II) with a chlorinating agent, such as $POCl_3$ provides intermediates of formula (III). Hydroxy derivatives of formula (II) are known in the art (WO 2018/104419 A1) or can be synthesized by conventional methods.



Scheme 2

According to **Scheme 2**, etherification between alcohols of formula (IV) and intermediates of formula (III) can be accomplished in the presence of a suitable base, such as K_2CO_3 in a suitable solvent, such as acetonitrile to form a compound of formula (V). Compounds of the general formula (I-a), wherein R^2=H were obtained after removal of the protective group of formula (V) using acid, such as ethyl acetate saturated with hydrogen chloride or TFA in dichloromethane. Compounds of the general formula (I-a), wherein R^2= alkyl, optionally substituted with -$S(O)_2$-alkyl, cycloalkyl or heterocycle; cycloalkyl; heterocycle were obtained from those compounds of the general formula (I-a), wherein R^2=H by alkylation. Compounds of the general formula (I-a), wherein R^2= heteroaryl were obtained from those compounds of the general formula (I-a), wherein R^2=H by arylation. Compounds of the general formula (I-a), wherein R^2= heterocycle, optionally substituted with alkyl were obtained from those compounds of the general formula (I-a), wherein R^2=H by condensation with benzotriazole and a carbonyl compound, followed by a nucleophilic reaction using Grignard reagents. Alcohol of formula (IV) can be purchased or can be prepared by conventional methods.

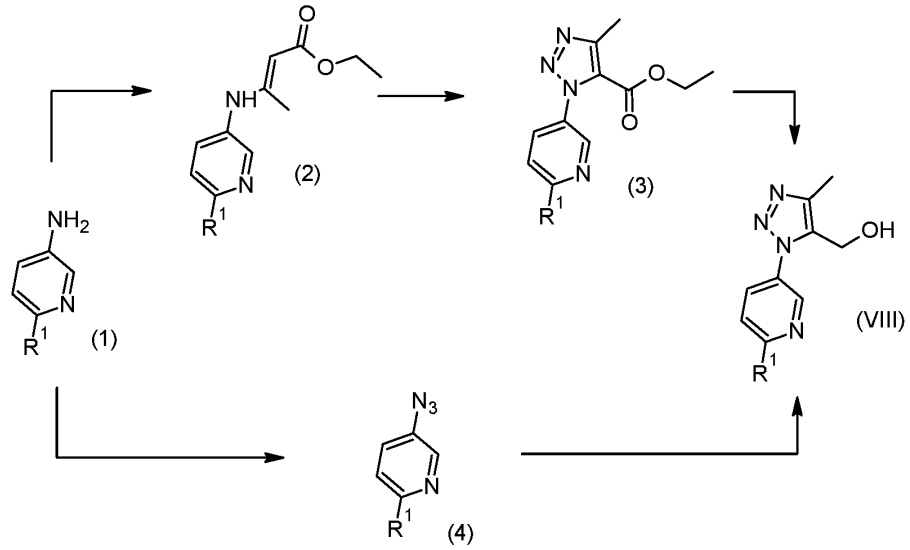
The compounds of formula (I-a) wherein X=N, R^1 and R^2 are as defined in any of the embodiments described above can be prepared according to **Scheme 3**.



Scheme 3

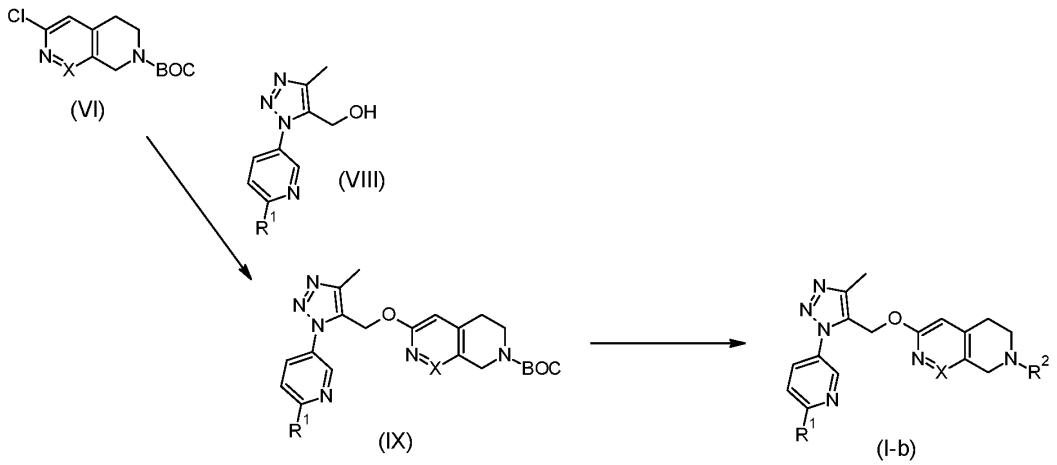
According to **Scheme 3**, etherification between chloro derivatives of formula (VI) and hydroxy derivatives of formula (II) can be carried out by a palladium-mediated process in the presence of a suitable base, such as Cs_2CO_3 to provide a compound of formula (VII). Compounds of the general formula (I-a), wherein R^2=H were obtained after removal of the protective group of formula (VII) using acid, such as ethyl acetate saturated with hydrogen chloride or TFA in dichloromethane. Compounds of the general formula (I-a), wherein R^2= alkyl, optionally substituted with -$S(O)_2$-alkyl, cycloalkyl or heterocycle; cycloalkyl; heterocycle were obtained from those compounds of the general formula (I-a), wherein R^2=H by alkylation. Compounds of the general formula (I-a), wherein R^2= heteroaryl were obtained from those compounds of the general formula (I-a), wherein R^2=H by arylation. Compounds of the general formula (I-a), wherein R^2= heterocycle, optionally substituted with alkyl were obtained from those compounds of the general formula (I-a), wherein R^2=H by condensation with benzotriazole and a carbonyl compound, followed by a nucleophilic reaction using Grignard reagents. Chloro derivative of formula (VI) can be purchased or can be prepared by conventional methods.

The compounds of formula (I-b) wherein X, R^1 and R^2 are as defined in any of the embodiments described above can be prepared according to **Scheme 4 and 5**.



Scheme 4

In a first step, a compound of formula (1) is reacted with ethyl acetoacetate in a suitable solvent, such as DMSO to give a compound of formula (2) which is coupled with N-tosylhydrazide in the presence of KI and TBHP to give a compound of formula (3) (Huang et al. *Adv. Synth. Catal.* 2018, 360:3117-3123). Treatment of a compound of formula (3) with a reducing agent such as DIBAL-H in a suitable solvent such as toluene gives a compound of formula (VIII). Alternatively, a compound of formula (1) is converted to a diazonium salt, which is further reacted with trimethylsilyl azide to give a compound of formula (4). Compounds of formula (4) reacted with 2-butyn-1-ol give a compound of formula (VIII).



Scheme 5

According to **Scheme 5**, etherification between chloro derivatives of formula (VI) and hydroxy derivatives of formula (VIII) can be carried out by a palladium-mediated process in the presence of a suitable base, such as Cs_2CO_3 to provide a compound of formula (IX). Compounds of the general formula (I-b), wherein R^2=H were obtained after removal of the protective group of formula (IX) using acid, such as ethyl acetate saturated with hydrogen chloride or TFA in dichloromethane. Compounds of the general formula (I-b), wherein R^2= alkyl, optionally substituted with -$S(O)_2$-alkyl, cycloalkyl or heterocycle; cycloalkyl; heterocycle were obtained from those compounds of the general formula (I-b), wherein R^2=H by alkylation. Compounds of the general formula (I-b), wherein R^2= heteroaryl were obtained from those compounds of the general formula (I-b), wherein R^2=H by arylation. Compounds of the general formula (I-b), wherein R^2= heterocycle, optionally substituted with alkyl were obtained from those compounds of the general formula (I-b), wherein R^2=H by condensation with benzotriazole and a carbonyl compound, followed by a nucleophilic reaction using Grignard reagents. Chloro derivative of formula (VI) can be purchased or can be prepared by conventional methods.

The reagents and detailed process steps required for the above reactions are set forth in the Intermediates and Examples.

The present invention thus relates to a process for the preparation of compounds of formula (I) as defined above, comprising

step (i) a coupling reaction, selected from the group consisting of

(a-1) reacting a compound of formula (IV) with a compound of formula (III), to give a compound of formula (V), wherein X=CH and R^1 and R^2 are as defined above;

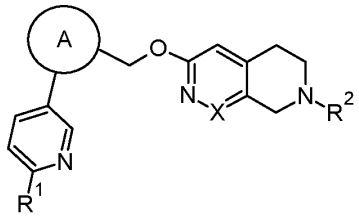
(a-2) reacting a compound of formula (VI) with a compound of formula (II), to give a compound of formula (VII), wherein X=N and R^1 and R^2 are as defined above; and

(b) reacting a compound of formula (VI) with a compound of formula (VIII), to give a compound of formula (IX), wherein X, R^1 and R^2 are as defined above

step (ii) deprotection of a compound of formula (V), (VII) or (IX) to obtain a compound of formula (I) wherein A, X, and R^1 are as defined above and R^2 is hydrogen, and

step (iii) optionally transforming a compound of formula (I) wherein R^2 is hydrogen to a compound of formula (I) wherein A, X, and R^1 are as defined as above and R^2 is an alkyl group optionally substituted with -$S(O)_2$-alkyl, a cycloalkyl or a heterocycle; a cycloalkyl group; a heterocycle group optionally substituted with an alkyl; or a heteroaryl group.

In an aspect, the present invention provides novel intermediates of formula (I'') synthesised in the process for preparing the compound of general formula (I) wherein A, X, and R^1 are as defined above and R^2 is an amino protecting group (Peter G. M. Wuts: Greene's Protective Groups in Organic Synthesis: Fifth Edition, Chapter 7. Protection for the Amino Group, pages 895-1193), such as a carbamate (methyl, 9-fluorenylmethyl, 2,2,2-trichloroethyl, tert-butyl, 2-(trimethylsilyl)ethyl, allyl, benzyl), trifluoroacetamide, benzylamine, allylamine, or tritylamine, preferably a carbamate, most preferably *tert*-butyloxycarbonyl protecting group.



(I'')

In a further aspect, the present invention provides novel intermediates of formula (V) synthesised in the process for preparing the compound of general formula (I) wherein X is CH, R^1 and R^2 are as defined above with the proviso that the compound is not *tert*-butyl 6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate, or *tert*-butyl 6-({5-methyl-3-[6-(trifluoromethyl)pyridin-5 3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate.

In another further aspect, the present invention provides novel intermediates of formula (VII) synthesised in the process for preparing the compound of general formula (I) wherein X is N, R^1 and R^2 are as defined above.

In one embodiment, the present invention relates to the intermediates of formula (VII) selected from the group consisting of:

tert-butyl 2-methyl-5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]pyridine-2-carboxylate, and

tert-butyl 5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine-2-carboxylate.

In yet another aspect, the present invention provides novel intermediates of formula (IX) synthesised in the process for preparing the compound of general formula (I) wherein X, R^1 and R^2 are as defined above.

In one embodiment, the present invention relates to the intermediates of formula (IX) selected from the group consisting of:

tert-butyl 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate,

tert-butyl 6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate,

tert-butyl 6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate,

tert-butyl 6-{[1-(6-methoxypyridin-3-yl)-4-methyl-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate, and

tert-butyl 2-methyl-5-[4-methyl-5-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1H-1,2,3-triazol-1-yl]pyridine-2-carboxylate.

The activity data of each of the compounds of formula (I) of the present invention are determined *in vitro* by the methods described below.

