NAPHTHYRIDINE AND PYRIDO[3,4-*c*]PYRIDAZINE DERIVATIVES AS $GABA_A$ 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 Cl^--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 (α5$GABA_A$Rs) 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.

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. In addition, SH-053-2'F-R-CH3 and MP-III-022 reversed 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 irritability. 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 these 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 α5, β3 and γ3 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 Gabra$\alpha 5^{-/-}$ and RDX, the genes for the α5$GABA_AR$ and its anchoring protein

radixin, further supporting a α5GABA$_A$R 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 α5GABA$_A$R selective tracer [^{11}C]Ro154513 across multiple brain regions suggesting reduced level of α5GABA$_A$R 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 α5GABA$_A$R (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 α5 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 α5GABA$_A$R 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 α5GABA$_A$R 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 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 under 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 (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; Gill et al., *Neuropsychopharmacology* 2011, 36:1903-1911; Hauser et al., *Mol Psychiatry* 2005, 10:201-207; 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 (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),

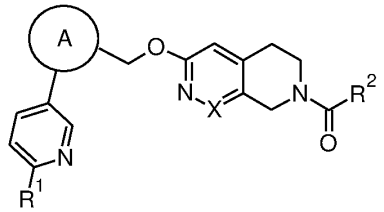
Alzheimer's disease related neuropsychiatric symptoms (Xu et al., *Psychopharmacology* 2018, 235:1151-1161), stroke (Clarkson et al., *Nature* 2010, 468:305-309; Lake et al., *J Cereb Blood Flow Metab* 2015, 35:1601-1609), neuropathic pain (Hérnandez-Reyes et al., *Pain* 2019, 160:1448-1458) and inflammatory 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). 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

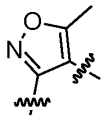
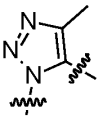
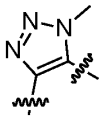
The present invention provides compounds of formula (I)



(I)

wherein

A is represented by

 group,  group, or  group,

R^1 is a C_{1-4}alkyl or halo-C_{1-4}alkyl group,

R^2 is a C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{1-4}alkyl-$S(O)_2$-C_{1-4}alkyl, C_{1-4}alkoxy, C_{3-7}cycloalkyl, C_{6-10}aryl, optionally substituted C_{3-10}heterocycle, C_{5-10}heteroaryl, or NR^3R^4 group wherein R^3 and R^4 is each independently H, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-10}heterocycle group,

X is CH or N

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

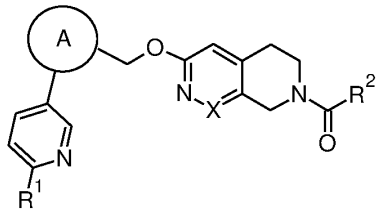
The present invention provides a process for the manufacture of the compounds of formula (I), as defined above and intemediates of the preparation process as well.

The present invention also provides a 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

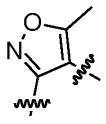
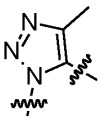
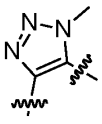
The present invention provides compounds of formula (I) having affinity and selectivity for the alpha 5 subunit-containing gamma-aminobutyric acid A receptor ($GABA_A$ α5 receptor) and act as $GABA_A$ α5 receptor positive allosteric modulators, thereby useful in the treatment or prevention of diseases 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)



wherein

A is represented by

 group,  group, or  group,

R^1 is a C_{1-4}alkyl or halo-C_{1-4}alkyl group,

R^2 is a C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{1-4}alkyl-$S(O)_2$-C_{1-4}alkyl, C_{1-4}alkoxy, C_{3-7}cycloalkyl, C_{6-10}aryl, optionally substituted C_{3-10}heterocycle, C_{5-10}heteroaryl, or NR^3R^4 group wherein R^3 and R^4 is each independently H, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-10}heterocycle group,

X is CH or N

and/or salts thereof and/or stereoisomers thereof and/or enantiomers thereof and/or racemates thereof and/or diastereomers thereof and/or biologically active metabolites thereof and/or prodrugs thereof and/or solvates thereof and/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 "C_{1-4}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 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 preferred. Methyl group is most preferred.

The term "C_{1-4}alkoxy" refers alone or in combination with other groups to -O-C_{1-4}alkyl group, wherein the C_{1-4}alkyl is as defined above. Examples include, but are not limited to, methoxy, ethoxy, *i*-propoxy, *n*-propoxy or *t*-butoxy.

The term "C_{1-4}alkyl-$S(O)_2$-C_{1-4}alkyl" refers alone or in combination with other groups to C_{1-4}alkyl group substituted with -$S(O)_2$-C_{1-4}alkyl wherein any C_{1-4}alkyl is as defined above. Preferred is methylsulfonylmethane or ethylsulfonylmethane group.

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 fluoro (fluorine).

The term "halo-C_{1-4}alkyl" refers alone or in combination with other groups to a C_{1-4}alkyl as defined above substituted with one or more identical or different halogens on any carbon atoms of said C_{1-4}alkyl, including vicinal and/or germinal halo-substitutions as well, such as perhaloalkyl groups. The term "perhaloalkyl" refers to a C_{1-4}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 monohalo-C_{1-4}alkyl groups, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, difluoromethyl or trifluoromethyl. Preferred halo-C_{1-4}alkyl group is a halo-methyl group, more preferably difluoromethyl or trifluoromethyl, most preferably trifluoromethyl.

The term "C_{3-7}cycloalkyl group" refers to monovalent monocyclic saturated carbocyclic groups comprising 3 to 7 carbon ring atoms. Examples include cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane. C_{3-4}cycloalkyl groups are preferred.

The term "C_{6-10}aryl group" refers to monovalent, mono- or bicyclic aromatic carbocyclic groups comprising 6 to 10 carbon ring atoms. Bicyclic aryl groups comprise at least one aromatic carbocyclic group. Examples include phenyl, dihydro-indene, indene, naphthyl, dialin, tetralin, anthryl, azulenyl, indanyl and the like. Phenyl is preferred.

The term "C_{3-10}heterocyclic group" 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. C_{4-6}heterocyclic groups comprising 1 or 2 ring heteroatoms independently selected from N, O and S are preferred.

The term "C_{5-10}heteroaryl group" 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. C_{5-6}heteroaryl groups comprising 1 or 2 ring heteroatoms independently selected from N, O and S are preferred.

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

The term "salt" refers to pharmaceutically acceptable and/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, 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. These salts often exhibit more favorable solubility properties than the compounds used for their preparation and are therefore more suitable for use in the preparation of various pharmaceutical formulations.

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. Such decomposing groups associated with the compounds of formula (I) of the present invention, in particular those suitable for prodrugs, are known in the art and may also be applied for the compounds of the present invention (Rautio et al., *Nature Reviews - Drug Discovery* 2008, 7:255-270).

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 liposomes transfer the active agent selectively to the target organ, which absorbs it.

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. The dose required to achieve the appropriate therapeutic effect may vary widely and must always be adapted to individual needs with regard to the degree of disease, the condition and weight of

the patient being treated and the sensitivity to the active ingredient, the way of dosage regimen and the numbers of daily treatments.

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 0.01 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.

Another embodiment of the present invention relates to the use of special binders that can improve the solubility, dissolution, penetration, absorption or bioavailability of the active ingredient(s), such as, but not limited to, hydrophilic polymers, hot melting extruding excipients, surfactants, buffering agents, complexing agents, emulsifying agents, lyophilization excipients, disintegrants, microencapsulating agents, penetration promoters, solubilizers, cosolvents, 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 ”diseases related to the $GABA_A$ α5 receptor” refers to diseases, conditions or 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 diseases include, but not limited to, neurodevelopmental disorders, neurodegenerative disorders, neurocognitive disorders, schizophrenia, mood disorders, pain disorders, substance-related and addictive disorders 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), bipolar disorders, 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, or bronchoconstrictive diseases (such as asthma, chronic obstructive pulmonary disease, and bronchopulmonary dysplasia).

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), bipolar disorders, 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, or bronchoconstrictive diseases (such as asthma, chronic obstructive pulmonary disease, and bronchopulmonary dysplasia).

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 diseases 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 diseases 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 neurodevelopmental disorders, neurodegenerative disorders, neurocognitive disorders, schizophrenia, mood disorders, pain disorders, substance-related and addictive disorders or other diseases, 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 neurodevelopmental disorders, neurodegenerative disorders, neurocognitive disorders, schizophrenia, mood disorders, pain disorders, substance-related and addictive disorders or other diseases, 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 neurodevelopmental disorders, neurodegenerative disorders, neurocognitive disorders, schizophrenia, mood disorders, pain disorders, substance-related and addictive disorders or other diseases, 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.

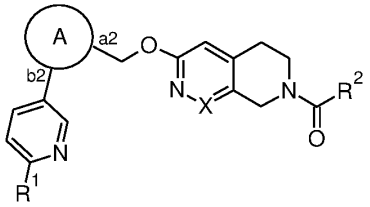
The term “treatment” refers to the alleviation of a specific pathological condition, the elimination or reduction of one or more of the symptoms of the condition, the slowing or elimination of the progression of the disease state, and the prevention or delay of recurrency of the pathological condition 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 stereoisomers thereof and/or enantiomers thereof and/or racemates thereof and/or diastereomers thereof and/or biologically active metabolites thereof and/or prodrugs thereof and/or solvates thereof and/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 exact therapeutically effective amount of the compound of formula (I), as defined above depends on a number of factors including, but not limited to, the age and body weight of the subject (patient), the precise type of disease requiring treatment and its seriousness, the nature of the medicinal product and the route of administration.

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.

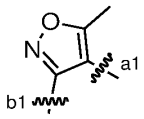
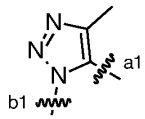
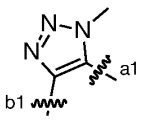
In one embodiment, the present invention relates to compounds of formula (I')



(I')

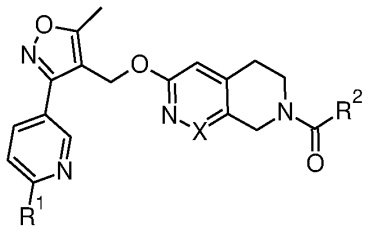
wherein

A is represented by

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

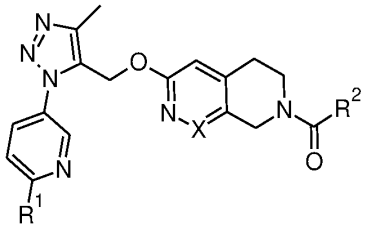
In one embodiment, the present invention relates to compounds of formula (I-a)



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

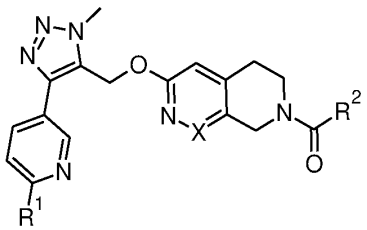
In one embodiment, the present invention relates to compounds of formula (I-b)



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

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



(I-c)

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

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^1 is a $C_{1\text{-}4}$alkyl group.

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

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is a C_{1-4}alkyl group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is a halo-C_{1-4}alkyl group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is a C_{1-4}alkyl-$S(O)_2$-C_{1-4} alkyl group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is a C_{1-4}alkoxy group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is a C_{3-7}cycloalkyl group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is a C_{6-10}aryl group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is an optionally substituted C_{3-10}heterocyclic group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is a C_{5-10}heteroaryl group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^2 is a NR^3R^4 group wherein R^3 and R^4 is each independently H, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-10}heterocycle group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^1 is a C_{1-2}alkyl or halo-methyl group, and R^2 is a C_{1-4}alkyl, halo-methyl, C_{1-2}alkyl-$S(O)_2CH_3$, C_{1-4}alkoxy, C_{3-5}cycloalkyl, phenyl, optionally substituted C_{4-6}heterocycle, C_{5-6}heteroaryl, or NR^3R^4 group wherein R^3 and R^4 is each independently H, C_{1-2}alkyl, C_{3-5}cycloalkyl or C_{4-7}heterocycle group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^1 is a methyl, difluoromethyl or trifluoromethyl group, and R^2 is a C_{1-4}alkyl, halo-methyl, C_{1-2}alkyl-$S(O)_2CH_3$, C_{1-4}alkoxy, C_{3-5}cycloalkyl, phenyl, optionally substituted C_{4-6}heterocycle, C_{5-6}heteroaryl, or NR^3R^4 group wherein R^3 and R^4 is each independently H, C_{1-2}alkyl, C_{3-5}cycloalkyl or C_{4-6}heterocycle group.

In one embodiment, the present invention relates to compounds of formula (I) wherein R^1 is a methyl, difluoromethyl or trifluoromethyl group, and R^2 is a methyl, fluoromethyl, trifluoromethyl, methylsulfonylmethane, *tert*-butoxy, C_{3-4}cycloalkyl, phenyl, optionally

substituted C_{4-6}heterocycle comprising 1 or 2 ring heteroatoms independently selected from N, O and S, C_{5-6}heteroaryl comprising 1 or 2 ring heteroatoms independently selected from N, O and S, or NR^3R^4 group wherein R^3 and R^4 is each independently H, methyl, C_{3-4}cycloalkyl or C_{5-6}heterocycle group.