Biological example 1: Binding assay

The $GABA_A$ α5β3γ2 protein used for the receptor binding assay was derived from membranes produced from HEK cells (Millipore CYL3073) expressing the human recombinant $GABA_A$ α5β3γ2 receptor. Cells were stored and cultured in-house according to the instructions provided by the vendor (Millipore). Cell pellet was homogenized in 10 times modified Krebs Henseleit buffer (membrane preparation buffer): 20 mM Tris, 120 mM NaCl, 100 mM KCl, 25 mM $CaCl_2$ and 25 mM $MgCl_2$ pH=7.4 at 4 °C using Ultra Turrax (Janke&Kunkel) maximal speed for 15 seconds. The homogenate was centrifuged at 40,000 *g* for 30 minutes at 4 ºC. Supernatant was discarded and the resulting pellet was washed in membrane preparation buffer. Pellet was resuspended in membrane preparation buffer and aliquots of 1.4 mL ampules were stored at -70 ºC until use.

Receptor binding assays were performed in 96-well format in deep-well plates. For each 96-well plate one ampule of membrane homogenate was thawed and diluted in binding buffer (50 mM Tris pH=7.4, 100 mM KCl) and 200 µL was dispensed into each well. Radioligand [^{3}H]Ro151788 (Perkin Elmer: NET757250UC) was prepared in binding buffer and added to each well in 50 µL volume to give final concentration of 0.5 nM. Test compounds in suitable concentration(s) were added in additional 50 µL. The final assay volume was 300 µL. Incubation was carried out for 60 minutes at 4°C. For non-specific binding 10 µM unlabeled

diazepam was used. After incubation samples were filtered over UniFilter® GF/B™ using Filtermate Harvester (Perkin Elmer) and washed with 5x1 mL binding buffer. The plate was dried at 40 °C for an hour and 40 µL Microscint (Perkin Elmer) scintillation cocktail was added to each well. The plate was read in Microbeta (Perkin Elmer).

The specific radioligand binding (SB) was defined as the difference between total binding (Tot) and the non-specific binding (NSB). Results are expressed as a percent inhibition of specific binding obtained in the presence of compound of interest.

For IC_{50} and K_i determination a minimum of six drug concentrations in triplicate were used. IC_{50} values (i.e., concentration of compound giving 50% inhibition of specific binding) were calculated from concentration-displacement curves by sigmoidal fitting using Origin 7.5 software. K_i values (i.e., inhibition constants) were calculated using the Cheng-Prusoff equation $K_i = IC_{50}/[1+(L/K_D)]$, where [L] is the radioligand concentration and K_D the affinity of the labelled ligand for receptor. K_D was determined from the Saturation analyses.

The compounds of the present invention were tested in the above described assay, and all were found to have high affinity for the $GABA_A$ α5 receptor (K_i< 150 nM).

Table 1 showing representative $hGABA_A$ α5 K_i test results, obtained by the above described binding assay:

Ex.	$hGABA_A$ α5 K_i (nM)	Ex.	$hGABA_A$ α5 K_i (nM)	Ex.	$hGABA_A$ α5 K_i (nM)
1	3.9	17	17.6	33	29.5
2	37.0	18	12.7	34	51.6
3	4.2	19	35.5	35	88.8
4	4.5	20	26.5	36	53.5
5	7.4	21	23.0	37	37.9
6	8.4	22	22.7	38	20.9
7	29.3	23	7.3	39	21.4
8	11.2	24	8.3	40	28.5
9	4.9	25	128	41	61.5
10	4.5	26	93.8	42	28.0
11	7.4	27	63.2	43	19.0
12	28.2	28	5.9	44	40.4

13	6.6	29	29.7	45	99.5
14	3.2	30	3.3	46	61.5
15	17.1	31	36.0		
16	5.6	32	44.5		

Biological example 2: Functional assay

Human HEK293 cell lines expressing $GABA_A$ α5β3γ2 receptors were used in functional assays using the QPatch automated patch clamp system.

HEK293 cell lines stably expressing human recombinant $GABA_A$ α5β3γ2 receptor subunits (Millipore, CYL3053) were cultured in DMEM supplemented with 10% FBS (Gibco), passed two times per week and plated on Petri dishes previously coated with poly-d-lysine.

Automated whole-cell patch clamp recordings were made from cells 2-4 days after plating. Cells were detached using trypsin/EDTA (Sigma) treatment (2 minutes in 0.25% trypsin at 37 ºC), then, after centrifugation (125 *g*, 3 min, 2x), resuspended in a serum-free based media (Gibco, CHO-S-SFM-II) containing 12.5 mM HEPES, 1× penicillin-streptomycin-amphotericin (SigmaMix) and soybean trypsin inhibitor (Sigma, 0.04 mg/ml).

Cell suspension, as well as the extracellular solution (130 mM NaCl, 5 mM KCl, 5.1 mM HEPES, 4.9 mM HEPES-Na, 10 mM $CaCl_2$, 2 mM $MgCl_2$, 10 mM glucose and 0.1% DMSO, pH=7.35-7.4) and the intracellular solution (80 mM KCl, 50 mM KF, 36 mM KOH, 10 mM EGTA, 10 mM HEPES, 1.75 mM $MgCl_2$, 0.5 mM $CaCl_2$, 4 mM Na_2ATP. 14 mM phosphocreatine, 50 U/ml creatine-phosphokinase, 0.3 mM GTP, pH=7.25-7.3) were added to the QPatch-HTX automated patch clamp system (Sophion) in single-cell mode at room temperature. Inward currents were evoked at a holding potential of -80 mV by 3-s-long applications of the control agonist GABA at 1 µM at 2-4-min intervals first in concentration-matched DMSO (0.1 or 0.3%) control solution for five times, then in the presence of the test compound for four times, finally in control solution again for three times (wash-out). At the end of the experiment 100 µM GABA was applied to saturate the GABA-response and to assess the efficacy of the control GABA application. Current signals were low-pass filtered at 100 Hz and recorded at a sampling rate of 1 kHz.

The percentage modulation was calculated from the comparison of GABA-evoked peak current amplitudes in the presence and absence of the test compound.

The compounds of the present invention were tested at 1 µM in the above described assay, and all were found to possess $GABA_A$ α5 positive allosteric modulator activity.

Table 2 showing representative $hGABA_A$ α5 functional efficacy test results, obtained by the above described assay:

Ex.	$hGABA_A$ α5 efficacy (%)	Ex.	$hGABA_A$ α5 efficacy (%)	Ex.	$hGABA_A$ α5 efficacy (%)
1	155	16	146	32	155
2	100	19	129	33	71
7	125	20	111	34	62
8	133	21	134	37	53
9	106	22	68	40	86
10	131	24	88	42	99
11	114	25	73	43	85
13	129	29	102	44	96
14	126	30	59	45	97
15	115	31	115	46	76

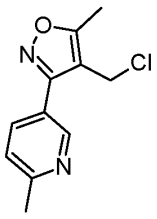
Examples

The present invention will be further illustrated by the following Intermediates and Examples without limiting the scope of the present invention to them. From the above description and from the Intermediates and Examples, the person skilled in the art may ascertain the essential features of the invention and without departing from its essence and scope, may make certain changes and modifications in order to adapt the invention to various applications and conditions. As a result, the invention is not limited to the following illustrative examples, but rather to the scope determined by the appended claims.

In general, the compounds of formula (I) can be prepared according to the common general knowledge of the person skilled in the art and/or the methods described for the working examples and/or intermediates. Solvents, temperatures, pressures and other reaction conditions can be easily selected by the person skilled in the art. Starting materials are commercially available and/or can be easily prepared by the person skilled in the art according to literature procedure. During the preparation of compounds combinatorial techniques can be used, for example, where intermediates are suitable for the use of these methods.

Intermediate 1

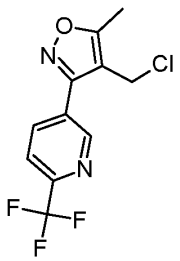
5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine



1.00 g (4.89 mmol) of [5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methanol (WO 2018/104419 A1, Hoffmann-La Roche) was dissolved in 30 mL of phosphorus oxychloride. The reaction mixture was stirred for 2 hours at 115°C, then evaporated to dryness. Ethyl acetate was added and washed with saturated sodium hydrogen carbonate solution and with water, dried over anhydrous sodium sulfate, and evaporated to obtain 0.95 g (87%) of the title compound. MS (ESI) m/z: 223.1 $[M+H]^+$.

Intermediate 2

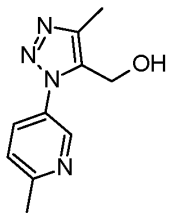
5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine



In analogy of Intermediate 1, {5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methanol (WO 2018/104419 A1, Hoffmann-La Roche) was converted into the title compound. MS (ESI) m/z: 277.1 $[M+H]^+$.

Intermediate 3

[4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol



Method A

a: methyl (2E)-3-[(6-methylpyridin-3-yl)amino]but-2-enoate

To a mixture of 1.00 g (9.20 mmol) of commercially available 6-methylpyridine-3-amine and 1.40 mL (1.11 mmol) of ethyl acetoacetate in 30 mL of ethanol, 1.67 g (13.9 mmol) of anhydrous magnesium sulfate and 0.10 mL (1.85 mmol) of acetic acid was added. The reaction mixture was refluxed for 10 hours. After cooling, filtration of inorganics and concentration of the filtrate under reduced pressure afforded the residue which was used in the next step without further purification. MS (ESI) m/z: 207.1 $[M+H]^+$.

b: ethyl 4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazole-5-carboxylate

To a mixture of 8.31 g (37.7 mmol) of methyl (2E)-3-[(6-methylpyridin-3-yl)amino]but-2-enoate, 8.43 g (45.3 mmol) of methylbenzenesulfonehydrazide, 6.26 g (37.7 mmol) of potassium iodide in 70 mL of DMSO, 7.31 mL (75.5 mmol) of TBHP (70% solution in water) was added slowly. Then the mixture was stirred at 70°C for 24 hours. After the reaction was completed (monitored by TLC), 140 g of sodium dithionite dissolved in 300 mL of water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate. The combined organic layers were then dried over $MgSO_4$, filtered, and then concentrated in vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: DCM:MeOH, 0-10% gradient) afforded the desired product. Yield: 6.35 g (68 %), MS (ESI) m/z: 247.1 $[M+H]^+$.

c: [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol

6.35 g (25.8 mmol) of ethyl 4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazole-5-carboxylate was dissolved in 80 mL of anhydrous THF and cooled to 0 °C. 103 mL of DIBAL-H (1 M solution in toluene) was added dropwise under argon and the reaction mixture was stirred at room temperature for 1 hour. After cooling it was quenched with 71 mL of water and acidificated with 135 mL of 1M HCl. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated in vacuo. The crude product was crystallised from isopropanol to obtain the title compound as a white solid. Yield: 3.42 g, (65%), MS (ESI) m/z: 205.1 [M+H]+.

Method B

a: 5-azido-2-methylpyridine

5.0 g (46 mmol) of commercially available 6-methylpyridine-3-amine was diisolved in a mixture of 14 mL of cc. HCl and 14 mL of water and cooled to 0 °C. 3.19 g (46.2 mmol) of $NaNO_2$ dissolved in 12 mL of water was added dropwise. The reaction mixture was stirred at 0 °C for

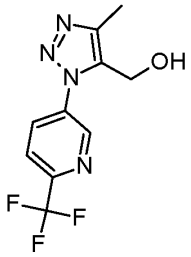
20 min then 10.6 mL (80 mmol) of trimethylsylil azide was added dropwise slowly and the reaction mixture was stirred at room temperature for 1.5 hour. After completion 70 mL of ethyl acetate was added and washed three times with 30 mL of saturated sodium carbonate solution and with water, dried over anhydrous sodium sulfate, and evaporated. The crude product was used in the next step without further purification.

b: [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol

5.81 g (43.3 mmol) of 5-azido-2-methylpyridine was dissolved in 3.24 mL (43.3 mmol) of 2-butyn-1-ol and the reaction mixture was stirred at 100°C for 10 h. The residue was purified by flash coloumn chromatography (silica gel, eluent: cyclohexane:EtOAc 40-80 % gradient). Yield: 2.30 g (26 %), white solid. MS (ESI) m/z: 205.1 [M+H]+.

Intermediate 4

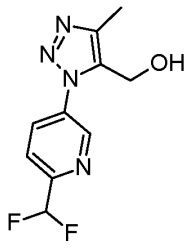
{4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1*H*-1,2,3-triazol-5-yl}methanol



The compound was synthesized according to the procedure described for intermediate 3 using commercially available 6-(trifluoromethyl)pyridin-3-amine in step a. MS (ESI) m/z: 259.1 [M+H]+.

Intermediate 5

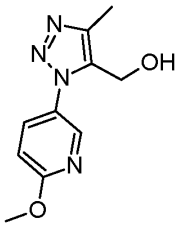
{1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methanol



The compound was synthesized according to the procedure described for intermediate 3 using commercially available 6-(difluoromethyl)pyridin-3-amine in step a. MS (ESI) m/z: 241.1 [M+H]+.

Intermediate 6

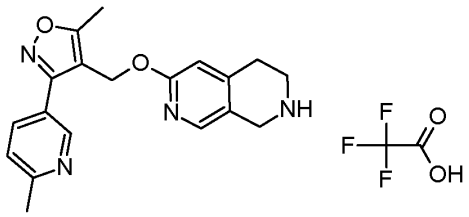
[1-(6-methoxypyridin-3-yl)-4-methyl-1*H*-1,2,3-triazol-5-yl]methanol



The compound was synthesized according to the procedure described for intermediate 3 using commercially available 6-methoxypyridin-3-amine in step a. MS (ESI) m/z: 221.1 [M+H]+.

Example 1

6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine trifluoroacetic acid salt



A: *tert*-butyl 6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate

1.96 g (8.80 mmol) of 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1), and 2.20 mg (8.80 mmol) of commercially available tert-butyl 6-hydroxy-3,4-dihydro-2,7-naphthyridine-2(1H)-carboxylate were dissolved in 120 mL of anhydrous acetonitrile. Then, 3.65 mg (26.40 mmol) of anhydrous potassium-carbonate was added to the solution, and the suspension was stirred under reflux for 12 h. The conversion was followed by TLC (EtOAc:cyclohexane=1:1 as eluent, silica plate). After the reaction completed, the mixture was filtered, and evaporated to give an oily crude product, which was purified by

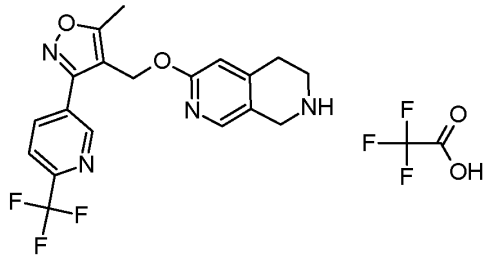
flash coloumn chromatography (silica gel, eluent: EtOAc:cyclohexane=1:1). Yield: 640 mg (16.6 %) white solid. MS (ESI) m/z: 437.3 $[M+H]^+$.

B: 6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine trifluoroacetic acid salt

97.97 mg (0.22 mmol) of tert-butyl 6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate was dissolved in 10 mL of DCM. Then, 1489 mg (13.06 mmol) of trifluoroacetic acid was added to the solution, and the suspension was stirred at rt for 6 h. After the reaction completed, the mixture was evaporated to give the title compound. Yield: 90 mg (91%) yellow solid. MS (ESI) m/z: 337.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 8.96-9.07 (br m, 2H), 8.81 (br d, J=2.0 Hz, 1H), 8.12 (dd, J=8.1, 2.3 Hz, 1H), 8.06 (s, 1H), 7.49 (d, J=8.1 Hz, 1H), 6.73 (s, 1H), 5.27 (s, 2H), 4.25 (br t, J=4.5 Hz, 2H), 3.31-3.39 (m, 2H), 2.95 (t, J=6.3 Hz, 2H), 2.57 (s, 3H), 2.56 (s, 3H).

Example 2

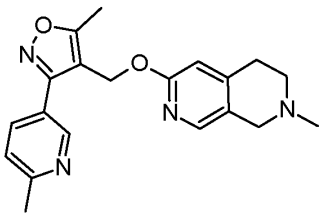
6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine trifluoroacetic acid salt



The title compound prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine (Intermediate 2) in step a. MS (ESI) m/z: 391.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.11 (d, J=1.9 Hz, 1H), 8.82-9.03 (br m, 2H), 8.48 (dd, J=8.1, 1.7 Hz, 1H), 8.11 (d, J=8.1, 1H), 8.04 (s, 1H), 6.73 (s, 1H), 5.33 (s, 2H), 4.24 (br t, 2H), 3.31-3.38 (br m, 2H), 2.94 (t, J=6.3 Hz, 2H), 2.61 (s, 3H).

Example 3

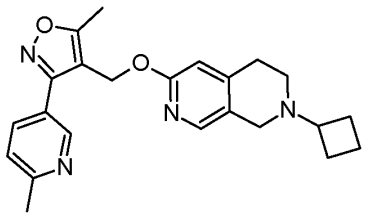
2-methyl-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



450 mg (1.0 mmol) of 6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine trifluoroacetic acid salt (Example 1) was added to a solution of saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo. The obtained base was dissolved in 2 mL of water and 240 mg (4.0 mmol) of acetic acid, 122 mg (1.5 mmol) of formaldehyde solution (37% in water) and 131 mg (2.0 mmol) of zinc powder was added. The reaction mixture was stirred at 30°C for 48 hours. After the reaction was completed (monitored by TLC), the reaction mixture was neutralized with ammonia solution, and the resulting mixture was extracted with DCM. The combined organic layers were then dried over $MgSO_4$, filtered, and then concentrated in vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: DCM:MeOH=10:1) afforded the desired product. Yield: 59.3 mg (16.9 %), MS (ESI) m/z: 351.2 $[M+H]^+$.

Example 4

2-cyclobutyl-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine

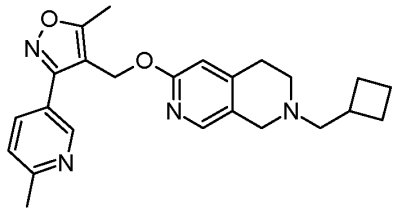


To a solution of 200 mg (0.44 mmol) of 6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine trifluoroacetic acid salt (Example 1) in 4 mL of 2,2,2-triluoroethanol 112 mg (1.33 mmol) of $NaHCO_3$ was added and stirred for 30 min, then 32 mg (0.44 mmol) of cyclobutanone was added in one portion and the reaction mixture was warmed up to 45°C. The so obtained solution was stirred for 5 min, then 16.8 mg (0.44 mmol) of sodium borohydride was added. The reaction mixture was stirred at 45°C for 3 hours. After completion the solvent was evaporated, the residue was dissolved in DCM and washed with brine. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated in

vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: EtOAc:MeOH=10:1) afforded the desired product. Yield: 28.1 mg (16.1 %), MS (ESI) m/z: 393.2 $[M+H]^+$.

Example 5

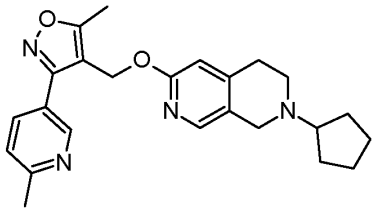
2-(cyclobutylmethyl)-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 4 using commercially available cyclobutanecarbaldehyde. MS (ESI) m/z: 405.2 $[M+H]^+$.

Example 6

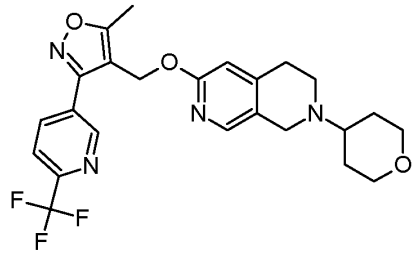
2-cyclopentyl-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 4 using commercially available cyclopentanone. MS (ESI) m/z: 405.2 $[M+H]^+$.

Example 7

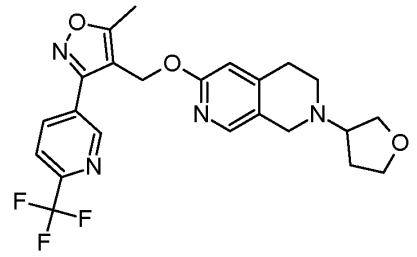
6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 4 using 6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine trifluoroacetic acid salt (Example 2) and commercially available tetrahydropyran-4-one. MS (ESI) m/z: 475.2 $[M+H]^+$.

Example 8

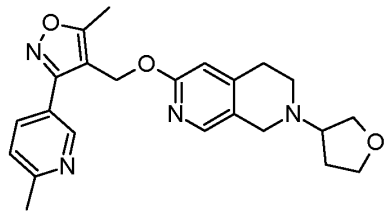
6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 4 using 6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine trifluoroacetic acid salt (Example 2) and commercially available 3-oxotetrahydrofuran. MS (ESI) m/z: 461.2 $[M+H]^+$.

Example 9

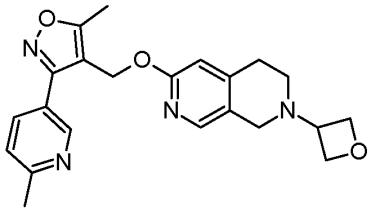
6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 4 using commercially available 3-oxotetrahydrofuran. MS (ESI) m/z: 407.2 $[M+H]^+$.

Example 10

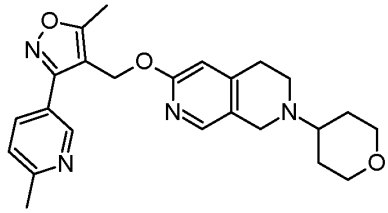
6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxetan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 4 using commercially available 3-oxetanone. MS (ESI) m/z: 393.2 $[M+H]^+$.

Example 11

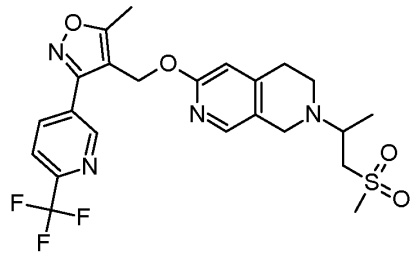
6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 4 using commercially available 4-oxotetrahydropyran. MS (ESI) m/z: 421.2 $[M+H]^+$.

Example 12

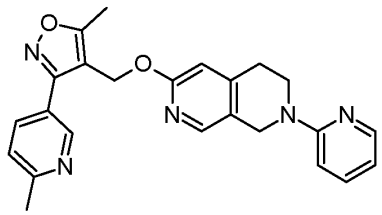
2-(1-methanesulfonylpropan-2-yl)-6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine



183.6 mg (0.36 mmol) of 6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine trifluoroacetic acid salt (Example 2) was added to a solution of saturated Na_2CO_3 and extracted with DCM. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo. The obtained base was added to a stirred solution of 49 mg (0.36 mmol) of methanesulfonylacetone in 1 mL of methanol and 1 mL of 2,2,2-triluoroethanol at room temperature. The mixture was stirred for 1 h. 84 mg (0.72 mmol) of triethylsilicon was added by syringe and followed by 57 mg (0.26 mmol) of indium(III) chloride (Lee et al., *J. Org. Chem.* 2008, 73, 22, 8829–8837). The reaction was allowed to stir at room temperature and was monitored by TLC. When the reaction was completed, the mixture was quenched by 1 mL of saturated K_2CO_3 solution. The mixture was extracted with EtOAc. The combined organic layer was washed with brine and finally was dried over Na_2SO_4. The crude product was purified by flash column chromatography (silica gel, eluent: cyclohexane:EtAOc=1:1). Yield: 21 mg (11 %), MS (ESI) m/z: 511.1 $[M+H]^+$.

Example 13

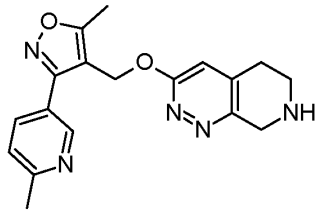
6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(pyridin-2-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



283 mg (0.63 mmol) of 6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine trifluoroacetic acid salt (Example 1) was dissolved in 2 mL of 2-fluoropyridine the reaction mixture was stirred at 120°C for 3 h. The residue was purified by flash coloumn chromatography (silica gel, eluent: DCM:MeOH=10:1). Yield: 50 mg (19.2 %). MS (ESI) m/z: 414.2 $[M+H]^+$.