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

1-[6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl]ethanone,

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,

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

1-[6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl]ethanone,

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

2-cyclopropanecarbonyl-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-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(pyridine-3-carbonyl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

4-(6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carbonyl)-1lambda6-thiane-1,1-dione,

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

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

2-cyclobutanecarbonyl-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-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxolane-3-carbonyl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

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

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

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

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

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

2-(3-methyl-1,2-oxazole-5-carbonyl)-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-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxane-3-carbonyl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

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

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

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

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

1-(3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl)ethan-1-one,

3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-N-(oxan-4-yl)-5H,6H,7H,8H-pyrido[3,4-c]pyridazine-7-carboxamide,

4-(3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-5H,6H,7H,8H-pyrido[3,4-c]pyridazine-7-carbonyl)morpholine,

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

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

1-(3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl)propan-1-one,

2-fluoro-1-(3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl)ethan-1-one,

2-methyl-1-(3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl)propan-1-one,

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

N-cyclopropyl-3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-5H,6H,7H,8H-pyrido[3,4-c]pyridazine-7-carboxamide,

1-[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]ethan-1-one,

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

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

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

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

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

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

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

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

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

2-cyclopropanecarbonyl-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-cyclobutanecarbonyl-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-(oxane-4-carbonyl)-1,2,3,4-tetrahydro-2,7-naphthyridine,

1-[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]ethan-1-one,

1-[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]propan-1-one,

2-fluoro-1-[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]ethan-1-one,

2-methyl-1-[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]propan-1-one,

2-cyclopropanecarbonyl-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,

1-[3-{[4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methoxy}-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl]ethanone,

1-[3-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1*H*-1,2,3-triazol-5-yl}methoxy)-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl]ethanone,

1-[3-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methoxy)-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl]ethanone,

1-[6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methoxy)-3,4 dihydro-2,7-naphthyridin-2(1*H*)-yl]ethanone,

1-[6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methoxy)-3,4 dihydro-2,7-naphthyridin-2(1*H*)-yl]propan-1-one,

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

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

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

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

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

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

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

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

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

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

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

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

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

1-(6-{[1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl]ethanone.

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

AcCN = acetonitrile

Cs_2CO_3 = cesium carbonate

DCM = dichloromethane

DIBAL-H = diisobutylaluminium hydride

DIPEA = *N*-ethyl-*N*-(propan-2-yl)propan-2-amine

DMF = *N,N*-Dimethylformamide

DMSO = dimethyl sulfoxide

K_2CO_3 = potassium carbonate

$LiAlH_4$ = lithium aluminium hydride

LiHMDS = lithium bis(trimethylsilyl)amide

$POCl_3$ = phosphorus oxychloride

TBAF = tetrabutylammonium fluoride

TBHP = *tert*-butyl hydroperoxide

Tf_2O = trifluoromethanesulfonic acid anhydride

THF = tetrahydrofuran

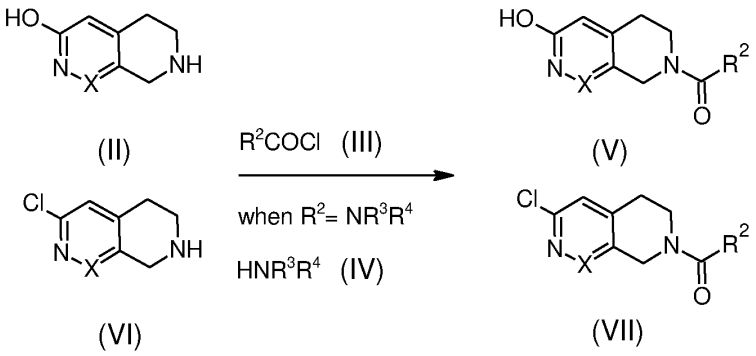
TLC = thin layer chromatography

brine = high-concentration solution of salt (usually sodium chloride)

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

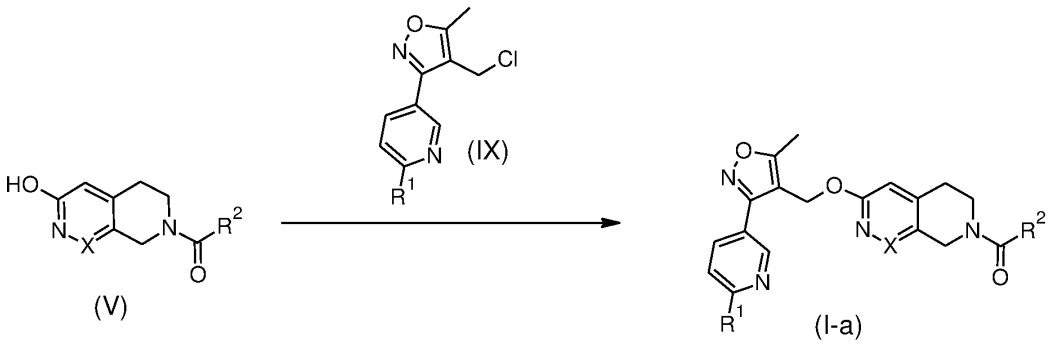
The present invention also relates to a process for the preparation of compounds of formula (I) as defined above, comprising:

(i) reacting amine derivatives of formula (II) or bicyclic amine derivatives of formula (VI) with R^2COCl of formula (III) wherein R^2 is a C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{1-4}alkyl-$S(O)_2$-C_{1-4}alkyl, C_{1-4}alkoxy, C_{3-7}cycloalkyl, C_{6-10}aryl, optionally substituted C_{3-10}heterocycle, C_{5-10}heteroaryl, or with HNR^3R^4 of formula (IV) wherein R^3 and R^4 is each independently H, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-10}heterocycle group to give the intermediates of formula (V) or (VII) wherein X and R^2 is as defined for formula (I)

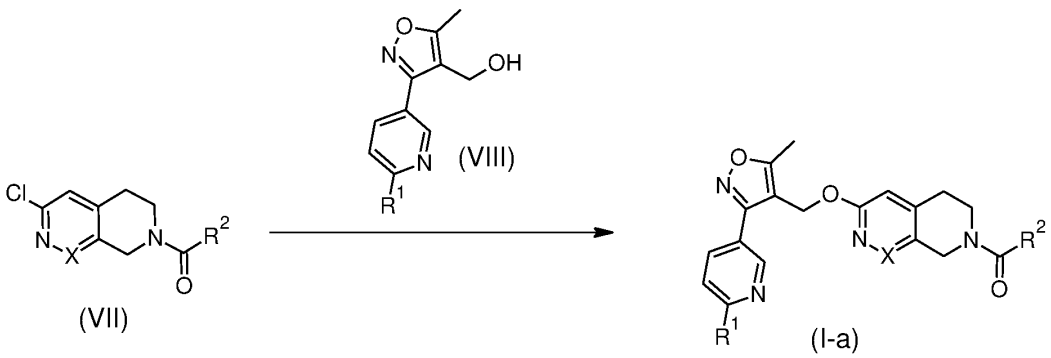


(ii) reacting the intermediates of formula (V) or (VII) with a compound of formula (VIII), (IX), (X), or (XI) to provide a compound of formula (I), according to step (a1), (a2), (b) or (c):

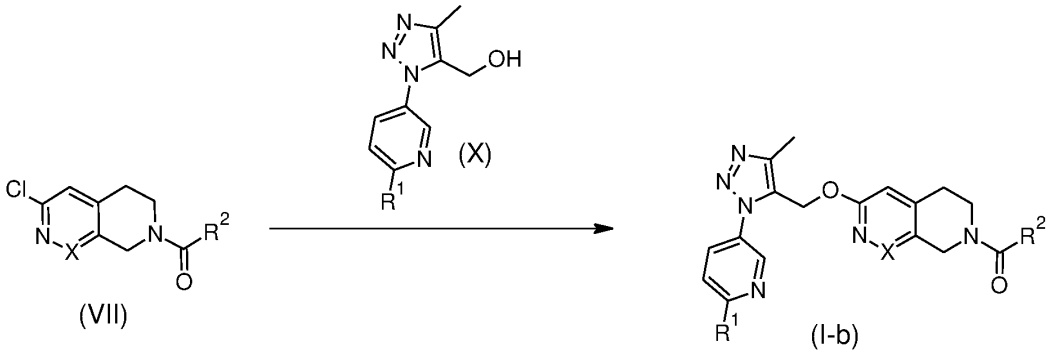
(a1) reacting a compound of formula (V) with a compound of formula (IX), to give a compound of formula (I-a), wherein X=CH and R^1 and R^2 are as defined above, or



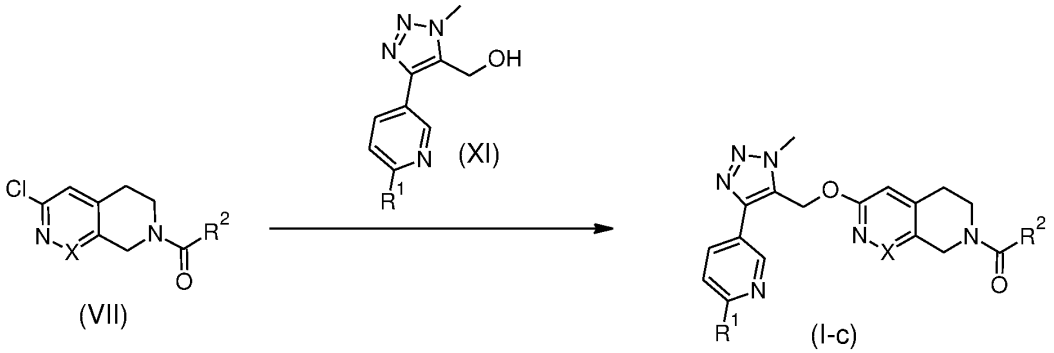
(a2) reacting a compound of formula (VII) with a compound of formula (VIII), to give a compound of formula (I-a), wherein X=N and R^1 and R^2 are as defined above, or



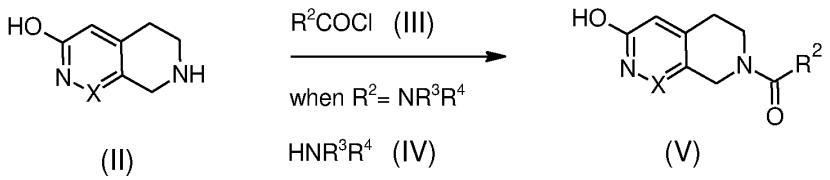
(b) reacting a compound of formula (VII) with a compound of formula (X), to give a compound of formula (I-b), wherein X, R^1 and R^2 are as defined above



(c) reacting a compound of formula (VII) with a compound of formula (XI), to give a compound of formula (I-c), wherein X, R^1 and R^2 are as defined above.



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, 2, and 3**.



Scheme 1

According to **Scheme 1**, acylation of commercially available bicyclic amine derivatives of formula (II) with R^2COCl of formula (III) in a suitable base, such as Et_3N provides the amide derivatives of formula (V); or when $R^2 = NR^3R^4$, amine derivatives of formula (II) can also be reacted with HNR^3R^4 of formula (IV) wherein R^3 and R^4 is as defined above, using triphosgene in the presence of a suitable base, such as DIPEA to form compound of formula (V). The acyl chlorides of formula (III) and amines of formula (IV) are commercially available or can be

prepared by conventional methods, wherein the definition of R^2 is the same as described above for formula (I).

In an 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 or N, and R^2 is a C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{1-4}alkyl-$S(O)_2$-C_{1-4}alkyl, C_{1-4}alkoxy, C_{3-7}cycloalkyl, C_{6-10}aryl, optionally substituted C_{3-10}heterocycle, C_{5-10}heteroaryl, or NR^3R^4 group wherein R^3 and R^4 is each independently H, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-10}heterocycle group; preferably R^2 is a C_{1-4}alkyl, halo-methyl, C_{1-2}alkyl-$S(O)_2CH_3$, C_{1-4}alkoxy, C_{3-5}cycloalkyl, phenyl, optionally substituted C_{4-6}heterocycle, C_{5-6}heteroaryl, or NR^3R^4 group wherein R^3 and R^4 is each independently H, C_{1-2}alkyl, C_{3-5}cycloalkyl or C_{4-7}heterocycle group; more preferably R^2 is a methyl, fluoromethyl, trifluoromethyl, methylsulfonylmethane, C_{3-4}cycloalkyl, phenyl, optionally substituted C_{4-6}heterocycle comprising 1 or 2 ring heteroatoms independently selected from N, O and S, C_{5-6}heteroaryl comprising 1 or 2 ring heteroatoms independently selected from N, O and S, or NR^3R^4 group wherein R^3 and R^4 is each independently H, methyl, C_{3-4}cycloalkyl or C_{5-6}heterocycle group. The compounds 2, 5, 6, 8-tetrahydro-3-oxo-pyrido[3,4-*c*]pyridazine-7(3*H*)-carboxylic acid ethyl ester; 2, 5, 6, 8-tetrahydro-3-oxo-pyrido[3,4-*c*]pyridazine-7(3*H*)-carboxylic acid methyl ester; 2, 5, 6, 8-tetrahydro-3-oxo-pyrido[3,4-*c*]pyridazine-7(3*H*)-carboxylic acid 1,1-dimethylethyl ester and 3, 4, 6, 7-tetrahydro-6-oxo-2,7-naphthyridine-2(1*H*)-carboxylic acid 1,1-dimethylethyl ester are known in the art (CN 102924452 A, WO 2006/065215 A1).