Example 14

2-methyl-5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]pyridine



A: tert-butyl 2-methyl-5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]pyridine-2-carboxylate

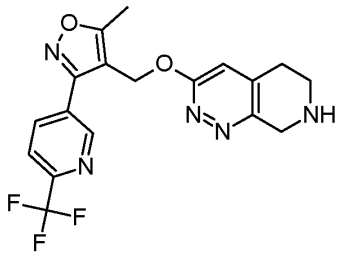
Under argon atmosphere a flask was charged with 660 mg (2.45 mmol) of commercially available tert-butyl 3-chloro-5,8-dihydropyrido[3,4-c]pyridazine-7(6H)-carboxylate, 500 mg (2.45 mmol) of {5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methanol (WO 2018/104419 A1, Hoffmann-La Roche), 1595 mg (4.89 mmol) of Cs_2CO_3, 98 mg (0.25 mmol) of rac-2-(di-*tert*-butylphosphino)-1,11-binaphthyl, 55 mg (0.24 mmol) of $Pd(OAc)_2$ and 20 mL of anhydrous toluene. The mixture was stirred at 100°C for 12 h. The conversion was checked by TLC (cyclohexane:EtOAc=1:1 as eluent, silica plate). The reaction mixture was filtered through a celite pad, washed with acetone, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by flash coloumn chromatography (silica gel, eluent: cyclohexane:EtAOc=1:1). Yield: 342 mg (32 %), white, amorphous solid. MS (ESI) m/z: 438.2 $[M+H]^+$.

B: 2-methyl-5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]pyridine

342 mg (0.78 mmol) of tert-butyl 2-methyl-5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]pyridine-2-carboxylate was dissolved in 50 mL of DCM. Then, 1782 mg (15.63 mmol) of trifluoroacetic acid was added to the solution, and the suspension was stirred at rt for 24 h. After completion the mixture was evaporated, the residue was dissolved in DCM and washed with saturated Na_2CO_3 solution and water. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: EtOAc:MeOH=10:1) afforded the desired product. Yield: 132 mg (50 %), MS (ESI) m/z: 338.2 $[M+H]^+$.

Example 15

5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine



A: tert-butyl 5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine-2-carboxylate

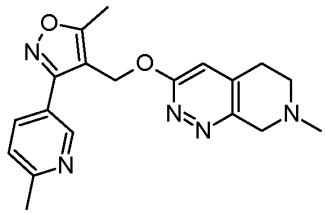
Under argon atmosphere a flask was charged with 668 mg (2.48 mmol) of commercially available tert-butyl 3-chloro-5,8-dihydropyrido[3,4-c]pyridazine-7(6H)-carboxylate, 639 mg (2.48 mmol) of 5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methanol (WO 2018/104419 A1, Hoffmann-La Roche), 1614 mg (4.95 mmol) of Cs_2CO_3, 99 mg (0.25 mmol) of rac-2-(di-*tert*-butylphosphino)-1,11-binaphthyl, 56 mg (0.25 mmol) of $Pd(OAc)_2$ and 20 mL of anhydrous toluene. The mixture was stirred at 100°C for 12 h. The conversion was checked by TLC (cyclohexane:EtOAc=1:1 as eluent, silica plate). The reaction mixture was filtered through a celite pad, washed with acetone, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by flash coloumn chromatography (silica gel, eluent: cyclohexane:EtAOc=1:1). Yield: 395 mg (32.5 %). MS (ESI) m/z: 492.2 $[M+H]^+$.

B: 5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine

395 mg (0.80 mmol) of tert-butyl 5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine-2-carboxylate was dissolved in 20 mL of DCM. Then, 916 mg (8.03 mmol) of trifluoroacetic acid was added to the solution, and the suspension was stirred at rt for 24 h. After completion the mixture was evaporated, the residue was dissolved in DCM and washed with saturated Na_2CO_3 solution and water. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: EtOAc:MeOH=10:1) afforded the desired product. Yield: 175 mg (56 %), MS (ESI) m/z: 392.1 [M+H]+.

Example 16

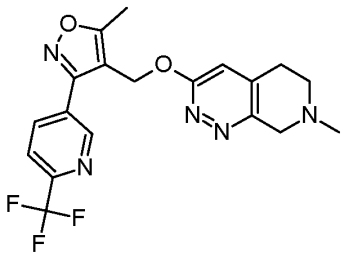
2-methyl-5-{5-methyl-4-[({7-methyl-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl}oxy)methyl]-1,2-oxazol-3-yl}pyridine



To a solution of 74 mg (0.22 mmol) of 2-methyl-5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]pyridine (Example 14) in 5 mL of methanol 27 mg (0.33 mmol) of formaldehyde solution (37% in water) was added and the reaction mixture was warmed up to 50°C, then 93 mg (0.44 mmol) of sodium triacetoxyborohydride was added in one portion. The reaction mixture was stirred at 50°C for 5 hours. After completion the solvent was evaporated, the residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ solution. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: EtOAc:MeOH=10:1) afforded the desired product. Yield: 40 mg (52 %), MS (ESI) m/z: 352.2 $[M+H]^+$.

Example 17

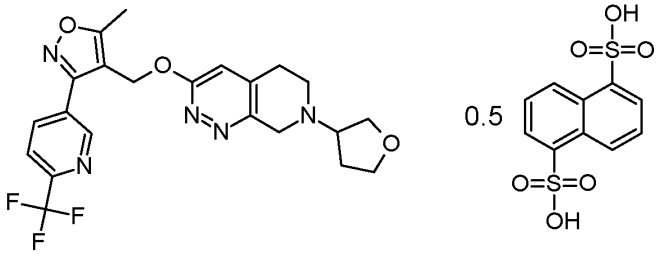
5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine



The title compound prepared according to the procedure described for Example 16 using 5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine (Example 15). MS (ESI) m/z: 406.1 $[M+H]^+$.

Example 18

5-[5-methyl-4-({[7-(oxolan-3-yl)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl]oxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine heminapadisylate salt



A: Synthesis of the free base

To a solution of 130 mg (0.33 mmol) of 5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine (Example 15) in 5 mL of 2,2,2-trifluoroethanol 29 mg (0.34 mmol) of 3-oxotetrahydrofuran and 13 mg (0.34 mmol) of sodium borohydride was added. The reaction mixture was stirred at 45°C for 12 hours. After completion the solvent was evaporated, the residue was dissolved in DCM and washed with water. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: DCM:MeOH=10:1) afforded the free base as an oil. Yield: 23 mg (15 %), MS (ESI) m/z: 462.2 $[M+H]^+$

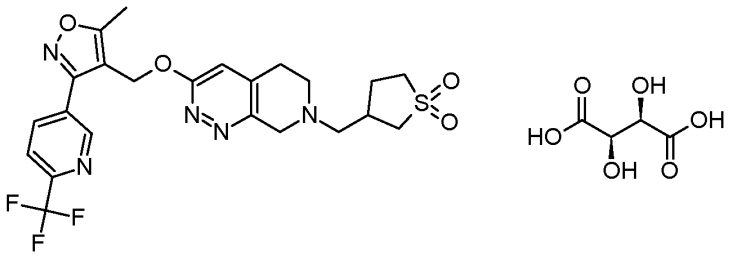
B: Synthesis of the heminapadisylate salt

23 mg (0.05 mmol) of 5-[5-methyl-4-({[7-(oxolan-3-yl)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl]oxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine was dissolved in 2 mL of ethanol and 18 mg (0.05 mmol) of 1,5-naphthalenedisulfonic acid tetrahydrate was added and stirred

at 60°C for 10 minutes, then allowed to cool to rt. The precipitated product was collected by filtration, washed with cold ethanol and dried in vacuum to obtain the title compound as a white solid. Yield: 17 mg (56 %), MS (ESI) m/z: 462.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 10.05-10.50 (br m, 1H), 9.12 (d, J=1.7 Hz, 1H), 8.49 (dd, J=8.1, 1.7 Hz, 1H), 8.10 (br d, J=8.2 Hz, 1H), 7.21 (br s, 1H), 4.40-4.85 (br m, 2H), 4.07-4.34 (br m, 2H), 3.91-4.06 (br m, 1H), 3.76-3.89 (m, 1H), 3.30-3.74 (br m, 5H), 3.00-3.18 (br m, 2H), 2.64 (s, 3H), 2.12-2.43 (br m, 2H); napadisylate (acid/base molar ratio 1:2) signals: 8.85 (dd, J=8.5, ~1 Hz, 2H), 7.91 (dd, J=7.0 Hz, 1.1 Hz, 2H), 7.38 (dd, J=8.5, 7.1 Hz, 2H).

Example 19

3-{[3-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl]methyl}-1lambda6-thiolane-1,1-dione tartarate salt



A: Synthesis of the free base

In a microwave tube 100 mg (0.256 mmol) of 5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine (Example 15) was dissolved in 3 mL of acetonitrile, then 66 mg (0.51 mmol) of N,N-diisopropylethylamine and 54.6 mg (0.256 mmol) of 3-bromomethyltetrahydrothiophene 1,1-dioxide was added. The tube was placed in a microwave reactor and heated at 100°C with stirring for 3 hours. After the reaction completed, the mixture was evaporated and purified by flash coloumn chromatography (silica gel, eluent: DCM:MeOH=10:1) to obtain 34 mg product as an oil. Yield: 38 mg (28.4 %), MS (ESI) m/z: 524.1 $[M+H]^+$.

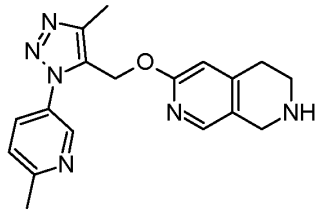
B: Synthesis of the tartarate salt

11.2 mg (0.021 mmol) of 3-{[3-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl]methyl}-1lambda6-thiolane-1,1-dione was dissolved in 1 mL of ethanol and 3.2 mg (0.021 mmol) of L-(+)-tartaric acid was added and stirred at 60°C for 10 minutes, then allowed to cool to rt. The precipitated product was

collected by filtration, washed with cold ethanol and dried in vacuum to obtain the title compound as a white solid. Yield: 12.5 mg (86.7 %), MS (ESI) m/z: 524.1 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 11.40-13.60 (br m, 1H), 9.12 (d, J=1.7 Hz, 1H), 8.46 (dd, J=8.0 Hz, 1.8 Hz, 1H), 8.09 (d, J=8.0 Hz, 1H), 7.00 (s, 1H), 5.48 (s, 2H), 3.75 (s, 2H), 3.14-3.26 (m, 2H), 3.00-3.09 (m, 1H), 2.82 (t, J=5.4 Hz, 2H), 2.74-2.81 (m, 2H), 2.54-2.73 (m, 4H), 2.63 (s, 3H), 2.20-2.29 (m, 1H), 1.73-1.83 (m, 1H); tartarate (acid/base ratio 1:1) signal: 4.28 (s, 2H).

Example 20

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



A: *tert*-butyl 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate

Under argon atmosphere a flask was charged with 504 mg (1.88 mmol) of commercially available tert-butyl 6-chloro-3,4-dihydro-2,7-naphthyridine-2(1H)-carboxylate, 383 mg (1.88 mmol) of [4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methanol (Intermediate 3), 1220 mg (3.75 mmol) of Cs_2CO_3, 74.7 mg (0.18 mmol) of rac-2-(di-*tert*-butylphosphino)-1,11-binaphthyl, 42 mg (0.18 mmol) of $Pd(OAc)_2$ and 20 mL of anhydrous toluene. The mixture was stirred at 100°C for 12 h. The conversion was checked by TLC (cyclohexane:EtOAc=1:1 as eluent, silica plate). The reaction mixture was filtered through a celite pad, washed with acetone, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by flash coloumn chromatography (silica gel, eluent: cyclohexane:EtAOc 30-70% gradient). Yield: 287 mg (35 %). MS (ESI) m/z: 437.2 $[M+H]^+$.

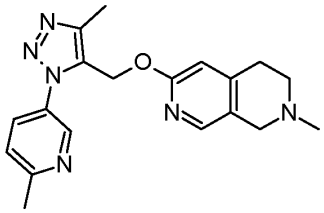
B: 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine

287 mg (0.65 mmol) of tert-butyl 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate was dissolved in 12 mL of ethyl acetate. 12 mL of ethyl acetate saturated with hydrogen chloride was added dropwise to the solution. The reaction mixture was stirred for 30 minutes at room temperature. The white

precipitate formed was filtered out, washed with small portion of ethyl acetate. The hydrochloride salt was added to a solution of saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: DCM:MeOH=10:1) afforded the desired product. Yield: 78 mg (35 %), MS (ESI) m/z: 337.2 [M+H]+.

Example 21

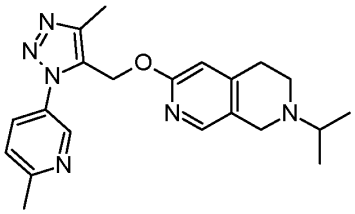
2-methyl-6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 16 using 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 20). MS (ESI) m/z: 351.1 $[M+H]^+$.

Example 22

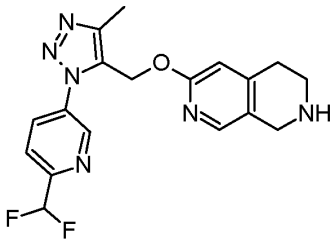
6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(propan-2-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 18, Step A using 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 20) and commercially available acetone. MS (ESI) m/z: 379.2 $[M+H]^+$.

Example 23

6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine



A: *tert*-butyl 6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate

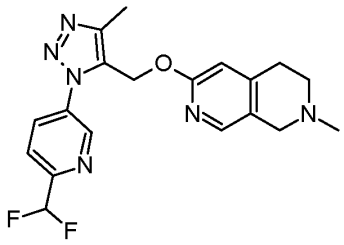
Under argon atmosphere a flask was charged with 91.3 mg (0.34 mmol) of commercially available tert-butyl 6-chloro-3,4-dihydro-2,7-naphthyridine-2(1H)-carboxylate, 81.6 mg (0.34 mmol) of {1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methanol (Intermediate 5), 226 mg (0.69 mmol) of Cs_2CO_3, 13.8 mg (0.034 mmol) of rac-2-(di-*tert*-butylphosphino)-1,11-binaphthyl, 7.8 mg (0.034 mmol) of $Pd(OAc)_2$ and 10 mL of anhydrous toluene. The mixture was stirred at 100°C for 12 h. The conversion was checked by TLC (cyclohexane:EtOAc=1:2 as eluent, silica plate). The reaction mixture was filtered through a celite pad, washed with acetone, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by flash coloumn chromatography (silica gel, eluent: cyclohexane:EtAOc=1:2). Yield: 90 mg (56 %). MS (ESI) m/z: 473.2 $[M+H]^+$.

B: 6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine

90 mg (0.19 mmol) of tert-butyl 6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate was dissolved in 10 mL of DCM. Then, 652 mg (5.71 mmol) of trifluoroacetic acid was added to the solution, and the suspension was stirred at rt for 3 h. After completion the mixture was evaporated, the residue was dissolved in DCM and washed with saturated Na_2CO_3 solution and water. The organic layer was separated, dried over MgSO4, filtered and evaporated in vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: DCM:MeOH=10:1) afforded the desired product. Yield: 28.4 mg (40 %), MS (ESI) m/z: 373.2 [M+H]+.

Example 24

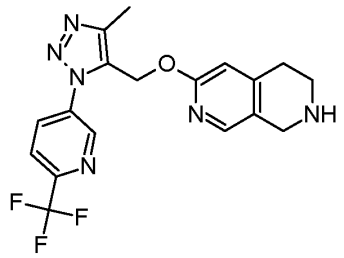
6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-2-methyl-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 16 using 6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 23). MS (ESI) m/z: 387.2 $[M+H]^+$.

Example 25

6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine



A: *tert*-butyl 6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate

Under argon atmosphere a flask was charged with 521 mg (1.94 mmol) of commercially available tert-butyl 6-chloro-3,4-dihydro-2,7-naphthyridine-2(1H)-carboxylate, 500 mg (1.94 mmol) of 4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methanol (intermediate 4), 1260 mg (3.87 mmol) of Cs_2CO_3, 77.2 mg (0.194 mmol) of rac-2-(di-*tert*-butylphosphino)-1,11-binaphthyl, 43.5 mg (0.194 mmol) of $Pd(OAc)_2$ and 30 mL of anhydrous toluene. The mixture was stirred at 100°C for 12 h. The conversion was checked by TLC (DCM:MeOH=9:1 as eluent, silica plate). The reaction mixture was filtered through a celite pad, washed with acetone, dried over anhydrous sodium sulfate, and evaporated. The residue

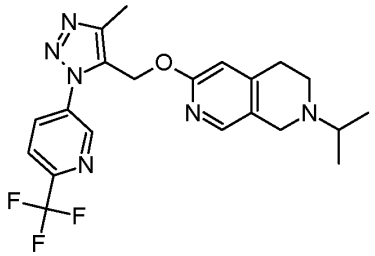
was purified by flash coloumn chromatography (silica gel, eluent: DCM:MeOH=9:1). Yield: 710 mg (74.8 %), amorphous solid. MS (ESI) m/z: 491.2 $[M+H]^+$.

B: 6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine

710 mg (1.45 mmol) of tert-butyl 6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate was dissolved in 15 mL of DCM. Then, 3300 mg (29 mmol) of trifluoroacetic acid was added to the solution, and the suspension was stirred at rt for 24 h. After completion the mixture was evaporated, the residue was dissolved in DCM and washed with saturated Na_2CO_3 solution and water. The organic layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: DCM:MeOH=9:1) afforded the desired product. Yield: 320 mg (56.6 %), MS (ESI) m/z: 391.2 $[M+H]^+$.

Example 26

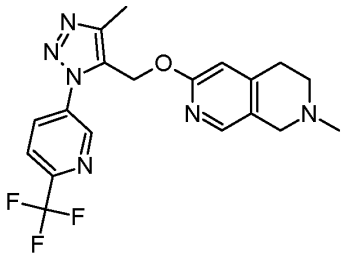
6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(propan-2-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



To a solution of 160 mg (0.41 mmol) of 6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 25) in 5 mL of 2,2,2-trifluoroethanol 23.8 mg (0.41 mmol) of acetone and 15.5 mg (0.41 mmol) of sodium borohydride was added. The reaction mixture was stirred at 45°C for 12 hours. After completion the solvent was evaporated, the residue was dissolved in DCM and washed with water. The organic layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: DCM:MeOH=9:1) afforded the title compound. Yield: 61 mg (34 %), MS (ESI) m/z: 433.2 $[M+H]^+$.

Example 27

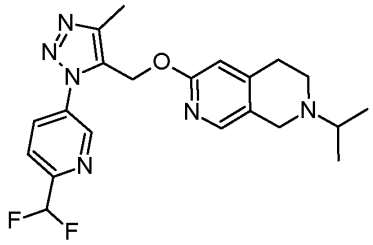
2-methyl-6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 16 using 6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 25, Step B). MS (ESI) m/z: 405.1 $[M+H]^+$.

Example 28

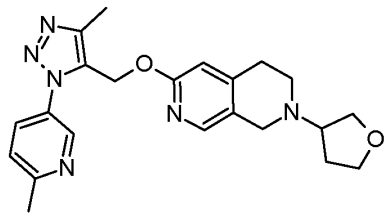
6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-2-(propan-2-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 18, Step A using 6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 23) and commercially available acetone. MS (ESI) m/z: 415.2 $[M+H]^+$.

Example 29

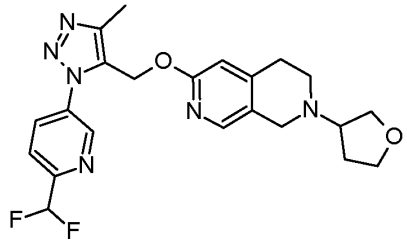
6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 18, Step A using 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 20) and commercially available 3-oxotetrahydrofuran. MS (ESI) m/z: 407.2 $[M+H]^+$.

Example 30

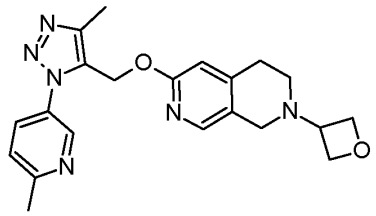
6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 18, Step A using 6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 23) and commercially available 3-oxotetrahydrofuran. MS (ESI) m/z: 443.2 $[M+H]^+$.

Example 31

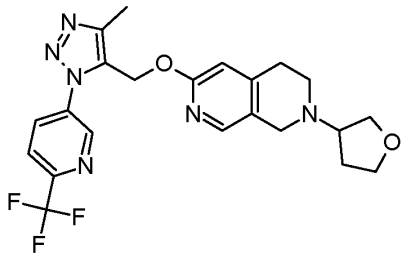
6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxetan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 18, Step A using 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 20) and commercially available 3-oxetanone. MS (ESI) m/z: 393.2 $[M+H]^+$.

Example 32

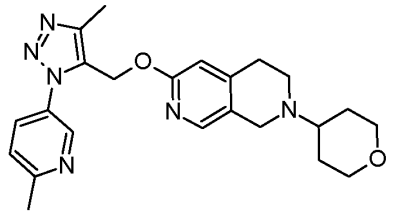
6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 26 using commercially available 3-oxotetrahydrofuran. MS (ESI) m/z: 461.2 $[M+H]^+$.

Example 33

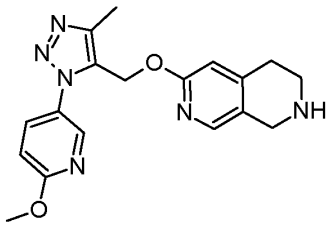
6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 18, Step A using 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 20) and commercially available 4-oxotetrahydropyran. MS (ESI) m/z: 421.2 $[M+H]^+$.

Example 34

6-{[1-(6-methoxypyridin-3-yl)-4-methyl-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



A: *tert*-butyl 6-{[1-(6-methoxypyridin-3-yl)-4-methyl-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate

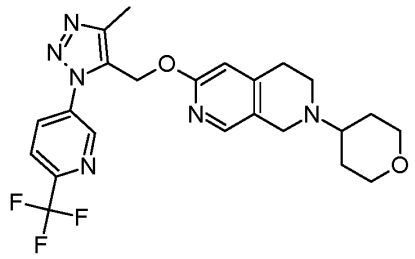
Under argon atmosphere a flask was charged with 300 mg (1.12 mmol) of commercially available tert-butyl 6-chloro-3,4-dihydro-2,7-naphthyridine-2(1H)-carboxylate, 246 mg (1.12 mmol) of [1-(6-methoxypyridin-3-yl)-4-methyl-1H-1,2,3-triazol-5-yl]methanol (Intermediate 6), 727 mg (2.23 mmol) of Cs_2CO_3, 44.5 mg (0.11 mmol) of rac-2-(di-*tert*-butylphosphino)-1,11-binaphthyl, 25 mg (0.11 mmol) of $Pd(OAc)_2$ and 20 mL of anhydrous toluene. The mixture was stirred at 100°C for 12 h. The conversion was checked by TLC (cyclohexane:EtOAc=1:1 as eluent, silica plate). The reaction mixture was filtered through a celite pad, washed with acetone, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by flash coloumn chromatography (silica gel, eluent: cyclohexane:EtAOc=1:1). Yield: 200 mg (39.5 %). MS (ESI) m/z: 453.2 $[M+H]^+$.