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

1-(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)ethanone,

1-(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-(methylsulfonyl)ethanone,

cyclopropyl(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methanone,

(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(pyridin-3-yl)methanone,

(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methanone,

(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(pyridin-4-yl)methanone,

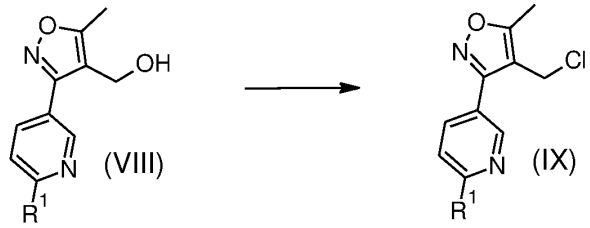
(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydro-2*H*-pyran-4-yl)methanone,

cyclobutyl(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methanone,

(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydrofuran-3-yl)methanone,

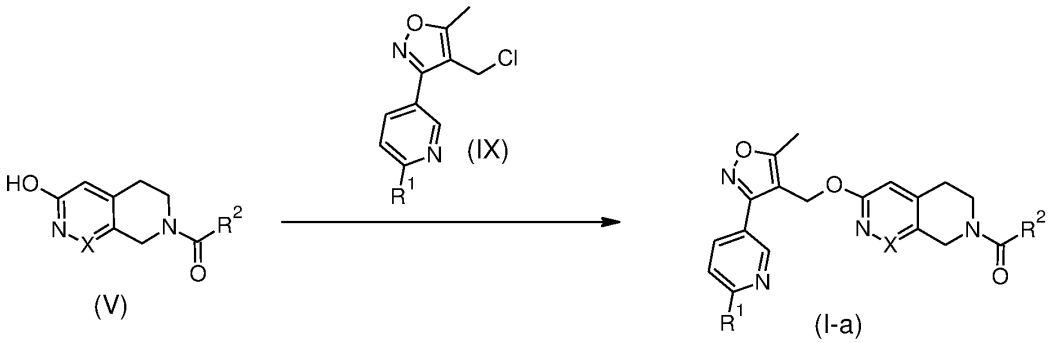
4-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-methylpyrrolidin-2-one,

4-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-(propan-2-yl)pyrrolidin-2-one,
(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(4-methyl-1,2-oxazol-5-yl)methanone,
(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(3-methyl-1,2-oxazol-5-yl)methanone,
(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydro-2*H*-pyran-3-yl)methanone,
5-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-methylpiperidin-2-one,
(5*R*)-5-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-methylpyrrolidin-2-one,
(5*S*)-5-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-methylpyrrolidin-2-one,
1-ethyl-4-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]pyrrolidin-2-one,
(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(pyrrolidin-1-yl)methanone, and
6-hydroxy-*N*,*N*-dimethyl-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxamide.



Scheme 2

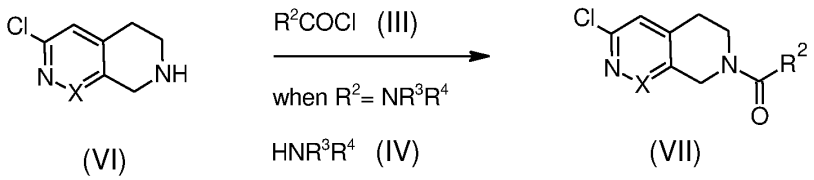
According to **Scheme 2**, reacting a compound of formula (VIII) with a chlorinating agent, such as $POCl_3$ provides intermediates of formula (IX). Both hydroxy derivatives of formula (VIII) and intermediates of formula (IX) are known in the art (WO 2018/104419 A1; WO 2019/238633 A1) or can be synthesized by conventional methods.



Scheme 3

According to **Scheme 3**, etherification between alcohols of formula (V) and intermediates of formula (IX) 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 (I-a).

The compounds of formula (I-a) wherein X=N and 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

According to **Scheme 4**, acylation of commercially available bicyclic amine derivatives of formula (VI) with R^2COCl of formula (III) in a suitable base, such as Et_3N provides the amide derivatives of formula (VII); or when $R^2 = NR^3R^4$, amine derivatives of formula (VI) can also be reacted with HNR^3R^4 of formula (IV) wherein R^3 and R^4 is as defined above using triphosgene in the presence of a suitable base, such as DIPEA to form compound of formula (VII). The acyl chlorides of formula (III) and amines of formula (IV) are commercially available or can be prepared by conventional methods, wherein the definition of R^2 is the same as described above for formula (I).

In an 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 CH or N and R^2 is a C_{1-4}alkyl, halo-C_{1-4}alkyl, C_{1-4}alkyl-$S(O)_2$-C_{1-4}alkyl, C_{1-4}alkoxy, C_{3-7}cycloalkyl, C_{6-10}aryl, optionally substituted C_{3-10}heterocycle, C_{5-10}heteroaryl, or NR^3R^4 group wherein R^3 and R^4 is each independently H, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-10}heterocycle group; preferably R^2 is a C_{1-4}alkyl, halo-methyl, C_{1-2}alkyl-$S(O)_2CH_3$, C_{1-4}alkoxy, C_{3-5}cycloalkyl, phenyl, optionally substituted C_{4-6}heterocycle, C_{5-6}heteroaryl, or NR^3R^4 group wherein R^3 and R^4 is each independently H, C_{1-2}alkyl, C_{3-5}cycloalkyl or C_{4-7}heterocycle group; more preferably R^2 is a methyl, fluoromethyl, trifluoromethyl, methylsulfonylmethane, C_{3-4}cycloalkyl, phenyl, optionally substituted C_{4-6}heterocycle comprising 1 or 2 ring heteroatoms independently selected from N, O and S, C_{5-6}heteroaryl comprising 1 or 2 ring heteroatoms independently selected from N, O and S, or NR^3R^4 group wherein R^3 and R^4 is each independently H, methyl, C_{3-4}cycloalkyl or C_{5-6}heterocycle group with the proviso when X is CH and R^2 is a 3-pyridinyl or [6-methyl-4-[(1-methylcyclopropyl)amino]furo[2,3-*d*]pyrimidin-5-yl] group; and when R^2 is a *tert*-butoxy group.

The compounds (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)[6-methyl-4-[(1-methylcyclopropyl)amino]furo[2,3-*d*]pyrimidin-5-yl]-methanone; (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-3-pyridinyl-methanone; 3-chloro-5,8-dihydro-pyrido[3,4-*c*]pyridazine-7(6*H*)-carboxylic acid 1,1-dimethylethyl ester; and 6-chloro-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylic acid 1,1-dimethylethyl ester are known in the art (WO 2019/104285 A1, US 2016/102088 A1, US 2017/057966 A1, WO 2012/129344 A1).

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

1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)ethanone,

1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-fluoroethanone,

1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-methylpropan-1-one,

1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2,2-dimethylpropan-1-one,

1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-3-methylbutan-1-one,

(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(phenyl)methanone,

1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)propan-1-one,

(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(cyclopropyl)methanone,

(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(cyclobutyl)methanone,

(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydro-2*H*-pyran-4-yl)methanone,

1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)ethanone,

(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)(morpholin-4-yl)methanone,

(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)(tetrahydro-2*H*-pyran-4-yl)methanone,

(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)(cyclopropyl)methanone,

1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)propan-1-one,

1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)-2-fluoroethanone,

1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)-2-methylpropan-1-one,

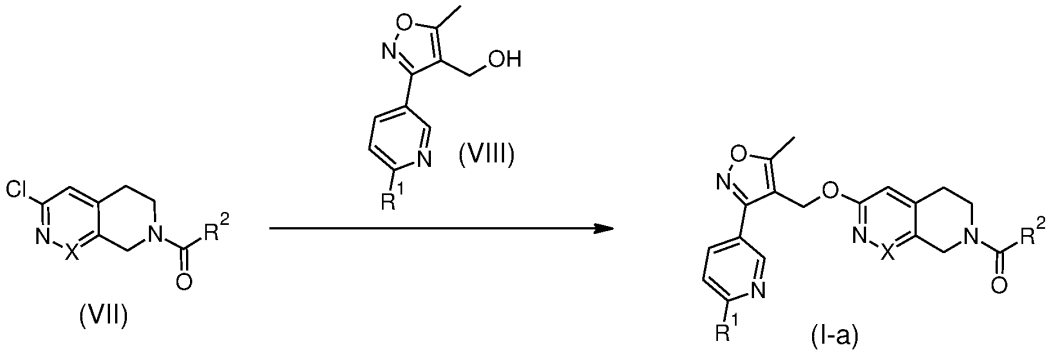
(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)(cyclobutyl)methanone,

1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)-2-(methylsulfonyl)ethanone,

1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)-2,2,2-trifluoroethanone,

3-chloro-*N*-(tetrahydro-2*H*-pyran-4-yl)-5,8-dihydropyrido[3,4-*c*]pyridazine-7(6*H*)-carboxamide, and

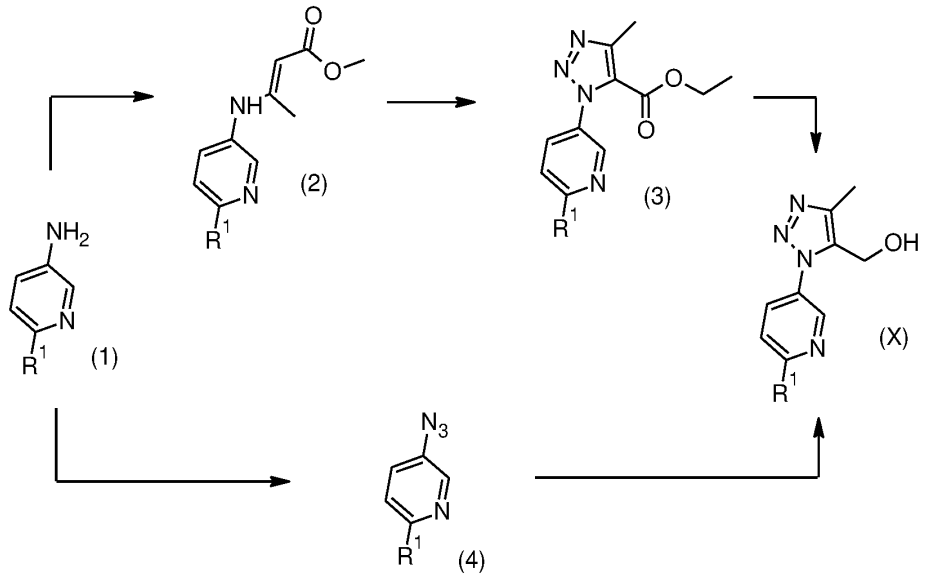
3-chloro-*N*-cyclopropyl-5,8-dihydropyrido[3,4-*c*]pyridazine-7(6*H*)-carboxamide.



Scheme 5

According to **Scheme 5**, etherification between amide derivatives of formula (VII) 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 (I-a).

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 6 and 7**.



Scheme 6

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 (4) with a

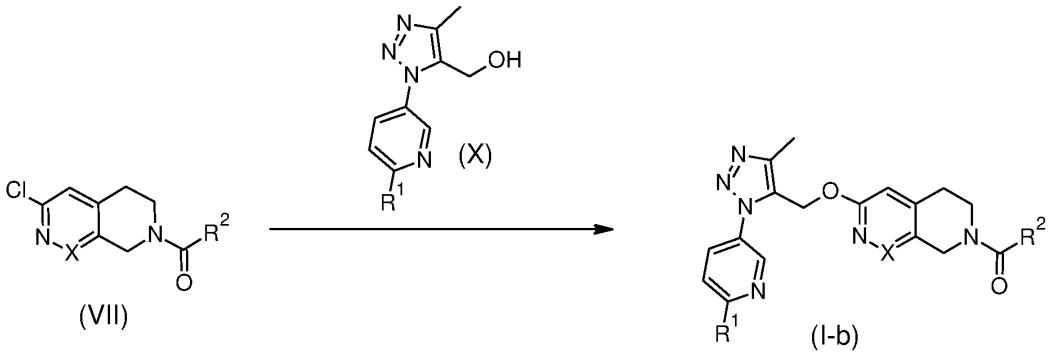
reducing agent such as DIBAL-H in a suitable solvent such as toluene gives a compound of formula (X). Alternatively, a compound of formula (1) is converted to a diazonium salt, which is further reacted with trimethylsilyl azide to give a compound of formula (4). Compounds of formula (4) reacted with 2-butyn-1-ol give a compound of formula (X).