B: 6-{[1-(6-methoxypyridin-3-yl)-4-methyl-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine

200 mg (0.44 mmol) of tert-butyl 6-{[1-(6-methoxypyridin-3-yl)-4-methyl-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate was dissolved in in 7 mL of ethyl acetate. 7 mL of ethyl acetate saturated with hydrogen chloride was added dropwise to the solution. The reaction mixture was stirred for 30 minutes at room temperature. The white precipitate formed was filtered out, washed with small portion of ethyl acetate. The hydrochloride salt was added to a solution of saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated in vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: DCM:MeOH=10:1) afforded the desired product. Yield: 115 mg (74 %), MS (ESI) m/z: 353.2 [M+H]+.

Example 35

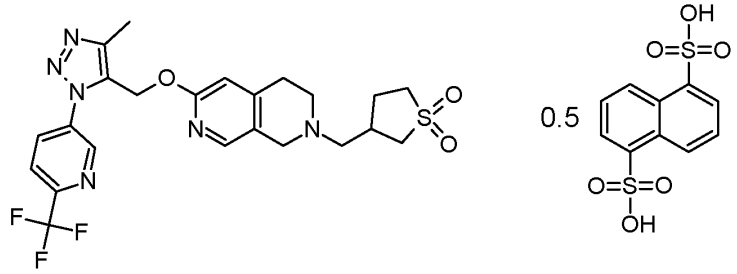
6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound prepared according to the procedure described for Example 26 using commercially available 4-oxotetrahydropyran. MS (ESI) m/z: 475.3 $[M+H]^+$.

Example 36

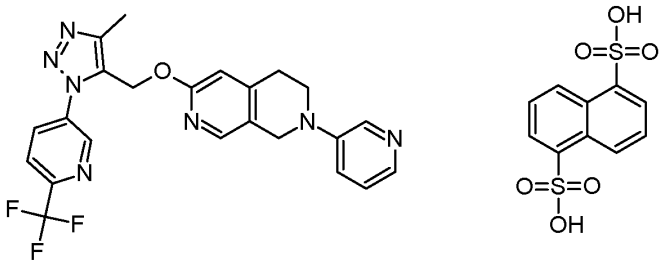
3-{[6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl]methyl}-1lambda6-thiolane-1,1-dione heminapadisylate salt



The free base of the title compound prepared according to the procedure described for Example 19, Step A using 6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 25). The heminapadisylate salt prepared according to the procedure described for Example 18 in Step B. MS (ESI) m/z: 523.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.45-9.70 (br m, 1H), 9.09 (d, J=2.4 Hz, 1H), 8.47 (dd, J=8.3 Hz, 2.2 Hz, 1H), 8.23 (d, J=8.3 Hz, 1H), 7.93-7.99 (br m, 1H), 6.72 (br s, 1H), 5.51 (s, 2H), 4.50-4.68 (m, 1H), 4.14-4.29 (br m, 1H), 3.60-3.76 (br m, 1H), 3.21-3.54 (br m, 5H), 3.00-3.12 (m, 3H), 2.84-3.00 (br m, 2H), 2.43 (s, 3H), 2.29-2.40 (br m, 1H), 1.77-1.91 (br m, 1H); napadisylate (acid/base molar ratio 1:2) signals: 8.85 (dd, J=8.5, ~1 Hz, 2H), 7.91 (dd, J=7.0 Hz, 1.1 Hz, 2H), 7.39 (dd, J=8.5, 7.1 Hz, 2H).

Example 37

6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(pyridin-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine napadysilate salt



A: Synthesis of the free base

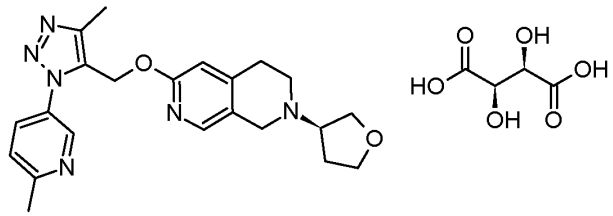
In a microwave tube, under argon atmosphere 239 mg (0.612 mmol) of 6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 25), 117 mg (0.741 mmol) of 3-bromopyridine, 141 mg (1.26 mmol) of potassium tert-butoxide, 38 mg (0.061 mmol) of 2,2-bis(Diphenylphosphino)-1,1'-binaphthalene, 13.7 mg (0.061 mmol) of $Pd(OAc)_2$ and 5 mL of anhydrous toluene. The tube was placed in a microwave reactor and heated at 120 °C with stirring for 1 hours. After the reaction completed, the mixture was evaporated and purified by flash coloumn chromatography (silica gel, eluent: DCM:MeOH=10:1) to obtain 19 mg product as an oil. Yield: 19 mg (6.6 %), MS (ESI) m/z: 468.2 $[M+H]^+$.

B: Synthesis of the napadisylate salt

19 mg (0.041mmol) of 6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(pyridin-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine was dissolved in 2 mL of methanol and 14.7 mg (0.041 mmol) of 1,5-naphthalenedisulfonic acid tetrahydrate was added and stirred at 60° C for 10 minutes, then allowed to cool to rt. The precipitated product was collected by filtration, washed with cold methanol, and dried in vacuum to obtain the title compound as a yellow solid. Yield: 11 mg (36 %), MS (ESI) m/z: 468.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.09 (d, J=2.4 Hz, 1H), 8.46 (dd, J=8.4 Hz, 2.2 Hz, 1H), 8.43 (d, J=2.8 Hz, 1H), 8.21(d, J=8.4 Hz, 1H), 8.17 (d, J=5.3 Hz, 1H), 8.06 (dd, J=8.8 Hz, 2.7 Hz, 1H), 7.96 (s, 1H), 7.85 (dd, J=8.9 Hz, 5.4 Hz, 1H), 6.69 (s, 1H), 5.49 (s, 2H), 4.55 (s, 2H), 3.65 (t, J=6.0 Hz, 2H), 2.92 (t, J=6.0 Hz, 2H), 2.43 (s, 3H); napadisylate (acid/base molar ratio 1:1) signals: 8.86 (dd, J=8.5 Hz, ~1 Hz, 2H), 7.92 (dd, J=7.0 Hz, 1.1 Hz, 2H), 7.40 (dd, J=8.5 Hz, 7.1 Hz, 2H).

Example 38

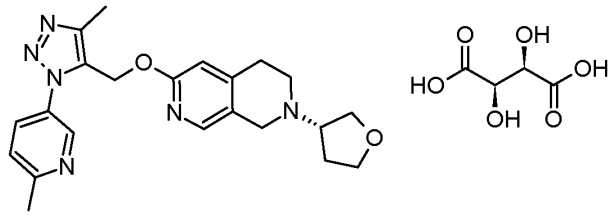
6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-[(3S)-oxolan-3-yl]-1,2,3,4-tetrahydro-2,7-naphthyridine or enantiomer, tartarate salt



Separation of the enantiomers of the racemic 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 29) by chiral HPLC (column: Lux i-Amylose-1 5µm 150×21,2mm) afforded the enantiopure title compound. MS (ESI) m/z: 407.2 $[M+H]^+$. The tartarate salt prepared according to the procedure described for Example 19 in Step B. MS (ESI) m/z: 407.2 $[M+H]^+$.

Example 39

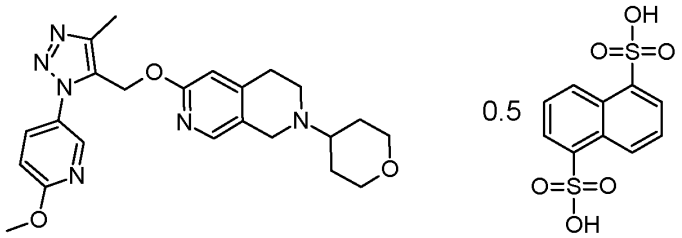
6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-[(3R)-oxolan-3-yl]-1,2,3,4-tetrahydro-2,7-naphthyridine or enantiomer, tartarate salt



Separation of the enantiomers of the racemic 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 29) by chiral HPLC (column: Lux i-Amylose-1 5µm 150×21,2mm) afforded the enantiopure title compound. MS (ESI) m/z: 407.2 $[M+H]^+$. The tartarate salt prepared according to the procedure described for Example 19 in Step B. MS (ESI) m/z: 407.2 $[M+H]^+$.

Example 40

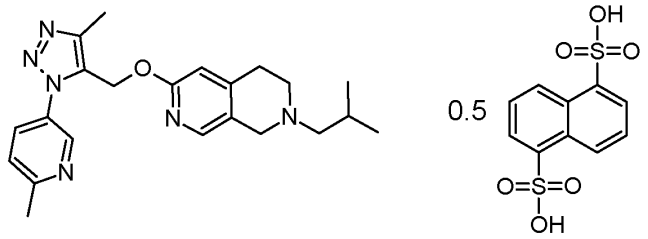
6-{[1-(6-methoxypyridin-3-yl)-4-methyl-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine heminapadisylate salt



The free base of the title compound prepared according to the procedure described for Example 18, Step A using 6-{[1-(6-methoxypyridin-3-yl)-4-methyl-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 34) and commercially available 4-oxotetrahydropyran. MS (ESI) m/z: 437.2 $[M+H]^+$. The heminapadisylate salt prepared according to the procedure described for Example 18 in Step B. MS (ESI) m/z: 437.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 800 MHz) δ (ppm): 9.70-9.77 (br m, 1H), 8.41 (d, J=2.8 Hz, 1H), 8.01 (s, 1H), 7.97 (dd, J=8.8, 2.7 Hz, 1H), 7.06 (d, J=8.8 Hz, 1H), 6.74 (s, 1H), 5.35-5.41 (AB d, J=13.5 Hz, 2H), 4.52 (d, J=14.6, 1H), 4.31 (dd, J=15.0, 8.3 Hz, 1H), 3.98 (br d, J=11.1 Hz, 2H), 3.94 (s, 3H), 3.70-3.74 (m, 1H), 3.49-3.55 (m, 1H), 3.26-3.35 (m, 3H), 3.01-3.10 (m, 2H), 2.39 (s, 3H), 2.04 (br d, J=12.0 Hz, 1H), 1.99 (br d, J=12.2 Hz, 1H), 1.63-1.73 (m, 2H); napadisylate (acid/base molar ratio 1:2) signals: 8.85 (dd, J=8.4, 1.0 Hz, 2H), 7.91 (dd, J=7.0, 1.0 Hz, 2H), 7.38 (dd, J=8.4, 7.0 Hz, 2H).

Example 41

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(2-methylpropyl)-1,2,3,4-tetrahydro-2,7-naphthyridine heminapadisylate salt

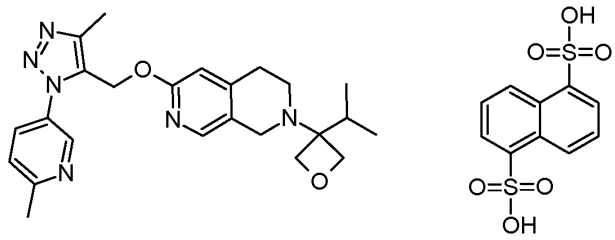


The free base of the title compound prepared according to the procedure described for Example 18, Step A using 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 20) and commercially available isobutyraldehyde. MS (ESI) m/z: 393.3 $[M+H]^+$. The heminapadisylate salt prepared according to the procedure described for Example 18 in Step B. MS (ESI) m/z: 393.3 $[M+H]^+$. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.22-9.40 (br m, 1H), 8.67 (d, J=2.4 Hz, 1H), 7.99 (s, 1H), 7.98

(dd, J=8.3, 2.6 Hz, 1H), 7.52 (d, J=8.3 Hz, 1H), 6.72 (s, 1H), 5.39 (s, 2H), 4.56 (br d, J=14.43 Hz, 1H), 4.19 (dd, J=15.1, 7.7 Hz, 1H), 3.62-3.71 (m, 1H), 3.22-3.36 (m, 1H), 2.97-3.15 (m, 4H), 2.58 (s, 3H), 2.39 (s, 3H), 2.15 (sep, J=6.7, 1H), 0.98 (t, J=6.1 Hz, 6H); napadisylate (acid/base molar ratio 1:2) signals: 8.85 (dd, J=8.4, 1.2 Hz, 2H), 7.91 (dd, J=7.0, 1.2 Hz, 2H), 7.38 (dd, J=8.4, 7.0 Hz, 2H).

Example 42

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-[3-(propan-2-yl)oxetan-3-yl]-1,2,3,4-tetrahydro-2,7-naphthyridine napadisylate salt



A: 2-[3-(1H-1,2,3-benzotriazol-1-yl)oxetan-3-yl]-6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine

To a solution of 1030 mg (3.06 mmol) of 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine (Example 20) in 30 mL of DCM 243 mg (3.37 mmol) of 3-oxetanone and 383 mg (3.21 mmol) of 1H-benzotriazole was added. The reaction mixture was stirred at rt for 12 hours. After completion the solvent was evaporated to dryness to obtain the title compound as a white solid. Yield: 1540 mg (98.7 %), MS (ESI) m/z: 510.2 $[M+H]^+$.

B: 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-[3-(propan-2-yl)oxetan-3-yl]-1,2,3,4-tetrahydro-2,7-naphthyridine

Under argon atmosphere a solution of 520 mg (1.02 mmol) of 2-[3-(1H-1,2,3-benzotriazol-1-yl)oxetan-3-yl]-6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine in 10 mL of THF was added to 593 mg (4.08 mmol) of isopropylmagnesium chloride lithium chloride complex solution in one portion. The reaction mixture was stirred at rt for 10 min. After the reaction completed, the mixture was quenched with water and extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered, and evaporated in vacuo. Purification of the residue by flash coloumn chromatography

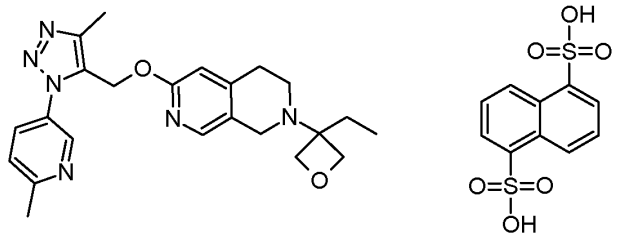
(silica gel, eluent: hexane:EtOAc: 2%Et_3N, 30-60% gradient) afforded the title compound. Yield: 177 mg (40 %), MS (ESI) m/z: 435.2 $[M+H]^+$.

C: 6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-[3-(propan-2-yl)oxetan-3-yl]-1,2,3,4-tetrahydro-2,7-naphthyridine napadisylate salt

The heminapadisylate salt prepared according to the procedure described for Example 36 in Step B. MS (ESI) m/z: 435.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 500 MHz) δ (ppm): 9.60-10.50 (br m, 1H), 8.71 (d, J=2.4 Hz, 1H), 8.04 (dd, J=8.3 Hz, 2.4 Hz, 1H), 7.99 (s, 1H), 7.57 (d, J=8.3 Hz, 1H), 6.75 (s, 1H), 5.41 (s, 2H), 4.69 (AB d, J=8.8 Hz, 2H), 4.66 (AB d, J=8.8 Hz, 2H), 4.35-4.61 (br m, 2H), 3.44-3.83 (br m, 2H), 3.04-3.17 (br m, 2H), 2.60 (s, 3H), 2.40 (s, 3H), 2.34-2.44 (m, 1H), 1.13 (d, J=6.7 Hz, 6H); napadisylate (acid/base molar ratio 1:1) signals: 8.85 (br d, J=8.6 Hz, 2H), 7.91 (d, J=7.0 Hz, 2H), 7.40 (dd, J=8.4 Hz, 7.3 Hz, 2H).

Example 43

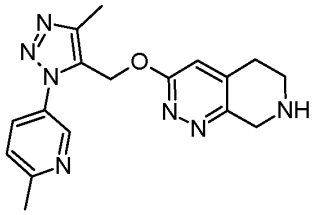
2-(3-ethyloxetan-3-yl)-6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine napadisylate salt



The title compound prepared according to the procedure described for Example 42 using ethylmagnesium bromide solution in Step B. MS (ESI) m/z: 421.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 500 MHz) δ (ppm): 10.54-10.96 (br m, 1H), 8.70 (d, J=2.4 Hz, 1H), 8.02 (dd, J=8.3 Hz, 2.6 Hz, 1H), 7.95 (s, 1H), 7.56 (d, J=8.3 Hz, 1H), 6.75 (s, 1H), 5.41 (s, 2H), 4.80 (br d, 2H), 4.57 (d, J=8.1 Hz, 2H), 4.24-4.44 (br m, 2H), 3.26-3.52 (br m, 2H), 3.02-3.18 (br m, 2H), 2.60 (s, 3H), 2.40 (s, 3H), 1.78-1.96 (br m, 2H), 1.23 (t, J=7.3 Hz, 3H); napadisylate (acid/base molar ratio 1:1) signals: 8.85 (br d, J=8.5 Hz, 2H), 7.91 (dd, J=7.0 Hz, 0.9 Hz, 2H), 7.39 (dd, J=8.5 Hz, 7.1 Hz, 2H).

Example 44

2-methyl-5-[4-methyl-5-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1H-1,2,3-triazol-1-yl]pyridine



A: *tert*-butyl 2-methyl-5-[4-methyl-5-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1H-1,2,3-triazol-1-yl]pyridine-2-carboxylate

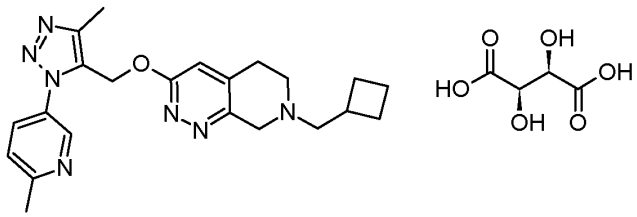
In a microwave tube, under argon atmosphere 135 mg (0.50 mmol) of commercially available tert-butyl 3-chloro-5,8-dihydropyrido[3,4-c]pyridazine-7(6H)-carboxylate, 102 mg (0.50 mmol) of [4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methanol (Intermediate 3), 112 mg (1.00 mmol) of potassium tert-butoxide, 20 mg (0.05 mmol) of rac-2-(di-*tert*-butylphosphino)-1,11-binaphthyl, 11.2 mg (0.05 mmol) of $Pd(OAc)_2$ and 10 mL of anhydrous toluene was added. The tube was placed in a microwave reactor and heated at 120°C with stirring for 3 hours. After the reaction completed, the mixture was filtered through a celite pad, washed with acetone, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by flash coloumn chromatography (silica gel, eluent: cyclohexane:EtAOc=1:1). Yield: 57 mg (26 %). MS (ESI) m/z: 438.2 $[M+H]^+$.

B: 2-methyl-5-[4-methyl-5-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1H-1,2,3-triazol-1-yl]pyridine

138 mg (0.31 mmol) of tert-butyl 2-methyl-5-[4-methyl-5-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1H-1,2,3-triazol-1-yl]pyridine-2-carboxylate was dissolved in 10 mL of DCM. Then, 360 mg (3.16 mmol) of trifluoroacetic acid was added to the solution, and the suspension was stirred at rt for 48 h. After completion the mixture was evaporated, the residue was dissolved in DCM and washed with saturated Na_2CO_3 solution and water. The organic layer was separated, dried over MgSO4, filtered and evaporated in vacuo. Purification of the residue by flash coloumn chromatography (silica gel, eluent: DCM:MeOH=10:1) afforded the desired product. Yield: 77 mg (72 %), MS (ESI) m/z: 338.1 [M+H]+.

Example 45

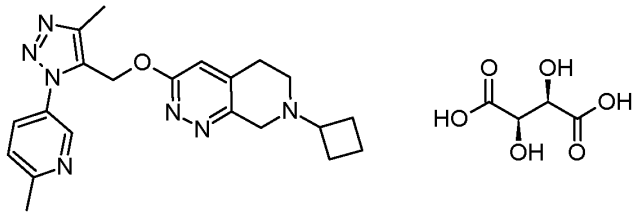
5-[5-({[7-(cyclobutylmethyl)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl]oxy}methyl)-4-methyl-1H-1,2,3-triazol-1-yl]-2-methylpyridine tartarate salt



The free base of the title compound prepared according to the procedure described for Example 18, Step A using 2-methyl-5-[4-methyl-5-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1H-1,2,3-triazol-1-yl]pyridine (Example 44) and commercially available cyclobutanecarboxaldehyde. MS (ESI) m/z: 406.3 $[M+H]^+$. The tartarate salt prepared according to the procedure described for Example 19 in Step B. MS (ESI) m/z: 406.3 $[M+H]^+$. ^1H NMR (DMSO-d_6, 500 MHz) δ (ppm): 8.67 (d, J=2.5 Hz, 1H), 7.97 (dd, J=8.3 Hz, 2.6 Hz, 1H), 7.49 (d, J=8.3 Hz, 1H), 6.96 (s, 1H), 5.53 (s, 2H), 3.68 (s, 2H), 2.80 (t, J=5.8 Hz, 2H), 2.64 (t, J=5.9 Hz, 2H), 2.55-2.62 (m, 1H), 2.57 (d, J=7.0 Hz, 2H), 2.56 (s, 3H), 2.41 (s, 3H), 2.00-2.08 (m, 2H), 1.75-1.93 (m, 2H), 1.64-1.73 (m, 2H); tartarate (acid/base ratio 1:1) signal: 4.28 (s, 2H).

Example 46

5-{5-[({7-cyclobutyl-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl}oxy)methyl]-4-methyl-1H-1,2,3-triazol-1-yl}-2-methylpyridine tartarate salt



The free base of the title compound prepared according to the procedure described for Example 18, Step A using 2-methyl-5-[4-methyl-5-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1H-1,2,3-triazol-1-yl]pyridine (Example 44) and commercially available cyclobutanone. MS (ESI) m/z: 392.2 $[M+H]^+$. The tartarate salt prepared according to the procedure described for Example 19 in Step B. MS (ESI) m/z: 392.2 $[M+H]^+$. ^1H NMR (DMSO-d_6, 500 MHz) δ (ppm): 8.67 (d, J=2.5 Hz, 1H), 7.98 (dd, J=8.3 Hz, 2.6 Hz, 1H), 7.50 (d, J=8.3 Hz, 1H), 6.97 (s, 1H), 5.53 (s, 2H), 3.58 (s, 2H), 2.95 (qui, J=7.6 Hz, 1H), 2.81 (br t, J=5.8 Hz, 2H), 2.57 (s, 3H), 2.52 (br t, J=5.8 Hz, 2H), 2.41 (s, 3H), 2.03-2.11 (m, 2H), 1.82-1.91 (m, 2H), 1.63-1.71 (m, 2H); tartarate (acid/base ratio 1:1) signal: 4.28 (s, 2H).

Pharmaceutical preparation examples

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	q.s.
Osmotic agent	0 – 50%
Preservatives	q.s.

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	q.s.

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	q.s.

VII., Eye drops

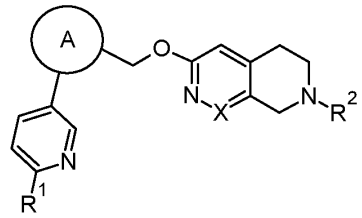
Active ingredient(s)	0.01 – 50%
Water	0 – 99.9%
Solvent	0 – 99.9%
Osmotic agent	0 – 20%
Viscosity enhancer	0 – 20%
Buffering agent	q.s.
Preservatives	q.s.