In an aspect, the present invention provides novel intermediates of formula (X) synthesised in the process for preparing the compound of general formula (I) wherein R^1 is a C_{1-4}alkyl or halo-C_{1-4}alkyl group, preferably a C_{1-2}alkyl or halo-methyl group, more preferably the intermediate of formula (X) is

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

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

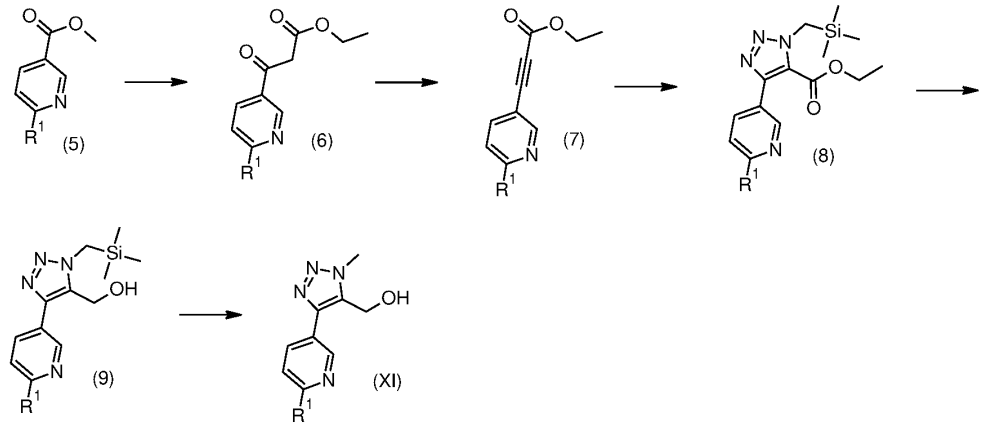
{1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methanol.



Scheme 7

According to **Scheme 7**, etherification between amide derivatives of formula (VII) and hydroxy derivatives of formula (X) 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 (I-b).

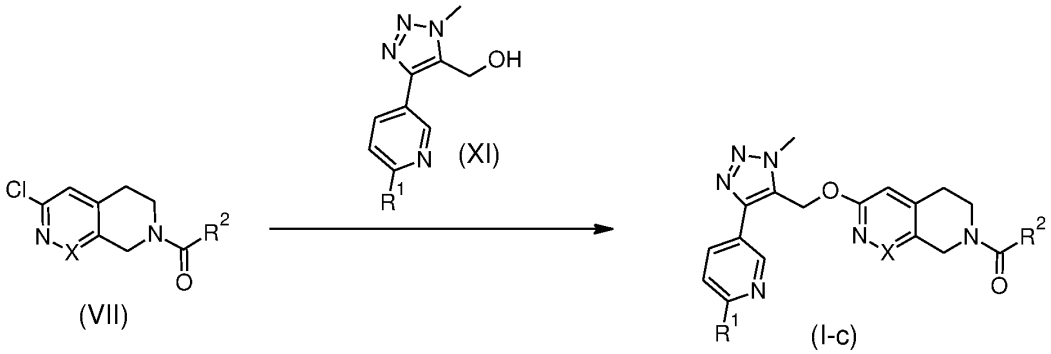
The compounds of formula (I-c) wherein X, R^1 and R^2 are as defined in any of the embodiments described above can be prepared according to **Scheme 8 and 9**.



Scheme 8

In a first step, a compound of formula (5) is reacted with ethyl acetate in a presence of a suitable base, such as LiHMDS to give a compound of formula (6) which then reacted with triphenylphosphine oxide and Tf_2O in the presence of a base, such as triethylamine in a suitable solvent, such as 1,2-dichloroethane to give a compound of formula (7). Compound of formula (7) reacted with trimethylsilylmethyl azide in the presence of a base, such as DIPEA in a suitable solvent, such as DMF gives a compound of formula (8). Treatment of a compound of formula (8) with a reducing agent such as $LiAlH_4$ in a suitable solvent such as THF gives a compound of formula (9), which treated with TBAF in a suitable solvent, such as THF gives a compound of formula (XI).

In an aspect, the present invention provides novel intermediates of formula (XI) synthesised in the process for preparing the compound of general formula (I) wherein R^1 is a C_{1-4}alkyl or halo-C_{1-4}alkyl group, preferably a C_{1-2}alkyl or halo-methyl group, most preferably a methyl, difluoromethyl or trifluoromethyl group. In one embodiment, the intermediate of formula (XI) is [1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methanol.



Scheme 9

According to **Scheme 9**, etherification between amide derivatives of formula (VII) and hydroxy derivatives of formula (XI) 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 (I-c).

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

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 (Ki< 100 nM).

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

Example	$hGABA_A$ α5 K_i (nM)	Example	$hGABA_A$ α5 K_i (nM)
1	1.7	34	8.1
2	38.0	37	7.9
4	9.7	38	6.6
5	3.5	39	30.0
7	6.0	41	48.0
8	16.0	43	20.0
9	10.0	44	22.0
10	17.0	47	25.0
12	7.2	48	33.0
15	8.3	49	15.0
16	11.0	50	44.0
20	9.0	51	31.0
21	5.7	53	99.1
22	9.4	55	1.1
23	6.9	56	1.6
24	2.3	57	0.9
26	13.0	60	22.0
27	10.0	62	33.0
28	4.4	63	43.0
29	6.0	65	52.0
30	1.9	68	9.1
31	4.3	70	37.2
33	2.2		

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 (125G, 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:

Example	$hGABA_A$ α5 efficacy (%)	Example	$hGABA_A$ α5 efficacy (%)
1	127	34	92
2	61	37	80
4	96	38	100
5	120	39	142
7	131	41	157
8	151	43	103
9	152	44	103
10	179	47	95
12	113	48	94
15	114	49	82
16	133	50	112
20	172	51	100
21	225	53	61
22	174	55	41
23	153	56	56
24	114	57	45
26	164	60	60
27	143	62	124
28	172	63	89
29	160	65	114
30	102	68	103
31	152	70	82
33	135		

Examples

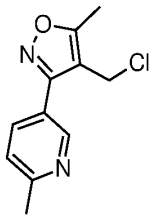
The present invention will be further illustrated by the following Intermediates and Examples without limiting the scope of the present invention to them. From the above description and from the Intermediates and Examples, the person skilled in the art may ascertain the essential features of the invention 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, such as the compounds of formula (II), (III), (IV), (VI), (1) and (5) 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

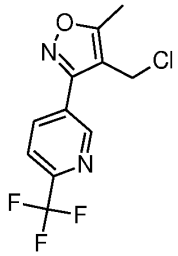
5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine



1.00 g (4.89 mmol) of [5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methanol (WO 2018/104419 A1) 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

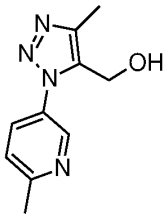
5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine



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

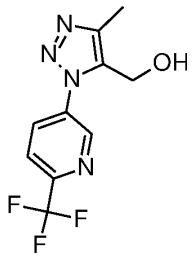
5.0 g (46 mmol) of commercially available 6-methylpyridine-3-amine was dissolved in a mixture of 14 mL of cc. HCl and 14 mL of water and cooled to 0 °C. 3.19 g (46.2 mmol) of $NaNO_2$ dissolved in 12 mL of water was added dropwise. The reaction mixture was stirred at 0 °C for 20 min then 10.6 mL (80 mmol) of trimethylsilyl 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

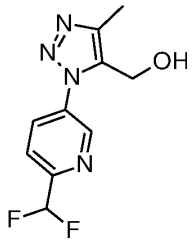
{4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1*H*-1,2,3-triazol-5-yl}methanol



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

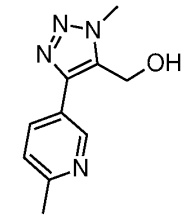
{1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methanol



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



a: ethyl 3-(6-methylpyridin-3-yl)-3-oxopropanoate

25 g (170 mmol) of commercially available methyl-6-methylnicotinate was dissolved in 97 mL (992 mmol) of ethyl acetate and cooled to -50°C under argon atmosphere. 165 mL of lithium bis(trimethylsilyl)amide (1M solution in THF) was added dropwise to the solution. The cooling bath was removed, and the mixture was allowed to warm up to room temperature. The conversion was checked by TLC (cyclohexane:EtOAc =1:1 as eluent, silica plate). The reaction mixture was washed with saturated sodium carbonate solution and with water, dried over anhydrous sodium sulfate, and evaporated. The obtained residue was purified by flash coloumn chromatography (silica gel, eluent: cyclohexane:EtOAc 50% gradient). Yield: 22.71 g (66 %). MS (ESI) m/z: 208.1 $[M+H]^+$.

b: ethyl 3-(6-methylpyridin-3-yl)prop-2-ynoate

Under argon atmosphere 25 g (90 mmol) of triphenylphosphine oxide was dissolved in 100 mL of 1,2-dichloroethane, cooled with an ice-water bath and 15.5 mL (92 mmol) of

trifluoromethanesulfonic acid anhydride was added dropwise. After stirring for 15 min, a solution of 7.94 g (38.3 mmol) of ethyl 3-(6-methylpyridin-3-yl)-3-oxopropanoate in 70 mL of 1,2-dichloroethane was added, followed by a dropwise addition of 25 mL (180 mmol) of triethylamine. After the addition completed the reaction mixture was refluxed for 1h. The conversion was checked by TLC (cyclohexane:EtOAc =1:1 as eluent, silica plate). The reaction mixture was washed with water, dried over anhydrous sodium sulfate, and evaporated. The obtained residue was purified by flash coloumn chromatography (silica gel, eluent: cyclohexane:EtOAc 50% gradient). Yield: 2.90 g (40 %). MS (ESI) m/z: 190.1 $[M+H]^+$.

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

To a suspension of 584 mg (3.07 mmol) of copper(I)iodide in 35 mL of DMF was added 2.61 mL (15.3 mmol) of DIPEA and 2.90 g (15 mmol) of ethyl 3-(6-methylpyridin-3-yl)prop-2-ynoate, then 11.6 g (90 mmol) of trimethylsilylmethyl azide was added at room temperature. The reaction mixture was stirred at 120°C for 3 h. The mixture was poured into water, extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate, and evaporated. The obtained residue was purified by flash coloumn chromatography (reversed phase silica gel, eluent: AcCN:H_2O 50% gradient). Yield: 1.53 g (31 %). MS (ESI) m/z: 319.2 $[M+H]^+$.

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

Under argon atmosphere 1.53 g (4.80 mmol) of ethyl 1-trimethylsilanylmethyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazole-5-carboxylate was dissolved in 30 mL of anhydrous THF and cooled to 0 °C. 179 mg (5.28 mmol) of $LiAlH_4$ was added in portions. After the addition completed, the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was poured into an ice-cooled solution of saturated sodium carbonate solution, ethyl acetate was added and filtrated over celite. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated in vacuo. The crude product was used in the next step without further purification. Yield: 1.25 g, (94 %), MS (ESI) m/z: 277.2 $[M+H]^+$.

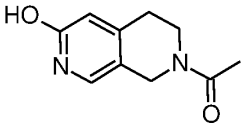
e: [1-methyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol

To a solution of 1.25 g (4.52 mmol) of [1- trimethylsilanylmethyl -4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol in 20 mL of THF, 1.42 g (5.06 mmol) of tetrabutylammonium fluoride hydrate was added dropwise at room temperature and stirred for 1 h. The THF was evaporated, the residue was dissolved in ethyl acetate and washed with water. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated in vacuo. Purification of the

residue by flash coloumn chromatography (silica gel, eluent: DCM:MeOH, 0-10% gradient) afforded the desired product. Yield: 0.48 g (52 %), MS (ESI) m/z: 205.1 $[M+H]^+$.

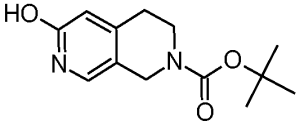
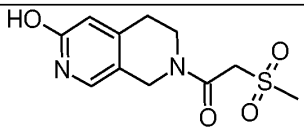
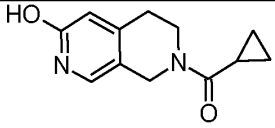
Intermediate 7

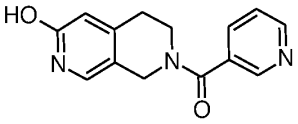
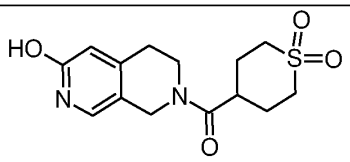
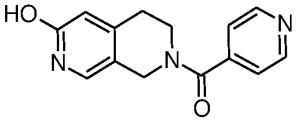
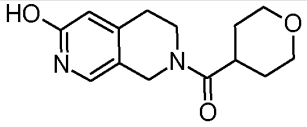
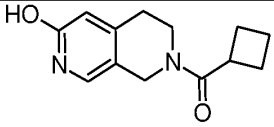
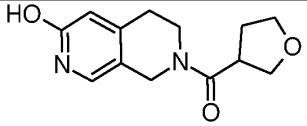
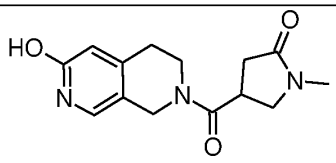
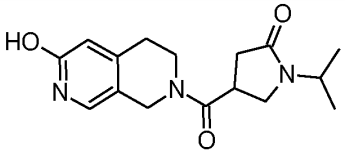
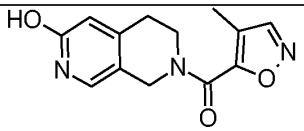
1-(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)ethanone

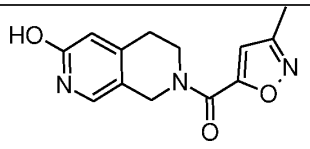
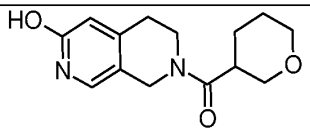
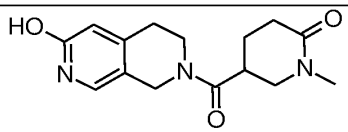
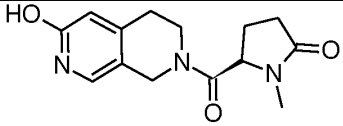
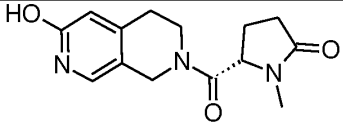
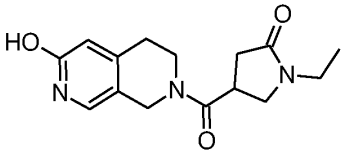
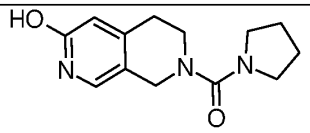
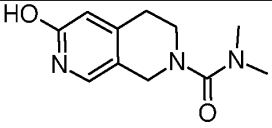


370 mg (2.46 mmol) of commercially available 5,6,7,8-tetrahydro-2,7-naphthyridin-3-ol was dissolved in 30 mL of anhydrous dichloromethane. 1.37 mL (9.85 mmol) of anhydrous triethyl amine was added in one portion to the solution, and the reaction mixture was cooled with an ice-water bath. A solution of 0.19 mL (2.46 mmol) of acetyl chloride in 5 mL of anhydrous dichloromethane was added dropwise to the stirred reaction mixture. The cooling bath was removed, and the mixture was allowed to warm up to room temperature. The conversion was checked by TLC (DCM:MeOH=95:5 as eluent, silica plate). The reaction mixture was evaporated and purified by flash coloumn chromatography (silica gel, eluent: DCM:MeOH, 0-5% gradient) afforded the desired product. Yield: 0.20 g (42 %), MS (ESI) m/z: 193.1 $[M+H]^+$.

Table 3 showing Intermediates synthesized according to the procedure described for intermediate 7.

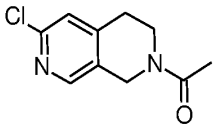
Intermediate	Structure	MS m/z $[M+H]^+$	Name
8		251.2	*tert*-butyl 6-hydroxy-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate
9		271.1	1-(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-(methylsulfonyl)ethanone
10		219.1	cyclopropyl(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methanone

11		256.1	(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(pyridin-3-yl)methanone
12		311.1	(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methanone
13		256.1	(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(pyridin-4-yl)methanone
14		263.1	(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydro-2*H*-pyran-4-yl)methanone
15		233.1	cyclobutyl(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methanone
16		249.1	(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydrofuran-3-yl)methanone
17		276.1	4-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-methylpyrrolidin-2-one
18		304.2	4-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-(propan-2-yl)pyrrolidin-2-one
19		260.1	(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(4-methyl-1,2-oxazol-5-yl)methanone

20		260.1	(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(3-methyl-1,2-oxazol-5-yl)methanone
21		263.1	(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydro-2*H*-pyran-3-yl)methanone
22		290.2	5-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-methylpiperidin-2-one
23		276.1	(5*R*)-5-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-methylpyrrolidin-2-one
24		276.1	(5*S*)-5-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-methylpyrrolidin-2-one
25		290.2	1-ethyl-4-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]pyrrolidin-2-one
26		248.1	(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(pyrrolidin-1-yl)methanone
27		222.1	6-hydroxy-*N*,*N*-dimethyl-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxamide

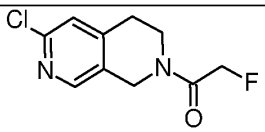
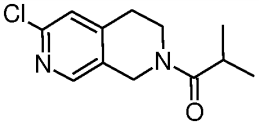
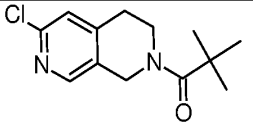
Intermediate 28

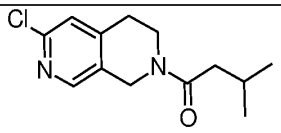
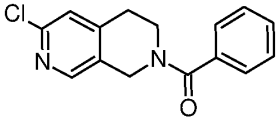
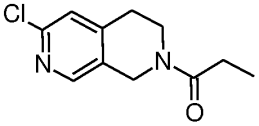
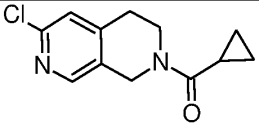
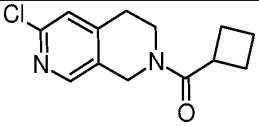
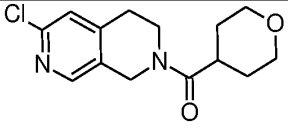
1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)ethanone



500 mg (2.44 mmol) of 6-chloro-1,2,3,4-tetrahydro-2,7-naphthyridine hydrochloride was dissolved in 30 mL of anhydrous dichloromethane. 542 mg (0.75 mL, 5.36 mmol) of anhydrous triethyl amine was added in one portion to the solution, and the reaction mixture was cooled with an ice-water bath. A solution of 191 mg (0.174 mL, 2.44 mmol) of acetyl chloride in 5 mL of anhydrous dichloromethane was added dropwise to the stirred reaction mixture during 10 minutes. The cooling bath was removed, and the mixture was allowed to warm up to room temperature. The conversion was checked by TLC (DCM:MeOH=95:5 as eluent, silica plate). The reaction mixture was washed with saturated sodium hydrogen carbonate solution and with water, dried over anhydrous sodium sulfate, and evaporated. Yield: 420 mg (82 %), white solid identical to the title compound. MS (ESI) m/z: 211.1 $[M+H]^+$.

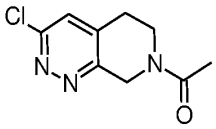
Table 4 showing Intermediates synthesized according to the procedure described for intermediate 28.

Intermediate	Structure	MS m/z $[M+H]^+$	Name
29		229.1	1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-fluoroethanone
30		239.1	1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-methylpropan-1-one
31		253.1	1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2,2-dimethylpropan-1-one

32		253.1	1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-3-methylbutan-1-one
33		273.1	(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(phenyl)methanone
34		225.1	1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)propan-1-one
35		237.1	(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(cyclopropyl)methanone
36		251.1	(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(cyclobutyl)methanone
37		281.1	(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydro-2*H*-pyran-4-yl)methanone

Intermediate 38

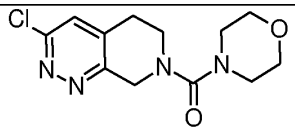
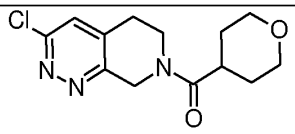
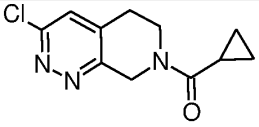
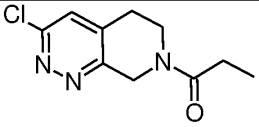
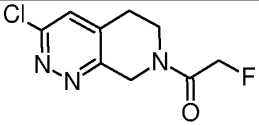
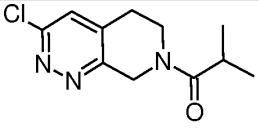
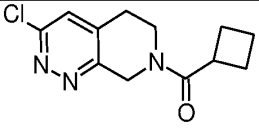
1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)ethanone

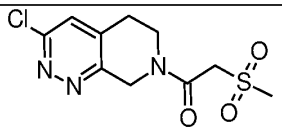
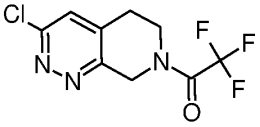


530 mg (2.57 mmol) of 3-chloro-5,6,7,8-tetrahydropyrido[3,4-*c*]pyridazine hydrochloride was dissolved in 20 mL of anhydrous dichloromethane. 520 mg (0.716 mL, 5.14 mmol) of anhydrous triethyl amine was added in one portion to the solution, and the reaction mixture was cooled with an ice-water bath. A solution of 264 mg (2.59 mmol) of acetyl chloride in 5 mL of anhydrous dichloromethane was added dropwise to the stirred reaction mixture during 10 minutes. The cooling bath was removed, and the mixture was allowed to warm up to room temperature. The conversion was checked by TLC (DCM:MeOH=9:1 as eluent, silica plate).

The reaction mixture was washed with saturated sodium hydrogen carbonate solution and with water, dried over anhydrous sodium sulfate, and evaporated. The crude product was purified by flash coloumn chromatography (silica gel, eluent: DCM:MeOH, 0-10% gradient) afforded the desired product. Yield: 340 mg (62.5 %), MS (ESI) m/z: 212.1 $[M+H]^+$.

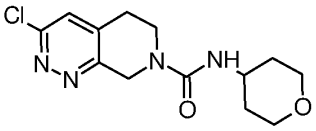
Table 5 showing Intermediates synthesized according to the procedure described for intermediate 38.

Intermediate	Structure	MS m/z $[M+H]^+$	Name
39		283.1	(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)(morpholin-4-yl)methanone
40		282.1	(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)(tetrahydro-2*H*-pyran-4-yl)methanone
41		238.1	(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)(cyclopropyl)methanone
42		226.1	1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)propan-1-one
43		230.1	1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)-2-fluoroethanone
44		240.1	1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)-2-methylpropan-1-one
45		252.1	(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)(cyclobutyl)methanone

46		290.1	1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)-2-(methylsulfonyl)ethanone
47		266.1	1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)-2,2,2-trifluoroethanone

Intermediate 48

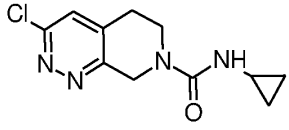
3-chloro-*N*-(tetrahydro-2*H*-pyran-4-yl)-5,8-dihydropyrido[3,4-*c*]pyridazine-7(6*H*)-carboxamide



To a solution of 125 mg (1.24 mmol) of 4-aminotetrahydropyran in 15 mL of anhydrous dichloromethane 528 mg (0.712 mL, 3.02 mmol) of DIPEA was added in one portion, and the reaction mixture was cooled with an ice-water bath, then 148 mg (0.50 mmol) of bis(trichloromethyl)carbonate was added in one portion. The so obtained solution was stirred for 30 minutes, then 230 mg (1.07 mmol) of 3-chloro-5,6,7,8-tetrahydropyrido[3,4-*c*]pyridazine hydrochloride was added in portions during 5 minutes. The cooling bath was removed, and the mixture was allowed to warm up to room temperature and stirred for 8 hours. The reaction mixture was washed with saturated sodium hydrogen carbonate solution and with water, dried over anhydrous sodium sulfate, and evaporated. The obtained residue was purified by flash coloumn (silica gel, eluent: DCM:MeOH, 0-10% gradient). Yield: 154 mg (38 %), white, amorphous solid identical to the title compound. MS (ESI) m/z: 297.1 $[M+H]^+$.

Intermediate 49

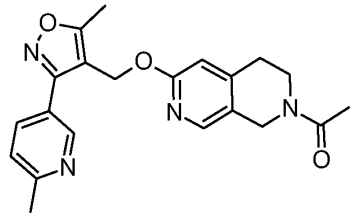
3-chloro-*N*-cyclopropyl-5,8-dihydropyrido[3,4-*c*]pyridazine-7(6*H*)-carboxamide



The compound was prepared according to the procedure described for Intermediate 48 using commercially available cyclopropylamine. Yield: 143 mg (51 %), MS (ESI) m/z: 253.1 $[M+H]^+$.

Example 1

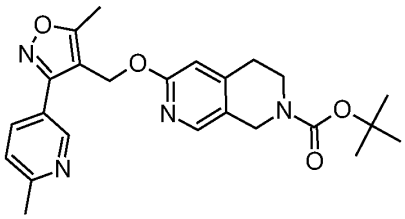
1-[6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl]ethanone



232 mg (1.04 mmol) of 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1), and 200 mg (1.04 mmol) of 1-(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)ethanone (Intermediate 7) were dissolved in 20 mL of anhydrous acetonitrile. Then, 431 mg (3.12 mmol) of anhydrous potassium-carbonate was added to the solution, and the suspension was stirred under reflux for 2 h. The conversion was followed by TLC (DCM:MeOH=10:1 as eluent, silica plate). After the reaction completed, the mixture was filtered, and evaporated to give 410 mg of oily crude product, which was purified by flash coloumn chromatography (silica gel, eluent: DCM:MeOH, 0-10% gradient). Yield: 100 mg (25.4 %) white solid. MS (ESI) m/z: 379.2 $[M+H]^+$.

Example 2

***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**

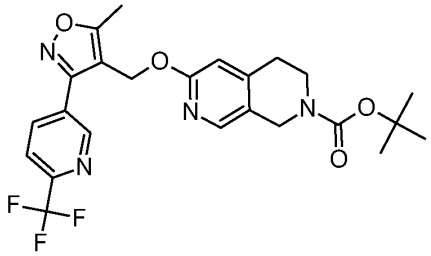


The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and *tert*-butyl

6-hydroxy-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate (Intermediate 8). MS (ESI) m/z: 437.3 $[M+H]^+$.

Example 3

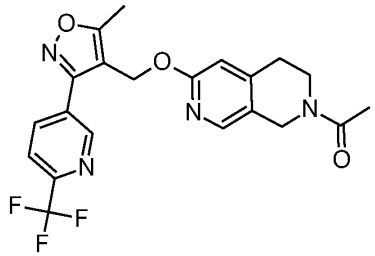
***tert*-butyl 6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxylate**



The title compound was 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) and *tert*-butyl 6-hydroxy-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate (Intermediate 8). MS (ESI) m/z: 491.2 $[M+H]^+$.

Example 4

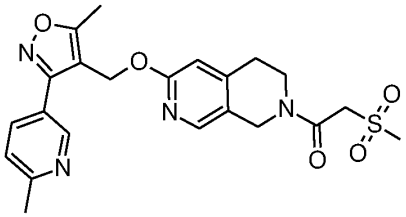
1-[6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl]ethanone



The title compound was 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) and 1-(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)ethanone (Intermediate 7). MS (ESI) m/z: 433.1 $[M+H]^+$.

Example 5

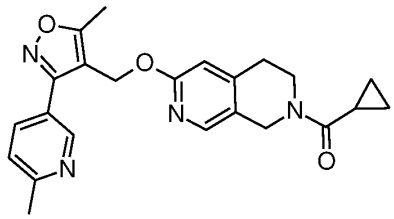
2-methanesulfonyl-1-(6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)ethan-1-one



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and 1-(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-(methylsulfonyl)ethanone (Intermediate 9). MS (ESI) m/z: 457.1 $[M+H]^+$.

Example 6

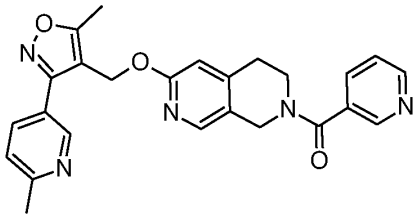
2-cyclopropanecarbonyl-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and cyclopropyl(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methanone (Intermediate 10). MS (ESI) m/z: 405.2 $[M+H]^+$.

Example 7

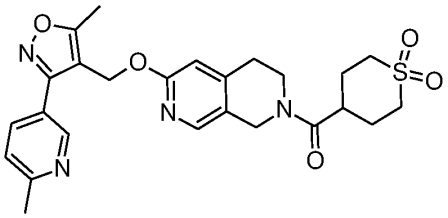
6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(pyridine-3-carbonyl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(pyridin-3-yl)methanone (Intermediate 11). MS (ESI) m/z: 442.2 $[M+H]^+$.

Example 8

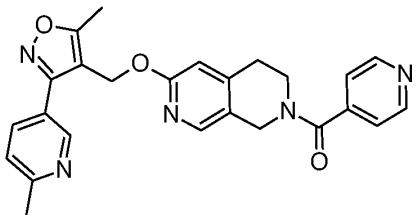
4-(6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carbonyl)-1lambda6-thiane-1,1-dione



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methanone (Intermediate 12). MS (ESI) m/z: 497.2 $[M+H]^+$.

Example 9

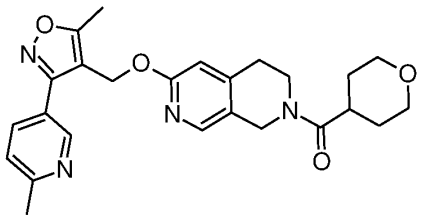
6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(pyridine-4-carbonyl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(pyridin-4-yl)methanone (Intermediate 13). MS (ESI) m/z: 442.2 $[M+H]^+$.

Example 10

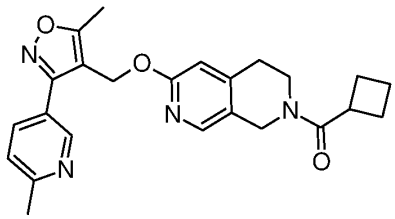
6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxane-4-carbonyl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydro-2*H*-pyran-4-yl)methanone (Intermediate 14). MS (ESI) m/z: 449.3 $[M+H]^+$.

Example 11

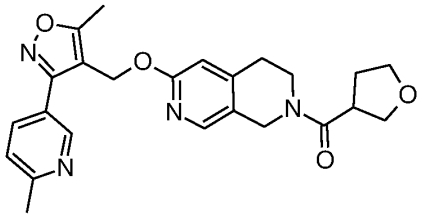
2-cyclobutanecarbonyl-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and cyclobutyl(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)methanone (Intermediate 15). MS (ESI) m/z: 419.2 $[M+H]^+$.

Example 12

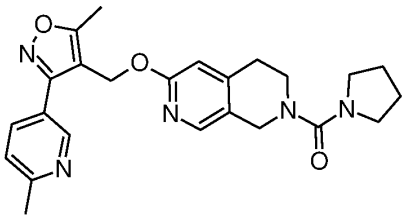
6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxolane-3-carbonyl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydrofuran-3-yl)methanone (Intermediate 16). MS (ESI) m/z: 435.2 $[M+H]^+$.

Example 13

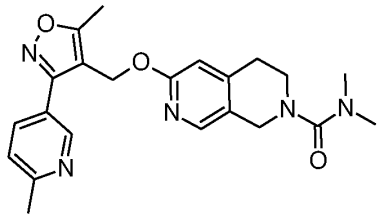
6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(pyrrolidine-1-carbonyl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(pyrrolidin-1-yl)methanone (Intermediate 26). MS (ESI) m/z: 434.3 $[M+H]^+$.

Example 14

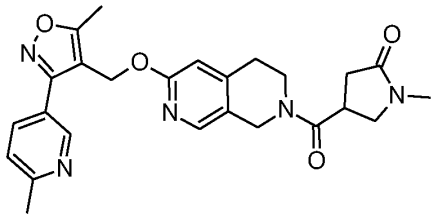
N,N-dimethyl-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carboxamide



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and 6-hydroxy-*N*,*N*-dimethyl-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxamide (Intermediate 27). MS (ESI) m/z: 408.1 $[M+H]^+$.

Example 15

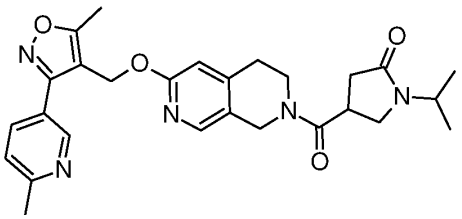
1-methyl-4-(6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carbonyl)pyrrolidin-2-one



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and 4-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-methylpyrrolidin-2-one (Intermediate 17). MS (ESI) m/z: 462.3 $[M+H]^+$.

Example 16

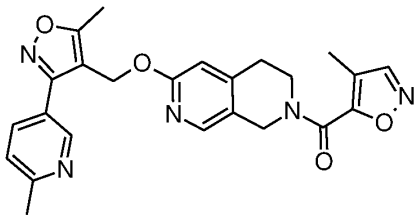
4-(6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carbonyl)-1-(propan-2-yl)pyrrolidin-2-one



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and 4-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-(propan-2-yl)pyrrolidin-2-one (Intermediate 18). MS (ESI) m/z: 490.2 $[M+H]^+$.

Example 17

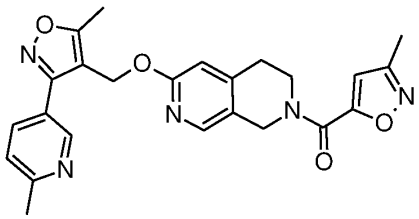
2-(4-methyl-1,2-oxazole-5-carbonyl)-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(4-methyl-1,2-oxazol-5-yl)methanone (Intermediate 19). MS (ESI) m/z: 446.2 $[M+H]^+$.

Example 18

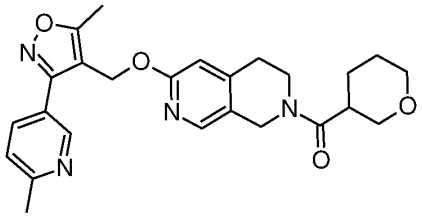
2-(3-methyl-1,2-oxazole-5-carbonyl)-6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(3-methyl-1,2-oxazol-5-yl)methanone (Intermediate 20). MS (ESI) m/z: 446.2 $[M+H]^+$.

Example 19

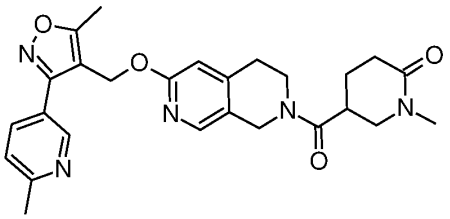
6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-2-(oxane-3-carbonyl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydro-2*H*-pyran-3-yl)methanone (Intermediate 21). MS (ESI) m/z: 449.2 $[M+H]^+$.

Example 20

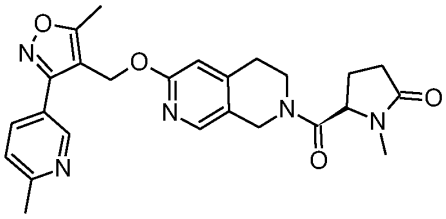
1-methyl-5-(6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carbonyl)piperidin-2-one



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and 5-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-methylpiperidin-2-one (Intermediate 22). MS (ESI) m/z: 476.3 $[M+H]^+$.

Example 21

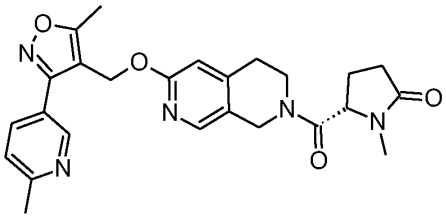
(5R)-1-methyl-5-(6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carbonyl)pyrrolidin-2-one



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (5*R*)-5-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-methylpyrrolidin-2-one (Intermediate 23). MS (ESI) m/z: 462.2 $[M+H]^+$.

Example 22

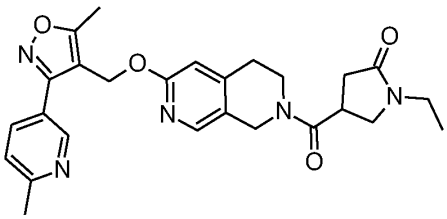
(5S)-1-methyl-5-(6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carbonyl)pyrrolidin-2-one



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (5*S*)-5-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]-1-methylpyrrolidin-2-one (Intermediate 24). MS (ESI) m/z: 462.2 $[M+H]^+$.

Example 23

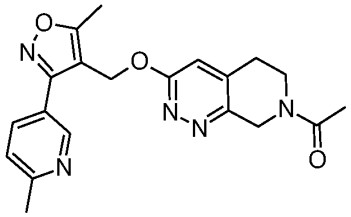
1-ethyl-4-(6-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine-2-carbonyl)pyrrolidin-2-one



The title compound was prepared according to the procedure described for Example 1 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and 1-ethyl-4-[(6-hydroxy-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)carbonyl]pyrrolidin-2-one (Intermediate 25). MS (ESI) m/z: 476.2 $[M+H]^+$.

Example 24

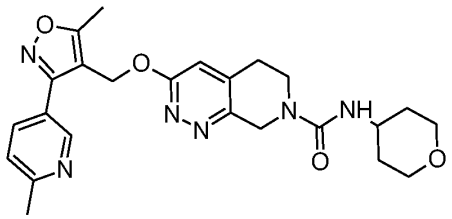
1-(3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl)ethan-1-one



Under argon atmosphere a flask was charged with 196 mg (0.926 mmol) of 1-(3-chloro-5,8-dihydropyrido[3,4-c]pyridazin-7(6*H*)-yl)ethanone (Intermediate 38), 189 mg (0.926 mmol) of 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1), 603 mg (1.85 mmol) of Cs_2CO_3, 37 mg (0.093 mmol) of rac-2-(di-*tert*-butylphosphino)-1,11-binaphthyl, 21 mg (0.094 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=1:1 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: 71 mg (20 %), white, amorphous solid. MS (ESI) m/z: 380.3 $[M+H]^+$.

Example 25

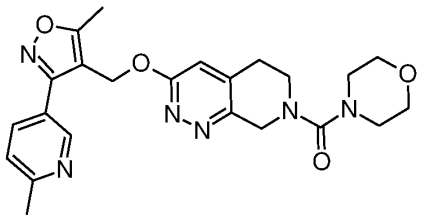
3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-N-(oxan-4-yl)-5H,6H,7H,8H-pyrido[3,4-c]pyridazine-7-carboxamide



The title compound was prepared according to the procedure described for Example 24 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and 3-chloro-*N*-(tetrahydro-2*H*-pyran-4-yl)-5,8-dihydropyrido[3,4-c]pyridazine-7(6*H*)-carboxamide (Intermediate 48). MS (ESI) m/z: 465.3 $[M+H]^+$.

Example 26

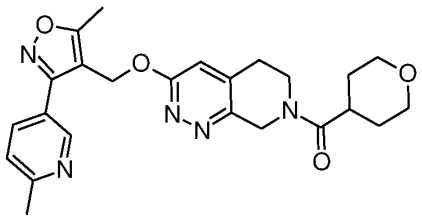
4-(3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-5H,6H,7H,8H-pyrido[3,4-c]pyridazine-7-carbonyl)morpholine



The title compound was prepared according to the procedure described for Example 24 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)(morpholin-4-yl)methanone (Intermediate 39). MS (ESI) m/z: 451.2 $[M+H]^+$.

Example 27

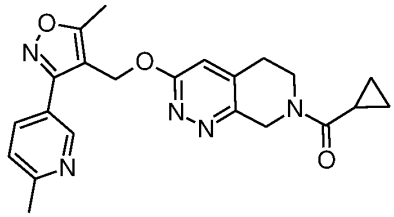
2-methyl-5-[5-methyl-4-({[7-(oxane-4-carbonyl)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl]oxy}methyl)-1,2-oxazol-3-yl]pyridine



The title compound was prepared according to the procedure described for Example 24 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)(tetrahydro-2*H*-pyran-4-yl)methanone (Intermediate 40). MS (ESI) m/z: 450.2 $[M+H]^+$.

Example 28

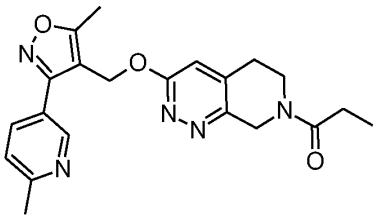
5-{4-[({7-cyclopropanecarbonyl-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl}oxy)methyl]-5-methyl-1,2-oxazol-3-yl}-2-methylpyridine



The title compound was prepared according to the procedure described for Example 24 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)(cyclopropyl)methanone (Intermediate 41). MS (ESI) m/z: 406.2 $[M+H]^+$.

Example 29

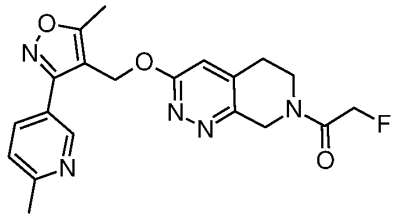
1-(3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl)propan-1-one



The title compound was prepared according to the procedure described for Example 24 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and 1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)propan-1-one (Intermediate 42). MS (ESI) m/z: 394.2 $[M+H]^+$.

Example 30

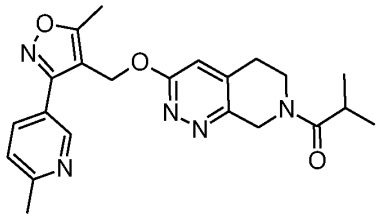
2-fluoro-1-(3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl)ethan-1-one



The title compound was prepared according to the procedure described for Example 24 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and 1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)-2-fluoroethanone (Intermediate 43). MS (ESI) m/z: 398.2 $[M+H]^+$.

Example 31

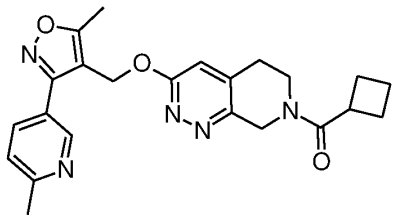
2-methyl-1-(3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl)propan-1-one



The title compound was prepared according to the procedure described for Example 24 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and 1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)-2-methylpropan-1-one (Intermediate 44). MS (ESI) m/z: 408.2 $[M+H]^+$.

Example 32

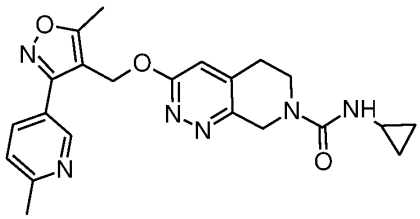
5-{4-[({7-cyclobutanecarbonyl-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-3-yl}oxy)methyl]-5-methyl-1,2-oxazol-3-yl}-2-methylpyridine



The title compound was prepared according to the procedure described for Example 24 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and (3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)(cyclobutyl)methanone (Intermediate 45). MS (ESI) m/z: 420.1 $[M+H]^+$.

Example 33

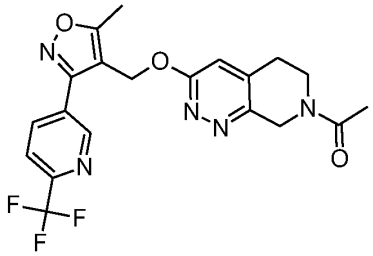
N-cyclopropyl-3-{[5-methyl-3-(6-methylpyridin-3-yl)-1,2-oxazol-4-yl]methoxy}-5H,6H,7H,8H-pyrido[3,4-c]pyridazine-7-carboxamide



The title compound was prepared according to the procedure described for Example 24 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-methylpyridine (Intermediate 1) and 3-chloro-N-cyclopropyl-5,8-dihydropyrido[3,4-c]pyridazine-7(6H)-carboxamide (Intermediate 49). MS (ESI) m/z: 421.2 $[M+H]^+$.

Example 34

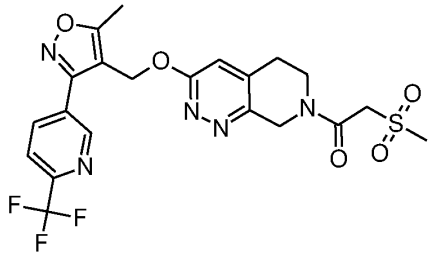
1-[3-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-5H,6H,7H,8H-pyrido[3,4-c]pyridazin-7-yl]ethan-1-one



The title compound was prepared according to the procedure described for Example 24 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine (Intermediate 2) and 1-(3-chloro-5,8-dihydropyrido[3,4-c]pyridazin-7(6*H*)-yl)ethanone (Intermediate 38). MS (ESI) m/z: 434.2 $[M+H]^+$.

Example 35

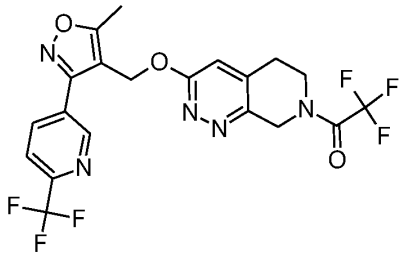
2-methanesulfonyl-1-[6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl]ethan-1-one



The title compound was prepared according to the procedure described for Example 24 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine (Intermediate 2) and 1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)-2-(methylsulfonyl)ethanone (Intermediate 46). MS (ESI) m/z: 511.1 $[M+H]^+$.

Example 36

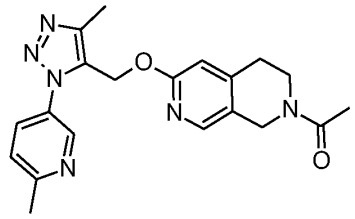
2,2,2-trifluoro-1-[6-({5-methyl-3-[6-(trifluoromethyl)pyridin-3-yl]-1,2-oxazol-4-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl]ethan-1-one



The title compound was prepared according to the procedure described for Example 24 using 5-[4-(chloromethyl)-5-methyl-1,2-oxazol-3-yl]-2-(trifluoromethyl)pyridine (Intermediate 2) and 1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)-2,2,2-trifluoroethanone (Intermediate 47). MS (ESI) m/z: 487.2 $[M+H]^+$.

Example 37

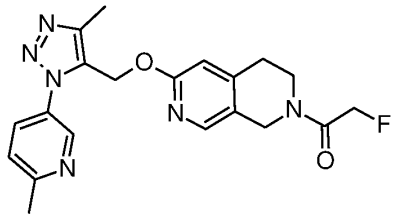
1-(6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)ethan-1-one



The title compound was prepared according to the procedure described for Example 24 using [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 3) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)ethanone (Intermediate 28). MS (ESI) m/z: 379.2 $[M+H]^+$.

Example 38

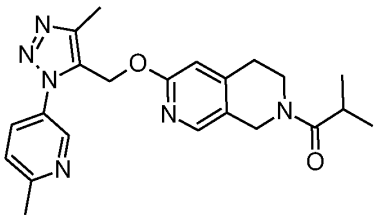
2-fluoro-1-(6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)ethan-1-one



The title compound was prepared according to the procedure described for Example 24 using [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 3) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-fluoroethanone (Intermediate 29). MS (ESI) m/z: 397.1 $[M+H]^+$.

Example 39

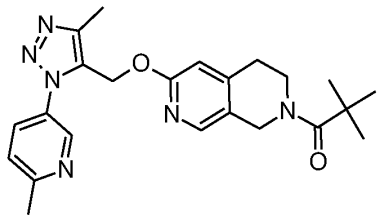
2-methyl-1-(6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)propan-1-one



The title compound was prepared according to the procedure described for Example 24 using [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 3) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-methylpropan-1-one (Intermediate 30). MS (ESI) m/z: 407.2 $[M+H]^+$.

Example 40

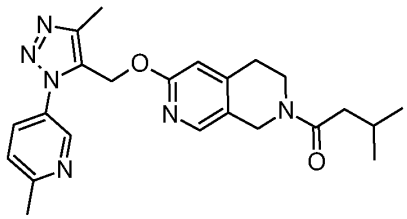
2,2-dimethyl-1-(6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)propan-1-one



The title compound was prepared according to the procedure described for Example 24 using [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 3) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2,2-dimethylpropan-1-one (Intermediate 31). MS (ESI) m/z: 421.2 $[M+H]^+$.

Example 41

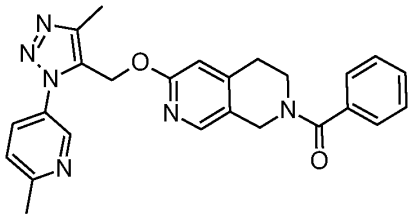
3-methyl-1-(6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)butan-1-one



The title compound was prepared according to the procedure described for Example 24 using [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 3) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-3-methylbutan-1-one (Intermediate 32). MS (ESI) m/z: 421.2 $[M+H]^+$.

Example 42

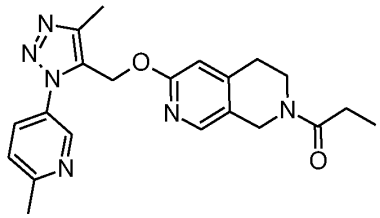
2-benzoyl-6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 24 using [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 3) and (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(phenyl)methanone (Intermediate 33). MS (ESI) m/z: 441.2 $[M+H]^+$.

Example 43

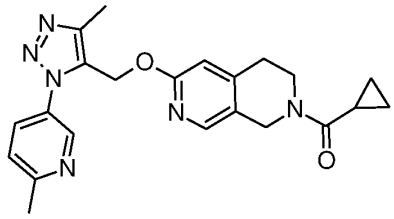
1-(6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)propan-1-one



The title compound was prepared according to the procedure described for Example 24 using [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 3) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)propan-1-one (Intermediate 34). MS (ESI) m/z: 393.2 $[M+H]^+$.

Example 44

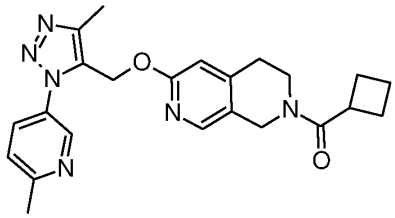
2-cyclopropanecarbonyl-6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 24 using [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 3) and (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(cyclopropyl)methanone (Intermediate 35). MS (ESI) m/z: 405.2 $[M+H]^+$.

Example 45

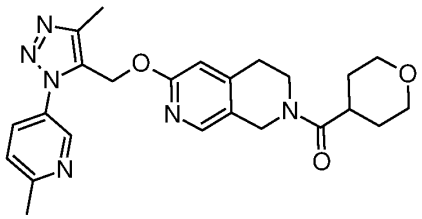
2-cyclobutanecarbonyl-6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 24 using [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 3) and (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(cyclobutyl)methanone (Intermediate 36). MS (ESI) m/z: 419.2 $[M+H]^+$.

Example 46

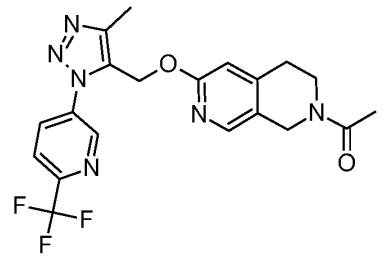
6-{[4-methyl-1-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxane-4-carbonyl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 24 using [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 3) and (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydro-2*H*-pyran-4-yl)methanone (Intermediate 37). MS (ESI) m/z: 449.2 $[M+H]^+$.

Example 47

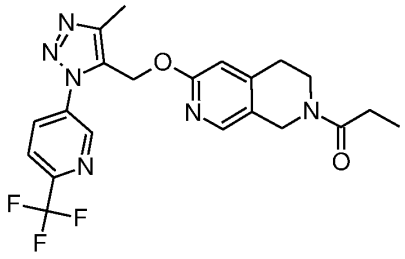
1-[6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl]ethan-1-one



The title compound was prepared according to the procedure described for Example 24 using [{4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1*H*-1,2,3-triazol-5-yl}methanol (Intermediate 4) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)ethanone (Intermediate 28). MS (ESI) m/z: 433.2 $[M+H]^+$.

Example 48

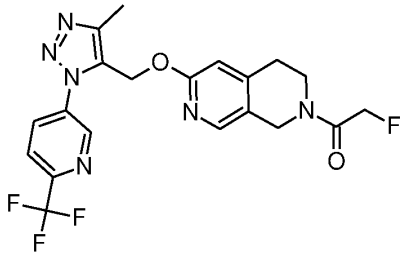
1-[6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl]propan-1-one



The title compound was prepared according to the procedure described for Example 24 using [{4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1*H*-1,2,3-triazol-5-yl}methanol (Intermediate 4) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)propan-1-one (Intermediate 34). MS (ESI) m/z: 447.2 $[M+H]^+$.

Example 49

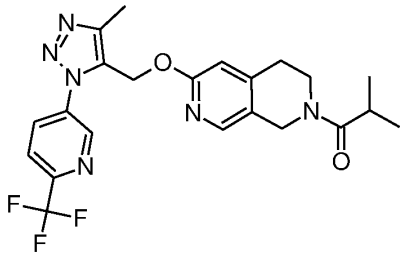
2-fluoro-1-[6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl]ethan-1-one



The title compound was prepared according to the procedure described for Example 24 using [{4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1*H*-1,2,3-triazol-5-yl}methanol (Intermediate 4) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-fluoroethanone (Intermediate 29). MS (ESI) m/z: 451.1 $[M+H]^+$.

Example 50

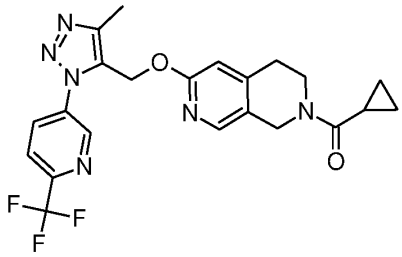
2-methyl-1-[6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl]propan-1-one



The title compound was prepared according to the procedure described for Example 24 using [{4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1*H*-1,2,3-triazol-5-yl}methanol (Intermediate 4) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-methylpropan-1-one (Intermediate 30). MS (ESI) m/z: 461.2 $[M+H]^+$.

Example 51

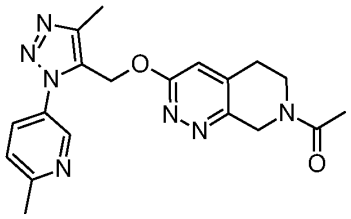
2-cyclopropanecarbonyl-6-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 24 using [{4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1*H*-1,2,3-triazol-5-yl}methanol (Intermediate 4) and (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(cyclopropyl)methanone (Intermediate 35). MS (ESI) m/z: 459.2 $[M+H]^+$.

Example 52

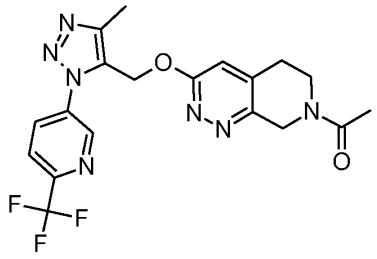
1-[3-{[4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methoxy}-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl]ethanone



The title compound was prepared according to the procedure described for Example 24 using [4-methyl-1-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 3) and 1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)ethanone (Intermediate 38). MS (ESI) m/z: 380.2 $[M+H]^+$.

Example 53

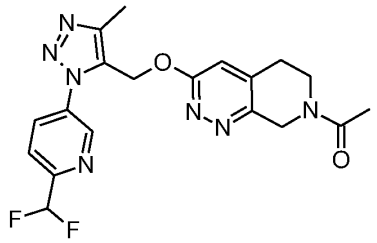
1-[3-({4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1*H*-1,2,3-triazol-5-yl}methoxy)-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl]ethanone



The title compound was prepared according to the procedure described for Example 24 using [{4-methyl-1-[6-(trifluoromethyl)pyridin-3-yl]-1*H*-1,2,3-triazol-5-yl}methanol (Intermediate 4) and 1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)ethanone (Intermediate 38). MS (ESI) m/z: 434.2 $[M+H]^+$.

Example 54

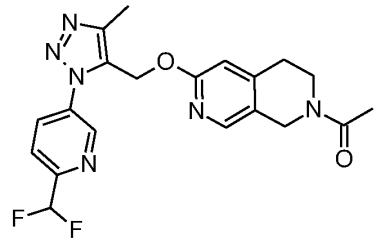
1-[3-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methoxy)-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl]ethanone



The title compound was prepared according to the procedure described for Example 24 using {1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methanol (Intermediate 5) and 1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)ethanone (Intermediate 38). MS (ESI) m/z: 416.2 $[M+H]^+$.

Example 55

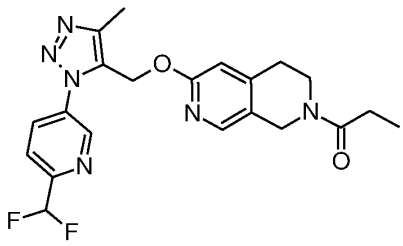
1-[6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methoxy)-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl]ethanone



The title compound was prepared according to the procedure described for Example 24 using {1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methanol (Intermediate 5) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)ethanone (Intermediate 28). MS (ESI) m/z: 415.2 $[M+H]^+$.

Example 56

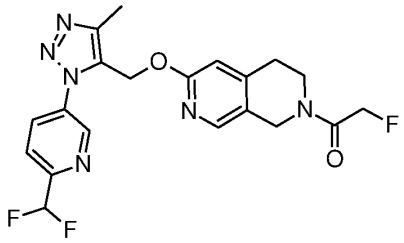
1-[6-({1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methoxy)-3,4 dihydro-2,7-naphthyridin-2(1*H*)-yl]propan-1-one



The title compound was prepared according to the procedure described for Example 24 using {1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methanol (Intermediate 5) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)propan-1-one (Intermediate 34). MS (ESI) m/z: 429.2 $[M+H]^+$.

Example 57

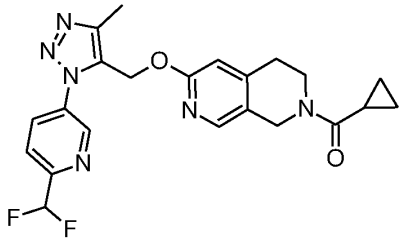
2-fluoro-1-[6-({4-methyl-1-[6-(difluoromethyl)pyridin-3-yl]-1H-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl]ethan-1-one



The title compound was prepared according to the procedure described for Example 24 using {1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methanol (Intermediate 5) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-fluoroethanone (Intermediate 29). MS (ESI) m/z: 433.2 $[M+H]^+$.

Example 58

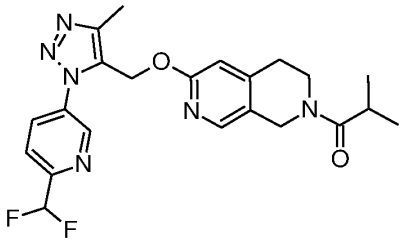
2-cyclopropanecarbonyl-6-({4-methyl-1-[6-(difluoromethyl)pyridin-3-yl]-1*H*-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 24 using {1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methanol (Intermediate 5) and (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(cyclopropyl)methanone (Intermediate 35). MS (ESI) m/z: 441.2 $[M+H]^+$.

Example 59

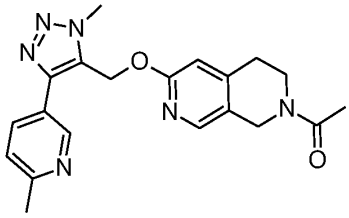
2-methyl-1-[6-({4-methyl-1-[6-(difluoromethyl)pyridin-3-yl]-1*H*-1,2,3-triazol-5-yl}methoxy)-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl]propan-1-one



The title compound was prepared according to the procedure described for Example 24 using {1-[6-(difluoromethyl)pyridin-3-yl]-4-methyl-1*H*-1,2,3-triazol-5-yl}methanol (Intermediate 5) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-methylpropan-1-one (Intermediate 30). MS (ESI) m/z: 443.2 $[M+H]^+$.

Example 60

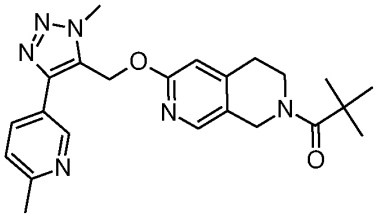
1-(6-{[1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)ethan-1-one



The title compound was prepared according to the procedure described for Example 24 using [1-methyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 6) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)ethanone (Intermediate 28). MS (ESI) m/z: 379.2 $[M+H]^+$.

Example 61

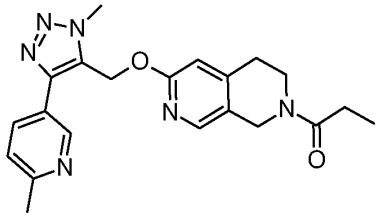
2,2-dimethyl-1-(6-{[1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)propan-1-one



The title compound was prepared according to the procedure described for Example 24 using [1-methyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 6) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2,2-dimethylpropan-1-one (Intermediate 31). MS (ESI) m/z: 421.2 $[M+H]^+$.

Example 62

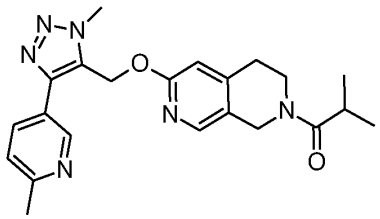
1-(6-{[1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)propan-1-one



The title compound was prepared according to the procedure described for Example 24 using [1-methyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 6) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)propan-1-one (Intermediate 34). MS (ESI) m/z: 393.2 $[M+H]^+$.

Example 63

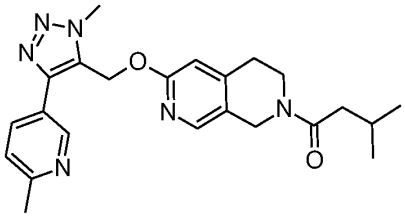
2-methyl-1-(6-{[1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)propan-1-one



The title compound was prepared according to the procedure described for Example 24 using [1-methyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 6) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-methylpropan-1-one (Intermediate 30). MS (ESI) m/z: 407.2 $[M+H]^+$.

Example 64

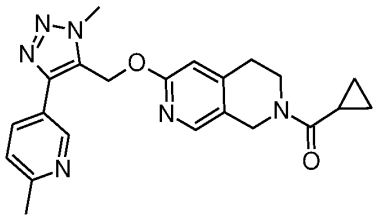
3-methyl-1-(6-{[1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)butan-1-one



The title compound was prepared according to the procedure described for Example 24 using [1-methyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 6) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-3-methylbutan-1-one (Intermediate 32). MS (ESI) m/z: 421.2 $[M+H]^+$.

Example 65

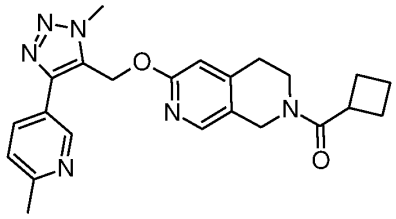
2-cyclopropanecarbonyl-6-{[1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 24 using [1-methyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 6) and (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(cyclopropyl)methanone (Intermediate 35). MS (ESI) m/z: 405.2 $[M+H]^+$.

Example 66

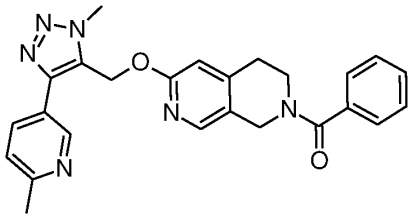
2-cyclobutanecarbonyl-6-{[1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 24 using [1-methyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 6) and (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(cyclobutyl)methanone (Intermediate 36). MS (ESI) m/z: 419.2 $[M+H]^+$.

Example 67

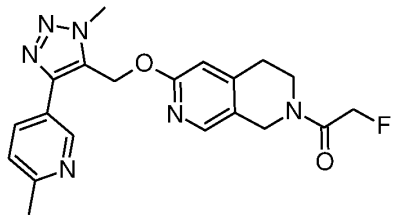
2-benzoyl-6-{[1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 24 using [1-methyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 6) and (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(phenyl)methanone (Intermediate 33). MS (ESI) m/z: 441.2 $[M+H]^+$.

Example 68

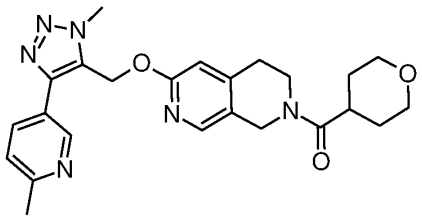
2-fluoro-1-(6-{[1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-1,2,3,4-tetrahydro-2,7-naphthyridin-2-yl)ethan-1-one



The title compound was prepared according to the procedure described for Example 24 using [1-methyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 6) and 1-(6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)-2-fluoroethanone (Intermediate 29). MS (ESI) m/z: 397.2 $[M+H]^+$.

Example 69

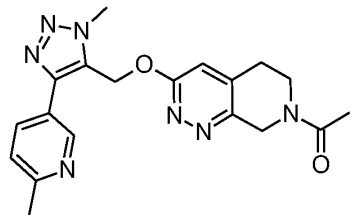
6-{[1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-2-(oxane-4-carbonyl)-1,2,3,4-tetrahydro-2,7-naphthyridine



The title compound was prepared according to the procedure described for Example 24 using [1-methyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 6) and (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1*H*)-yl)(tetrahydro-2*H*-pyran-4-yl)methanone (Intermediate 37). MS (ESI) m/z: 397.2 $[M+H]^+$.

Example 70

1-(6-{[1-methyl-4-(6-methylpyridin-3-yl)-1H-1,2,3-triazol-5-yl]methoxy}-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl]ethanone



The title compound was prepared according to the procedure described for Example 24 using [1-methyl-4-(6-methylpyridin-3-yl)-1*H*-1,2,3-triazol-5-yl]methanol (Intermediate 6) and 1-(3-chloro-5,8-dihydropyrido[3,4-*c*]pyridazin-7(6*H*)-yl)ethanone (Intermediate 38). MS (ESI) m/z: 408.2 $[M+H]^+$.

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.