VIII., Nasal drops or spray

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

Claims

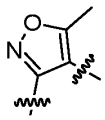
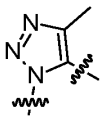
1. A compound of formula (I)



(I)

wherein

A is represented by

 group, or  group;

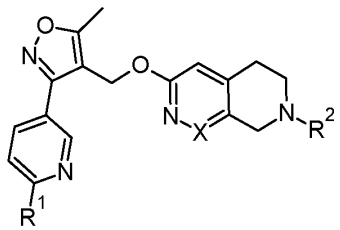
R^1 is an alkyl, an alkoxy, or a haloalkyl group;

R^2 is hydrogen; an alkyl group optionally substituted with $-S(O)_2$-alkyl, cycloalkyl or heterocycle; a cycloalkyl group; a heterocycle group optionally substituted with an alkyl; or a heteroaryl group;

X is CH, or N;

and/or salts thereof and/or stereoisomers thereof and/or enantiomers thereof and/or racemates thereof or diastereomers thereof and/or biologically active metabolites thereof or prodrugs thereof or solvates thereof or hydrates thereof and/or polymorphs thereof.

2. The compound according to claim 1,



(I-a)

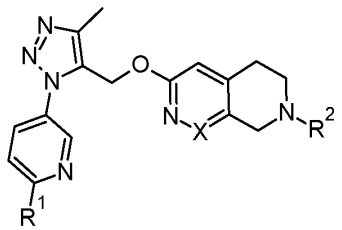
wherein

R^1 is an alkyl, an alkoxy, or a haloalkyl group;

R^2 is hydrogen; an alkyl group optionally substituted with -$S(O)_2$-alkyl, cycloalkyl or heterocycle; a cycloalkyl group; a heterocycle group optionally substituted with an alkyl; or a heteroaryl group;

X is CH, or N.

3. The compound according to claim 1,



(I-b)

wherein

R^1 is an alkyl, an alkoxy, or a haloalkyl group;

R^2 is hydrogen; an alkyl group optionally substituted with -$S(O)_2$-alkyl, cycloalkyl or heterocycle; a cycloalkyl group; a heterocycle group optionally substituted with an alkyl; or a heteroaryl group;

X is CH, or N.

4. The compound according to any one of claims 1 to 3, wherein

R^1 is a C_{1-6}alkyl, a C_{1-6}alkoxy, or a halo-C_{1-6}alkyl group;

R^2 is hydrogen; a C_{1-6}alkyl group optionally substituted with -$S(O)_2$-C_{1-6}alkyl, C_{3-7}cycloalkyl or a monovalent saturated or partly unsaturated monocyclic, bicyclic, fused, bridged or spiro ring system of 3 to 10 ring atoms comprising 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon; a C_{3-7}cycloalkyl group; a monovalent saturated or partly unsaturated monocyclic, bicyclic, fused, bridged or spiro ring system of 3 to 10 ring atoms comprising 1, 2, 3 or 4 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon optionally substituted with a C_{1-6}alkyl; or a monovalent, heterocyclic aromatic, mono- or bicyclic ring system of 5 to 10 ring atoms,

comprising 1, 2 or 3 heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon;

X is CH or N.

5. The compound according to any one of claims 1 to 4, wherein R^1 is a C_{1-4}alkyl, a C_{1-4}alkoxy, or a halo-C_{1-4}alkyl group.

6. The compound according to any one of claims 1 to 5, wherein R^1 is a C_{1-2}alkyl, a C_{1-2}alkoxy, or a halo-C_{1-2}alkyl group.

7. The compound according to any one of claims 1 to 6, wherein R^2 is hydrogen; a C_{1-4}alkyl group optionally substituted with -$S(O)_2$-C_{1-4}alkyl, a C_{4-6}cycloalkyl or a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising 1, or 2 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon; a C_{4-6}cycloalkyl group; a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising 1, or 2 ring heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon optionally substituted with a C_{1-4}alkyl; or a monovalent, heterocyclic aromatic, monocyclic ring system of 5 to 6 ring atoms, comprising 1, or 2 heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon.

8. The compound according to any one of claims 1 to 7, wherein R^2 is hydrogen; a C_{1-4}alkyl group optionally substituted with -$S(O)_2$-C_{1-2}alkyl, C_{4-6}cycloalkyl or a a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising one ring heteroatom selected from O and S, the remaining ring atoms being carbon; a C_{4-6}cycloalkyl group; a monovalent saturated monocyclic ring of 3 to 7 ring atoms comprising one ring heteroatom selected from O and S, the remaining ring atoms being carbon optionally substituted with a C_{1-4}alkyl; or a monovalent, heterocyclic aromatic, monocyclic ring system of 6 ring atoms, comprising 1, or 2 heteroatoms independently selected from N, O and S, the remaining ring atoms being carbon.

9. The compound according to any one of claims 1 to 8, wherein R^2 is hydrogen.

10. The compound according to any one of claims 1 to 9, wherein X is CH.

11. The compound according to any one of claims 1 to 9, wherein X is N.

12. The compound according to any one of claims 1 to 11 selected from the group consisting of

6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-methyl-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-cyclobutyl-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-(cyclobutylmethyl)-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-cyclopentyl-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxetan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-(1-methanesulfonylpropan-2-yl)-6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(pyridin-2-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-methyl-5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]pyridine,

5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine,

2-methyl-5-{5-methyl-4-[({7-methyl-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl}oxy)methyl]-1,2-oxazol-3-yl}pyridine,

5-[5-methyl-4-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine,

5-[5-methyl-4-({[7-(oxolan-3-yl)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl]oxy}methyl)-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine,

3-{[3-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl]methyl}-1lambda6-thiolane-1,1-dione,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-methyl-6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(propan-2-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-2-methyl-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(propan-2-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-methyl-6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-2-(propan-2-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1H-1,2,3-triazol-5-yl}methoxy)-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxetan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(oxolan-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[1-(6-methoxypyridin-3-yl)-4-methyl-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

3-{[6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl]methyl}-1lambda6-thiolane-1,1-dione,

6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-2-(pyridin-3-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-[(3S)-oxolan-3-yl]-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-[(3R)-oxolan-3-yl]-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[1-(6-methoxypyridin-3-yl)-4-methyl-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxan-4-yl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(2-methylpropyl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-[3-(propan-2-yl)oxetan-3-yl]-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-(3-ethyloxetan-3-yl)-6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine,

2-methyl-5-[4-methyl-5-({5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yloxy}methyl)-1H-1,2,3-triazol-1-yl]pyridine,

5-[5-({[7-(cyclobutylmethyl)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl]oxy}methyl)-4-methyl-1H-1,2,3-triazol-1-yl]-2-methylpyridine, and

5-{5-[({7-cyclobutyl-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl}oxy)methyl]-4-methyl-1H-1,2,3-triazol-1-yl}-2-methylpyridine

and/or salts thereof and/or stereoisomers thereof and/or enantiomers thereof and/or racemates thereof or diastereomers thereof and/or biologically active metabolites thereof or prodrugs thereof or solvates thereof or hydrates thereof and/or polymorphs thereof.

13. The compound according to any one of claims 1 to 12, for use as medicament.

14. The compound according to any one of claims 1 to 12, for use in the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

15. The compound according to claim 14, for use wherein the disease related to the $GABA_A$ α5 receptor is selected from the group consisting of a neurodevelopmental disorder, a neurodegenerative disorder, a neurocognitive disorder, schizophrenia, a mood disorder, a pain disorder, a substance-related and addictive disorder and other disease.

16. The compound according to claim 15, for use wherein the disease related to the $GABA_A$ α5 receptor is selected from the group consisting of autism spectrum disorder (ASD), Angelman syndrome, Fragile X disorder, Prader-Willi syndrome, Rett syndrome, Alzheimer's disease (AD), cognition deficiency disorders, memory deficits, age-associated memory impairment or cognitive decline, dementia, mild cognitive impairment (MCI), bipolar disorders, negative and/or cognitive symptoms associated with schizophrenia, epilepsy, post-traumatic stress disorder, amyotrophic lateral sclerosis.

17. The compound according to any one of claims 1 to 12 in combination with one or more other active ingredients, for use in the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

18. Use of a compound according to any one of claims 1 to 12, for the manufacture of a medicament for the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

19. The use according to claim 18, wherein the disease related to the $GABA_A$ α5 receptor is selected from the group consisting of a neurodevelopmental disorder, a neurodegenerative disorder, a neurocognitive disorder, schizophrenia, a mood disorder, a pain disorder, a substance-related and addictive disorder and other disease.

20. The use according to claim 19, wherein the disease related to the $GABA_A$ α5 receptor is selected from the group consisting of autism spectrum disorder (ASD), Angelman syndrome, Fragile X disorder, Prader-Willi syndrome, Rett syndrome, Alzheimer's disease (AD), cognition deficiency disorders, memory deficits, age-associated memory impairment or cognitive decline, dementia, mild cognitive impairment (MCI), bipolar disorders, negative and/or cognitive symptoms associated with schizophrenia, epilepsy, post-traumatic stress disorder, amyotrophic lateral sclerosis.

21. Use of a compound according to any one of claims 1 to 12 in combination with one or more other active ingredients, for the manufacture of a medicament for the treatment or prevention of diseases related to the $GABA_A$ α5 receptor.

22. A method of treating or preventing a disease related to the $GABA_A$ α5 receptor, comprising administering to a subject in need of such treatment or prevention an effective amount of at least one compound according to any one of claims 1 to 12.

23. The method according to claim 22, wherein the disease related to the $GABA_A$ α5 receptor is selected from the group consisting of a neurodevelopmental disorder, a neurodegenerative disorder, a neurocognitive disorder, schizophrenia, a mood disorder, a pain disorder, a substance-related and addictive disorder and other disease.

24. The method according to claim 23, wherein the disease related to the $GABA_A$ α5 receptor is selected from the group consisting of autism spectrum disorder (ASD), Angelman syndrome, Fragile X disorder, Prader-Willi syndrome, Rett syndrome, Alzheimer's disease (AD), cognition deficiency disorders, memory deficits, age-associated memory impairment or cognitive decline, dementia, mild cognitive impairment (MCI), bipolar disorders, negative and/or cognitive symptoms associated with schizophrenia, epilepsy, post-traumatic stress disorder, amyotrophic lateral sclerosis.

25. A method of treating or preventing a disease related to the $GABA_A$ α5 receptor comprising administering to a subject in need of such treatment or prevention an effective amount of at least one compound according to any one of claims 1 to 12 in combination with one or more other active ingredients.

26. A pharmaceutical composition comprising as active ingredient at least one compound according to any one of claims 1 to 12 and at least one physiologically or pharmaceutically acceptable excipient.

27. The pharmaceutical composition according to claim 26, wherein the composition further comprises one or more other active ingredients.

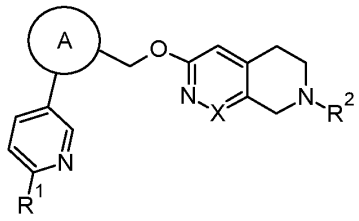
28. The pharmaceutical composition according to claim 26 or 27, for use in the treatment or prevention of a disease related to the $GABA_A$ α5 receptor.

29. The pharmaceutical composition according to claim 28, for use wherein the disease related to the $GABA_A$ α5 receptor is selected from the group consisting of a neurodevelopmental disorder, a neurodegenerative disorder, a neurocognitive disorder, schizophrenia, a mood disorder, a pain disorder, a substance-related and addictive disorder and other disease.

30. The pharmaceutical composition according to claim 29, for use wherein the disease related to the $GABA_A$ α5 receptor is selected from the group consisting of autism spectrum disorder (ASD), Angelman syndrome, Fragile X disorder, Prader-Willi syndrome, Rett

syndrome, Alzheimer's disease (AD), cognition deficiency disorders, memory deficits, age-associated memory impairment or cognitive decline, dementia, mild cognitive impairment (MCI), bipolar disorders, negative and/or cognitive symptoms associated with schizophrenia, epilepsy, post-traumatic stress disorder, amyotrophic lateral sclerosis.

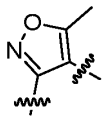
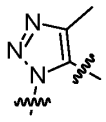
31. A compound of formula (I''),



(I'')

wherein

A is represented by

 group, or  group;

R^1 is an alkyl, an alkoxy, or a haloalkyl group;

R^2 is an amino protecting group;

X is CH or N;

with the proviso that the compound is not

tert-butyl 6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate, or

tert-butyl 6-({5-methyl-3-[6-(trifluoromethyl)pyridin-5 3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate.