NOVEL HETEROARYL-UREA COMPOUNDS AS KV7.2 INHIBITORS

Field of the invention

The present invention relates to novel compounds, particularly pyridine compounds, useful as Kv7.2 enhancers (or positive modulators), their manufacture, pharmaceutical compositions, kits comprising the compounds, and their use as medicaments for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2. These disorders, diseases, or disabilities can be selected from behavioral disorders, mood disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus.

Background of the invention

The potassium channel family 7, or Q, contains five proteins that in humans are encoded by the genes KCNQ1, KCNQ2, KCNQ3, KCNQ4, and KCNQ5. The KCNQ proteins form homo- and hetero-tetrameric channels that respond to membrane voltage changes and open to let potassium ions flow out of cell membranes. Homomeric Kv7.2 channels as well as heteromeric Kv7.2 and Kv7.3 channels have been investigated because of their unique distribution and their potential role as primary regulators of neuronal excitability in many CNS and PNS pathways (Wang *et al.*, 1998). KCNQ2 channels control the neuronal resting membrane potential, the spike frequency adaptation of neuronal firing, and presynaptic release. Impairment in their function leads to network instability even when lost exclusively in inhibitory neurons (Soh *et al.*, 2018).

A significant percentage of childhood epilepsies are associated with KCNQ2 mutations (Lee *et al.*, 2019). Human genetic studies identify de novo mutations in KCNQ2 as the third most robust link to epileptic encephalopathy (EE) (Zhao *et al.*, 2020). Whether primary or secondary EEs, seizure activity worsens clinical outcomes and alters normal neurodevelopment (von Deimling, Helbig and Marsh, 2017). Pediatric epilepsies affect about 1 in 200 children (Waaler *et al.*, 2000) driving cognitive, behavioral and neurological deficits (Simkin and Kiskinis, 2018). In the case of specific pathogenic KCNQ2 mutations, despite most individuals eventually becoming seizure-free,

developmental delays are experienced by the majority of patients (Kato *et al.*, 2013). Targeting Kv7 channels offers a genetically validated target against epilepsy with a differentiated mode of action amongst anti-epileptics (Gunthorpe, Large and Sankar, 2012). Kv7.2 enhancers show the potential to transform neurodevelopmental trajectories by treating the neural network instability responsible for EEs (Kessi *et al.*, 2020).

The connection between epilepsy and autism is robust (Srivastava and Sahin, 2017) and derives from the convergent phenotypes driven by a multitude of small genetic contributors, in combination with environmental factors. KCNQ2 is one of the top 5 ion channels associated with Autism Spectrum Disorder (ASD) and one of the top 30 of all de novo mutations known in ASD (Zhao *et al.*, 2020).

Another defining feature of ASD, Atypical Sensory Processing (ASP) (Thye *et al.*, 2018), is also driven by convergent genetics as seen in co-twin-control studies (Neufeld *et al.*, 2021). The biology responsible for increased sensory sensitivity has been studied in preclinical models. There, multi-sensory neuronal hyper-excitability emerges regardless of the genetic manipulation that originally drives pathological neurodevelopment. Some genes whose manipulation leads to sensory sensitivity include CNTNAP2 (Peñagarikano *et al.*, 2011), SHANK3 (Holder and Quach, 2016) and GABRB3 (Tanaka *et al.*, 2012). Kv7.2 enhancers show the potential to correct neurodevelopmental trajectories in ASD by normalizing network stability, neural information processing, and sensory abnormalities, ultimately responsible for atypical social and repetitive behaviors in ASD. It is also interesting that KCNQ2 knock-out mice show repetitive behaviors and aberrant exploratory and social behaviors (Kim *et al.*, 2019).

Kv7.2 enhancers also showed promise in syndromic neurodevelopmental disorders in part because of the prevalence and impact of epilepsies (Budisteanu *et al.*, 2020). For example, epilepsy is prevalent (>80%) in Angleman syndrome, mostly starting before 3 years of age (Fiumara *et al.*, 2010).

Another neurodevelopmental disorder, Dup15q syndrome (Dup15q), is caused by the partial duplication of Chromosome 15 that confers a considerable risk for autism spectrum disorder,

epilepsy, and intellectual disability. Dup15q patient-derived induced pluripotent cells show KCNQ2 anomalies, and Retigabine, a pan-Kv7 channel opener, partially corrects their phenotype (Fink *et al.*, 2018). Epilepsies are central to Dup15q, with Kv7.2 enhancers showing potential to transform this neurodevelopmental disorder.

In Fragile X syndrome, about 15% of individuals experience epilepsy (Berry-Kravis, 2002) together with abnormal sensory processing (McCullagh *et al.*, 2020). KCNQ2 (Kv7.2 gene) is downregulated in the absence of Fragile X Mental Retardation Protein (FMRP) in rodent models (Zhang *et al.*, 2018). Therefore, Kv7.2 enhancers could positively impact Fragile X by acting on both epilepsies and sensory processing.

Infantile epilepsies are associated with intellectual disabilities, and KCNQ2 de novo mutations are significantly associated with intellectual disability (Zhao *et al.*, 2020). Kv7.2 enhancement may addressthe underlying biology that exacerbates the disability.

For all these neurodevelopmental disorders, early diagnosis and the identification of the correct antiepileptic treatment is at the core of the strategies aiming at normalizing neurodevelopmental trajectories.

Within behavioral disorders, Kv7.2 enhancers showed promise in attention-deficit hyperactivity disorder (ADHD) as well as major depressive disorder (MDD, depression). Some patients with KCNQ2 mutations and mild epilepsy phenotype, show cognitive delay and ADHD (Lee *et al.*, 2019). Kv7.2 enhancers were suggested to treat the neural network instability and the behavioral impulsivity linked to ADHD. In the MDD space, Retigabine (Kv7 opener) showed antidepressant efficacy in patients by acting on the brain's reward centers (Tan *et al.*, 2018). The significant reduction in depressive symptoms observed with retigabine places Kv7.2 enhancers as therapeutic candidates in MDD.

The therapeutic potential of Kv7.2 enhancers in pain sensitivity is supported by the localization of Kv7.2 channels in dorsal root ganglia and their established role in pain perception (Brown and Passmore, 2009). Non-selective Kv7.2 enhancers showed efficacy in reducing the excitability of human peripheral axons (Lang *et al.*, 2008). Retigabine has already shown some

efficacy in preclinical pain models (Korsgaard *et al.*, 2005; Xu *et al.*, 2010; Wu *et al.*, 2017). Retigabine also shows efficacy in controlling spreading depression, a wave of cellular depolarization associated with migraines (Aiba and Noebels, 2021).

Within sensory abnormalities, aberrant plasticity of KCNQ2 channels is strongly linked to the induction of tinnitus (Li, Choi and Tzounopoulos, 2013). This link is based on the localization of Kv7.2 channels in the cochlea (Jin *et al.*, 2009) and how cochlear damage depends on neuronal excitability driven by the closure of Kv7.2 channels (Liu, Glowatzki and Fuchs, 2015). Retigabine prevents the development of tinnitus in preclinical models (Li, Choi and Tzounopoulos, 2013). As evidence in support of how KCNQ2 pathologies are connected between indications, it is interesting to find that tinnitus and hyperacusis are more prevalent in ASD than in the general population (Danesh *et al.*, 2015).

In neurodegenerative diseases, dysregulated K+ homeostasis in chronic neuro-inflammatory conditions is central to disease progression. For example, in amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease of the motor nervous system (Hardiman *et al.*, 2017), diverse genetics converge onto motorneuron excitotoxicity (Kanai *et al.*, 2006; Pasinelli and Brown, 2006) and specifically axonal hyperexcitability predicts survival (Kanai *et al.*, 2012). Patient-derived motor neurons show membrane hyperexcitability and the tool compound Retigabine (pan-Kv7 enhancer) rescues phenotype (Wainger *et al.*, 2014). The motorneuron hyperexcitability was found early in presymptomatic in vivo systems (Kuo *et al.*, 2004) where it is a contributor to disease progression. Recently, clinical trials in ALS with Retigabine showed efficacy on functional biomarkers of ALS (Wainger *et al.*, 2021) and preclinically protects against peripheral neuropathy (Nodera *et al.*, 2011).

In Alzheimer's disease (AD), neuronal hyperexcitability and network instability (Frere and Slutsky, 2018)are early features of both IPSC models of sporadic AD (Ghatak *et al.*, 2019), and genetic in vivo models (Palop *et al.*, 2007; Kazim *et al.*, 2017; Styr and Slutsky, 2018). Network instability worsens proteinopathy (Dolev *et al.*, 2013; Frere and Slutsky, 2018) with consequences for patients (Vossel *et al.*, 2013; Lam *et al.*, 2017).

Because motor neuron and cortical neuron degeneration can be meaningfully slowed down by reducing aberrant neuronal activity, Kv7.2 enhancement could be an effective way to stop such aberrant activity, changing the neurodegenerative trajectory of the disease.

Therefore, enhancing the activity of Kv7.2 is a promising strategy for the treatment or prevention of diseases associated with Kv7.2. These include neurodevelopmental disorders like autism and Fragile X, epilepsy, intellectual disability, depression, attention deficit hyperactivity disorder, motor neuron excitability, pain, migraine, and sensory processing disorders.

WO2020/163268 relates to pyridine urea derivatives as KCNQ potentiators.

US5,384,330 relates to pharmacologically active 1,2,4-triaminobenzene derivatives modulating potassium ion channels Kv7.2-Kv7.5 (KCNQ2-KCNQ5) for the treatment of drug-resistant epilepsy. The compounds showed tolerability issues and other side effects.

Furthermore, the bioactivation of drugs to produce chemically reactive metabolites is an undesirable property for a drug intended for use in patients because of the observation that most drugs that cause serious idiosyncratic clinical adverse reactions form reactive metabolites capable of covalent binding to protein (Park *et al.*, 2011). Some reactive metabolites can form adducts with glutathione (GSH) when used as trapping agent in *in vitro* experiments. The formation of GSH adducts in human liver microsomes can therefore provide valuable information on the potential of molecules to undergo bioactivation to reactive metabolites (Dieckhaus *et al.*, 2005; Brink *et al.*, 2014) and, since GSH adduct formation translates with high probability into increased levels of covalent binding to hepatic microsomal protein, GSH adduct formation could further serve as a surrogate marker for covalent binding to human hepatic protein (Evans *et al.*, 2004). Compounds that do not to form GSH adducts when incubated in human liver microsomes under the conditions of metabolic activation *in vitro* may therefore be deemed to pose a low risk for reactive metabolite formation in humans (Brink *et al.*, 2017).

To date, no agents acting on Kv7.2 are approved for the treatment of any of the diseases, disorders, or disabilities described herein, and thus there remains a need for modulators of Kv7.2 which provide a therapeutic benefit. Further, it would be beneficial to have modulators of Kv7.2

which are highly selective over other Kv7 channels. There is a need for Kv7.2 modulators which provide for a combination of favorable pharmacological properties, such as for example potency, selectivity, and metabolic stability.

It is, therefore, an object of this invention to provide selective Kv7.2 enhancers with favorable pharmacological properties useful as Kv7.2 enhancers (or positive modulators) for the therapeutic and/or prophylactic treatment of disorders, diseases, or disabilities associated with Kv7.2, and preferably demonstrating beneficial low propensity to form GSH adducts when incubated in human liver microsomes under the conditions of metabolic activation.

REFERENCES:

Aiba, I. and Noebels, J. L. (2021) "Kcnq2/Kv7.2 controls the threshold and bihemispheric symmetry of cortical spreading depolarization," *Brain: a journal of neurology*. doi: 10.1093/brain/awab141.

Berry-Kravis, E. (2002) "Epilepsy in fragile X syndrome," *Developmental medicine and child neurology*. Wiley Online Library, 44(11), pp. 724–728.

Brown, D. A. and Passmore, G. M. (2009) "Neural KCNQ (Kv7) channels," *British journal of pharmacology*, 156(8), pp. 1185–1195.

Brink, A., *et al.* (2014); *Rapid Commun. Mass Spectrom.*, *28*, 2695–2703.

Brink, A., *et al.* (2017); *Drug Discovery Today*, *22*, 751-756.

Budisteanu, M. *et al.* (2020) "Treatment of Epilepsy Associated with Common Chromosomal Developmental Diseases," *Open life sciences*. Walter de Gruyter GmbH, 15(1), pp. 21–29.

Danesh, A. A. *et al.* (2015) "Tinnitus and hyperacusis in autism spectrum disorders with emphasis on high functioning individuals diagnosed with Asperger's Syndrome," *International journal of pediatric otorhinolaryngology*, 79(10), pp. 1683–1688.

von Deimling, M., Helbig, I. and Marsh, E. D. (2017) "Epileptic Encephalopathies-Clinical Syndromes and Pathophysiological Concepts," *Current neurology and neuroscience reports*, 17(2), p. 10.

Dieckhaus, C.M., *et al.* (2005); *Chem. Res. Toxicol.*, *18*, 630-8.

Dolev, I. *et al.* (2013) "Spike bursts increase amyloid-β 40/42 ratio by inducing a presenilin-1 conformational change," *Nature neuroscience*, 16(5), pp. 587–595.

Evans, D.C. *et al.* (2004); *Chem. Res. Toxicol.*, *17*, 3-16.

Fink, J. J. *et al.* (2018) "Hyperexcitable phenotypes in iPSC-derived neurons from patients with 15q11-q13 duplication syndrome, a genetic form of autism," *BioRxiv*. biorxiv.org. Available at: https://www.biorxiv.org/content/10.1101/286336v1.abstract.

Fiumara, A. *et al.* (2010) "Epilepsy in patients with Angelman syndrome," *Italian Journal of Pediatrics*, p. 31. doi: 10.1186/1824-7288-36-31.

Frere, S. and Slutsky, I. (2018) "Alzheimer's Disease: From Firing Instability to Homeostasis Network Collapse," *Neuron*, 97(1), pp. 32–58.

Ghatak, S. *et al.* (2019) "Mechanisms of hyperexcitability in Alzheimer's disease hiPSC-derived neurons and cerebral organoids vs isogenic controls," *eLife*, 8. doi: 10.7554/eLife.50333.

Gunthorpe, M. J., Large, C. H. and Sankar, R. (2012) "The mechanism of action of retigabine (ezogabine), a first-in-class K+ channel opener for the treatment of epilepsy," *Epilepsia*, 53(3), pp. 412–424.

Hardiman, O. *et al.* (2017) "Amyotrophic lateral sclerosis," *Nature reviews. Disease primers*, 3, p. 17071.

Holder, J. L., Jr and Quach, M. M. (2016) "The spectrum of epilepsy and electroencephalographic abnormalities due to SHANK3 loss-of-function mutations," *Epilepsia*, 57(10), pp. 1651–1659.

Jin, Z. *et al.* (2009) "Expression and localization of K channels KCNQ2 and KCNQ3 in the mammalian cochlea," *Audiology & neuro-otology*, 14(2), pp. 98–105.

Kanai, K. *et al.* (2006) "Altered axonal excitability properties in amyotrophic lateral sclerosis: impaired potassium channel function related to disease stage," *Brain: a journal of neurology*, 129(Pt 4), pp. 953–962.

Kanai, K. *et al.* (2012) "Motor axonal excitability properties are strong predictors for survival in amyotrophic lateral sclerosis," *Journal of neurology, neurosurgery, and psychiatry*, 83(7), pp. 734–738.

Kato, M. *et al.* (2013) "Clinical spectrum of early onset epileptic encephalopathies caused by KCNQ2 mutation," *Epilepsia*, 54(7), pp. 1282–1287.

Kazim, S. F. *et al.* (2017) "Early-Onset Network Hyperexcitability in Presymptomatic Alzheimer's Disease Transgenic Mice Is Suppressed by Passive Immunization with Anti-Human APP/Aβ Antibody and by mGluR5 Blockade," *Frontiers in aging neuroscience*, 9, p. 71.

Kessi, M. *et al.* (2020) "Intellectual Disability and Potassium Channelopathies: A Systematic Review," *Frontiers in genetics*, 11, p. 614.

Kim, E. C. *et al.* (2019) "Heterozygous loss of epilepsy gene KCNQ2 alters social, repetitive, and exploratory behaviors," *Genes, Brain and Behavior*. doi: 10.1111/gbb.12599.

Korsgaard, M. P. G. *et al.* (2005) "Anxiolytic effects of Maxipost (BMS-204352) and retigabine via activation of neuronal Kv7 channels," *The Journal of pharmacology and experimental therapeutics*, 314(1), pp. 282–292.

Kuo, J. J. *et al.* (2004) "Hyperexcitability of cultured spinal motoneurons from presymptomatic ALS mice," *Journal of neurophysiology*. physiology.org, 91(1), pp. 571–575.

Lam, A. D. *et al.* (2017) "Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease," *Nature medicine*, 23(6), pp. 678–680.

Lang, P. M. *et al.* (2008) "Retigabine reduces the excitability of unmyelinated peripheral human axons," *Neuropharmacology*, 54(8), pp. 1271–1278.

Lee, I.-C. *et al.* (2019) "KCNQ2 mutations in childhood nonlesional epilepsy: Variable phenotypes and a novel mutation in a case series," *Molecular genetics & genomic medicine*, 7(7), p. e00816.

Li, S., Choi, V. and Tzounopoulos, T. (2013) "Pathogenic plasticity of Kv7.2/3 channel activity is essential for the induction of tinnitus," *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 110(24), pp. 9980–9985.

Liu, C., Glowatzki, E. and Fuchs, P. A. (2015) "Unmyelinated type II afferent neurons report cochlear damage," *Proceedings of the National Academy of Sciences of the United States of America*, 112(47), pp. 14723–14727.

McCullagh, E. A. *et al.* (2020) "Mechanisms underlying auditory processing deficits in Fragile X syndrome," *FASEB journal: official publication of the Federation of American Societies for Experimental Biology*. doi: 10.1096/fj.201902435R.

Neufeld, J. *et al.* (2021) "A co-twin-control study of altered sensory processing in autism," *Autism: the international journal of research and practice*, 25(5), pp. 1422–1432.

Ng, F. L *et al.* (2011). Expression and function of the K+ channel KCNQ genes in human arteries. *British Journal of Pharmacology*, *162*(1), 42–53.

Nodera, H. *et al.* (2011) "Neuroprotective effects of Kv7 channel agonist, retigabine, for cisplatin-induced peripheral neuropathy," *Neuroscience letters*, 505(3), pp. 223–227.

Palop, J. J. *et al.* (2007) "Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease," *Neuron*, 55(5), pp. 697–711.

Park, B.K., *et al.* (2011); *Nat. Rev. Drug Discov*, *10*, 292-306.

Pasinelli, P. and Brown, R. H. (2006) "Molecular biology of amyotrophic lateral sclerosis: insights from genetics," *Nature reviews. Neuroscience*, 7(9), pp. 710–723.

Peñagarikano, O. *et al.* (2011) "Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits," *Cell*, 147(1), pp. 235–246.

Simkin, D. and Kiskinis, E. (2018) "Modeling Pediatric Epilepsy Through iPSC-Based Technologies," *Epilepsy currents / American Epilepsy Society*, 18(4), pp. 240–245.

Soh, H. *et al.* (2018) "Deletion of KCNQ2/3 potassium channels from PV+ interneurons leads to homeostatic potentiation of excitatory transmission," *eLife*, 7. doi: 10.7554/eLife.38617.

Srivastava, S. and Sahin, M. (2017) "Autism spectrum disorder and epileptic encephalopathy: common causes, many questions," *Journal of neurodevelopmental disorders*, 9, p. 23.

Styr, B. and Slutsky, I. (2018) "Imbalance between firing homeostasis and synaptic plasticity drives early-phase Alzheimer's disease," *Nature neuroscience*, 21(4), pp. 463–473.

Tan, A. *et al.* (2018) "Effects of the KCNQ channel opener ezogabine on functional connectivity of the ventral striatum and clinical symptoms in patients with major depressive disorder," *Molecular psychiatry*. doi: 10.1038/s41380-018-0283-2.

Tanaka, M. *et al.* (2012) "GABRB3, Epilepsy, and Neurodevelopment," in Noebels, J. L. et al. (eds.) *Jasper's Basic Mechanisms of the Epilepsies*. Bethesda (MD): National Center for Biotechnology Information (US).

Thye, M. D. *et al.* (2018) "The impact of atypical sensory processing on social impairments in autism spectrum disorder," *Developmental cognitive neuroscience*. Elsevier, 29, pp. 151–167.

Vossel, K. A. *et al.* (2013) "Seizures and epileptiform activity in the early stages of Alzheimer disease," *JAMA neurology*, 70(9), pp. 1158–1166.

Waaler, P. E. *et al.* (2000) "Prevalence, classification, and severity of epilepsy in children in western Norway," *Epilepsia*, 41(7), pp. 802–810.

Wainger, B. J. *et al.* (2014) "Intrinsic membrane hyperexcitability of amyotrophic lateral sclerosis patient-derived motor neurons," *Cell reports*, 7(1), pp. 1–11.

Wainger, B. J. *et al.* (2021) "Effect of Ezogabine on Cortical and Spinal Motor Neuron Excitability in Amyotrophic Lateral Sclerosis: A Randomized Clinical Trial," *JAMA neurology*, 78(2), pp. 186–196.

Wang, H. S. *et al.* (1998) "KCNQ2 and KCNQ3 potassium channel subunits: molecular correlates of the M-channel," *Science*. American Association for the Advancement of Science, 282(5395), pp. 1890–1893.

Wu, Z. *et al.* (2017) "Activation of KCNQ Channels Suppresses Spontaneous Activity in Dorsal Root Ganglion Neurons and Reduces Chronic Pain after Spinal Cord Injury," *Journal of neurotrauma*, 34(6), pp. 1260–1270.

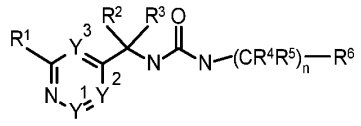
Xu, W. *et al.* (2010) "Activation of voltage-gated KCNQ/Kv7 channels by anticonvulsant retigabine attenuates mechanical allodynia of inflammatory temporomandibular joint in rats," *Molecular pain*, 6, p. 49.

Zhang, F. *et al.* (2018) "Fragile X mental retardation protein modulates the stability of its m6A-marked messenger RNA targets," *Human molecular genetics*. Oxford Academic, 27(22), pp. 3936–3950.

Zhao, G. *et al.* (2020) "Gene4Denovo: an integrated database and analytic platform for de novo mutations in humans," *Nucleic acids research*. Oxford Academic, 48(D1), pp. D913–D926.

Summary of the Invention

In some aspects, provided herein is a pharmaceutical composition comprising a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof:



(I'),

wherein R^1, R^2, R^3, R^4, R^5, Y^1, Y^2, Y^3, n and R^6 are as defined herein.

In a further aspect, the present invention provides compounds of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof.

In a further aspect, the present invention provides a process for the preparation of a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof.

In a further aspect, the present invention provides a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt, when manufactured according to a process described herein.

In a further aspect, the present invention provides a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the same, for use as therapeutically active substance.

In a further aspect, the present invention provides a compound of formula (I') , or a solvate or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the same, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2.

In a further aspect, the present invention provides the use of a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the same, in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2.

In a further aspect, the present invention provides the use of a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising

the same, for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2.

In a further aspect, the present invention provides a method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2, which method comprises administering a therapeutically effective amount of a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising the same.

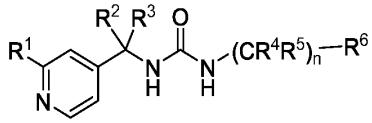
In a further aspect, the present invention provides a kit for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2, comprising:

a) a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or a pharmaceutical composition for use comprising the same; and
b) instructions for use.

In a further aspect, the present invention provides the invention as hereinbefore described.

The compounds of formula (I') , or a solvate or a pharmaceutically acceptable salts thereof, as described herein, provide for a combination of favorable pharmacological properties, such as for example potency, selectivity, and metabolic stability. A reasonable metabolic stability is important to ensure a suitable pharmacological half life, which is best achieved with compounds that have a human liver microsomal clearance below 20 uL/min/mg. Selectivity within the Kv7 family is desirable to avoid actions on tissues without therapeutic potential for the indications described in this invention. For example, actions on Kv7.4 and Kv7.5 in skeletal and smooth muscle impact the function of human arteries, where KCNQ2 expression is minimal or undetected in these tissues (Ng et al 2011).

The same embodiments as described above are included for a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein R^1, R^2, R^3, R^4, R^5, n and R^6 are as defined herein.

Detailed Description of the Invention

Definitions

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein, unless incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any embodiments explicitly disclosed herein. Any embodiment described in this application can be combined with any other embodiment. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, and abstract), or to any novel one, or any novel combination, of the any embodiment, or any steps of any method or process so disclosed.

"Administer", "administered", or "administering" when used for the therapeutic and/or prophylactic treatment of disorders, diseases, or disabilities as described herein means the giving of a compound of this invention to a patient or subject by any method, e.g. by infusion, inhalation, injection, paste, suppository, or tablet, etc..

As used herein, the terms "including", "containing", and "comprising" are used in their open, non-limiting sense.

The articles "a" and "an" as used in this disclosure may refer to one or more than one (e.g., to at least one) of the grammatical object of the article. By way of example, "an element" may mean one element or more than one element.

As described herein, compunds of the present disclosure may be "unsubstituted" or "substituted" with one or more substituents (e.g., 1, 2, 3, 4, or 5), such as those illustrated generally herein, or as exemplified by particular classes, subclasses, and species of the present disclosure. In general, the term "substituted" refers to the replacement of a hydrogen atom in a given structure with a specified substituent. In some embodiments, more than one hydrogen atom is replaced with a specified substituent (e.g. when two hydrogen atoms are replaced with one oxo substituent). Combinations of substituents envisioned by the present disclosure are typically those that result in the formation of stable or chemically feasible compounds. In one embodiment, an optionally substituted group has one substituent. In another embodiment, an optionally substituted group has two substituents. In another embodiment, an optionally substituted group has three substituents. In another embodiment, an optionally substituted group has substituents as described herein.

As used herein, the term "unsubstituted" may mean that the specified group bears no substituents beyond the moiety recited (e.g., where valency is satisfied by hydrogen).

The terms "effective amount" or "therapeutically effective amount" refers to an amount of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of the afore-mentioned, being sufficient to produce a desired therapeutic outcome, such as reducing the severity of duration of, stabilizing the severity of, or elimintating one or more signs, symptoms or causes of a disease, disorder, or disability. For therapeutic use, beneficial or desired results may include, for example, decreasing one or more symptoms resulting from the disease, disorder, or disability (biochemical, histologic and/or behavioral), including its complications and intermediate pathological phenotypes presenting

during development of the disease, disorder, or disability, increasing the quality of life of those suffering from the disease, disorder, or disability, decreasing the dose of other medications required to treat the disease, disorder, or disability, enhancing effect of another medication, delaying the progression of the disease, disorder, or disability and/or prolonging survival of patients.

The term "pharmaceutically acceptable salt" refers to those salts which retain the biological effectiveness and properties of the free bases or free acids, which are not biologically or otherwise undesirable. The salts are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, in particular hydrochloric acid, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, N-acetylcystein and the like. In addition these salts may be prepared by addition of an inorganic base or an organic base to the free acid. Salts derived from an inorganic base include, but are not limited to, the sodium, potassium, lithium, ammonium, calcium, magnesium salts and the like. Salts derived from organic bases include, but are not limited to salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, lysine, arginine, N-ethylpiperidine, piperidine, polyimine resins and the like.

The term “excipient” or “pharmaceutical excipients” as used herein refers to any pharmaceutically acceptable excipient that may be used in the production of a drug or pharmaceutical composition, such as a tablet containing a compound as described herein (or tautomer or pharmaceutically acceptable salt) as an active ingredient. Various substances may be embraced by the term excipient, including without limitation any substance used as a diluent, filler, extender, binder, disintegrant, glidant, humectant, coating, emulsifier or dispersing agent, compression/encapsulation aid, cream or lotion, lubricant, solution for parenteral administration, material for chewable tablets, sweetener or flavoring, suspending/gelling agent, or wet granulation agent. Disintegrant refers to excipients that expand and dissolve when wet causing the

tablet to break apart in the body and release the active ingredient for absorption. Examples include cross-linked polymers like crospovidone, croscarmellose sodium, etc. and modified starches like sodium starch glycolate. Filler refers to excipients that fill out the size of a tablet by increasing the bulk volume. Fillers make it possible for the final product to have the proper volume for patient handling. Examples of fillers are plant cellulose, lactose, starch, mannitol, etc. Specific examples are lactose monohydrate like Pharmatose 200M, microcrystalline cellulose (MCC) like Avicel PH101, or Avicel PH102 and spray dried lactose like Fast Flo 316™. Binders refers to excipients that hold the ingredients in a tablet together. Binders ensure that tablets and granules can be formed with required mechanical strength. Examples of binders are, polyvinlypyrrolidon (PV), hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), cellulose, sugar alcohols like sorbitol, proteins like gelatin and polymers like PVP, e.g. copovidone (PVP/VA 64), PEG, etc. Lubricants refer to excipients that prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine. Lubricants also ensure that tablet formation and ejection can occur with low fraction between active ingredient and wall. Examples of lubricants are minerals like talc or silica and fats like stearin, magnesium stearate, etc. Coatings may include, e.g., cellulose acetate phthalate, ethylcellulose, gellan gum, maltodextrin, enteric coatings, etc.; compression/encapsulation aids include e.g. calcium carbonate, dextrose, fructose dc (dc – "directly compressible"), honey dc, lactose (anhydrate or monohydrate; optionally in combination with aspartame, cellulose, or microcrystalline cellulose), starch dc, sucrose, etc. Creams or lotions include, e.g., maltodextrin, carrageenans, etc.. Materials for chewable tablets include, e.g. dextrose, fructose dc, lactose (monohydrate, optionally in combination with aspartame or cellulose), etc.. Suspending/gelling agents include, e.g., carrageenan, sodium starch glycolate, xanthan gum, etc.. Sweeteners include, e.g., aspartame, dextrose, fructose dc, sorbitol, sucrose dc, etc.. Wet granulation agents include, e.g., calcium carbonate, maltodextrin, microcrystalline cellulose, etc. In some cases, the term "excipient" ecompasses pharmaceutically acceptable carriers. The skilled person knows suitable pharmaceutical compositions to be used in the treatment of patients and how to produce them.

The term a "patient" or "subject" may encompass both mammals and non-mammals. Examples of mammals may include, but are not limited to, any member of the class *Mammalia*:

humans; nonhuman primates such as chimpanzees, monkeys, baboons, or rhesus monkeys, as well as other apes and monkey species; farm animals such as cattle, horses, sheep, goats, and swine; companion animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs; and the like. Examples of non-mammals include, but are not limited to, birds, fish, and the like. "Patient" or "subject" may include both human and animals. In some preferred embodiments, the "patient" or "subject" is a human.

As used herein, the terms "treat" or "treatment" are meant to indicate a postponement of development of one or more disease(s), disorder(s), or disability(ies); preventing the development of one or more disease(s), disorder(s), or disability(ies); and/or reducing severity of one or more symptoms of a disease, disorder, or disability that will or are expected to develop. Thus, these terms may include ameliorating one or more existing disease, disorder, or disability symptoms; preventing one or more additional symptoms; ameliorating or preventing the underlying causes of one or more symptoms; inhibiting the diseases, disorder, or disability, e.g., arresting the development of the diseases, disorder, or disability; relieving the diseases, disorder, or disability; causing regression of the diseases, disorder, or disability; relieving a symptom caused by the diseases, disorder, or disability; or stopping or alleviating the symptoms of the diseases, disorder, or disability.

Compounds of the invention and disclosure may exist as solvates. The term "solvate" may refer to a complex of variable stoichiometry formed by a solute and solvent. Such solvents for the purpose of the disclosure may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, MeOH, EtOH, and AcOH. Solvates wherein water is the solvent molecule are typically referred to as hydrates. Hydrates may include compositions containing stoichiometric amounts of water, as well as compositions containing variable amounts of water.

The term "prophylaxis" as used herein includes: preventing or delaying the appearance of clinical symptoms of diseases, disorder, or disability developing in a patient or subject, especially a human, that may be afflicted with or predisposed to the disease, disorder, or disability as

described herein, but does not yet experience or display clinical or subclinical symptoms of the disease, disorder, or disability.

As used herein, the term "about," when referring to a value is meant to encompass variations of, for example, in some embodiments ± 20%, in some embodiments ± 10%, in some embodiments ± 5%, in some embodiments ± 1%, in some embodiments ± 0.5%, and in some embodiments ± 0.1% from the specified amount, as such variations are appropriate to perform the disclosed methods or employ the disclosed compositions.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit, unless the context clearly dictates otherwise, between the upper and lower limit of the range and any other stated or intervening value in that stated range, is encompassed within the invention. The upper and lower limits of these small ranges which may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

Numerical ranges, as used herein, may include sequential integers. For example, a range expressed as "from 0 to 5" would include 0, 1, 2, 3, 4, and 5.

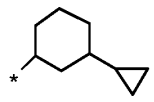
A "metabolite" is a product produced through metabolism in the body of a specified compound or salt thereof. Metabolites of a compound may be identified using routine techniques known in the art and their activities determined using tests such as those described herein. Such products may result e.g. from the oxidation, reduction, hydrolysis, amidation, deamidation, esterification, deesterification, enzymatic cleavage, and the like, of the administered compound. Accordingly, the invention includes metabolites of compounds of the invention, including compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof.

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications,

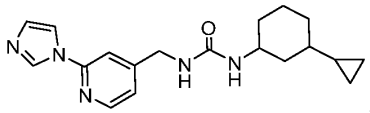
usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

The terms “compound of this invention,” and “compounds of the present invention” and “compounds or formuala (I’)”, or “compounds of formula (I)” include compounds of formula (I’) or formula (I), compounds selected from any of formulae (I*), (I**), (II), (III) etc., compounds selected from tables 1-9, solvates, pharmaceutically acceptable salts, stereoisomers, geometric isomers, tautomers, metabolites, prodrugs, polymorphs; and mixtures thereof.

The symbols "*" at the end of a bond or "- - - " drawn through a bond each refer to the point of attachment of a functional group or other chemical moiety to the rest of the molecule of which it is a part. Thus, for example:



means that the subsituent is attached to the rest of the molecule as shown



A bond drawn into ring system (as opposed to connected at a distinct vertex) indicates that the bond may be attached to any of the suitable ring atoms.

The term “optional” or “optionally” as used herein means that a 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. For example, “optionally substituted” means that the optionally substituted moiety may incorporate a hydrogen atom or a substituent. “Optionally substituted” means that a compound can be unsubstituted or substituted as defined herein. “Optionally substituted” means that a given substituent can be unsubstituted or futher be substituted with certain substituents as defined herein and listed in the different embodiments. E.g. as a non-limiting example, the wording R^6 can be

cyclobutyl optionally substituted with one or two C_{1-6}alkyl means that R^6 comprises unsubstituted cyclobutyl or cyclobutyl substituted with one or two C_{1-6}alkyl.

The term "independently" is used herein to indicate that a variable is applied in any one instance without regard to the presence or absence of a variable having that same or a different definition within the same compound. Thus, in a compound in which R" appears twice and is defined as "independently carbon or nitrogen", both R"s can be carbon, both R"s can be nitrogen, or one R" can be carbon and the other nitrogen. In an additon, e.g. in a compound in which e.g. R^2 and R^3 are independently selected from hydrogen and hydroxyC_{1-6}alkyl, both R^2 and R^3 can be hydrogen, or both can be hydroxyC_{1-6}alkyl, or one of R^2 and R^3 can be hydrogen and the other one hydroxyC_{1-6}alkyl.

In this application the units ul, uMol, C etc. mean µl, µMol, °C etc.

In this application, in the expression “forming a saturated monocyclic 3-5 membered cycloalkyl”, as formed by R^2/R^3 and/or R^4/R^5 as described herein, the “saturated monocyclic 3-5 membered cycloalkyl” means an optionally substituted cycloalkyl selected from cyclopropyl, cyclobutyl, and cyclopentyl, which are optionally substituted with halogen or haloC_{1-6}alkyl. In particular the cycloalkyl, e.g. cyclopropyl, is unsubstituted.

In this application in the expression “forming a saturated monocyclic 3-6 membered cycloalkyl”, as formed by R^2/R^3 and/or R^4/R^5 as described herein, the “saturated monocyclic 3-6 membered cycloalkyl” means an optionally substituted cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, which are optionally substituted with halogen or haloC_{1-6}alkyl. In particular, the cycloalkyl, e.g. cyclopropyl, is unsubstituted.

The term “EC_{50}” in this application is defined as: the agonistic effect of a compound can be determined by testing the compound in an in vitro assay as described herein, whereby the effect of the compound is measured across a range of compound concentrations. The resulting data is plotted as a concentration response curve, which typically follows a sigmoidal function, whereby the concentration of the compound is plotted on the x axis and the response (agonistic effect) is

plotted on the y axis. The term "EC_{50}" is the "half maximal effective concentration" and denotes the concentration of a particular compound required to obtain 50% of the maximum response (E_{max}) which is observed for that compound in the given in vitro assay.

A compound of this invention may exist in one or more stereoisomeric forms (e.g., it contains one or more asymmetric carbon atoms). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the subject matter disclosed herein. Likewise, it is understood that a compound or salt may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the subject matter disclosed herein. It is to be understood that the subject matter disclosed herein includes combinations and subsets of the particular groups described herein. The scope of the subject matter disclosed herein includes mixtures of stereoisomers as well as purified enantiomers or enantiomerically/ diastereomerically enriched mixtures. It is to be understood that the subject matter disclosed herein includes combinations and subsets of the particular groups defined herein.

A compound of this invention can contain several asymmetric centers and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereioisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates.

According to the Cahn-Ingold-Prelog Convention, the asymmetric carbon atom can be of the "R" or "S" configuration.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. Chiral separation of a racemate to its enantiomeric components may be performed to separate the eutomer and the distomer.

The term "stereoisomers" refers to compounds, which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, e.g. melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., *McGraw-Hill Dictionary of Chemical Terms* (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., New York, 1994. The compounds of the invention may contain asymmetric or chiral centers, and therefore exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of the invention, including but not limited to, diastereomers, enantiomers and atropisomers, as well as mixtures thereof such as racemic mixtures, form part of the present invention. Any organic compounds exist in optically active forms, i.e., they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L, or *R* and *S,* are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process.

The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and imine-enamine isomerizations. Valence tautomers include interconversions by reorganization of some of the bonding electrons.

It should be understood that individual enantiomers and diastereomers are included in the tables below by compound name, and their corresponding structures can be readily determined therefrom. In some instances, the enantiomers or diastereomers are identified by their respective properties, for example, retention times on a chiral HPLC or their biological activities (e.g., as described further in the Examples), and the absolute stereo configurations of one or more chiral centers are arbitrarily assigned (e.g., stereochemistry of all chiral centers is arbitrarily assigned, or stereochemistry of one chiral center is known and remaining chiral centers arbitrarily assigned, etc.).

In some embodiments of the invention only one of the possible enantiomers are used. In other embodiments mixtures of the possible enantiomers having different percentages for each component are used.

In some embodiments, compounds of this invention re isotopically-labeled by having one or more atoms therein replaced by an atom having a different atomic mass or mass number. Such isotopically-labeled (e.g.., radiolabeled) compounds of formula (I`) or (I), or a solvate or a pharmaceutically acceptable salts thereof, are considered to be within the scope of this disclosure. Examples of isotopes that can be incorporated into the compounds of formula (I`) or (I), or a solvate or a pharmaceutically acceptable salts thereof, include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine, and iodine, such as, but not limited to, ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{13}N, ^{15}N, ^{15}O, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, and ^{125}I, respectively. Certain isotopically-labeled compounds of formula (I`) or (I), or a solvate or a pharmaceutically acceptable salts thereof, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e., ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and

ready means of detection. For example, a compound of this invention can be enriched with 1, 2, 5, 10, 25, 50, 75, 90, 95, or 99 percent of a given isotope.

Substitution with positron emitting isotopes, such as ^{3}H, ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy. Isotopically-labeled compounds of this invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the Examples as set out below using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

In one embodiment, the present invention provides pharmaceutically acceptable salts of the compounds of this invention as described herein, especially pharmaceutically acceptable salts selected from hydrochlorides, fumarates, lactates (in particular derived from L-(+)-lactic acid), tartrates (in particular derived from L-(+)-tartaric acid) and trifluoroacetates. In yet a further particular embodiment, the present invention provides compounds of this inventio, as described herein (i.e., as "free bases" or "free acids", respectively).

When a bond in a compound formula herein is drawn in a non-stereochemical manner (e.g. flat), the atom to which the bond is attached includes all stereochemical possibilities. When a bond in a compound formula herein is drawn in a defined stereochemical manner (e.g. bold, bold-wedge, dashed or dashed-wedge), it is to be understood that the atom to which the stereochemical bond is attached is enriched in the absolute stereoisomer depicted unless otherwise noted. In one embodiment, the compound may be at least 51% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 80% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 90% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 95% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 97% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 98% the absolute stereoisomer depicted. In another embodiment, the compound may be at least 99% the absolute stereoisomer depicted.

The term "alkyl" refers to a mono- or multivalent, e.g., a mono- or bivalent, linear or branched saturated hydrocarbon group of 1 to 6 carbon atoms ("C_{1-6}alkyl"), e.g., 1, 2, 3, 4, 5, or 6

carbon atoms. In some embodiments, the alkyl group contains 1 to 3 carbon atoms, e.g., 1, 2 or 3 carbon atoms. Some non-limiting examples of methyl (CH_3-), ethyl (CH_3CH_2-), n-propyl ($CH_3CH_2CH_2$-), 2-propyl (isopropyl, $(CH_3)_2CH_2$-), n-butyl ($CH_3CH_2CH_2CH_2$-), iso-butyl ($(CH_3)_2CH_2CH_2$-), sec-butyl ($CH_3CH(CH_3)CH_2$-), and tert-butyl ($(CH_3)_3C$-). Preferred, yet non-limiting, examples of alkyl are tert-butyl ($(CH_3)_3C$-) or methyl (CH_3-). A preferred, yet non-limiting, example of alkyl is methyl (CH_3-). Another preferred, yet non-limiting, example of alkyl is tert-butyl ($(CH_3)_3C$-).

The term "alkoxy" refers to an alkyl group, as previously defined, attached to the parent molecular moiety via an oxygen atom. The alkoxy group contains 1 to 6 carbon atoms ("C_{1-6}alkoxy"), e.g. 1, 2, 3, 4, 5, or 6 carbon atoms. In other embodiments, the alkoxy group contains 1 to 4 carbon atoms. In still other embodiments, the alkoxy group contains 1 to 3 carbon atoms. Some non-limiting examples of alkoxy groups include CH_3O- (methoxy), CH_3CH_2O- (ethoxy), $CH_3CH_2CH_2O$- (n-propoxy), and $(CH_3)_3CO$- (tert-butoxy). A particularly preferred, yet non-limiting, example of alkoxy is methoxy (CH_3O-).

The term "C_{3-5}cycloalkylC_{1-6}alkoxy" as used herein refers to an alkoxy group, wherein at least one of the hydrogen atoms was replaced by a C_{3-5}cycloalkyl group. Preferably, "C_{3-5}cycloalkylC_{1-6}alkoxy" refers to an alkoxy group wherein one, two, or three hydrogen atoms of the alkoxy group have been replaced by a C_{3-5}cycloalkyl group. Preferably, "C_{3-5}cycloalkylC_{1-6}alkoxy" refers to an alkoxy group wherein one hydrogen atom of the alkoxy group has been replaced by a C_{3-5}cycloalkyl group. Preferably, the alkoxy group comprises one C-atom. Preferred, yet not-limiting, examples are 2-cyclopropylmethoxy and 2-cyclobutylmethoxy.

The term "cyanoC_{1-6}alkoxy" as used herein refers to an alkoxy group, wherein at least one of the hydrogen atoms was replaced by a cyano group. Preferably, "cyanoC_{1-6}alkoxy" refers to an alkoxy group wherein one, two, or three hydrogen atoms of the alkoxy group have been replaced by a cyano group. Preferably, "cyanoC_{1-6}alkoxy" refers to an alkoxy group wherein one hydrogen atom of the alkoxy group has been replaced by a cyano group. Preferably, the alkoxy group comprises one C-atom. In one embodiment, "cyanoC_{1-6}alkoxy" is selected from NC-CH_2O-, NC-CH_2CH_2O-, and NC$CH_2CH_2CH_2O$-. In a preferred embodiment, the cyanoC_{1-6}alkoxy is NC-

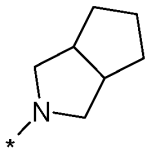
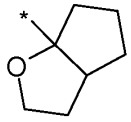
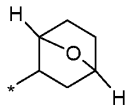
CH_2O-. A preferred, a yet not-limiting, example is NC-CH_2O-. A preferred example is 2-cyanomethoxy with the structure NC-CH_2O-.

The term "halogen" or "halo" refers to fluoro (F), chloro (Cl), bromo (Br), or iodo (I). Preferably, the term "halogen" or "halo" refers to fluoro (F), chloro (Cl) or bromo (Br). Particularly preferred, yet non-limiting examples of "halogen" or "halo" are fluoro (F) and chloro (Cl).

The term "cycloalkyl" as used herein refers to a monocyclic, or polycyclic, saturated or partly unsaturated, non-aromatic 3-10 membered monocyclic, or polycyclic hydrocarbon group of 3-10 ring carbon atoms ("C_{3-10}cycloalkyl"). In a preferred embodiment, the cycloalkyl is a 4-10 membered cycloalkyl. In some embodiments, the 4-10 membered cycloalkyl groups are monocyclic or bicyclic. In some embodiments, the cycloalkyl group is a saturated monocyclic 3-5 or a 4-6 membered hydrocarbon group of 3 to 5 or 4 to 6 ring carbon atoms, e.g., of 3, 4, or 5; or 4, 5, or 6 carbon atoms. In a preferred embodiment, the saturated monocyclic 3-6 or 4-6 membered cycloalkyl is selected from cyclobutyl, cyclopentyl, and cyclohexyl. In some embodiments, cycloalkyl comprises one or two non-aromatic double bond(s). In some embodiments, cycloalkyl comprises one non-aromatic double bond. In some embodiments, cycloakyl is a monocyclic 4-6 membered cycloalkenyl group with one non-aromatic double bond. In some embodiments, cycloalkenyl is selected from cyclobutenyl, cyclopentenyl, and cyclohexenyl. Polycyclic and bicyclic cycloalkyl groups may include fused, or bridged polycyclic or bicyclic moieties, wherein each ring is a saturated or partially unsaturated, non-aromatic hydrocarbon. Cycloalkyl comprises bicyclic cycloalkyl referring to 4-10 membered bridged cycloalkyl moieties consisting of two saturated carbocycles having two carbon atoms in common, i.e., the bridge separating the two rings is either a single bond or a chain of one or two ring atoms. In some embodiments the cycloalkyl is a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings. In one preferred embodiment, cycloalkyl is selected from a 4-10 membered bridged cycloalkyl, a saturated monocyclic 3-6 or 4-6 membered cycloalkyl group, a 6 membered cycloalkenyl group, or a 7-10 membered bicycylic fused cycloalkyl. In one particularily preferred embodiment, cycloalkyl is selected from a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl group, or a 7-10 membered

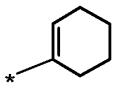
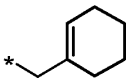
bicycylic fused cycloalkyl. In some examples the 4-10 membered bridged cycloalkyls are selected from bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and adamantane. In some examples the 4-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings are selected from bicyclo[3.1.0]hexanyl, octahydropentalenyl, bicyclo[3.2.0]heptanyl, bicyclo[3.2.1]octanyl, bicyclo[3.2.2]octanyl, and hexahydropentalenyl. In some cases, cycloalkyl does not include bicyclic or polycyclic spiro cycloalkyl ring systems. Some non-limiting examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexanyl, bicyclo[3.2.1]octanyl, adamantane, bicyclo[3.2.0]heptanyl, bicyclo[3.2.1]octanyl and hexahydropentalenyl and octahydropentalene. Other examples can be found in the tables of this application.

"Heterocycloalkyl" or "heterocyclyl" as used herein refers to non-aromatic, monocyclic, or polycyclic ring systems containing carbon and at least one ring heteroatom forming a 5-12 membered heterocycloalkyl. Heterocycles are for example described in Paquette, Leo A.; "Principles of Modern Heterocyclic Chemistry" (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; "The Chemistry of Heterocyclic Compounds, A series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. In some embodiments, the heterocycloalkyl is bicyclic. In some embodiments, the heteroatom is independently selected from the group consisting of N-atoms, O-atoms, and S-atoms. In some embodiments, the heteroatom is an O-atom. The heterocycloalkyl group may be saturated or partially unsaturated, and unless otherwise specified, may comprise 5, 6, 7, 8, 9, 10, 11, 12, or more ring atoms, where ring atoms refer to the sum of carbon and heteroatoms in the one or more rings (e.g., be a 5 membered, 6 membered, 7 membered, 8 membered, 9 membered, 10 membered, 11 membered, or 12 membered heterocycloalkyl). Heterocycloalkyl may include groups comprising 1 to 5 ring heteroatoms, 1 to 4 heteroatoms, 1 to 3 ring heteroatoms, 1 or 2 ring heteroatoms, or 1 ring heteroatom. In some embodiments, the 1 ring atom is an O-atom. In some embodiments the heterocycloalkyl is a monocyclic 4-6 membered heterocycloalkyl. In some embodiments, the heterocycloalkyl comprises one ring, two rings, three rings, four rings, or more, for example as a polycyclic fused

system. In some embodiments, the heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein one ring comprises one O-atom. In some embodiments, the heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring or two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, e.g. dihydrochromenyl . In some embodiments the bicyclic fused heterocycloalkyl comprises one or two non-aromatic double bond(s). In some embodiments, heterocycloalkyl comprises one non-aromatic double bond. In some embodiments, the heterocycloalkyl is a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, e.g. cyclopenta[c]pyrrolyl having the structure  or hexahydrocyclopenta[b]furan-6a-yl having e.g. the structure  . In some embodiments, heterocycloalkyl comprises a 7-10 membered bridged heterosystem, wherein the bridge comprises an O-atom, e.g. oxabicyclo[2.2.1]heptanyl e.g. having the structure  . In some embodiments, heterocycloalkyl is selected from bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom. In some particularily preferred embodiments heterocycloalkyl is selected froma 5-12 membered heterocycloalkyl, which heterocycloalkyl is a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom. In some cases, heterocycloalkyl does not include bicyclic or polycyclic spiro heterocycloalkyl ring systems. Preferered, but not

limiting, examples of heterocycloalkyl include, oxetanyl, dihydrochromenyl, hexahydrocyclopenta[b]furanyl. Other examples can be found in the tables of this application.

"Heterocyclyloxy" as used herein refers to a C_{1-6}alkoxy group, wherein a 4-6 membered heterocycloalkyl group is linked to an -O- to form an alkoxy group. Preferably, a yet not-limiting, example is oxetanyloxy (specifically oxetan-3-yloxy).

"C_{1-6}alkyl-6 membered cycloalkenyl" as used herein refers to a C_{1-6}alkyl group, wherein a 6 membered heterocycloalkyl group is linked to the alkyl group. Preferably, yet not-limiting, examples are  or  .

"Heteroaryl" as used herein refers to a 5 or 6 membered monocyclic, aromatic group comprising at least one ring heteroatom. In some embodiments, the heteroatom is independently selected from the group consisting of N-atoms, O-atoms, and S-atoms. The number of ring atoms refer to the sum of carbon and heteroatoms in the one ring. In some embodiment, heteroaryl is a 5 or 6 membered moncyclic, aromatic group with two N-atoms. In some embodiments, heteroaryl is a 5 or 6 membered monocyclic aromatic group comprising one N-atom. In some embodiments, heteroaryl is a 5 or 6 membered monocyclic aromatic group comprising one N-atom and one O-atom. Examples of 5 membered heteroaryl groups include, but are not limited to, pyrrolyl pyrazolyl, imidazolyl, oxazolyl, triazolyl, or furanyl. In some preferred embodiments, 5 membered heteroaryl is pyrazolyl, imidazolyl, or oxazolyl. In some more preferred embodiments, 5 membered heteroaryl is pyrazolyl or imidazolyl. Examples of 6 membered heteroaryl groups include, but are not limited to, pyrimidinyl, pyridinyl, pyrazinyl, or pyridazinyl. In some more preferred embodiments, 6 membered heteroaryl is pyrazinyl, pyridinyl or pyrimidinyl.

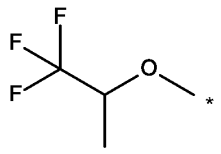
The term "cyano" refers to a –CN (nitrile) group.

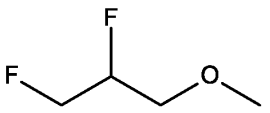
The term "oxo" refers to an =0 group.

The term "hydroxy" or "hydroxyl" refers to an OH group.

The term "haloalkyl" refers to a C_{1-6}alkyl group, with one to six C-atoms, wherein at least one of the hydrogen atoms of the alkyl group has been replaced by one or more halogen atoms. Preferably, "haloalkyl" refers to an alkyl group wherein 1, 2 or 3 hydrogen atoms of the alkyl group have been replaced by a halogen atom, i.e. haloalkyl includes monohaloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like. Halogen atoms may be fluoro (F), chloro (Cl), or bromo (Br). Particularly preferred, yet non-limiting, examples of "halogen" are fluoro (F) and chloro (Cl). More preferably, haloalkyl is substituted with fluoro (F). As described above, the alkyl part can be linear or branched. Preferred, yet non-limiting, examples of haloalkyl are $(CH_3)_2FC$- (1-fluoro-isopropyl), CF_3CH_2- (2,2,2-trifluoroethyl), CH_3CF_2- (1,1-difluoroethyl), CF_3- (trifluoromethyl), CH_2F- (fluoromethyl), or CHF_2- (difluromethyl). Particularily preferred is $(CH_3)_2CF$- (1-fluoro-isopropyl).

"Haloalkoxy", as used herein, refers to a C_{1-6}alkoxy group, wherein at least one of the hydrogen atoms has been replaced by halogen atoms. Preferably, "haloalkoxy" refers to an alkoxy group wherein 1, 2, or 3 hydrogen atoms of the alkyl group have been replaced by a halogen atom, i.e. haloalkoxy includes monohaloalkoxy, dihaloalkoxy, trihaloalkoxy, perhaloaloxy and the like. Halogen atoms may be fluoro (F), chloro (Cl) or bromo (Br). Particularly preferred, yet non-limiting, examples of "halogen" are fluoro (F) and chloro (Cl). More preferably, haloalky is substituted with fluoro (F). The alkyl part of haloalkoxy can be linear or branched as describe above, and the haloalkoxy for example have the structure:

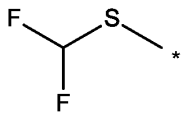


, or


. Preferred, yet non-limiting examples of haloalkoxy are CHF_2O-, CH_2FO- CF_3CH_2O-, CF_2HCH_2O-, $CH_3CF_2CH_2O$-, and CH_3CFHCH_2O-, $CH_3CF_2CH_2O$-, $CF_3CH(CH_3)O$-, or $FCHCH_2CHFCH_2O$-

"haloalkylthio" as used herein, refers to a thio group comprising a haloC_{1-6}alkyl group. Preferably, "haloalkylthio" refers to an alkylthio group wherein 1, 2, or 3 hydrogen atoms of the

alkyl group have been replaced by a halogen atom, i.e. haloalkylthio includes monohaloalkylthio, dihaloalkylthio, trihaloalkylthio, perhaloalkylthio and the like. Halogen atoms may be fluoro (F), chloro (Cl) or bromo (Br). Particularly preferred, yet non-limiting, examples of "halogen" are fluoro (F) and chloro (Cl). More preferably, haloalky is substituted with fluoro (F). The alkyl part of haloalkylthio can be linear or branched as describe above. Preferred, yet non-limiting examples of haloalkoxy are CHF_2S-, CH_2FS- CF_3CH_2S-, CF_2HCH_S-, $CH_3CF_2CH_2S$-, and CH_3CFHCH_2S-. A particularly preferred example has the structure:



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The term "hydroxyalkyl" refers to a C_{1-6}alkyl group, with one to six C-atoms, wherein at least one of the hydrogen atoms of the alkyl group has been replaced by one or more hydroxy. Preferably, "hydroxyalkyl" refers to an alkyl group wherein 1, 2 or 3 hydrogen atoms of the alkyl group have been replaced by hydroxy, i.e. hydroxyalkyl includes monohydroxyalkyl, dihydroxalkyl, trihydroxyalkyl, perhydroxyalkyl and the like. More preferably, "hydroxyalkyl" refers to a C_{1-6}alkyl group wherein one hydrogen atom has been replaced by hydroxy. The alkyl part of hydroxyalkyl can be linear or branched as describe above. Particularily prefered, yet not limiting examples of hydroxyalkyl are $HOCH_2$- (hydroxymethyl), $HOCH(CH_3)$-, $HOCH_2CH_2$- (hydroxyethyl), $HOCH_2CH_2CH_2$- (n-hydroxypropyl) and $HOCH_2CH_2CH_2CH_2$- (n-hydroxybutyl).

The term "mood disorder" as used herein relates to a mental health problem that primarily affects a person's emotional state. It is a disorder in which a person experiences long periods of extreme happiness, extreme sadness or both. Two of the most common mood disorders are depression and bipolar disorder.

The term "depression" as used herein relates to a mood disorder that causes a persistent feeling of sadness and loss of interest. It is also known as major depressive disorder (MDD).

The term "behavioral disorder" relates to disorders that involve a pattern of disruptive behaviors in children that last for at least 6 months and cause problems in school, at home and in social situations. Behavioral disorders involve a pattern of disruptive behaviors in children that last for at least 6 months and cause problems in school, at home and in social situations. The most important behavioral disorder is Attention deficit hyperactivity disorder" (ADHD).

The term "Attention deficit hyperactivity disorder" (ADHD) as used herein relates to a behavioral disorder characterized by inattention, or excessive activity and impulsivity. ADHD occurs more frequently in people with epilepsy than in the general population. Children with ADHD have an increased risk of seizures, with approximately 14% of children with ADHD developing seizures.

The term "developmental disorder" or "neurodevelopmental disorder" as used herein relates to a group of conditions caused by an impairment in physical, learning, language, or behavior areas. These conditions begin during the developmental period, may impact day-to-day functioning, and can last through a person's lifetime. Examples of neurodevelopment disorders include Autism Spectrum Disorder ("ASD") and syndromic developmental disorders.

The term "Autism Spectrum Disorder (ASD)" as used herein relates to a developmental disorder of variable severity that is characterized by difficulty in social interaction and communication and by restricted or repetitive patterns of thought and behavior. ASD encompasses mostly idiopathic but also syndromic forms and is currently diagnosed according to the diagnostic and statistical manual version 5 (DSM V).

The term "syndromic developmental disorder" as used herein relates to a development disorder with a clinically defined pattern of somatic abnormalities and a neurobehavioral phenotype that may include ASD. The diagnosis is typically confirmed by targeted genetic testing. Examples for syndromic development disorders include Dup15q syndrome (Dup15q), Fragile X syndrome (FXS) and Angelman syndrome.

The term "Dup15q syndrome" or "Duq15q" as used herein relates to the common name for chromosome 15q11.2-q13.1 duplication syndrome. This is a syndromic development disorder,

caused by the partial duplication of Chromosome 15, which confers a strong risk for autism spectrum disorder, epilepsy and intellectual disability.

The term "Fragile X syndrome" (FXS) as used herein relates to a genetic disorder characterized by mild-to-moderate intellectual disability. This disorder is typically caused by an expansion of the CGG triplet repeat within the FMR1 (fragile X mental retardation 1) gene on the X chromosome.

The term "Angelman syndrome" as used herein relates to a genetic disorder that mainly affects the nervous system due to a lack of function of part of chromosome 15 inherited from a person's mother. Characteristic features of this condition include delayed development, intellectual disability, severe speech impairment, and problems with movement and balance (ataxia). Most affected children also have recurrent seizures (epilepsy).

The term "Intellectual disability" (ID) used herein relates to a generalized neurodevelopmental disorder characterized by significantly impaired intellectual and adaptive functioning. It is defined by an IQ under 70, in addition to deficits in two or more adaptive behaviors that affect everyday, general living. ID is also known as a general learning disability and formerly known as mental retardation (MR).

The term "epilepsy" used herein relates to a neurological disorder marked by sudden recurrent episodes of sensory disturbance, loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain. Examples of epilepsies include broad pediatric epilepsies, West syndrome, Ohtahara syndrome and epileptic encephalopathy.

The term "neurodegenerative diseases" used herein relates to diseases that are related to e progressive loss of structure or function of neurons, including the death of neurons. Examples of neurodegenerative diseases include, but are not limited to, Alzheimer's disease and motor neuron diseases.

The term “motor neuron disease” used herein relates to a group of rare neurodegenerative disorders that selectively affect motor neurons. Examples of motor neuron diseases include, but are not limited to, amyotrophic lateral sclerosis (ALS).

The term “pain” as used herein relates to an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Examples of pain include, but are not limited to, nociceptive pain, chronic pain (including idiopathic pain), neuropathic pain including chemotherapy induced neuropathy, phantom pain and phsychogenic pain.

The term “migraine” as used herein relates to a moderate to severe headache disorder, causing throbbing or pulsating pain for hours or days.

The term “Tinnitus” as used herein relates to a symptom characterized by the perception of sound when no corresponding external sound is present.

Any disease, disorder, or disability described herein also includes any state or condition related to such disease, disorder, or disability.

Compounds of the invention

All compound names of compound structures were generated using OpenEye Lexichem, Version 1.2.0, OpenEye Scientific Software, Santa Fe, NM, USA; www.eyesopen.com.

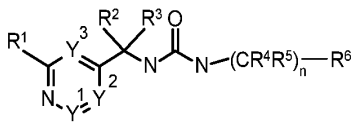
In all embodiments of this invention providing a compound of formula (I) or formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, the respective carbon atom and the respective substituents R^4 and R^5 are absent.

In some embodiments of this invention providing a compound of formula (I) or formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, R^2 and R^3, together with the one carbon atom to which they are attached to, do not form as saturated monocyclic cycloalkyl as described herein.

In some embodiments of this invention providing a compound of formula (I) or formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, the substituents R^4 or R^5 cannot be hydroxy.

In all embodiments of this invention providing a compound of formula (I) or formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2 or 3, the two or three pairs of R^4/R^5 can be identical or different as described herein.

The invention provides a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof:



(I')

Y^1 is CR^a or N;

Y^2 is CR^b or N;

Y^3 is CR^c or N;

provided that only 0 or 1 of Y^1, Y^2 and Y^3 is N and the others are CR^a, CR^b, or CR^c;

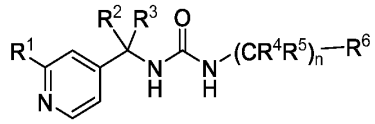
R^a is hydrogen or halogen;

R^b is hydrogen or halogen;

R^c is hydrogen or halogen;

and wherein R^1, R^2, R^3, R^4, R^5, n and R^6 are as described herein, for example as in claim 1.

In one particularily preferred embodiment, the invention provides a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, wherein zero of Y^1, Y^2, and Y^3 are N. In this embodiment Y^1, Y^2, and Y^3 are CR^a, CR^b or CR^c. In this embodiment the compound of formula (I') is of formula (I) with the structure:



(I)

wherein R^1, R^2, R^3, R^4, R^5, n and R^6 are as described herein.

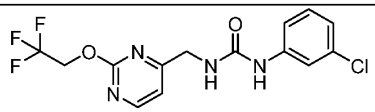
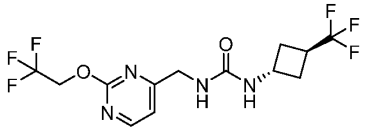
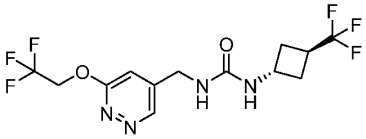
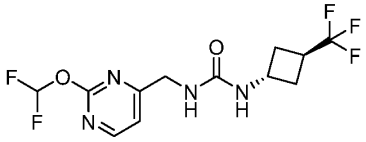
In one embodiment, the invention provides a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, wherein one of Y^1, Y^2, or Y^3 is N. In this embodiment the other ones of Y^1, Y^2, and Y^3 are are CR^a, CR^b or CR^c.

In one embodiment, the invention provides a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, wherein only Y^1 is N. In this embodiment, Y^2 and Y^3 are CR^b or CR^c.

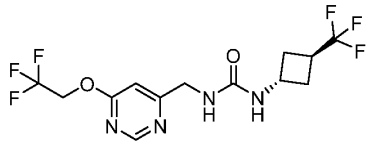
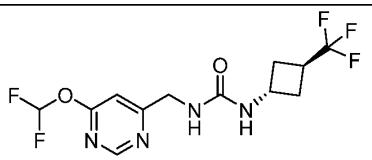
In one embodiment, the invention provides a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, wherein only Y^2 is N. In this embodiment, Y^1 and Y^3 are CR^a or CR^c.

In one embodiment, the invention provides a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof, wherein only Y^3 is N. In this embodiment, Y^1 and Y^2 are CR^a or CR^b.

This invention comprises the following compounds:

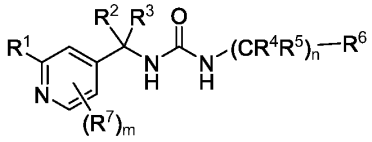
203	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]urea	
204	1-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
215	1-[[6-(2,2,2-trifluoroethoxy)pyridazin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
243	1-[[2-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-	

	(trifluoromethyl)cyclobutyl]urea	

279	1-[[6-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
282	1-[[6-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

All of the features and embodiments disclosed in this specification relating to Y^1, Y^2 and Y^3 (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

In one embodiment, the present invention provides a compound of formula (I*), or a solvate or pharmaceutically acceptable salt thereof:



(I*)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-}

$_{6}$alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

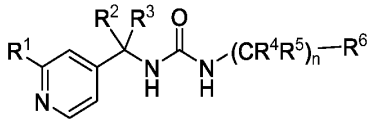
R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl;

n is 0, 1, 2, or 3;

R^7 is halogen, and

m is 0, 1, 2, or 3.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, haloC_{1-6}alkylthio, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl; wherein the 4-6 membered cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen; and wherein the haloC_{1-6}alkoxy is optionally substituted with C_{1-6}alkoxy.

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

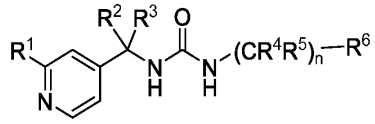
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, Si(C_{1-6}alkyl)$_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl, C_{2-6} alkynyl; and

n is 0, 1, 2, or 3.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl; wherein the 4-6 membered cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen; and wherein the haloC_{1-6}alkoxy is optionally substituted with C_{1-6}alkoxy.

R^2 and are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

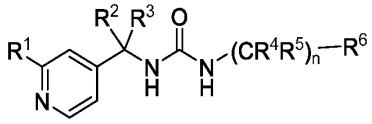
R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, Si(C_{1-6}alkyl)$_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted

with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl, C_{2-6} alkynyl; and

n is 0, 1, 2, or 3.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

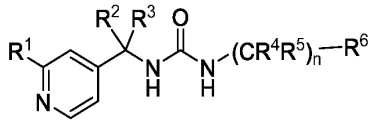
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, C_{1-6}alkyl-6 membered cycloalkenyl, C_{1-6}alkyl, Si(C_{1-6}alkyl)$_3$, haloC_{1-6}alkoxy and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, cycloalkenyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, hydroxy, oxo, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, , haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

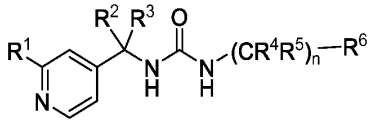
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, $Si(C_{1-6}alkyl)_3$, $haloC_{1-6}alkoxy$, and $haloC_{1-6}alkyl$, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, hydroxy, $hydroxyC_{1-6}alkyl$, and $haloC_{1-6}alkyl$; and

n is 0, 1, 2, or 3.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, $haloC_{1-6}alkoxy$, $haloC_{1-6}alkylthio$, a 4-6 membered heterocyclyloxy, halogen, $C_{3-5}cycloalkylC_{1-6}alkoxy$, and $cyanoC_{1-6}alkoxy$, wherein the heterocycloalkyl, $C_{3-5}cycloalkylC_{1-6}alkoxy$, or heterocyclyloxy are optionally substituted with one $C_{1-6}alkyl$ or $haloC_{1-6}alkyl$;

R^2 and R^3 are independently selected from hydrogen, deuterium, $C_{1-6}alkyl$, saturated monocyclic 3-5 membered cycloalkyl, $C_{1-6}alkoxy$, and $hydroxyC_{1-6}alkyl$; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

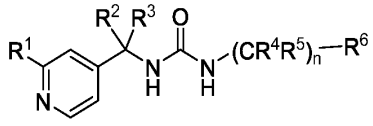
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, $Si(C_{1-6}alkyl)_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

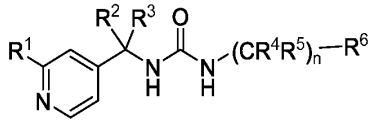
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, $Si(C_{1-6}alkyl)_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkyl, haloC_{1-6}alkoxy; and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

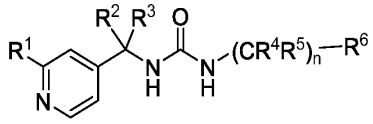
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, Si(C_{1-6}alkyl)$_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl,

heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkox, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

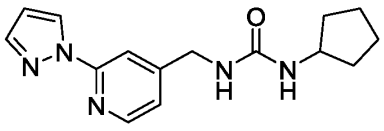
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, Si(C_{1-6}alkyl)$_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

provided that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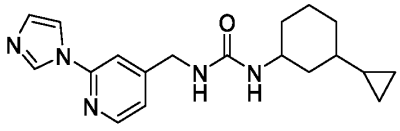
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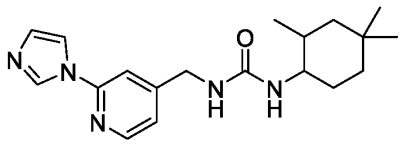
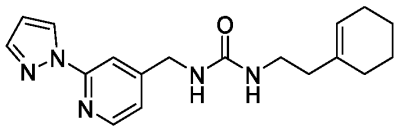
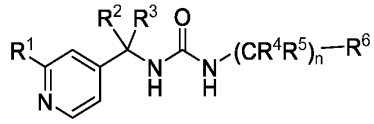


; and



are excluded.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

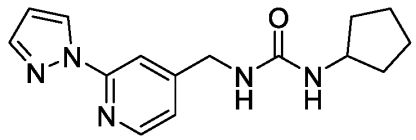
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, $Si(C_{1-6}alkyl)_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

provided that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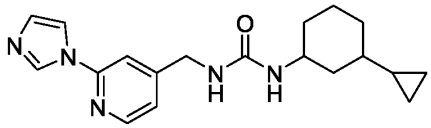
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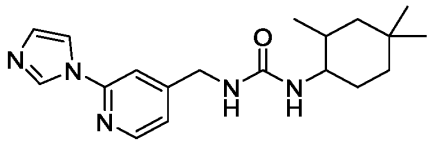
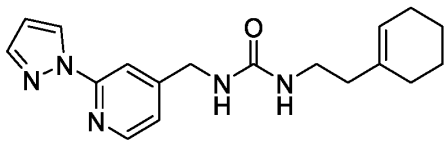
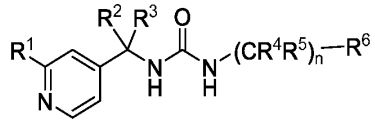

; and



are excluded.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, haloC_{1-6}alkoxy, haloC_{1-6}alkylthio, a 4-6 membered heterocyclyloxy, halogen, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

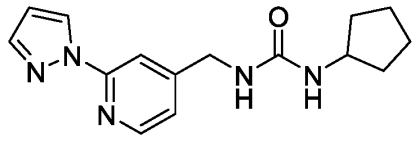
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, $Si(C_{1-6}alkyl)_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

provided that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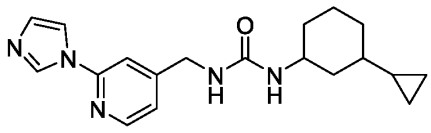
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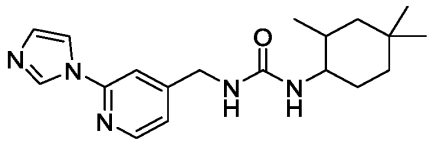
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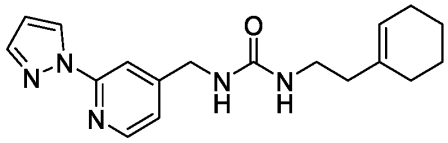
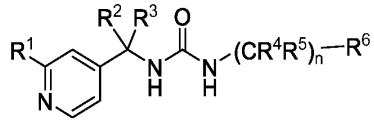


are excluded.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:


(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, a 4-6 membered heterocyclyloxy, halogen, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

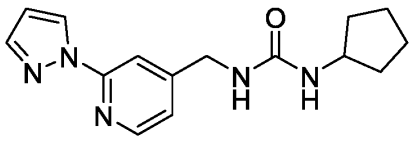
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, Si(C_{1-6}alkyl)$_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

provided that



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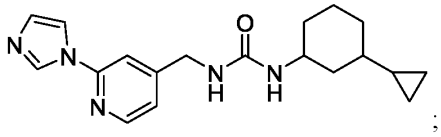
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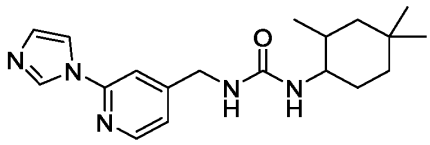
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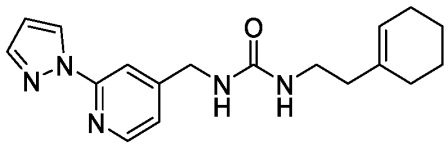
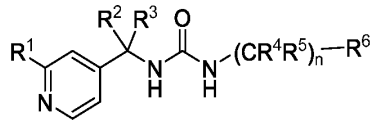


are excluded.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:


(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

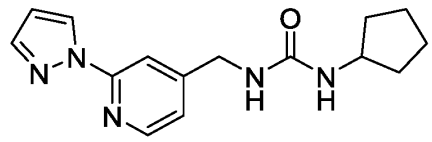
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, Si(C_{1-6}alkyl)$_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, haloC_{1-6}alkoxy, cyano, and hydroxy; and

n is 0, 1, 2, or 3;

provided that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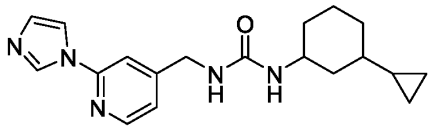
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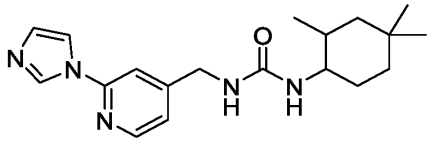
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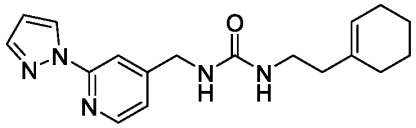
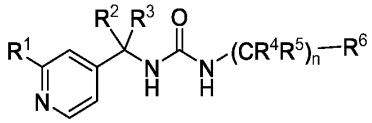


are excluded.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

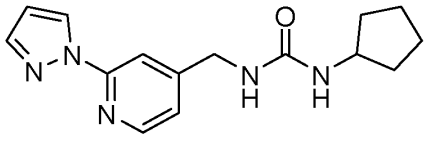
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, $Si(C_{1-6}alkyl)_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

provided that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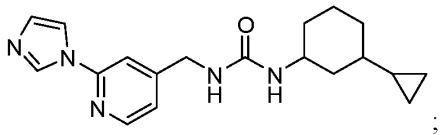
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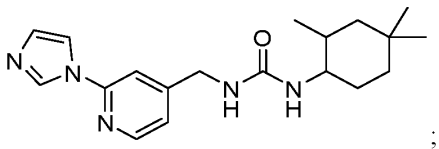
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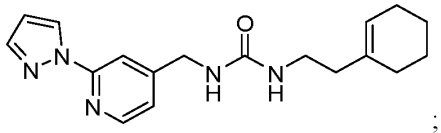
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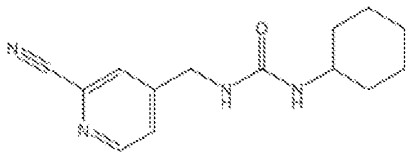
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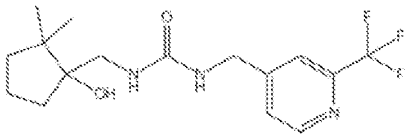
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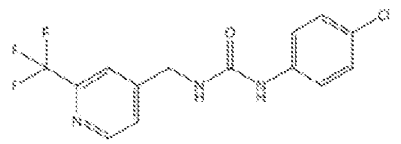
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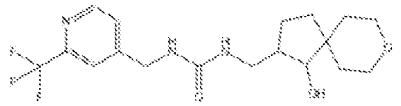
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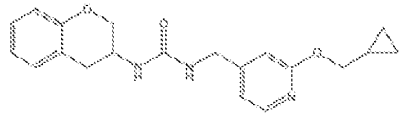
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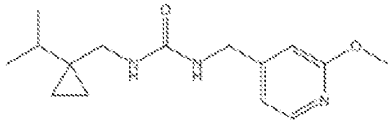
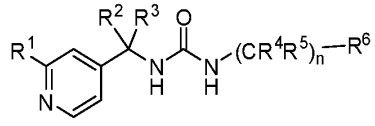


are excluded.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:


(I)

wherein:.

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

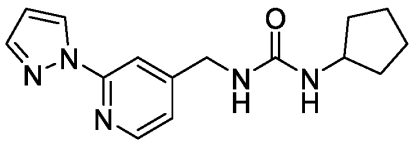
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, Si(C_{1-6}alkyl)$_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

provided that



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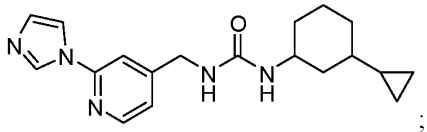
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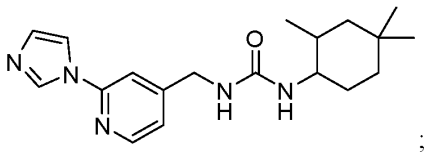
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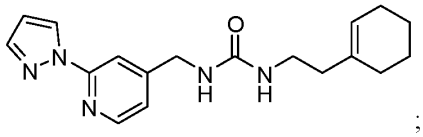
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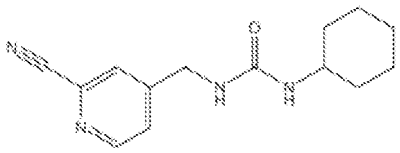
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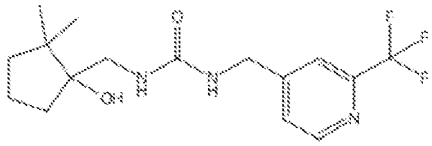
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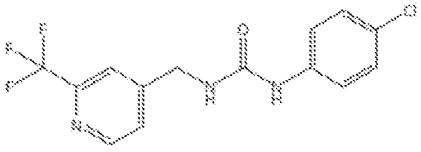
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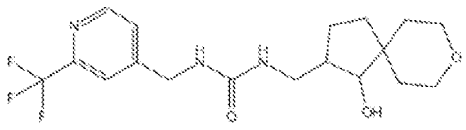
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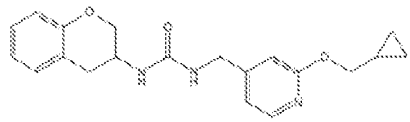

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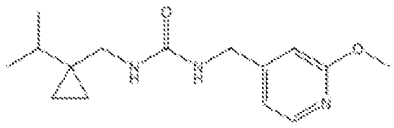
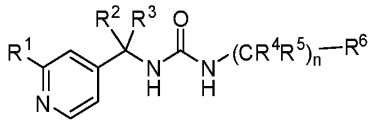


are excluded.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, CHF_2O-, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

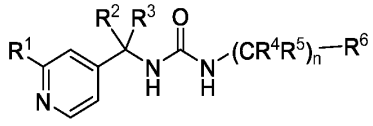
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, $Si(C_{1-6}alkyl)_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, CHF_2O-, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}aloxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

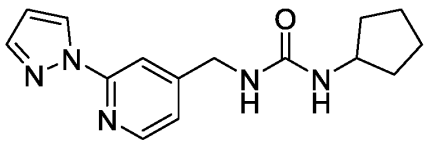
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, Si(C_{1-6}alkyl)$_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

provided that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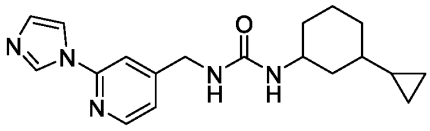
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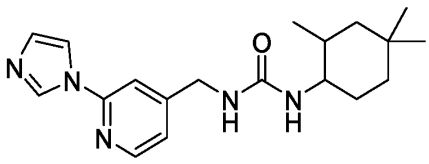
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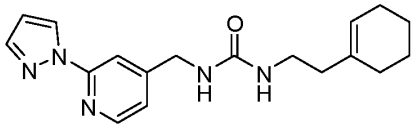
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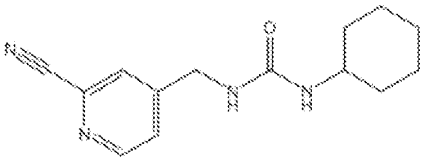
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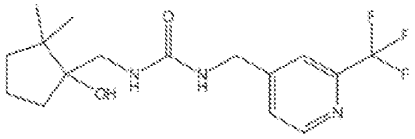
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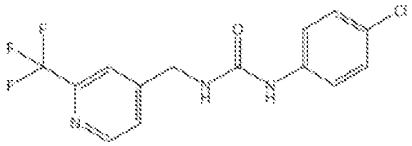
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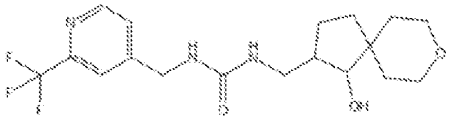
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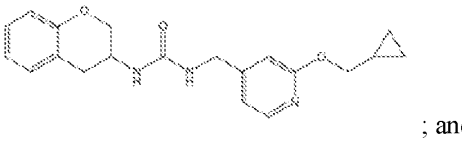
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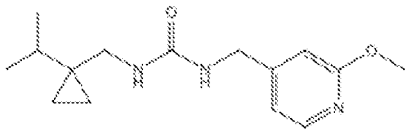
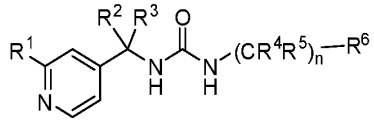


are excluded.

In some embodiments of the present invention, R^2 and R^3 together with the one carbon atom to which they are attached, do not form a saturated monocyclic 3-5 membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

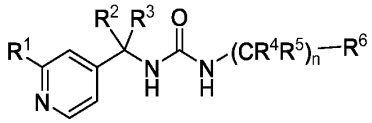
R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, $Si(C_{1-6}alkyl)_3$, and $haloC_{1-6}alkoxy$; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, $C_{3-6}cycloalkyl$, $C_{1-6}alkoxy$, $haloC_{1-6}alkoxy$, cyano, oxo, hydroxy, $hydroxyC_{1-6}alkyl$, and $haloC_{1-6}alkyl$; and

n is 0, 1, or 2.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, $haloC_{1-6}alkoxy$, $C_{1-6}alkoxy$, a 4-6 membered heterocyclyloxy, halogen, $haloC_{1-6}alkyl$, $haloC_{1-6}alkylthio$, $C_{3-5}cycloalkylC_{1-6}alkoxy$, $cyanoC_{1-6}alkoxy$, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, $C_{3-5}cycloalkylC_{1-6}alkoxy$, or heteroaryl are optionally substituted with one $C_{1-6}alkyl$ or $haloC_{1-6}alkyl$;

R^2 and R^3 are independently selected from hydrogen, $C_{1-6}alkyl$, and $hydroxyC_{1-6}alkyl$;

R^4 and R^5 are independently selected from hydrogen, $C_{1-6}alkyl$, a saturated monocyclic 3-5 membered cycloalkyl, $haloC_{1-6}alkyl$, $haloC_{1-6}alkoxy$, and $C_{1-6}alkoxy$; or

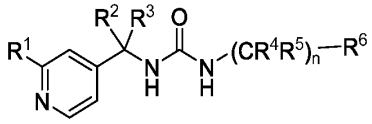
R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, $Si(C_{1-6}alkyl)_3$, and $haloC_{1-6}alkoxy$; wherein the

heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, haloC_{1-6}alkylthio , C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, heterocyclyloxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-

edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 3-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

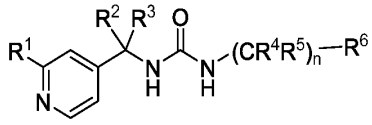
d) phenyl; and

e) haloC_{1-6}alkyl;

which bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, bicyclic edge-to-edge fused or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-}

$_{6}$alkoxy, heterocyclyloxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl; and

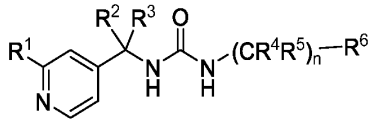
e) haloC_{1-6}alkyl;

which bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}

alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, heterocyclyloxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises

one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl; and

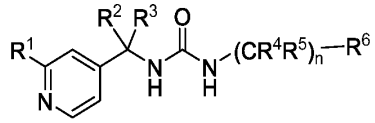
e) haloC_{1-6}alkyl;

which bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

In some preferred embodiments, n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-}

$_{6}$alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, heterocyclyloxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl; and

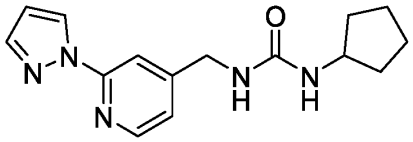
e) haloC_{1-6}alkyl;

which bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}

alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

provided that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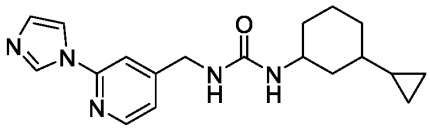
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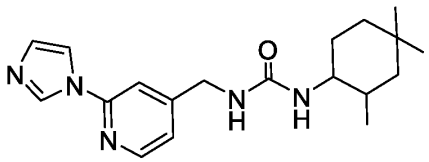
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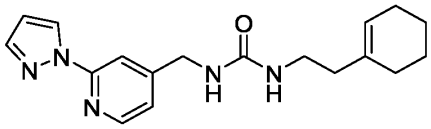
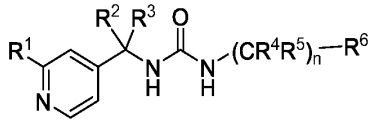


are excluded.

In some embodiments, n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl; and

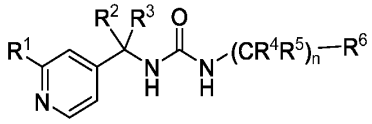
e) haloC_{1-6}alkyl;

which bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

In some preferred embodiments, n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

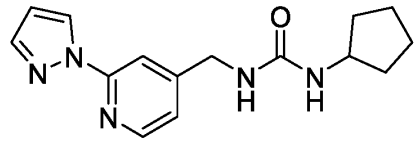
d) phenyl; and

e) haloC_{1-6}alkyl;

which bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

provided that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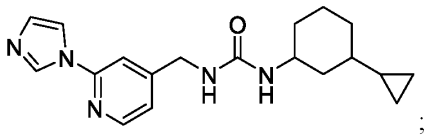
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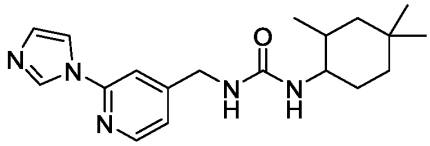
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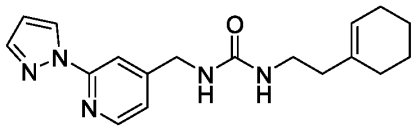
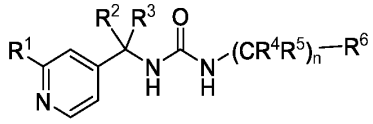


are excluded.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:


(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

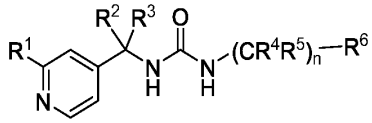
b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

which bicyclic edge-to-edge fused heterocycloalkyl; 7-10 membered bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, and hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl; and

n is 0, 1, or 2.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

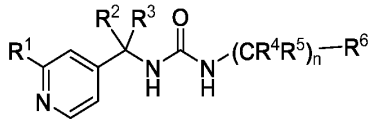
b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

which bicyclic edge-to-edge fused heterocycloalkyl; 7-10 membered bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, and hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl; and

n is 0, 1, or 2.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one

aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

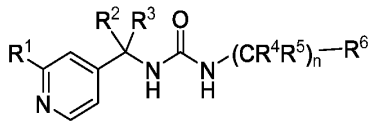
which bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one or two substituents independently selected from Cl-, F-, CH_3-, and CF_3-; and

n is 0, 1, or 2.

In some preferred embodiments, n is 0 or 1.

In some particularily preferred embodiments, R^6 is substituted with two F-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, C_{3-}

5cycloalkylC1-6alkoxy, or heteroaryl are optionally substituted with one C1-6alkyl or haloC1-6alkyl;

R^2 and R^3 are independently selected from hydrogen, C1-6alkyl, and hydroxyC1-6alkyl;

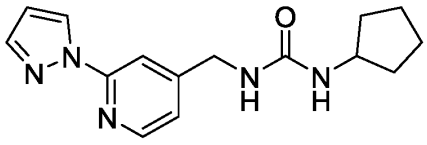
R^4 and R^5 are independently selected from hydrogen, C1-6alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C1-6alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; a 7-10 membered bridged heterocycloalkyl; a saturated monocyclic 4-6 membered cycloalkyl; phenyl; a 4-10 membered bridged cycloalkyl; a 7-10 membered fused cycloalkyl; tert-butyl; $(CH_3)_2CF$-; 6 membered heteroaryl, wherein the bicyclic fused heterocyloalkyls, bridged heterocycloalkyl, saturated monocylic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl, or 6 membered heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C1-6 alkyl, C3-6cycloalkyl, C1-6alkoxy, cyano, oxo, hydroxy, hydroxyC1-6alkyl, and haloC1-6alkyl; and

n is 0, 1, or 2;

provided that



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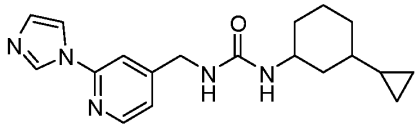
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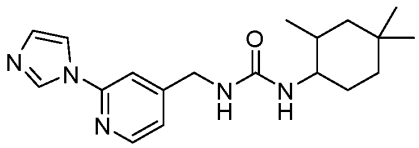
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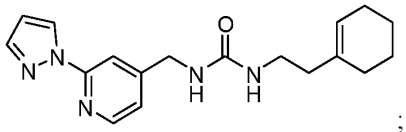
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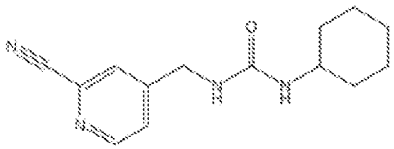
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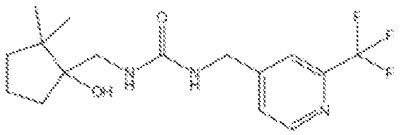
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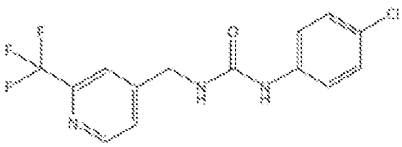
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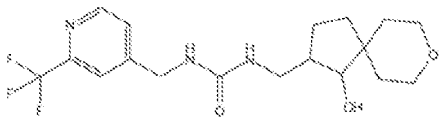
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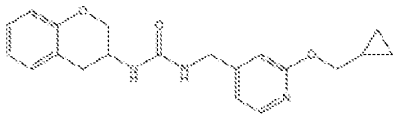

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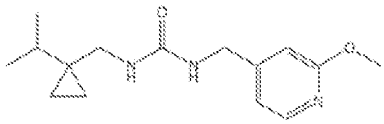


are excluded.

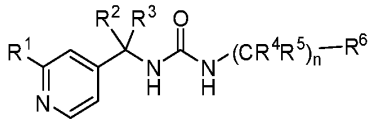
In some preferred embodiments, n is 0 or 1.

In some preferred embodiments, R^6 is substituted with one or two substituents independentyl selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In some preferred embodiments, R^6 is substituted with one or two substituents independentyl selected from Cl-, F-, CH_3-, and CF_3-.

In some preferred embodiments, R^6 is substituted with two F-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

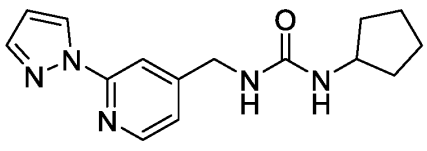
R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; a 7-10 membered bridged heterocycloalkyl; a saturated monocyclic 4-6 membered cycloalkyl; phenyl; a 4-10 membered bridged cycloalkyl; a 7-10 membered fused cycloalkyl; tert-butyl; $(CH_3)_2CF$-; and 6 membered heteroaryl, wherein the bicyclic fused heterocyloalkyl, bridged heterocycloalkyl, saturated monocylic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl, or 6 membered heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

provided that



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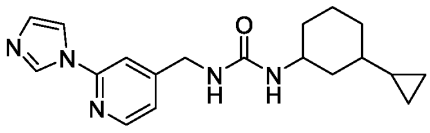

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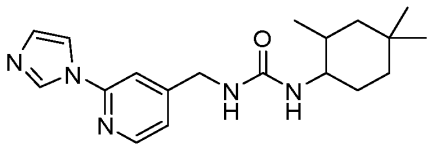
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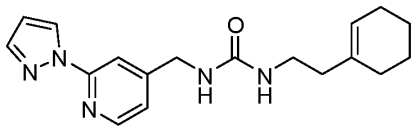
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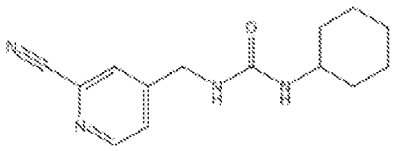
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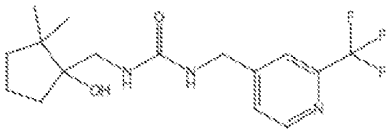
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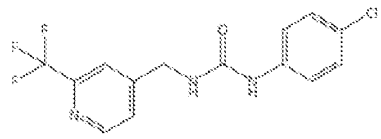
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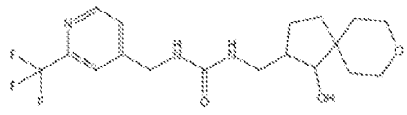
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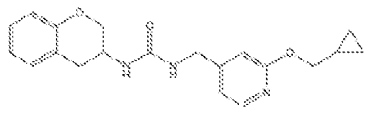
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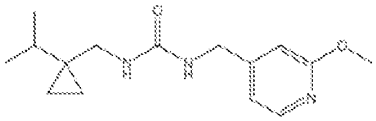
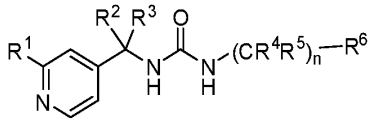


are excluded.

In some embodiments, n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, CHF_2O-, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

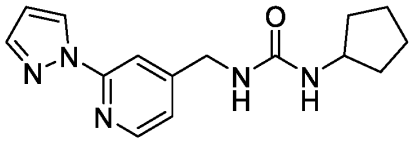
R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings,

wherein the one ring comprises one O-atom or one N-atom; a 7-10 membered bridged heterocycloalkyl; a saturated monocyclic 4-6 membered cycloalkyl; phenyl; a 4-10 membered bridged cycloalkyl; a 7-10 membered fused cycloalkyl; tert-butyl; $(CH_3)_2CF$-; 6 membered heteroaryl, wherein the bicyclic fused heterocyloalkyl, bridged heterocycloalkyl, saturated monocylic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

provided that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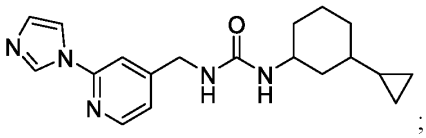
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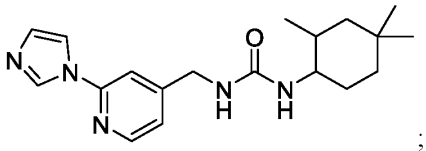
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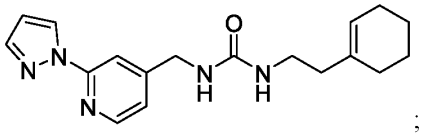
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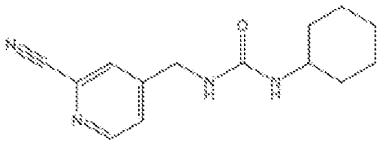
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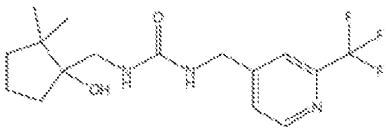
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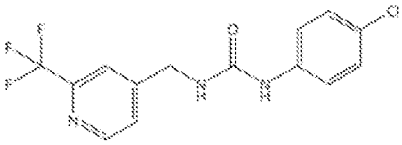
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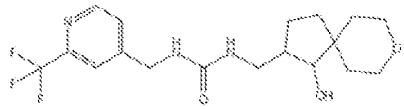
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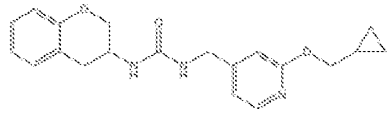
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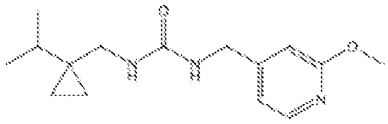
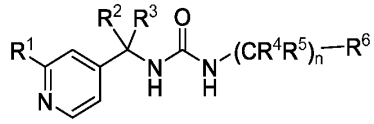


are excluded.

In some embodiments, n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, CHF_2O-, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

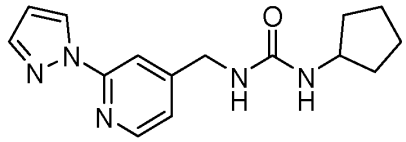
R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; a 7-10 membered bridged heterocycloalkyl; a saturated monocyclic 4-6 membered cycloalkyl; phenyl; a 4-10 membered bridged cycloalkyl; a 7-10 membered fused cycloalkyl; tert-butyl; $(CH_3)_2CF$-; 6 membered heteroaryl, wherein the bicyclic fused heterocyloalkyl, bridged heterocycloalkyl, saturated monocylic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from

halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

provided that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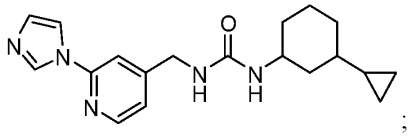
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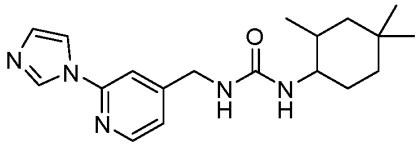
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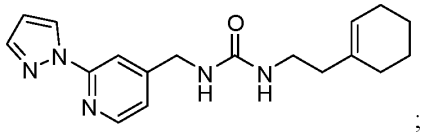
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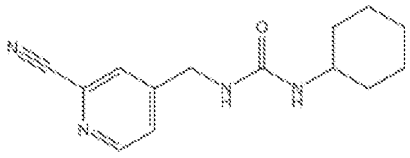
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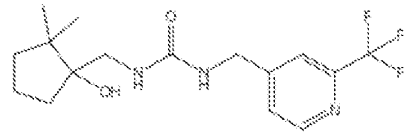
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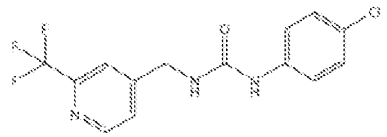
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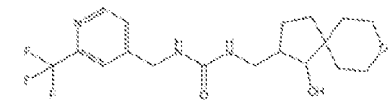
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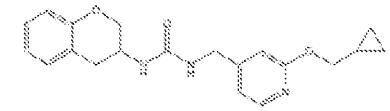
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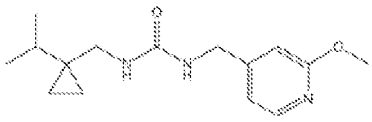
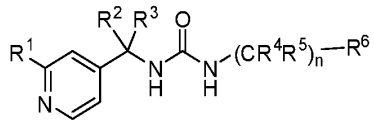


are excluded.

In some embodiments, n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:


(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyridinyl, and pyrimidinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyridinyl, or pyrimidinyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

In some preferred embodiments, n is 0 or 1.

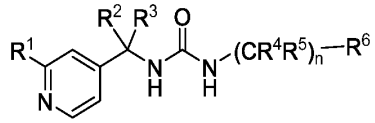
In some embodiments R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl.

In some preferred embodiments, R^6 is substituted with one or two substituents independentyl selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In some preferred embodiments, R^6 is substituted with one or two substituents independentyl selected from Cl-, F-, CH_3-, and CF_3-.

In some preferred embodiment, R^6 is substituted with two F-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

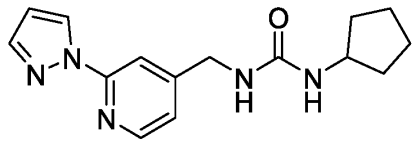
R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyridinyl, and pyrimidinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyridinyl, or pyrimidinyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

provided that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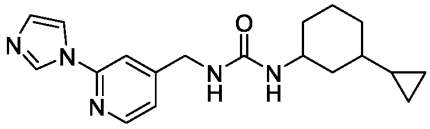
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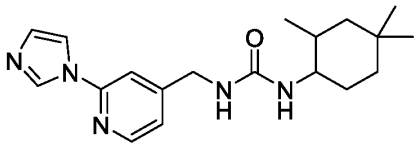
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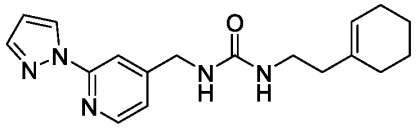
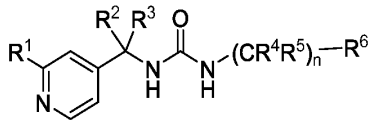


are excluded.

In some embodiments, n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

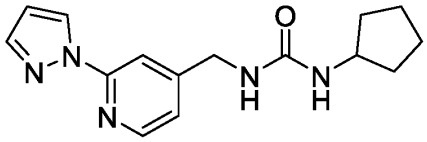
R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, hydroxy, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

provided that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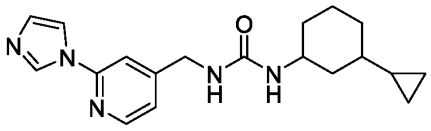
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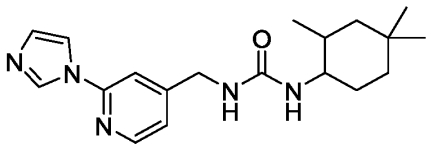
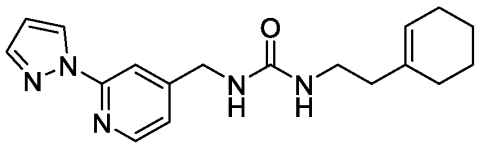
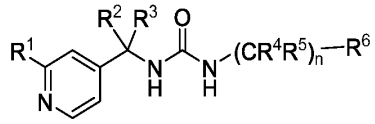

; and



are excluded.

In some embodiments, n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

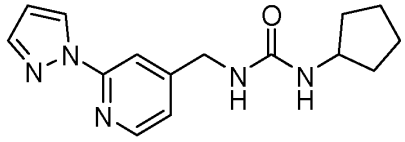
R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the

dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

provided that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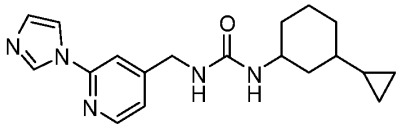
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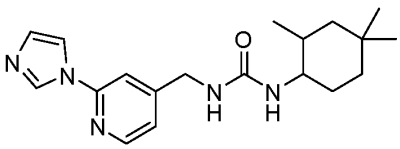
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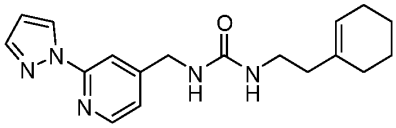
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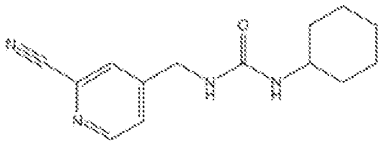
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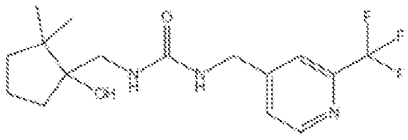

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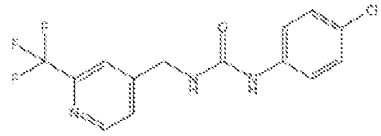

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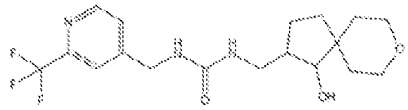

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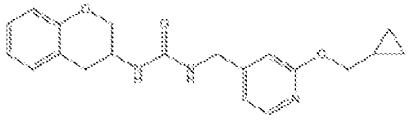
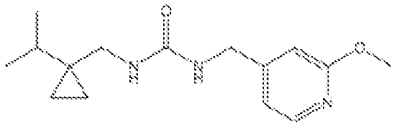


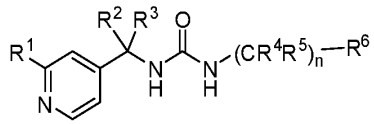
; and



are excluded.

In some embodiments, n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy; wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

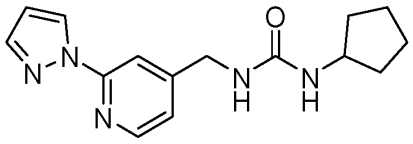
R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

provided that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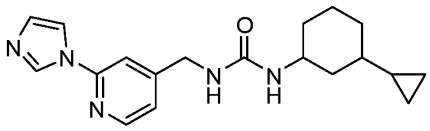
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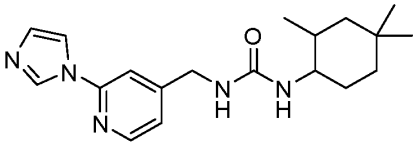
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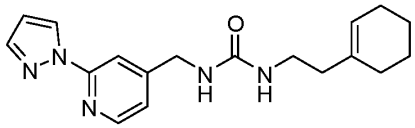
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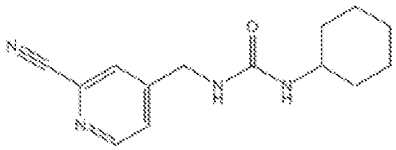
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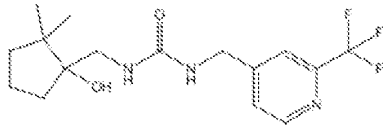
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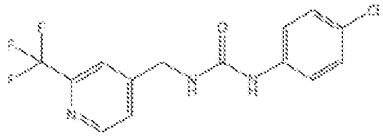
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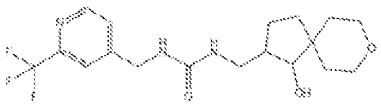

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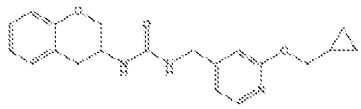

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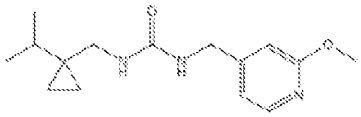
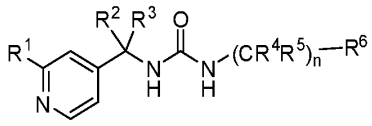


are excluded.

In some embodiments, n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, CHF_2O-, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, wherein the heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heterocyclyloxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, and hydroxyC_{1-6}alkyl, and hydroxy; or

R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

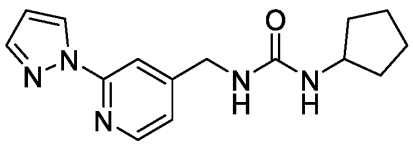
R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkoxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

provided that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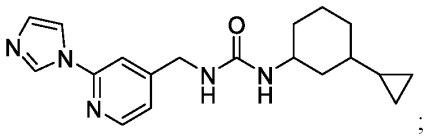
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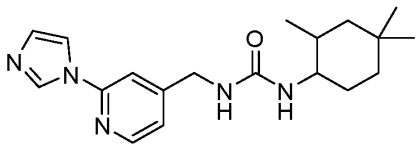
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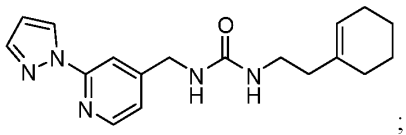
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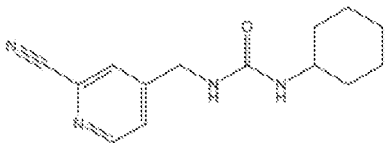
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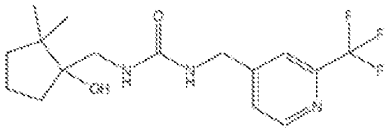
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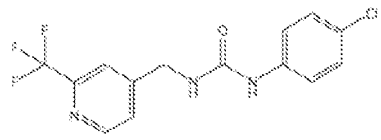
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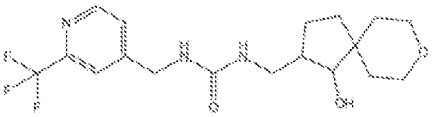
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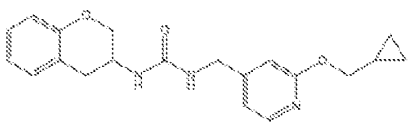
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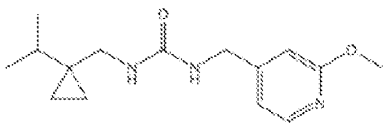
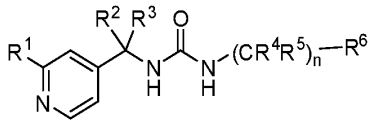


are excluded.

In some embodiments, n is 0 or 1.

In one embodiment the present invention provides a compound of formula (I) or a solvate or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising such a compound or solvate or pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is haloC_{1-6}alkoxy;

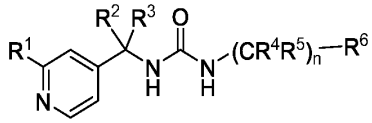
R^2 and R^3 are hydrogen;

R^4 and R^5 are independently selected from hydrogen, haloC_{1-6}alkyl;

R^6 is selected from a 3-10 membered cycloalkyl and a haloC_{1-6}alkyl;

n is 1.

In one embodiment the present invention provides a compound of formula (I) or a solvate or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising such a compound or solvate or pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

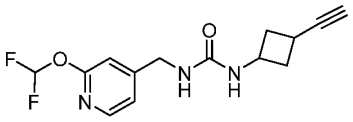
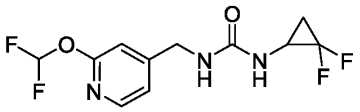
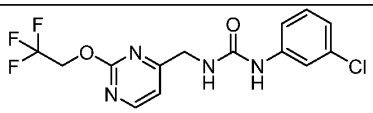
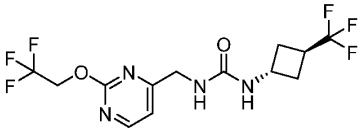
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

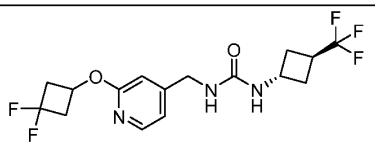
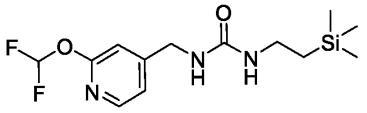
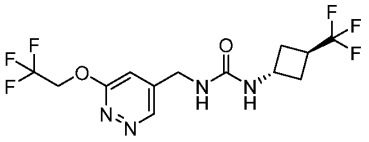
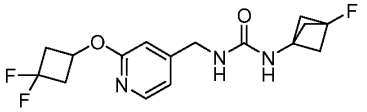
R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

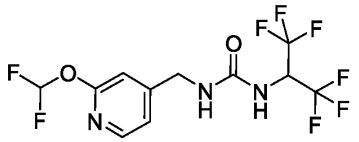
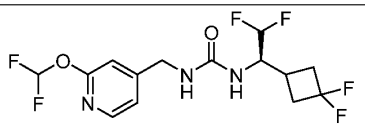
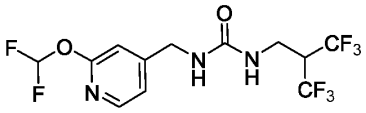
R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

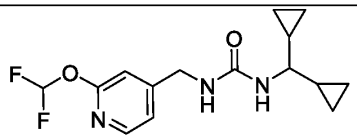
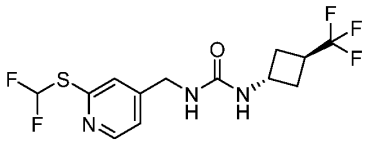
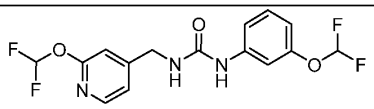
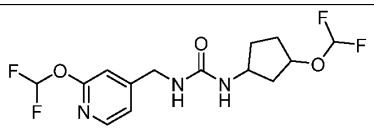
n is 0, 1, 2, or 3.

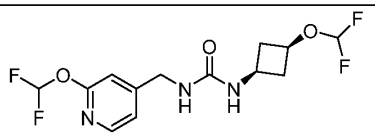
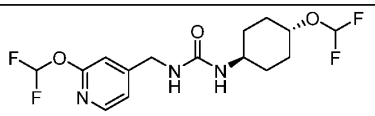
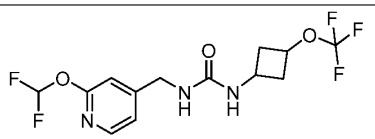
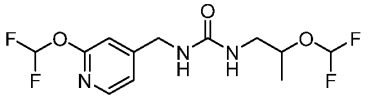
or a pharmaceutical composition comprising a compound selected from the following list or a solvate or a pharmaceutically acceptable salt thereof:

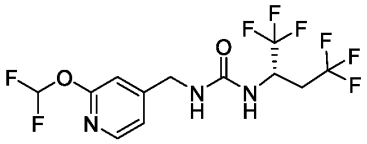
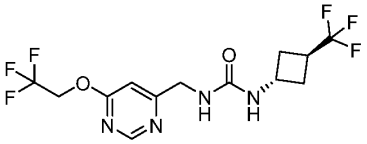
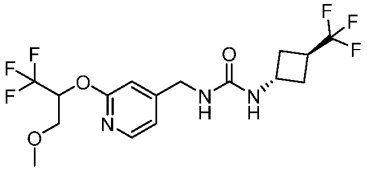
Example	Name	Structure
66	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethynylcyclobutyl)urea	
173	1-(2,2-difluorocyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
203	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]urea	
204	1-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

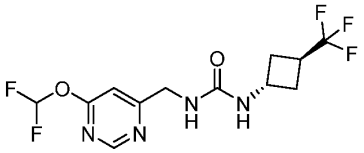
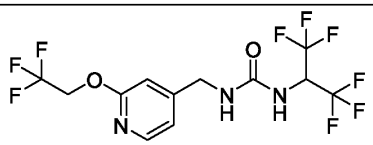
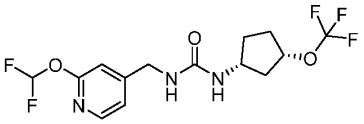
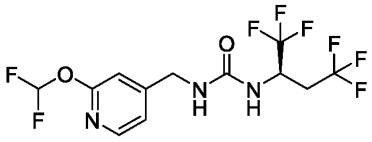
Example	Name	Structure
209	1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
212	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-trimethylsilylethyl)urea	
215	1-[[6-(2,2,2-trifluoroethoxy)pyridazin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
224	1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-(3-fluoro-1-	

Example	Name	Structure
	bicyclo[1.1.1]pentanyl)urea	
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea	
230	1-[(1R)-1-(3,3-difluorocyclobutyl)-2,2-difluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
252	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea	

Example	Name	Structure
253	1-(dicyclopropylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
260	1-[[2-(difluoromethylsulfanyl)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
262	1-[3-(difluoromethoxy)phenyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
264	1-[3-(difluoromethoxy)cyclopentyl]-3-[[2-(difluoromethoxy)	

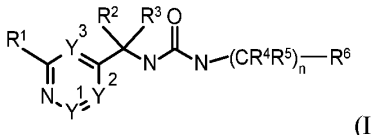
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
265	1-[(1s,3s)-3-(difluoromethoxy) cyclobutyl]-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
266	1-[(1r,4r)-4-(difluoromethoxy) cyclohexyl]-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
267	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[3-(trifluoromethoxy) cyclobutyl]urea	
268	1-[2-(difluoromethoxy) propyl]-3-[[2-(difluoromethoxy)	

Example	Name	Structure
	pyridin-4-yl]methyl]urea	
273	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	
279	1-[[6-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
281	1-[[2-(1,1,1-trifluoro-3-methoxypropan-2-yl)oxypyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	

Example	Name	Structure
282	1-[[6-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
285	1-(1,1,1,3,3,3-hexafluoropropan-2-yl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
288	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethoxy)cyclopentyl]urea	
294	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-	

Example	Name	Structure
	hexafluorobutan-2-yl]urea	

In one embodiment the present invention provides a compound of formula (I') or a solvate or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising such a compound or solvate or pharmaceutically acceptable salt thereof:



(I')

wherein:

Y^1, Y^2 and Y^3 are each independently selected from CH or N;

provided that only 0 or 1 of Y^1, Y^2 and Y^3 is N;

R^1 haloC_{1-6}alkoxy, haloC_{1-6} alkylthio, 4-6 membered cycloalkyloxy, wherein the 4-6 membered cycloalkyloxy is optionally substituted with one, two, or three substituents independently selected from halogen; wherein the haloC_{1-6}alkoxy is optionally substituted with C_{1-6}alkoxy;

R^2 and R^3 are independently selected from hydrogen;

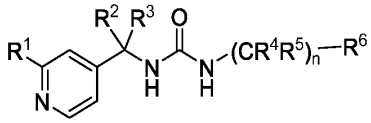
R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, and haloC_{1-6}alkyl;

R^6 is selected from a 3-10 membered cycloalkyl, phenyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, and triC_{1-6}alkylsilyl; wherein the cycloalkyl, or phenyl are optionally substituted with one, two,

or three substituents independently selected from halogen, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, C_{2-6} alkynyl; and

n is 0, 1 or 2.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three

substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is selected from cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy; wherein the heterocyclyloxy or cyloalkylalkoxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is selected from cyano, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is selected from cyano, CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, CF_3CH_2O-, CH_3CF_2-, CHF_2-, and CF_3-.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, and CF_3CH_2O-.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is CHF_2O- or CH_3CF_2O-.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is CHF_2O-.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is 5 membered heteroaryl selected from pyrazolyl and imidazolyl which are optionally substituted with one, two, or three substituents indendently selected from halogen and halo$C_{1\text{-}6}$alkyl.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is unsubstituted pyrazolyl or unsubstituted imidazolyl.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein (i) both R^2 and R^3 are hydrogen, or (ii) one of R^2 and R^3 is hydrogen and the other one is hydroxy$C_{1\text{-}6}$alkyl.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein one of R^2 and R^3 is hydrogen and the other one is hydroxy$C_{1\text{-}6}$alkyl selected from $HOCH_2$-, $HOCH_2CH_2$-, $HOCH_2CH_2CH_2$-, and $HOCH_2CH_2CH_2CH_2$-.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein the hydroxy$C_{1\text{-}6}$alkyl is $HOCH_2$- or $HOCH_2CH_2$-.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein both R^2 and R^3 are hydrogen.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein n is 0 or 1.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as describd herein, wherein n is 0.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein n is 1.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein n is 1 and (i) both R^4 and R^5 are hydrogen, (ii) one of R^4 and R^5 is hydrogen and the other one is C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, or C_{1-6}alkoxy.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein one of R^4 and R^5 is hydrogen and the other one is a methyl (CH_3-) or methoxy (CH_3O-).

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein the saturated monocyclic 3-5 membered cycloalkyl is unsubsituted cyclopropyl.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein n is 1 and both R^4 and R^5 are hydrogen.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, C_{1-6}alkyl, haloC_{1-6}alkyl, and phenyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^6 is optionally substituted with one, two, or three substituents independently selected from from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^6 is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CF_3-, cyclopropyl, and CH_3O-.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^6 is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, and CF_3-.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) C_{1-6}alkyl; and

e) haloC_{1-6}alkyl;

which are optionally substituted as described herein.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

which are optionally substituted as described herein.

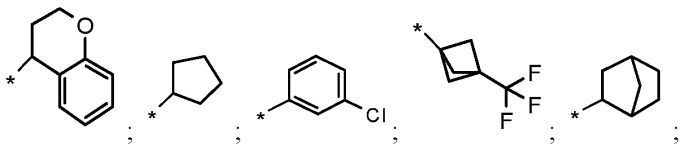
Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^6 is selected from:

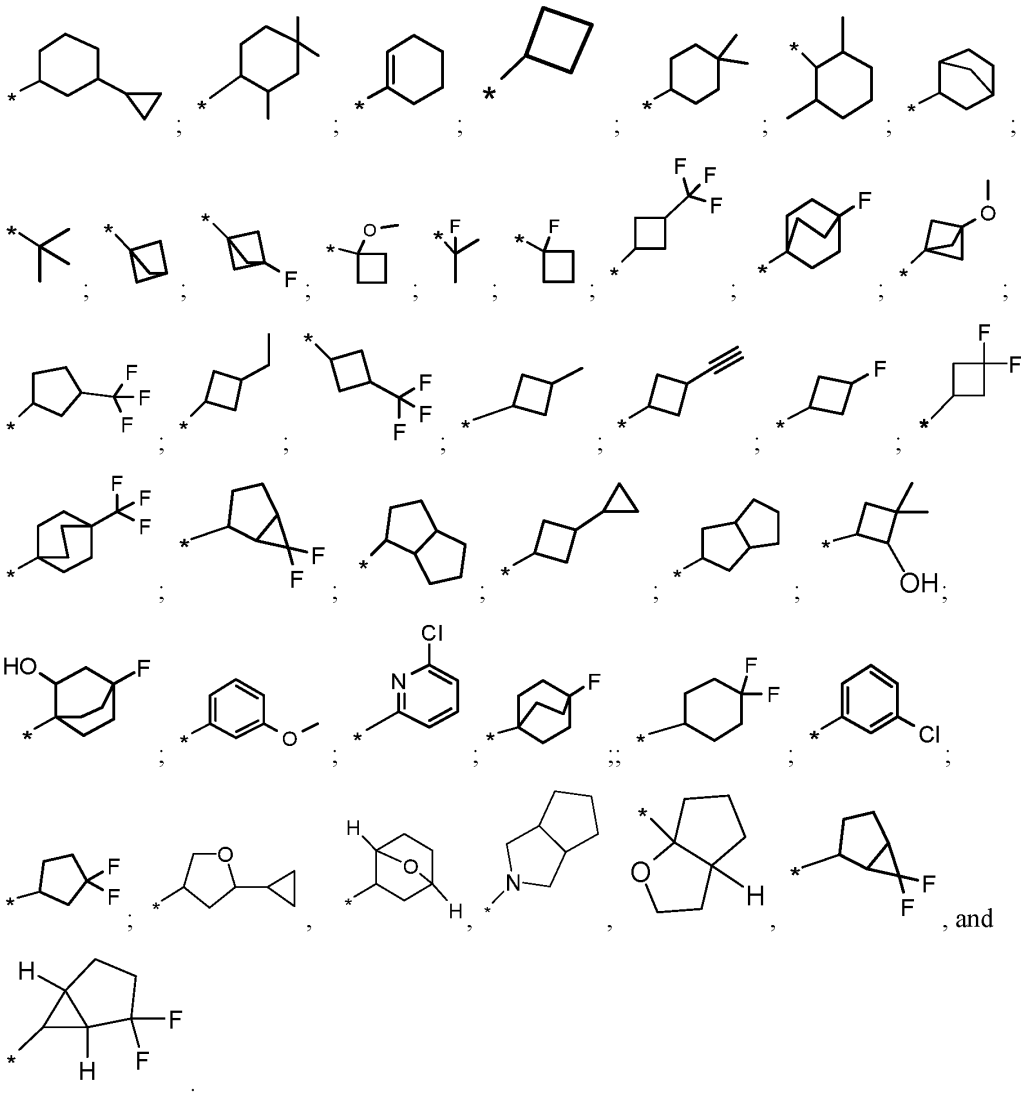
dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, which are optionally substituted as described herein.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^6 is selected from:

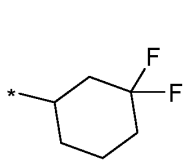
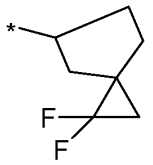
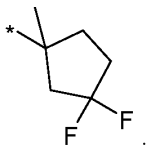
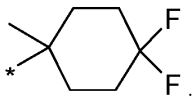
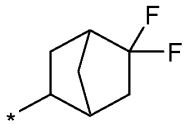
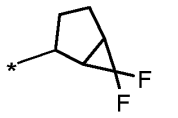
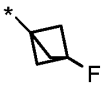
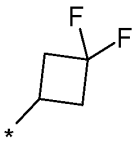
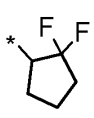
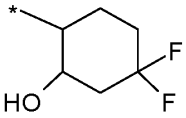
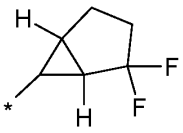
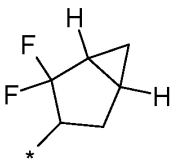
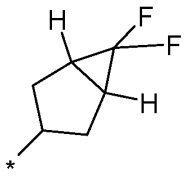
dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, which are optionally substituted as described herein.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^6 is selected from:



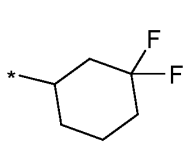
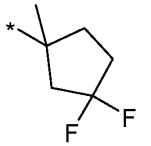
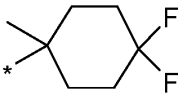
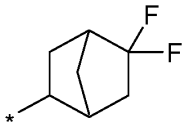
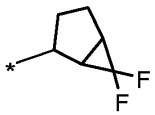
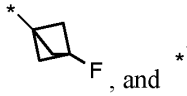
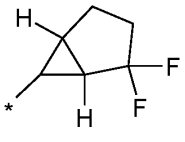


Some particularily preferred embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, where R^6 is as described herein substituted with one or two F- and wherein R^6 is selected from:

, and .

Some particularly preferred embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, where R^6 is as described herein substituted with one or two F- and wherein R^6 is selected from:

, and .

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is selected from CHF_2O-, unsubstituted pyrazolyl, unsubstituted imidazolyl, CH_3O-, $(CH_3)CF_2$-, CN-, CHF_2-, CF_3-, CF_3CH_2O-, CH_3CFHCH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, (i) R^4 and R^5 are hydrogen, or (ii) one of R^4 and R^5 are hydrogen and the other is cyclopropyl, or (iii) R^4 and R^5

together with the one carbon atom to which they are attached, form cyclopropyl, and R^6 is selected from a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, a 7-10 membered bridged heterosystem, wherein the bridge comprises an O-atom, a 6 membered heteroaryl; and a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, all optionally substituted as described herein.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is selected from CHF_2O- or unsubstituted imidazolyl, R^2 and R^3 are hydrogen, n is 0 or 1, (i) R^4 and R^5 are hydrogen, or (ii) one of R^4 and R^5 are hydrogen and the other is cyclopropyl, or (iii) R^4 and R^5 together with the one carbon atom to which they are attached, form cyclopropyl, and R^6 is selected from a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, a 7-10 membered bridged heterosystem, wherein the bridge comprises an O-atom, a 6 membered heteroaryl; and a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, all optionally substituted as described herein.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 37, wherein R^1 is selected from CHF_2O- or unsubstituted imidazolyl, R^2 and R^3 are hydrogen, n is 0; and R^6 is selected from a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, a 7-10

membered bridged heterosystem, wherein the bridge comprises an O-atom; a 6 membered heteroaryl; and a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, all optionally substituted as described herein.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is CHF_2O- and R^6 is optionally substituted with one or two Cl-, F-, CH_3-, and CF_3-

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is CHF_2O- and R^6 is optionally substituted with one or two F- or CF_3-.

Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is CHF_2O-, n is 0 or 1, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one or two F- or CF_3-.

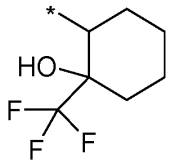
Some of the preferred embodiments of this invention comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, wherein R^1 is CHF_2O-, n is 0 or 1, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one or two CF_3-.

Some of the preferred embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CHF_2O- or unsubstituted imidazolyl, R^2 and R^3 are hydrogen, n is 0; and R^6 is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; a 7-10 membered bridged heterocycloalkyl; a saturated monocyclic 4-6 membered cycloalkyl;

phenyl; a 4-10 membered bridged cycloalkyl; a 7-10 membered fused cycloalkyl; tert-butyl; $(CH_3)_2CF$-; pyrazinyl, pyrimidinyl, and pyridinyl, wherein the bicyclic fused heterocyloalkyls, bridged heterocycloalkyl, saturated monocylic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one CF_3-.

In some preferred embodiments R^6 is substituted with one CF_3- and one other substituent of R^6 as described herein.

In some preferred embodiments, the other substituent of R^6 is hydroxy and R^6 has the structure:



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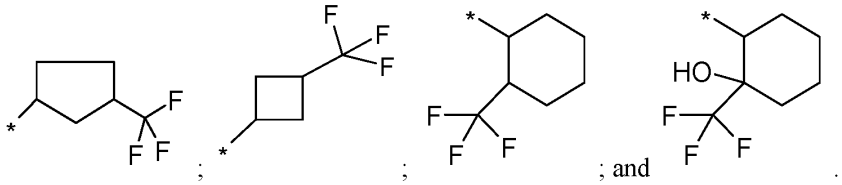
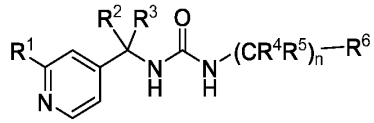
Some particularily preferred embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, where R^6 is as described herein substituted with one CF_3-, and wherein R^6 is selected from:



; ; ; and .

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, haloC_{1-6}alkyl and 5 membered unsubstituted heteroaryl;

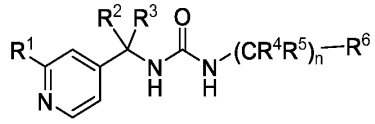
R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen;

R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, $(CH_3)_2CF$-, and 6 membered heteroaryl, wherein the bicyclic fused heterocycloalkyl, bridged cycloalkyl, cycloalkyl, phenyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0 or 1.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, haloC_{1-6}alkyl and 5 membered unsubstituted heteroaryl;

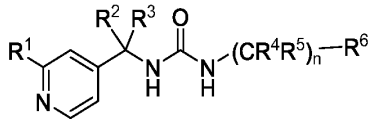
R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen;

R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, 6 membered heteroaryl, wherein the bicyclic fused heterocycloalkyl, bridged cycloalkyl, cycloalkyl, phenyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0 or 1.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, haloC_{1-6}alkyl and 5 membered unsubstituted heteroaryl;

R^2 and R^3 are hydrogen; or

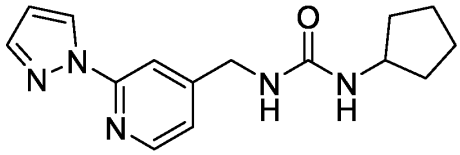
R^4 and R^5 are hydrogen;

R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring

comprises one O-atom or one N-atom; a 4-10 membered bridged cycloalkyl; a saturated monocyclic 4-6 membered cycloalkyl, phenyl; $(CH_3)_2CF$-; and 6 membered heteroaryl; wherein the bicyclic fused heterocycloalkyl; bridged cycloalkyl; cycloalkyl; phenyl; or heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0 or 1;

provided that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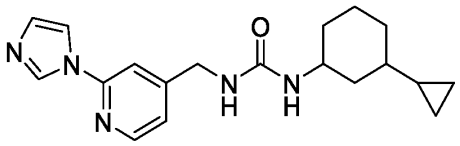
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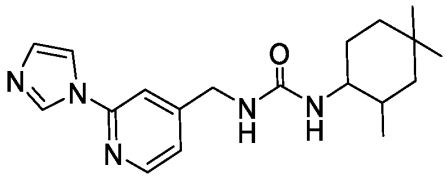
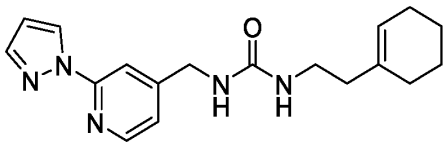
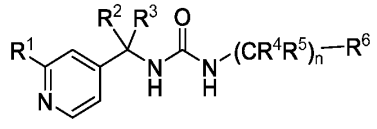

; and



are excluded.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, halo$_{1-6}$alkyl and 5 membered unsubstituted heteroaryl;

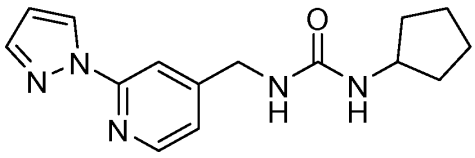
R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen;

R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; a 4-10 membered bridged cycloalkyl; a saturated monocyclic 4-6 membered cycloalkyl, phenyl; $(CH_3)_2CF$-; and 6 membered heteroaryl; wherein the bicyclic fused heterocycloalkyl; bridged cycloalkyl; cycloalkyl; phenyl; or heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0 or 1;

provided that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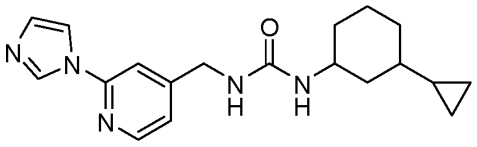
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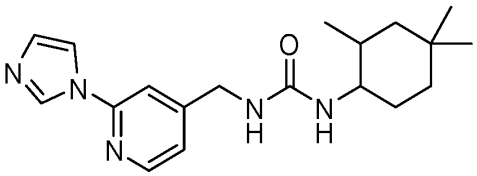
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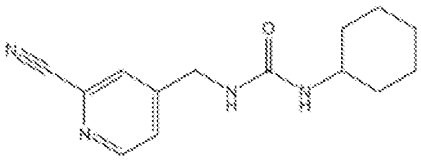
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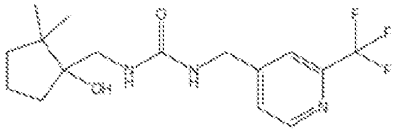
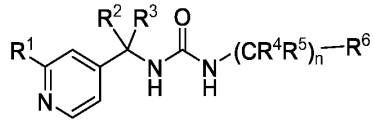

;

are excluded.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, haloC_{1-6}alkyl and 5 membered unsubstituted heteroaryl;

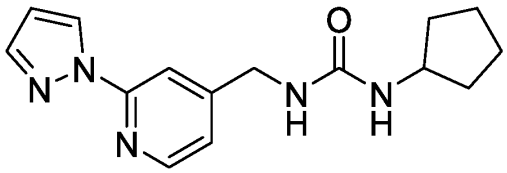
R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy; and

n is 0, or 1;

provided that



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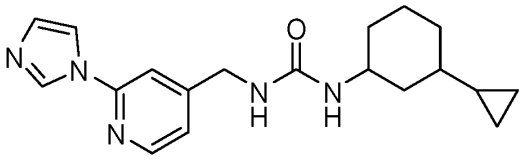
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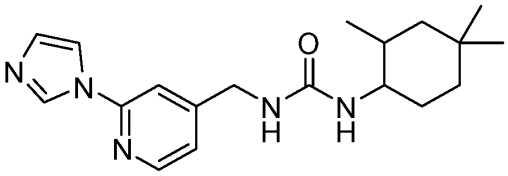
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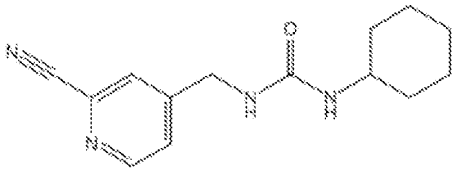
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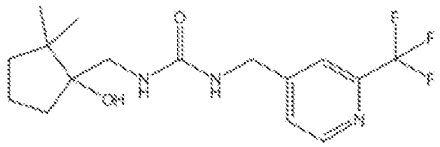
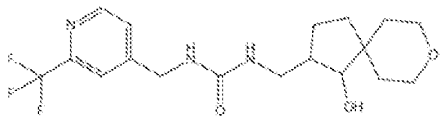
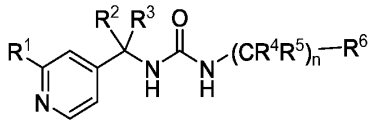

; and


;

are excluded.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selectd from cyano, CHF_2O-, CH_3CF_2-, CH_3O-, CH_3CFHCH_2O-, CF_3CH_2O-, CH_3CF_2-, CHF_2-, CF_3-, unsubstituted pyrazolyl, and unsubstituted imidazolyl;

R^2 and R^3 are hydrogen;

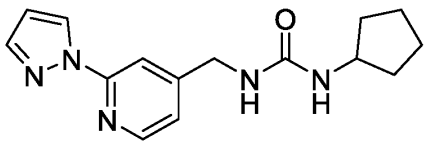
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; a 4-10 membered bridged cycloalkyl; a saturated monocyclic 4-6 membered cycloalkyl, phenyl; $(CH_3)_2CF$-; pyrazinyl, pyrimidinyl, and pyridinyl; wherein the bicyclic fused heterocycloalkyl; bridged cycloalkyl; cycloalkyl; phenyl; pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy; and

n is 0, or 1;

provided that



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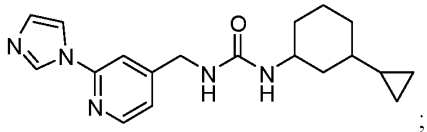
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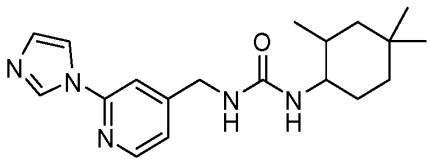
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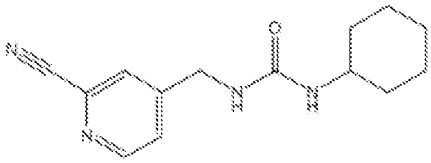
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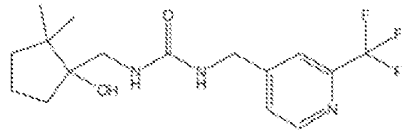
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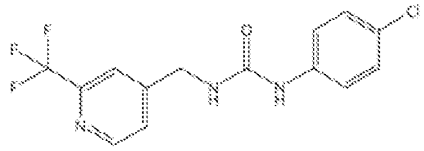
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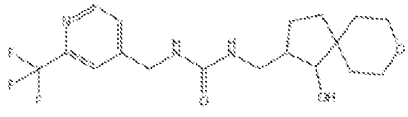
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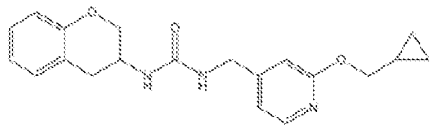
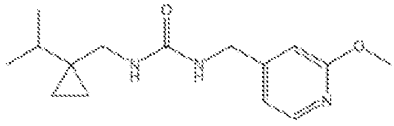
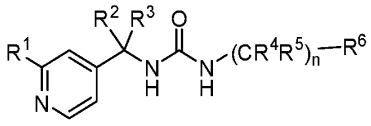


; and



are excluded

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from cyano, CHF_2O-, CH_3CF_2-, CH_3O-, CH_3CFHCH_2O-, CF_3CH_2O-, CH_3CF_2-, CHF_2-, CF_3-, unsubstituted pyrazolyl, and unsubstituted imidazolyl;

R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen; or

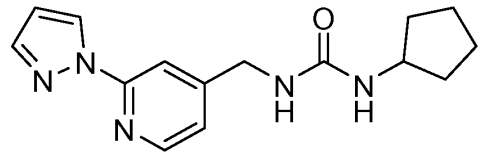
R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl,

hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy; and

n is 0, or 1;

provided that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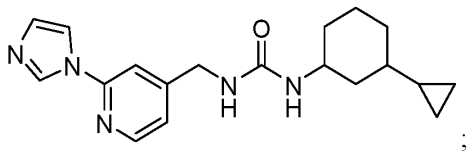
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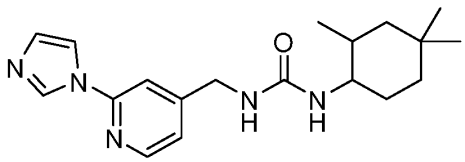
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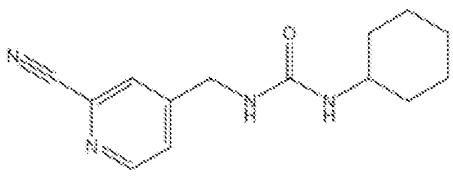
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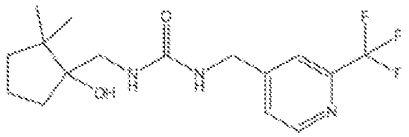
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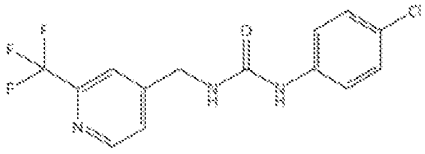
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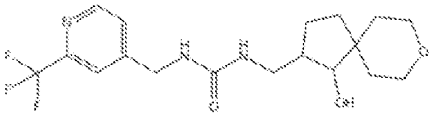
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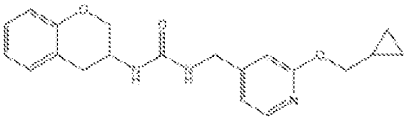
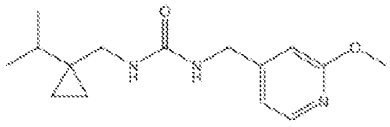
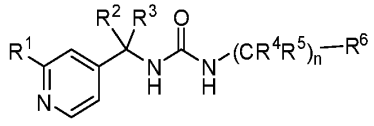

; and


;

are excluded.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:


(I)

wherein:

R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, CF_3CH_2O-, pyrazolyl, and imidazolyl; wherein the pyrazolyl and imidazolyl are unsubstituted or optionally substituted with one CF_3-;

R^2 and R^3 are hydrogen;

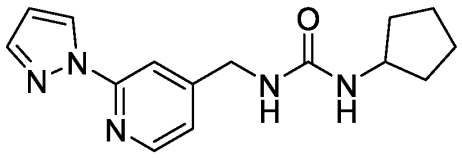
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy; and

n is 0, or 1;

provided that



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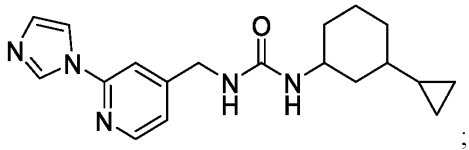
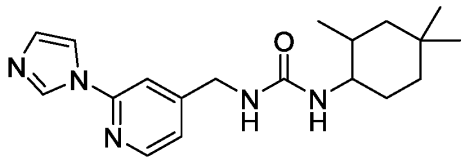
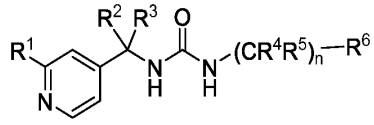

; and


;

are excluded.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:


(I)

wherein:

R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, and CF_3CH_2O-;

R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen; or

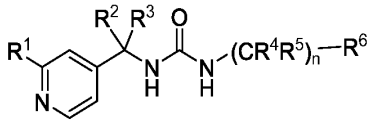
R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl,

bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, and CF_3CH_2O-;

R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen; or

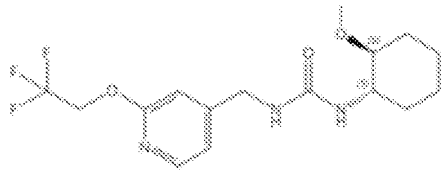
R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three

substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy; and

n is 0, or 1;

provided that



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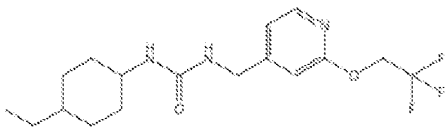

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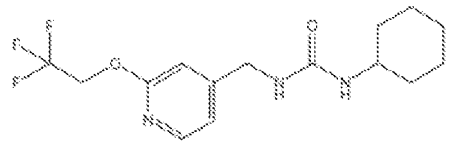

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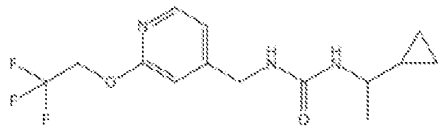

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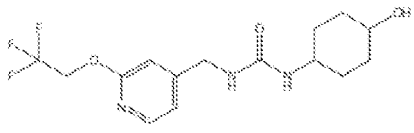

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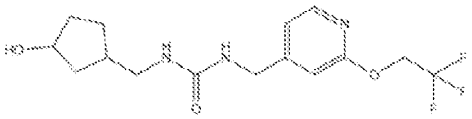
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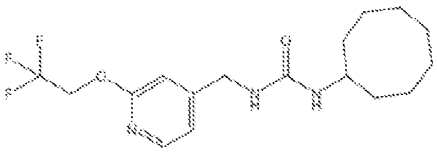
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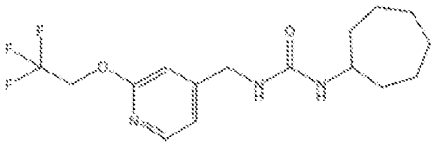
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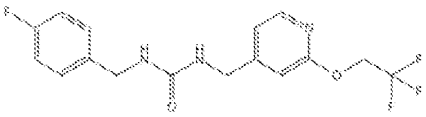
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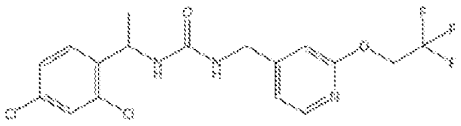
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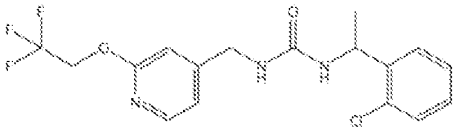
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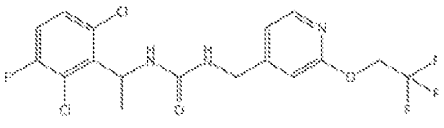
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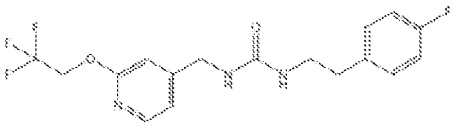
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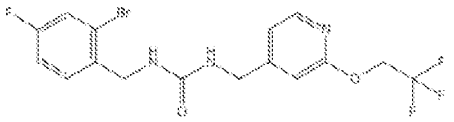
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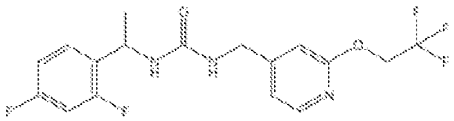
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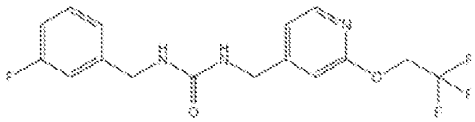
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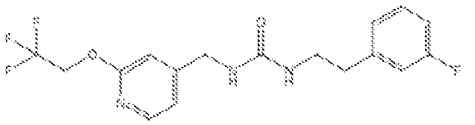
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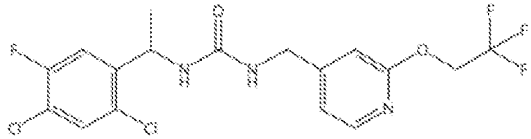
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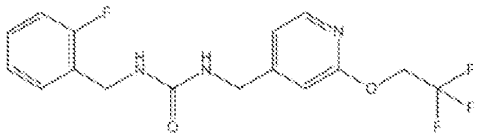

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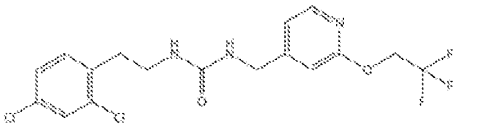

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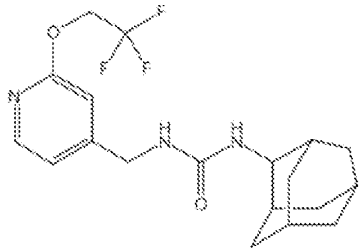

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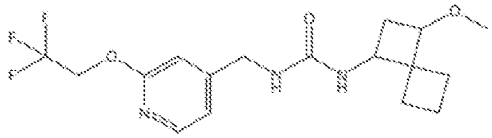
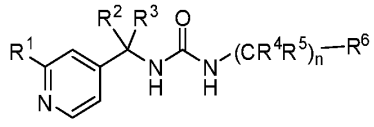


are excluded.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is CHF_2O- or unsubstituted imidazolyl;

R^2 and R^3 are hydrogen;

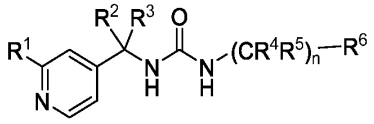
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexenyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, and pyridinyl wherein the bicyclo[1.1.1]pentanyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is CHF_2O- or unsubstituted imidazolyl;

R^2 and R^3 are hydrogen;

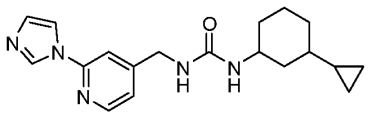
R^4 and R^5 are hydrogen; or

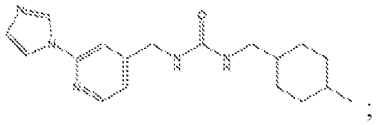
R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexenyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, and pyridinyl wherein the bicyclo[1.1.1]pentanyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy; and

n is 0, or 1;

provided that


;and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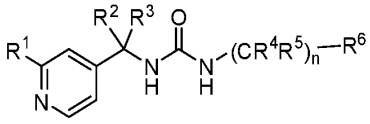
are excluded.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:


(I)

wherein:

R^1 is CHF_2O-;

R^2 and R^3 are hydrogen;

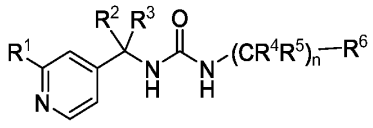
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexenyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, and pyridinyl wherein the bicyclo[1.1.1]pentanyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from C Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is CHF_2O-;

R^2 and R^3 are hydrogen;

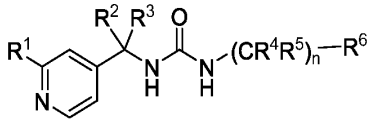
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexenyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the bicyclo[1.1.1]pentanyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, and CF_3-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is unsubstituted imidazolyl or imidazolyl substituted with one substituent selected from CH_3CF_2-, CF_3-, CH_2F, and CHF_2-;

R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen; or

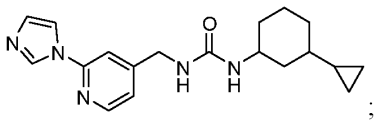
R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

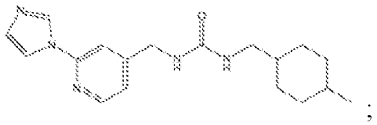
R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexenyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, and pyridinyl wherein the bicyclo[1.1.1]pentanyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl,

bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, and CF_3-; and

n is 0, or 1;

provided that


;and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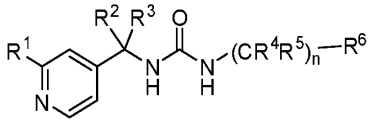
are excluded.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:


(I)

wherein:

R^1 is CHF_2O- or unsubstituted imidazolyl;

R^2 and R^3 are hydrogen;

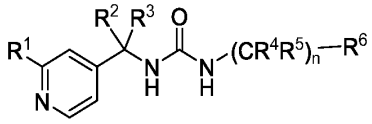
R^4 and R^5 are hydrogen;

R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexenyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl,

bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, and pyridinyl wherein the bicyclo[1.1.1]pentanyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, and CF_3-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is CHF_2O- or unsubstituted imidazolyl;

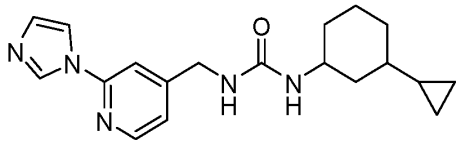
R^2 and R^3 are hydrogen;

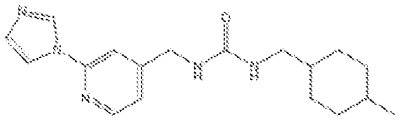
R^4 and R^5 are hydrogen;

R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexenyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, and pyridinyl wherein the bicyclo[1.1.1]pentanyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, and CF_3-; and

n is 0, or 1;

provided that


;and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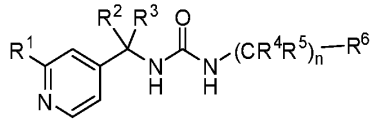
are excluded.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:


(I)

wherein:

R^1 is CHF_2O-;

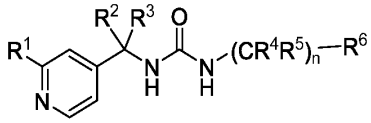
R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen;

R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexenyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, and pyridinyl wherein the bicyclo[1.1.1]pentanyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, and CF_3-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is CHF_2O-;

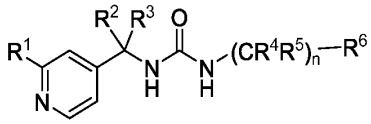
R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen;

R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexenyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, and pyridinyl wherein the bicyclo[1.1.1]pentanyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, and CF_3-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is unsubstituted imidazolyl or imidazolyl substituted with one substituent selected from CH_3CF_2-, CF_3-, CH_2F, and CHF_2-;

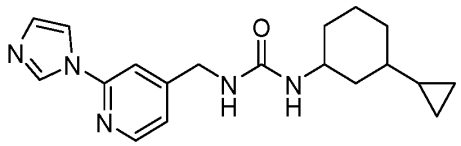
R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen;

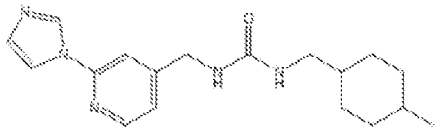
R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexenyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, pyrazinyl, pyrimidinyl, and pyridinyl wherein the bicyclo[1.1.1]pentanyl, cyclopentyl, cyclohexyl, cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, and bicyclo[2.2.2]octanyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, and CF_3-; and

n is 0, or 1;

provided that



; and



;

are excluded.

Features, integers, characteristics, compounds, chemical moieties or groups described in conjunction with a particular aspect, embodiment or example of the invention are to be understood to be applicable to any other aspect, embodiment or example described herein, unless

incompatible therewith. All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive. The invention is not restricted to the details of any embodiments described herein. Any embodiment described in this application can be combined with any other embodiment. For example, any embodiment herein relating to the compounds of formula (I), or a solvate or pharmaceutically acceptable salts thereof can be combined with any embodiment of pharmaceutical compositons, kits, medical use, or method of treatment. The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 5 membered heteroaryl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 5 membered heteroaryl, which is a 5 membered monocyclic, aromatic group with two N-atoms.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 5 membered heteroaryl, which is a 5 membered monocyclic, aromatic group comprising one N-atom and one O-atom.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is 5 membered heteroaryl, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is 5 membered heteroaryl, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl, wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is 5 membered heteroaryl, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) C_{1-6}alkyl; and

f) haloC_{1-6}alkyl;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, bicyclic edge-to-edge fused cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently

selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is 5 membered heteroaryl, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

wherein the bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 5 membered heteroaryl, and R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl,

bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 5 membered heteroaryl, and R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein the 5 membered heteroaryl is selected from pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, triazolyl, and furanyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein the 5 membered heteroaryl is selected from pyrazolyl, imidazolyl, and oxazolyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein the 5 membered heteroaryl is selected from pyrazolyl or imidazolyl, which pyrazolyl or imidazolyl are optionally substituted with one, two, or three substituents independently selected from $C_{1\text{-}6}$alkyl or halo$C_{1\text{-}6}$alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein the 5 membered heteroaryl is selected from pyrazolyl and imidazolyl, which pyrazolyl or imidazolyl are optionally substituted with one $C_{1\text{-}6}$alkyl or halo$C_{1\text{-}6}$alkyl.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted pyrazolyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from pyrazolyl and imidazolyl substituted with one, two, or three halo$C_{1\text{-}6}$alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl substituted with one halo$C_{1\text{-}6}$alkyl selected from $(CH_3)_2CF$-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl substituted with one CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl substituted with one $C_{1\text{-}6}$alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl substituted with one $C_{1\text{-}6}$alkyl selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl), n-butyl, sec-butyl, and tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl substituted with one CH_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl substituted with one, two, or three C_{1-6}alkyl or haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted imidazolyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl substituted with one haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl substituted with one haloC_{1-6}alkyl selected from $(CH_3)_2CF$-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl substituted with one CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl substituted with one C_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl substituted with one C_{1-6}alkyl selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, and tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl substituted with one CH_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is oxazolyl optionally substituted with one, two, or three C_{1-6}alkyl or haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted oxazolyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is oxazolyl substituted with one haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is oxazolyl substituted with one haloC_{1-6}alkyl selected from $(CH_3)_2CF$-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is oxazolyl substituted with one CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is oxazolyl substituted with one C_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is oxazolyl substituted with one C_{1-6}alkyl selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, and tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is oxazolyl substituted with one CH_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl, imidazolyl, or oxazolyl, which pyrazolyl, imidazolyl, or oxazolyl are unsubstituted or substituted as described herein, and R^2 and R^3 are hydrogen.

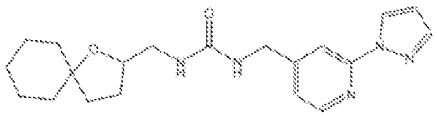
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from pyrazolyl, imidazolyl, and oxazolyl, which pyrazolyl, imidazolyl, or oxazolyl are unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, and n is 0, 1 or 2.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from pyrazolyl, imidazolyl, and oxazolyl, which pyrazolyl, imidazolyl, or oxazolyl are unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1 or 2, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, or a 4-10 membered bridged cycloalkyl, which fused heterocycloalkyl, saturated monocyclic cycloalkyl, phenyl, or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In the embodiments wherein n is 1 or 2, R^4 and R^5 are hydrogen.

In some preferred embodiments, n is 0 or 1.

In some embodiments the compound of formula (I) is not:



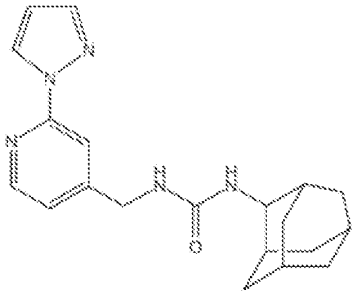
In some embodiments the above compound is not excluded for any medical use, kits, or pharmaceutical compositions.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl or imidazolyl, which pyrazolyl or imidazolyl are unsubstituted or substituted as described herein, R^2 and R^3 are

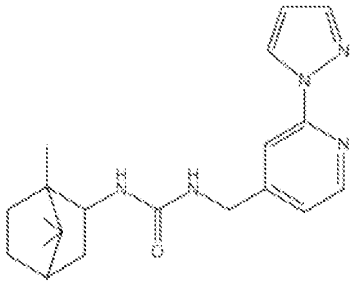
hydrogen, n is 0, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, or a 4-10 membered bridged cycloalkyl, which fused heterocycloalkyl, saturated monocyclic cycloalkyl, or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In some embodiments of the compound of formula (I), wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl the compound is not:



; or



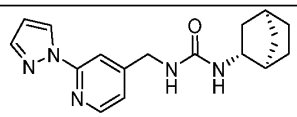
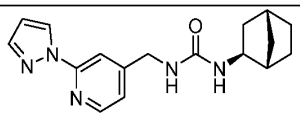
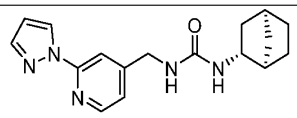
In some embodiments the above compounds are not excluded for any medical use, kits, or pharmaceutical compositions.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is an unsubstituted 4-10 membered bridged cycloalkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is unsubstituted bicyclo[2.2.1]heptanyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and and non-limiting examples are selected from:

7	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
15	1-[(1S,2S,4R)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
16	1-[(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, and R^6 is a monocyclic 4-6 membered cycloalkenyl group with one non-aromatic double bond, which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, and R^6 is an unsubstituted monocyclic 4-6 membered cycloalkenyl group with one non-aromatic double bond.

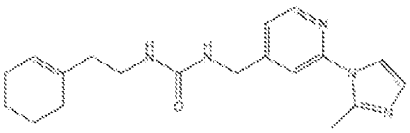
In some embodiments wherein n is 1 or 2, R^4 and R^5 are both hydrogen.

In some preferred embodiments n is 0 or 1.

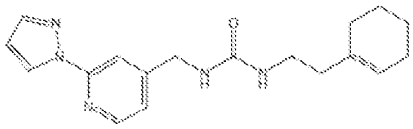
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 2, R^4 and R^5 are

hydrogen, and R^6 is a monocyclic 4-6 membered cycloalkenyl group with one non-aromatic double bond which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In some embodiments wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 2, R^4 and R^5 are hydrogen, and R^6 is a monocyclic 4-6 membered cycloalkenyl group with one non-aromatic double bond the compound of formula (I) is not:



; or



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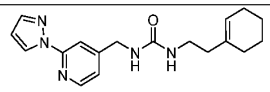
In some embodiments the above compounds are not excluded for any medical use, kits, or pharmaceutical compositions.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 2, R^4 and R^5 are hydrogen, and R^6 is an unsubstituted monocyclic 4-6 membered cycloalkenyl group selected from cyclobutenyl, cyclopentenyl, and cyclohexenyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 2, R^4 and R^5 are hydrogen, and R^6 is unsubstituted cyclohexenyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and a non-limiting example has the structure:

10	1-[2-(cyclohexen-1-yl)ethyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, which fused heterocycloalkyl is unsubstituted or substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

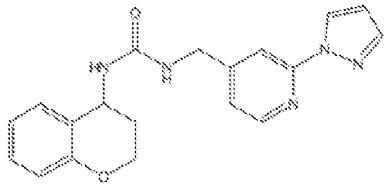
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, which fused heterocycloalkyl is unsubstituted or substituted with one, two, or three halogen or haloC_{1-6}alkyl.

In some embodiments, wherein n is 1 or 2, R^4 and R^5 are hydrogen.

In some preferred embodiments, n is 0 or 1.

In some other embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring

wherein one ring comprises one O-atom, which fused heterocycloalkyl is unsubstituted or substituted with one, two, or three halogen, or haloC_{1-6}alkyl, wherein the compound is not:



In some embodiments the above compound is not excluded for any medical use, kits, or pharmaceutical compositions.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, which fused heterocycloalkyl is unsubstituted or substituted with one, two, or three halogen or haloC_{1-6}alkyl.

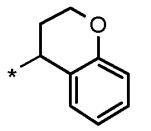
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, which fused heterocycloalkyl is unsubstituted or substituted with one halogen or haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, which fused heterocycloalkyl is optionally substituted with one Cl-, F-, CH_3-, and CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is an unsubstituted bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is unsubstituted dihydrochromenyl.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is



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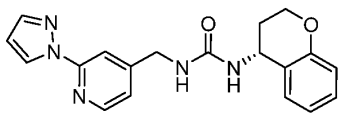
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and a non-limiting example has the structure:

1	1-[(4R)-3,4-dihydro-2H-chromen-4-yl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is

unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In some embodiments, wherein n is 1 or 2, R^4 and R^5 are hydrogen.

In some preferred embodiments, n is 0 or 1.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one, two, or three substituents independentyl selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

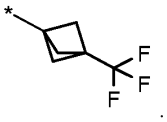
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is unsubstituted or substituted with one Cl-, F-, CH_3-, and CF_3-

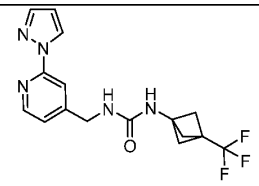
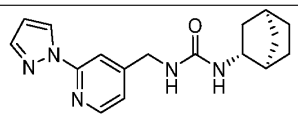
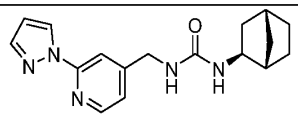
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from unsubstituted bicyclo[1.1.1]pentanyl and bicyclo[2.2.1]heptanyl.

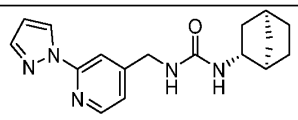
In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is unsubstituted bicyclo[1.1.1]pentanyl.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is



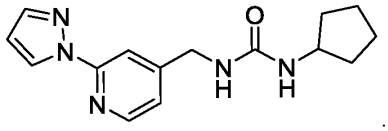
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and non-limiting examples have the structures:

6	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
7	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
15	1-[(1S,2S,4R)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	

16	1-[(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic 4-6 membered cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In some embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic 4-6 membered cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the compound is not;



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In some embodiments the above compound is not excluded for any medical use, kits, or pharmaceutical compositions.

In some embodiments, wherein n is 1 or 2, R^4 and R^5 are hydrogen.

In some preferred embodiments, n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic 4-6 membered cycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In some embodiments, the saturated monocyclic 4-6 membered cycloalkyl is unsubstituted.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which cycloalkyl is unsubstituted or substituted with one C_{1-6} alkyl selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, and tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which cycloalkyl is unsubstituted or substituted with one CH_3-.

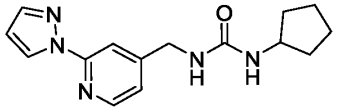
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are unsubstituted or substituted with one CH_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from unsubstituted cyclobutyl, cyclopentyl, and cyclohexyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is unsubstituted cyclobutyl or unsubstituted cyclopentyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is unsubstituted cyclopentyl.

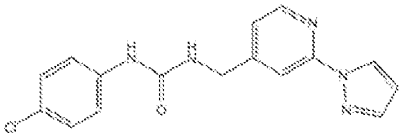
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and a non-limiting example has the structure:

2	1-cyclopentyl-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, and R^6 is phenyl which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In some embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, and R^6 is phenyl which is optionally substituted with one, two, or three substituents independently selected

from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the compound is not:



In some embodiments the above compound is not excluded for any medical use, kits, or pharmaceutical compositions.

In some embodiments, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, and R^6 is phenyl which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl, only for embodiments relating to medical use, kits, or pharmaceutical compositions.

In some embodiments, wherein n is 1 or 2, R^4 and R^5 are hydrogen.

In some preferred embodiments, n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is phenyl unsubstituted or substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

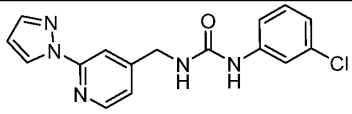
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is phenyl unsubstituted or substituted with one substituent selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is phenyl substituted with one halogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is phenyl substituted with one halogen selected from F-, Cl- or Br-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is phenyl substituted with one Cl-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazolyl which is unsubstituted or substituted as described herein, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and a non-limiting example has the structure:

4	1-(3-chlorophenyl)-3-[(2-pyrazol -1-ylpyridin-4-yl)methyl]urea	

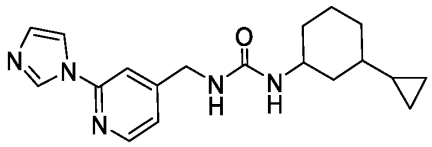
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, R^4 and R^5 are hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl or a 4-10 membered bridged cycloalkyl, which saturated monocyclic cycloalkyl or bridged cycloalkyl are optionally

substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In some embodiments, wherein n is 1 or 2, R^4 and R^5 are hydrogen.

In some preferred embodiments, n is 0 or 1.

In some embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, 1, or 2, R^4 and R^5 are hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl or a 4-10 membered bridged cycloalkyl, which saturated monocyclic cycloalkyl or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl, which compound is not selected from: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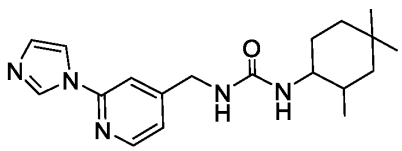
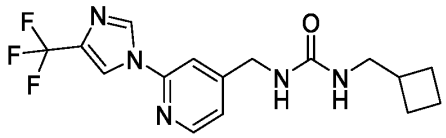

; and


.

In some embodiments, the compound is not excluded for any medical use, kits, or pharmaceutical compositions.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl or a 4-10 membered bridged cycloalkyl, which saturated monocyclic cycloalkyl or bridged cycloalkyl are unsubstituted or substituted with one, two, or three substituents independently selected from halogen, C_{3-6}cycloalkyl, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is unsubstituted or substituted with one C_{3-6}cycloalkyl.

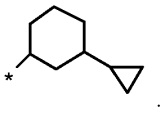
In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is unsubstituted or substituted with one C_{3-6}cycloalkyl selected from cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is unsubstituted or substituted with one cyclopropyl.

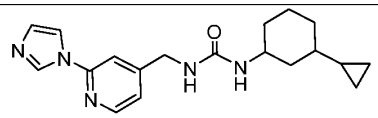
In one particularily prefered embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl

which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is cyclohexyl substituted with one cyclopropyl.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is



In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and a non-limiting example has the structure:

8	1-(3-cyclopropylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocylic cycloalkyl is unsubstituted or substituted with one, two, or three C_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is unsubstituted or substituted with three C_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is unsubstituted or substituted with three C_{1-6}alkyl selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, and tert-butyl.

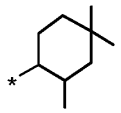
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is unsubstituted or substituted with three CH_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl which are substituted with two or three CH_3-.

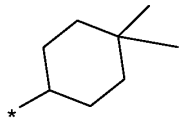
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is cyclohexyl substituted with two or three CH_3-.

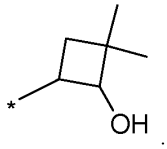
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is cyclohexyl substituted with two or three CH_3-, and one or two hydroxy.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl which is unsubstituted or substituted as described , R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from:

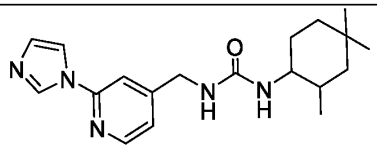
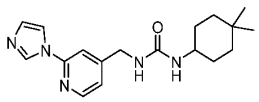
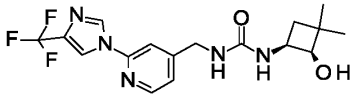


or





In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, R^1 is imidazolyl, which is unsubstituted or substituted as described herein, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and non-limiting examples have the structure :

9	1-[(2-imidazol-1-ylpyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	
37	1-(4,4-dimethylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea	
99	1-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	

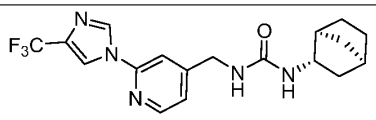
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl, which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, or a satuarated monocyclic 4-6 membered cycloalkyl, which are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidzolyl, which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is an unsubstituted 4-10 membered bridged cycloalkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidazolyl, which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is unsubstituted bicyclo[2.2.1]heptanyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is imidzolyl, which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl which is substituted by three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, R^1 is imidazolyl which is substituted or substituted as described herein, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and a non-limting example has the structure:

26	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-[4-	

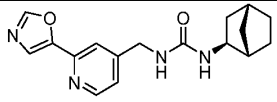
	(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is oxazolyl, which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

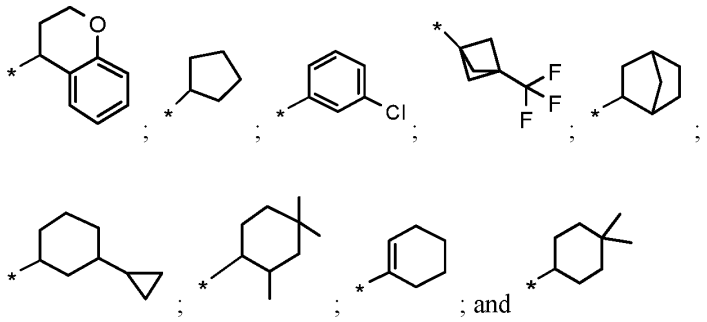
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is oxazolyl, which is unsubstituted or substituted as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is an unsubstituted 4-10 membered bridged cycloalkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is oxazolyl, which is substituted with one haloC_{1-6}alkyl as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is unsubstituted bicyclo[2.2.1]heptanyl.

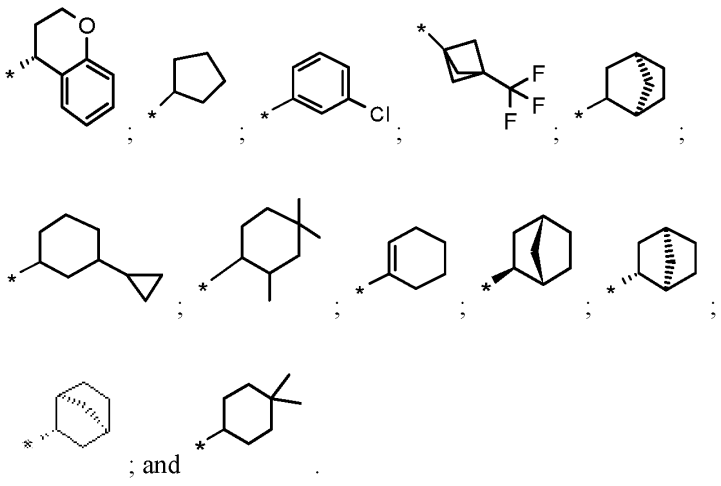
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, R^1 is oxazolyl which is substituted or substituted as described herein, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and a non-limiting example has the structure:

28	1-[[2-(1,3-oxazol-5-yl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	

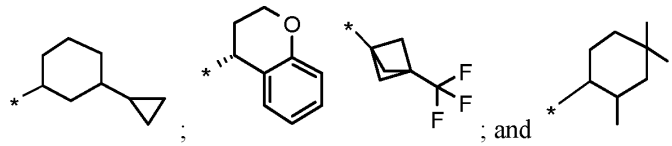
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from pyrazolyl, imidazolyl, and oxazolyl, which are unsubstituted or substituted as described herein, n, R^2, R^3, R^4 and R^5 are as described herein, and R^6 is selected from:



In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from pyrazolyl, imidazolyl, and oxazolyl, which are unsubstituted or substituted as described herein, n, R^2, R^3, R^4 and R^5 are as described herein, and R^6 is selected from:

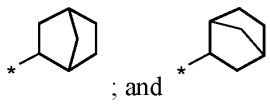


In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from pyrazolyl, imidazolyl, and oxazolyl, which are unsubstituted or substituted as described herein, n, R^2, R^3, R^4 and R^5 are as described herein, and R^6 is selected from:



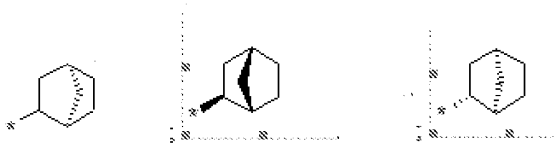
; ; and .

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from pyrazolyl, imidazolyl, or oxazolyl, which are unsubstituted or substituted as described herein, n, R^2, R^3, R^4 and R^5 are as described herein, and R^6 is selected from:



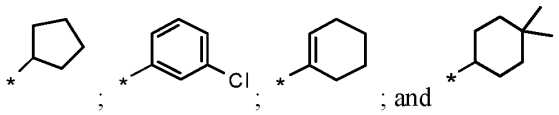
; and .

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from pyrazolyl, imidazolyl, and oxazolyl, which are unsubstituted or substituted as described herein, n, R^2, R^3, R^4 and R^5 are as described herein, and R^6 is selected from:

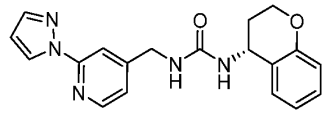
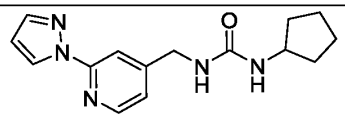
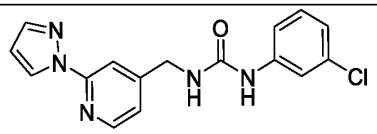
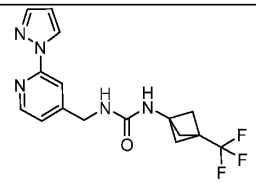
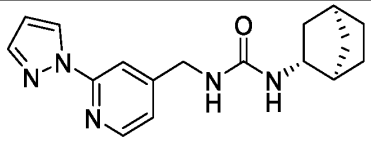


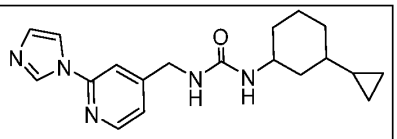
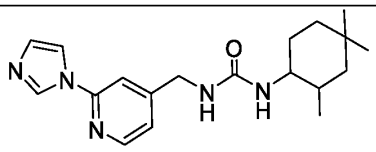
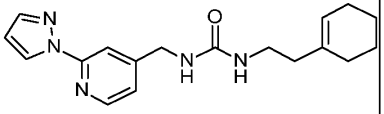
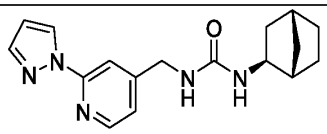
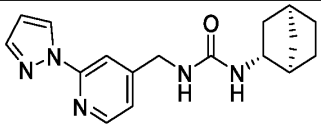
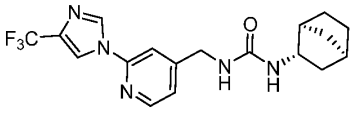
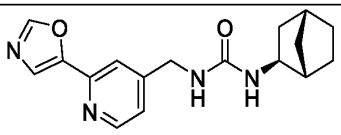
; ; and .

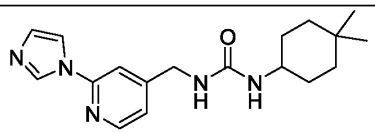
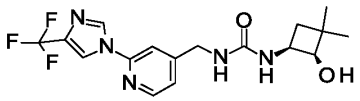
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from pyrazolyl, imidazolyl, and oxazolyl, which are unsubstituted or substituted as described herein, n, R^2, R^3, R^4 and R^5 are as described herein, and R^6 is selected from:



In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 5 membered heteroaryl selected from pyrazolyl, imidazolyl and oxazolyl, which are unsubstituted or substituted as described herein, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and non-limiting examples are selected from:

1	1-[(4R)-3,4-dihydro-2H-chromen-4-yl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
2	1-cyclopentyl-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
4	1-(3-chlorophenyl)-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
6	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
7	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	

8	1-(3-cyclopropylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea	
9	1-[(2-imidazol-1-ylpyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	
10	1-[2-(cyclohexen-1-yl)ethyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
15	1-[(1S,2S,4R)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
16	1-[(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
26	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	
28	1-[[2-(1,3-oxazol-5-yl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	

37	1-(4,4-dimethylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea	
99	1-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkyl, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkyl, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invntion provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkyl, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) C_{1-6}alkyl, and

e) haloC_{1-6}alkyl;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, bicyclic edge-to-edge fused cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invntion provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkyl, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or

one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

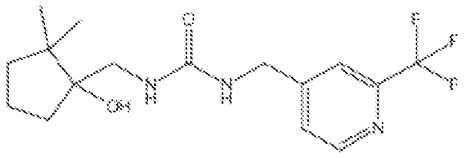
wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkyl, and R^6 is selected from is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

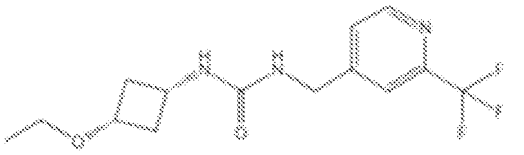
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkyl, and R^6 is selected from is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl,

oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In some embodiments, wherein R^1 is a haloC_{1-6}alkyl, the compound of formula (I) is not selected from:



; or



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In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkyl selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, or CHF_2-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CHF_2-, CF_3-, CF_3CH_2-, and CH_3CF_2-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3CF_2-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2-,

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-, R^2 and R^3 are hydrogen, n is 0, 1 or 2, and R^6 is a 4-10 membered bridged cycloalkyl, or a saturated monocyclic 4-6 membered cycloalkyl, wherein the bridged cycloalkyl, or saturated monocyclic cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-, R^2 and R^3 are hydrogen, n is 0, 1 or 2, and R^6 is a 4-10 membered bridged cycloalkyl, or a saturated monocyclic 4-6 membered cycloalkyl, wherein the bridged cycloalkyl, or saturated monocyclic cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In some embodiments, when n is 1 or 2, R^4 and R^5 are hydrogen.

In some embodiments n is 0 or 1.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, or CHF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, or a saturated monocyclic 4-6 membered cycloalkyl, wherein the

bridged cycloalkyl, or saturated monocyclic cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-, CF_3CH_2-, and CH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is an unsubstituted 4-10 membered bridged cycloalkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-, CF_3CH_2-, and CH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from an unsubstituted bicyclo[1.1.1]pentanyl and bicyclo[2.2.1]heptanyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-, CF_3CH_2-, and CH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is an unsubstituted bicyclo[2.2.1]heptanyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-, CF_3CH_2-, and CH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from bicyclo[1.1.1]pentanyl and bicyclo[2.2.1]heptanyl, which are substituted with one or two halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

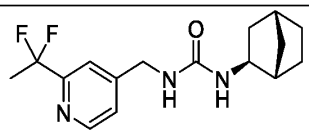
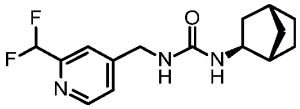
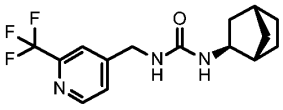
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-, CF_3CH_2-, and CH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is bicyclo[1.1.1]pentanyl and bicyclo[2.2.1]heptanyl, which are substituted with one or two F- or CF_3-.

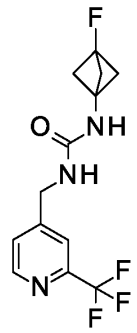
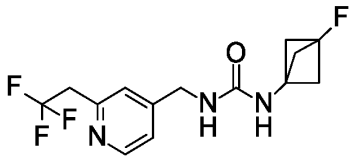
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-,

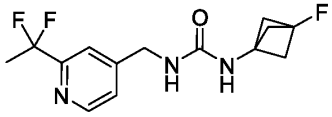
CF_3CH_2-, and CH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is an unsubstituted bicyclo[2.2.1]heptanyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-, CF_3CH_2-, andCH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is bicyclo[1.1.1]pentanyl and bicyclo[2.2.1]heptanyl, which are substituted with one for two F- or CF_3-.

In one preferred embdiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a halo$C_{1\text{-}6}$alkyl, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and non-limiting examples are selected from:

33	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
35	1-[[2-(difluoromethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
36	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	

153	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	
159	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	

200	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-, CF_3CH_2-, and CH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl .

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-,

CF_3CH_2-, and CH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-, CF_3CH_2-, and CH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are substituted with one haloC_{1-6}alkyl.

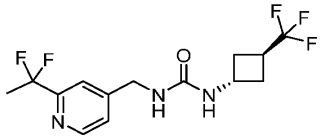
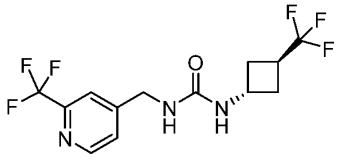
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-, CF_3CH_2-, and CH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are substituted with one haloC_{1-6}alkyl selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

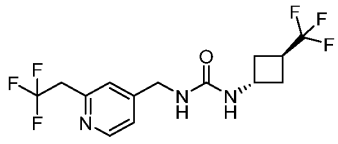
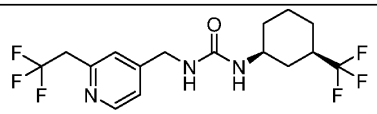
In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-, CF_3CH_2-, and CH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are substituted with one CF_3-.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3-, R^2 and R^3 are hydrogen, n is 0, and R^6 is cyclobutyl substituted with one CF_3-.

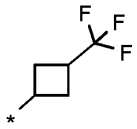
In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CF_3-, CHF_2-, CF_3CH_2-, and CH_3CF_2-, R^2 and R^3 are hydrogen, n is 0, and R^6 is is a saturated monocyclic 4-6 membered cycloalkyl selected from unsubstituted cyclobutyl, cyclopentyl, and cyclohexyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkyl, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and non-limiting examples are selected from:

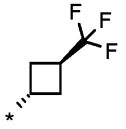
57	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
58	1-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	

64	1-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
276	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	

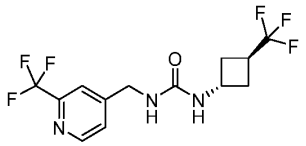
In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl having the structure:



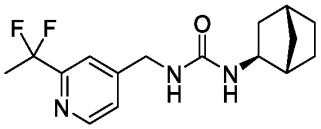
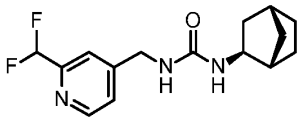
In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl having the structure:

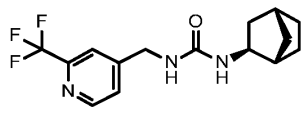
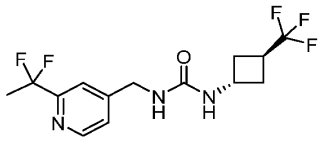
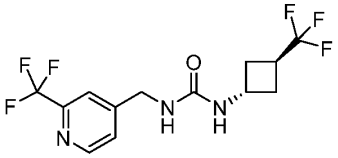
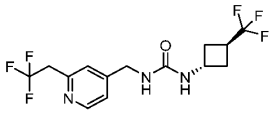
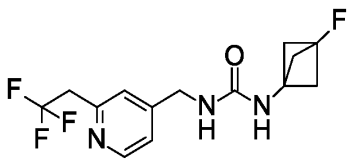


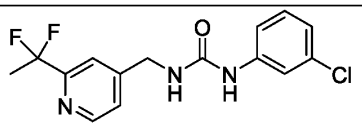
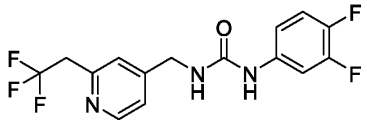
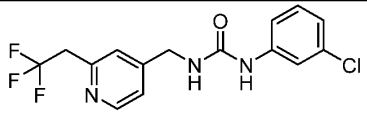
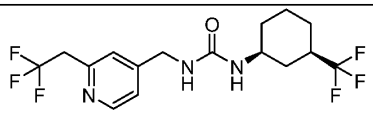
In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkyl, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and a non-limiting example has the structure:

58	1-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt, thereof, wherein R^1 is a haloC_{1-6}alkyl, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and non-limiting examples are selected from:

33	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
35	1-[[2-(difluoromethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	

36	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	
57	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
58	1-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	
64	1-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
159	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	

231	1-(3-chlorophenyl)-3-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]urea	
274	1-(3,4-difluorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
275	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
276	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein

the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) C_{1-6}alkyl; and

f) haloC_{1-6}alkyl;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, bicyclic edge-to-edge fused cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

wherein the bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, and is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, and R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, and R^2 and R^3 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, and n is 0, 1, or 2.

In some embodiments, when n is 1 or 2, R^4 and R^5 are hydrogen.

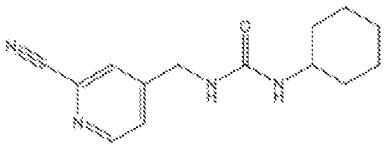
In some embodiments is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, and n is 0.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, or a saturated monocyclic 4-6 membered cycloalkyl, which bridged cycloalkyl or saturated monocyclic cycloalkyl are optionally

substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In some embodiments of the compound of formula (I), wherein R^1 is cyano, R^2 and R^3 are hydrogen n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, or a saturated monocyclic 4-6 membered cycloalkyl, which bridged cycloalkyl or saturated monocyclic cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl, and the compound is not:



In some embodiments, the above compound is not excluded for any medical use, kits, or pharmaceutical compositions.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, or a saturated monocyclic 4-6 membered cycloalkyl, which bridged cycloalkyl or saturated monocyclic cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, or haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, or a saturated monocyclic 4-6 membered cycloalkyl, which bridged cycloalkyl or saturated monocyclic cycloalkyl are optionally substituted with one, two, or three C_{1-6} alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl or a saturated monocyclic 4-6 membered cycloalkyl, which bridged cycloalkyl or saturated monocyclic cycloalkyl are optionally substituted with three C_{1-6} alkyl.

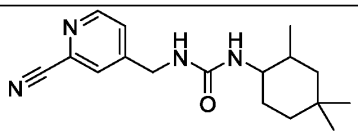
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with three C_{1-6} alkyl selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, and tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl are optionally substituted with three C_{1-6} alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with three CH_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is cyclohexyl, which cyclohexyl is substituted with three CH_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and a non-limiting example is:

5	1-[(2-cyanopyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl which is optionally substituted with one, two or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

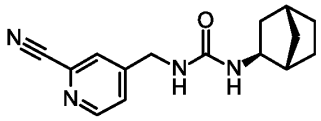
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl selected from bicyclo[1.1.1]pentanyl and bicyclo[2.2.1]heptanyl which are optionally substituted with one, two or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is an unsubstituted 4-10 membered bridged cycloalkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from unsubstituted bicyclo[1.1.1]pentanyl and bicyclo[2.2.1]heptanyl.

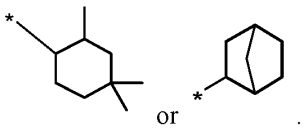
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is an unsubstituted bicyclo[2.2.1]heptanyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and a non-limiting example is:

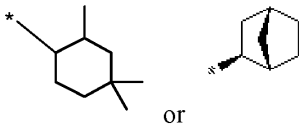
34	1-[(2-cyanopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl or saturated monocyclic 4-6 membered cycloalkyl which is optionally substituted with three CH_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl or a saturated monocyclic 4-6 membered cycloalkyl which are optionally substituted as described herein, and wherein non-limiting examples of the structures of R^6 are:

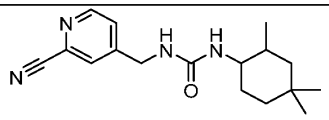
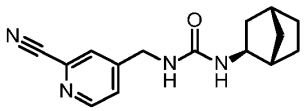
 or .

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, R^2 and R^3 are hydrogen, n is 0, and R^6 is an unsubituted 4-10 membered bridged cycloalkyl or a saturated monocyclic 4-6 membered cycloalkyl which is substituted with three CH_3-, and wherein non-limiting examples of the structures of R^6 are:



or .

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and non-limiting examples are selected from:

5	1-[(2-cyanopyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	
34	1-[(2-cyanopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyano$C_{1\text{-}6}$alkoxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyano$C_{1\text{-}6}$alkoxy, and R^6 is selected from is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, $C_{1\text{-}6}$alkyl, and halo$C_{1\text{-}6}$alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, $C_{1\text{-}6}$ alkyl, $C_{3\text{-}6}$cycloalkyl, $C_{1\text{-}6}$alkoxy, cyano, oxo, hydroxy, hydroxy$C_{1\text{-}6}$alkyl, and halo$C_{1\text{-}6}$alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyano$C_{1\text{-}6}$alkoxy, and R^6 is selected from is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10

membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyanoC_{1-6}alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) C_{1-6}alkyl; and

f) haloC_{1-6}alkyl;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, bicyclic edge-to-edge fused cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyanoC_{1-6}alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

wherein the bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, , heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyanoC_{1-6}alkoxy, and R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents

independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyanoC_{1-6}alkoxy, and R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyanoC_{1-6}alkoxy and R^2 and R^3 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyanoC_{1-6}alkoxy, R^2 and R^3 are hydrogen and n is 0, 1, or 2.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyanoC_{1-6}alkoxy, R^2 and R^3 are hydrogen and n is 0.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyanoC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three substituents independently

selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyanoC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl which saturated monocyclic cycloalkyl is optionally substituted with substituent selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl as defined herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyanoC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl which saturated monocyclic cycloalkyl is optionally substituted with one substituent selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl as defined herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyanoC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

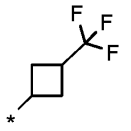
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a cyanoC_{1-6}alkoxy selected from NC-CH_2O-, NC-CH_2CH_2O-, and NC$CH_2CH_2CH_2O$-.

In a preferred emobidment, the cyanoC_{1-6}alkoxy is NC-CH_2O-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is NC-CH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is cyclobutyl substituted with one haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is NC-CH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is cyclobutyl substituted with one CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is NC-CH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 has the structure:



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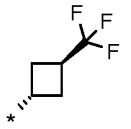
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is NC-CH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 has the structure:



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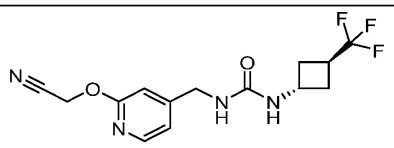
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is cyano$C_{1\text{-}6}$alkoxy, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and a non-limiting example has the structure:

63	1-[[2-(cyanomethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, and R^6 is selected from is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, and R^6 is selected from is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl, wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl; and

e) haloC_{1-6}alkyl;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

wherein the bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl, are optionally

substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

wherein the bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl, are optionally substituted with one or two substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or

one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

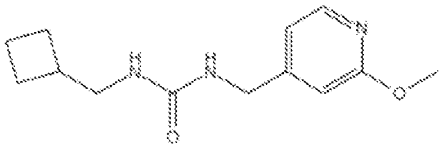
wherein the bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl, are optionally substituted with one or two substituents independently selected from Cl-, F-, CH_3-, and CF_3-.

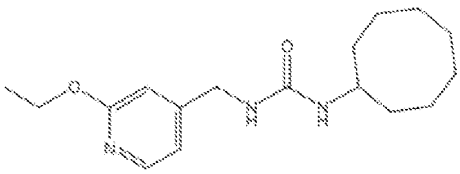
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, and R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

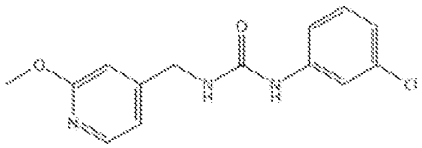
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, and R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl,

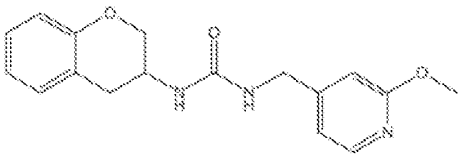
bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

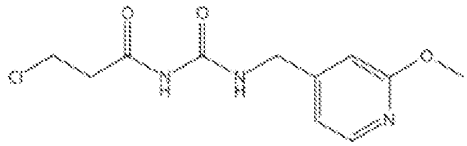
In some embodiments, some compounds as described below, wherein R^1 is C_{1-6}alkoxy, are excluded from the compounds of formula (I):

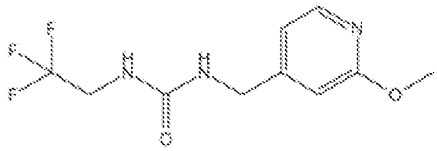


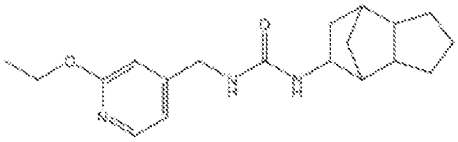












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In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy selected from CH_3O-, CH_3CH_2O-, $CH_3CH_2CH_2O$-, and $(CH_3)_3CO$-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, and R^2 and R^3 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, R^2 and R^3 are hydrogen, and n is 0, 1, or 2.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, R^2 and R^3 are hydrogen, n

is 0, 1, or 2 and R^6 is a 4-10 membered bridged cycloalkyl which is optionally substituted with one, two or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

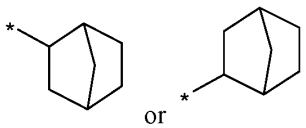
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl which is optionally substituted with one, two or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl selected from bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, and bicyclo[2.2.2]octanyl, which are optionally substituted with one, two or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is unsubstituted.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is an unsubstituted bicyclo[2.2.1]heptanyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0, and R^6 has the structure:



or

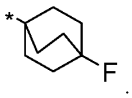
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0,

and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one or two substituents independentyl selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is bicyclo[2.2.2]octanyl optionally substituted with one or two substituents independentyl selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is bicyclo[2.2.2]octanyl optionally substituted with one or two F- or CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0, and R^6 has the structure:



In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 0, 1, or 2 and R^6 is a saturated monocyclic 4-6 membered cycloalkyl which is optionally substituted with one, two or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl which is optionally substituted with one, two or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which are optionally substituted with one, two or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

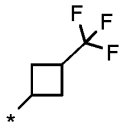
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which cycloalkyl is unsubstituted.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which cycloalkyl is optionally substituted with one or two substituents independently selected form halogen and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which are optionally substituted with one or two substituents independently selected from halogen and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl optionally substituted with one or two F- or CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0, and R^6 has the structure:



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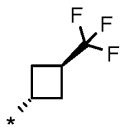
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3O-, R^2 and R^3 are hydrogen, n is 0, and R^6 has the structure:



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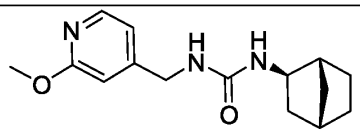
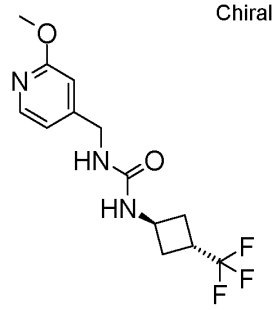
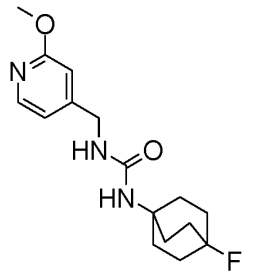
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $C_{1\text{-}6}$alkoxy, n, R^2, R^3 R^4, R^5, and R^6 are as described herein, and non-limiting examples have the structure:

14	1-[(2-methoxypyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
128	1-[(2-methoxypyridin-4-yl)methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	Chiral 

129	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[(2-methoxypyridin-4-yl)methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen, and R^6 is selected from is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen, and R^6 is selected from is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring,

wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) C_{1-6} alkyl; and

f) haloC_{1-6}alkyl;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, bicyclic edge-to-edge fused cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

wherein the bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl, are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen, and R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen, and R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen selected from Cl-, Br-, and F-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or pharmaceutically acceptable salt thereo, wherein R^1 is Br-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen, and R^2 and R^3 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen, R^2 and R^3 are hydrogen, and n is 0, 1, or 2.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen, R^2 and R^3 are hydrogen, and n is 0.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen, R^2 and R^3 are hydrogen, n is 0, 1, or 2, and R^6 is a 4-10 membered bridged cycloalkyl which is optionally substituted with one, two or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl which is optionally substituted with one, two or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

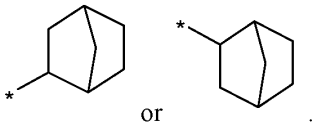
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is halogen, R^2 and R^3 are hydrogen, n is 0,

and R^6 is a 4-10 membered bridged cycloalkyl selected from bicyclo[1.1.1]pentanyl and bicyclo[2.2.1]heptanyl, which bicyclo[1.1.1]pentanyl and bicyclo[2.2.1]heptanyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

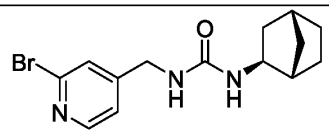
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is Br-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is unsubstituted.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is Br-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a bicyclo[2.2.1]heptanyl which is unsubstituted.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is Br-, R^2 and R^3 are hydrogen, n is 0, and R^6 has the structure:


or .

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{1-6}alkoxy, n, R^2, R^3, R^4, R^5 and R^6 are as described herein, and a non-limiting example has the structure:

27	1-[(2-bromopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	

In one embodiment, the pesent invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereo, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy, and R^6 is selected from is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy, and R^6 is selected from is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) C_{1-6} alkyl; and

f) haloC_{1-6}alkyl;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, bicyclic edge-to-edge fused cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is C_{3-5}cycloalkylC_{1-6}alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

wherein the bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl, are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

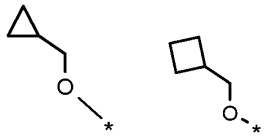
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy, and R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy, and R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the pesent invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereo, wherein R^1 the C_{3-5}cycloalkylC_{1-6}alkoxy selected from cyclopropylmethoxy and cyclobutylmethoxy.

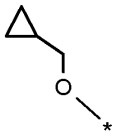
In one embodiment, the pesent invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereo, wherein R^1 selected from 2-cyclopropylmethoxy or 2-cyclobutylmethoxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereo, wherein R^1 a $C_{3\text{-}5}$cycloalkyl$C_{1\text{-}6}$alkoxy has the



structure or .

In one embodiment, the present invention provides a compound of formula (I), or a solvate or pharmaceutically acceptable salt thereo, wherein R^1 has the structure



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In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a $C_{3\text{-}5}$cycloalkyl$C_{1\text{-}6}$alkoxy, and R^2 and R^3 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a cycloalkyl$C_{1\text{-}6}$alkoxy, R^2 and R^3 are hydrogen, and n is 0, 1, or 2.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a $C_{3\text{-}5}$cycloalkyl$C_{1\text{-}6}$alkoxy, R^2 and R^3 are hydrogen, and n is 0.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a $C_{3\text{-}5}$cycloalkyl$C_{1\text{-}6}$alkoxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl are optionally substituted with one, two, or three substituents

independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one halogen, or haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one haloC_{1-6}alkyl selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is cyclobutyl, which cyclobutyl is optionally substituted with one CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, and R^2 and R^3 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, R^2 and R^3 are hydrogen, and n is 0.

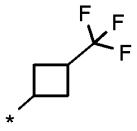
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl which saturated monocyclic cycloalkyl is optionally substituted with one haloC_{1-6}alkyl as defined herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl which saturated monocyclic cycloalkyl is optionally substituted with one haloC_{1-6}alkyl as defined herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 is cyclobutyl substituted with one CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy as described herein, R^2 and R^3 are hydrogen, n is 0, and R^6 has the structure:



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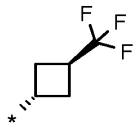
In particular R^6 has the structure:



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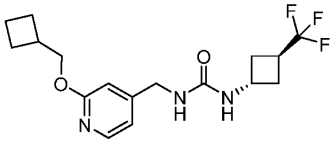
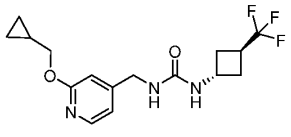
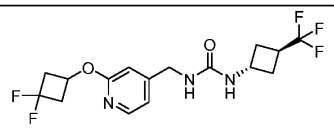
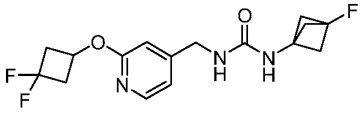
In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is a C_{3-5}cycloalkylC_{1-6}alkoxy, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and non-limiting examples are selected from:

54	1-[[2-(cyclobutylmethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
55	1-[[2-(cyclopropylmethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	

209	1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
224	1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	

In one embodiment, the pesent invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereo, wherein R^1 is a 4-6 membered heterocyclyloxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 4-6 membered heterocyclyloxy, and R^6 is selected from is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 4-6 membered heterocyclyloxy, and R^6 is selected from is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 4-6 membered heterocyclyloxy, and R^6 is selected from:

$_{6}$alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) C_{1-6} alkyl; and

f) haloC_{1-6}alkyl;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, bicyclic edge-to-edge fused cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 4-6 membered heterocyclyloxy, and R^6 is selected from:

a$_{6}$alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

wherein the bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

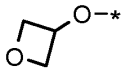
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 4-6 membered heterocyclyloxy, and R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 4-6 membered heterocyclyloxy, and R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereo, wherein R^1 is an oxetanyloxy which is optionally substituted with one CF_3- or F-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereo, wherein R^1 is an unsubstituted oxetanyloxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereo, wherein R^1 is unsubstituted oxetan-3yloxy with the structure;



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In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted oxetanyloxy, and R^2 and R^3 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted oxetanyloxy, R^2 and R^3 are hydrogen, and n is 0,

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted oxetanyloxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one or two C_{1-6}alkyl, or haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted oxetanyloxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one or two C_{1-6}alkyl or haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted oxetanyloxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one or two C_{1-6}alkyl or haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted oxetanyloxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, or cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one or two C_{1-6}alkyl, or haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted oxetanyloxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl optionally substituted with two haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted oxetanyloxy, R^2 and R^3

are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl optionally substituted with two haloC_{1-6}alkyl selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, or CHF_2-.

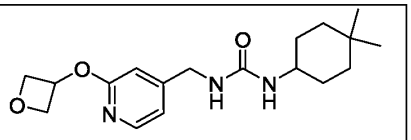
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted oxetanyloxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl optionally substituted with two C_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted oxetanyloxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl substituted with two C_{1-6}alkyl selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, and tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted oxetanyloxy, $R^2$and R^3 are hydrogen, n is 0, and R^6 is cyclohexyl optionally substituted with two CH_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is oxetan-3yloxy, R^2 and R^3 are hydrogen, n is 0, and R^6 is cyclohexyl optionally substituted with two CH_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a 4-6 membered heterocyclyloxy, n, R^2, R^3, R^4, R^5, and R^6 are as described herein, and a non-limting example has the structure:

18	1-(4,4-dimethylcyclohexyl)-3-[[2-(oxetan-3-yloxy)pyridin-4-yl]methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkoxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkoxy, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkoxy, and R^6 is selected from is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkoxy, and R^6 is selected from:

$_{6}$alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) C_{1-6} alkyl; and

f) haloC_{1-6}alkyl;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, bicyclic edge-to-edge fused cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkoxy, and R^6 is selected from:

$_{6}$alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

wherein the bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkoxy, and R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkoxy, and R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is a haloC_{1-6}alkoxy selected from CHF_2O-, CH_2FO-, CF_3CH_2O-, CF_2HCH_2O-, $CH_3CF_2CH_2O$-,and CH_3CFHCH_2O-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2FO-.

In another preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-.

In another embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_2HCH_2O-.

In another preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-.

In another embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3CFHCH_2O-.

In some embodiments, when CF_3CH_2O-, the compound of formula (I) excludes compounds for which R^2 and R^3 are hydrogen, n is 2, in the first pair of R^4 and R^5 both are hydrogen, and in the second pair of R^4 and R^5 one is hydrogen and the other one is hydroxy, and R^6 is $C_{1\text{-}6}$alkyl.

In some embodiments, when CF_3CH_2O-, the compound of formula (I) excludes compounds for which R^2 and R^3 are hydrogen, n is 2, in the first pair of R^4 and R^5 both are hydrogen, and in the second pair of R^4 and R^5 one is hydrogen and the other one is hydroxy, and R^6 is tert-butyl.

In some embodiments, when CF_3CH_2O-, the compound of formula (I) excludes compounds for which R^2 and R^3 are hydrogen, n is 2, in the first pair of R^4 and R^5 both are hydrogen, and in the second pair of R^4 and R^5 both are hydrogen, and R^6 is $C_{1\text{-}6}$alkyl.

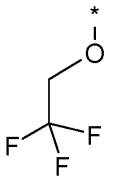
In some embodiments, when CF_3CH_2O-, the compound of formula (I) excludes compounds for which R^2 and R^3 are hydrogen, n is 3, wherein in the first and second pair of R^4 and R^5 both R^4 and R^5 are hydrogen, and the third pair of R^4 and R^5 together with the one carbon atom they are attached, form unsubstituted cyclopropyl, and R^6 is haloC_{1-6}alkyl.

In some embodiments, when CF_3CH_2O-, the compound of formula (I) excludes compounds for which R^2 and R^3 are hydrogen, n is 3, wherein in the first pair of R^4 and R^5 both R^4 and R^5 are hydrogen, in the second pair of R^4 and R^5 one is hydrogen and the other is hydroxy, and the third pair of R^4 and R^5 together with the one carbon atom they are attached, form unsubstituted cyclopropyl, and R^6 is haloC_{1-6}alkyl.

In some embodiments, when CF_3CH_2O-, the compound of formula (I) excludes compounds for which R^2 and R^3 are hydrogen, n is 3, wherein in the first and second pair of R^4 and R^5 both R^4 and R^5 are hydrogen, and the third pair of R^4 and R^5 together with the one carbon atom they are attached, form unsubstituted cyclopropyl, and R^6 is CF_3-.

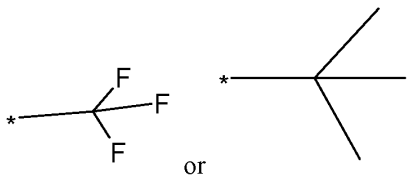
In some embodiments, when CF_3CH_2O-, the compound of formula (I) excludes compounds in which all of the following applies:

R^1 is



,

R^6 is:



or

,

n is 2 and R^4 and R^5 are (i) all hydrogen or (ii) within the first pair of R^4 and R^5 both R^4 and R^5 are hydrogen and within the second pair of R^4 and R^5 one is hydrogen and the other one is hydroxy.

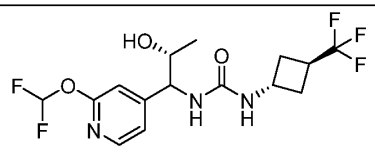
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy and one of R^2 and R^3 is hydrogen and the other one is hydroxyC_{1-6}alkyl.

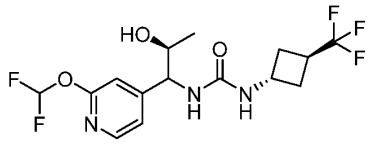
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy selected from CHF_2O-, CF_3CH_2O-, CF_2HCH_2O-, $CH_3CF_2CH_2O$-, and CH_3CFHCH_2O-, and one of R^2 and R^3 is hydrogen and the other one is hydroxyC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein the hydroxyC_{1-6}alkyl is linear.

7In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein the hydroxyC_{1-6}alkyl is branched,

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein the compounds have the structure:

286	1-[(2R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

287	1-[(2S)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, and R^3 is hydroxy$C_{1\text{-}6}$alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, and R^3 is hydroxy$C_{1\text{-}6}$alkyl selected from $HOCH_2$-, $HOCH(CH_3)$-, $HOCH_2CH_2$-, $HOCH_2CH_2CH_2$- and $HOCH_2CH_2CH_2CH_2$-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, and R^3 is $HOCH_2$- or $HOCH_2CH_2$-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, and R^3 is $HOCH(CH_3)$-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH(CH_3)$-, $HOCH_2$- or $HOCH_2CH_2$-, and n is 0, 1, or 2.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH(CH_3)$-, $HOCH_2$- or $HOCH_2CH_2$-, and n is 0.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH(CH_3)$-, $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$-, n is 0, and R^6 is selected from a 4-10 membered cycloalkyl and phenyl, which cycloalkyl, and phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$-, n is 0, and R^6 is selected from a 4-10 membered bridged cycloalkyl, and phenyl, which bridged cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$-, n is 0, and $R^6$is a 7-10 membered bridged cylcloalkyl, which bridged cycloalkyl is optionally substituted with one, two, or three substituents inpendently selected from R^2 is hydrogen, R^3 is $HOCH_2$-, n is 0, and R^6.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$-, n is 0, and R^6 is phenyl, which which phenyl is optionally substituted

with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- and n is 0, and R^6 is selected from bicyclo[2.2.2]octanyl, and phenyl, which bicyclo[2.2.2]octanyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- and n is 0, and R^6 is selected from bicyclo[2.2.2]octanyl, and phenyl, which bicyclo[2.2.2]octanyl, or phenyl are optionally substituted with one substituent selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- and n is 0, and R^6 is bicyclo[2.2.2]octanyl, which bicyclo[2.2.2]octanyl is optionally substituted with one substituent selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

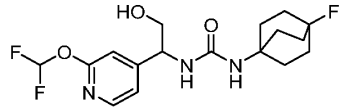
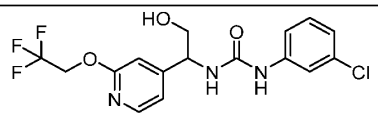
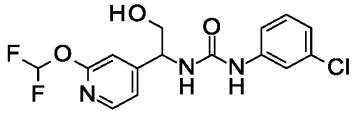
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- and n is 0, and R^6 is selected from bicyclo[2.2.2]octanyl, and phenyl, which bicyclo[2.2.2]octanyl, or phenyl are optionally substituted with one halogen selected from Cl-, F-, and Br-.

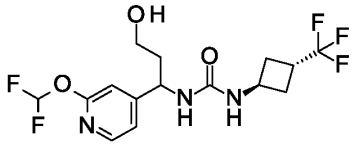
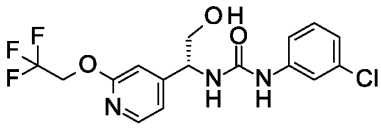
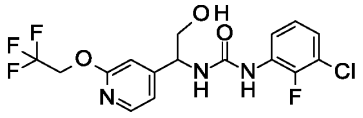
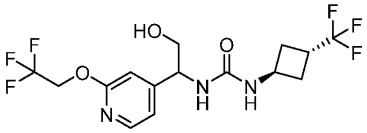
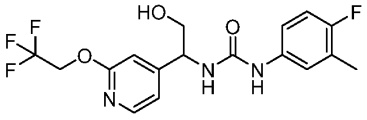
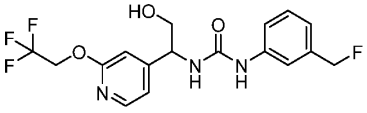
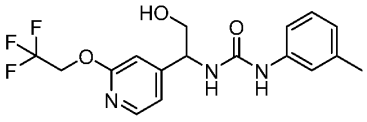
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- and n is 0, and R^6 is selected from bicyclo[2.2.2]octanyl, and phenyl, which bicyclo[2.2.2]octanyl, or phenyl are optionally substituted with one haloC_{1-6}alkyl selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, or CHF_2-.

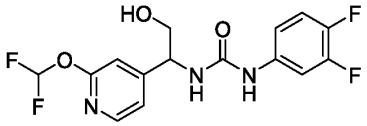
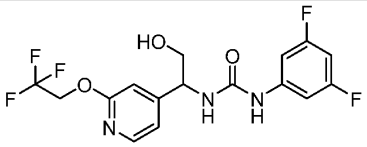
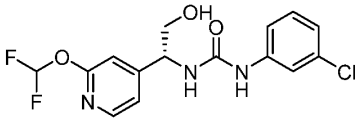
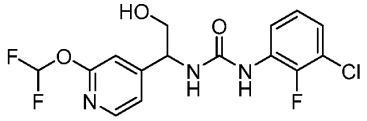
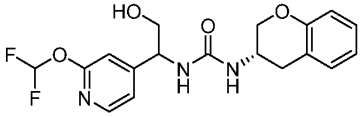
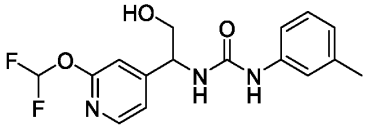
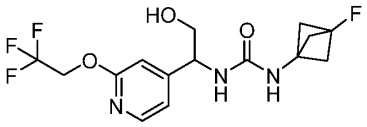
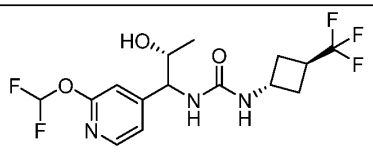
In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- and n is 0, and R^6 is selected from bicyclo[2.2.2]octanyl, and phenyl, which bicyclo[2.2.2]octanyl, or phenyl are optionally substituted with one Cl-, F- or CF_3-.

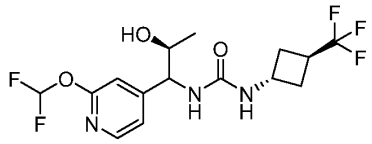
In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- and n is 0, and R^6 is selected from unsubstituted bicyclo[2.2.2]octanyl, and phenyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate, or pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, R^2 is hydrogen, R^3 is hydroxyC_{1-6}alkyl, n, R^4, R^5, and R^6 are as described herein, and non-limiting examples are selected from:

85	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
91	1-(3-chlorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	

117	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-3-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
150	1-(3-chloro-2-fluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
185	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
205	1-(4-fluoro-3-methylphenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
232	1-[3-(fluoromethyl)phenyl]-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
233	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-(3-methylphenyl)urea	

240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
256	1-(3,5-difluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
263	rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
270	1-(3-chloro-2-fluorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
278	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(3S)-3,4-dihydro-2H-chromen-3-yl]urea	
280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea	
283	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
286	1-[(2R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

287	1-[(2S)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 1, 2, or 3, and R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl.

The saturated monocyclic 3-5 membered cycloalkyl can be formed by R^4 and R^5 of pairs 1, 2, or 3. The remaining pairs of R^4 and R^5 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 1, and R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 2, and the first pair of R^4 and R^5 together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and the second pair of R^4 and R^5 are hydrogen.

In some embodiments, the saturated monocyclic 3-5 membered cycloalkyl formed is unsubstituted.

In some embodiments, the saturated monocyclic 3-5 membered cycloalkyl, in particular cyclopropyl, formed is substituted with one, two, three, or four, preferably one or two, substituents independently selected from halogen, haloC_{1-6}alkyl, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 1, and R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 1, and R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl, and wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 2, and the first pair of R^4 and R^5 together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and the second pair of R^4 and R^5 are hydrogen, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 2, and the first pair of R^4 and R^5 together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and the second pair of R^4 and R^5 are hydrogen, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl, and wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 1, and R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and R^6 is selected from a C_{1-6}alkyl and or a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, n is 2, and the first pair of R^4 and R^5 together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and the second pair of R^4 and R^5 are hydrogen, and R^6 is selected from a C_{1-6}alkyl and or a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl

In the above embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy selected from CHF_2O-, CF_3CH_2O-, CF_2HCH_2O-, $CH_3CF_2CH_2O$-, and CH_3CFHCH_2O-, R^2 and R^3 are hydrogen, n is 1 or 2, and R^4 and R^5 are as described herein, and R^6 is selected from a C_{1-6}alkyl and a

saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1 or 2, R^4 and R^5 are as described herein, and R^6 is selected from a C_{1-6}alkyl and an unsubstituted saturated monocyclic 4-6 membered cycloalkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1 or 2, R^4 and R^5 are as described herein, and R^6 is a C_{1-6}alkyl selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl, n-butyl, iso-butyl, sec-butyl, and tert-butyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1 or 2, R^4 and R^5 are as described herein, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl or cyclohexyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

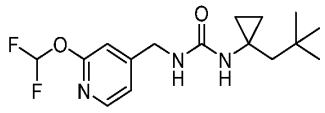
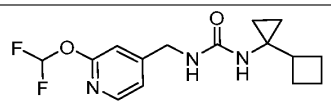
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1 or 2, R^4 and R^5 are as described herein, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, selected from cyclobutyl, cyclpentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, and CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1 or 2, R^4 and R^5 are as described herein, and R^6 is tert-butyl or cyclobutyl, which cyclobutyl is optionally substituted as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is is CHF_2O-, R^2 and R^3 are hydrogen, n is 1 or 2, R^4 and R^5 are as described herein, and R^6 is tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is is CHF_2O-, R^2 and R^3 are hydrogen, n is 1 or 2, R^4 and R^5 are as described herein, and R^6 is unsubstituted cyclobutyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, preferably CHF_2O-, R^4 and R^5, together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl, R^2, R^3, and R^6 are as described herein, and non-limiting examples are selected from:

44	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2-dimethylpropyl)cyclopropyl]urea	
50	1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-.

In some embodiments, wherein R^1 is CF_3CH_2O-, the compound of formula (I) excludes compounds for which R^2 and R^3 are hydrogen, n is 2, in the first pair of R^4 and R^5 both are hydrogen, and in the second pair of R^4 and R^5 one is hydrogen and the other one is hydroxy, and R^6 is C_{1-6}alkyl.

In some embodiments, wherein R^1 is CF_3CH_2O-, the compound of formula (I) excludes compounds for which R^2 and R^3 are hydrogen, n is 2, in the first pair of R^4 and R^5 both are

hydrogen, and in the second pair of R^4 and R^5 one is hydrogen and the other one is hydroxy, and R^6 is tert-butyl.

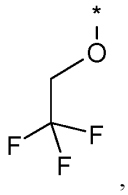
In some embodiments, wherein R^1 is CF_3CH_2O-, the compound of formula (I) excludes compounds for which R^2 and R^3 are hydrogen, n is 2, in the first pair of R^4 and R^5 both are hydrogen, and in the second pair of R^4 and R^5 both are hydrogen, and R^6 is C_{1-6}alkyl.

In some embodiments, wherein R^1 is CF_3CH_2O-, the compound of formula (I) excludes compounds for which R^2 and R^3 are hydrogen, n is 3, wherein in the first and second pair of R^4 and R^5 both R^4 and R^5 are hydrogen, and the third pair of R^4 and R^5 together with the one carbon atom they are attached, form unsubstituted cyclopropyl, and R^6 is haloC_{1-6}alkyl.

In some embodiments, wherein R^1 is CF_3CH_2O-, the compound of formula (I) excludes compounds for which R^2 and R^3 are hydrogen, n is 3, wherein in the first and second pair of R^4 and R^5 both R^4 and R^5 are hydrogen, and the third pair of R^4 and R^5 together with the one carbon atom they are attached, form unsubstituted cyclopropyl, and R^6 is CF_3-.

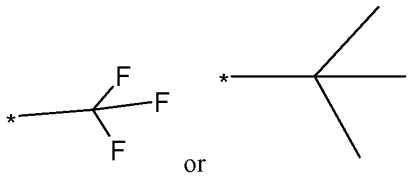
In some embodiments, wherein R^1 is CF_3CH_2O-, the compound of formula (I) excludes compounds in which all of the following applies:

R^1 is



,

R^6 is:



or ,

n is 2 and R^4 and R^5 are (i) all hydrogen or (ii) within the first pair of R^4 and R^5 both R^4 and R^5 are hydrogen and within the second pair of R^4 and R^5 one is hydrogen and the other one is hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, and n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, and n is 0.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl, which heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, or haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, hydroxy, and haloC_{1-6}alkyl and with the proviso that R^6 is not tert-butyl or CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and phenyl, which saturated monocyclic cycloalkyl, bridged cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and phenyl, which saturated monocyclic membered cycloalkyl, bridged cycloalkyl, or phenyl are optionally substituted with one halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and phenyl, which saturated monocyclic cycloalkyl, bridged cycloalkyl, or phenyl are optionally substituted with one halogen selected from F-, Cl-, or Br-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl and phenyl, which saturated monocyclic cycloalkyl, bridged cycloalkyl, or phenyl are optionally substituted with two halogen independently selected from F-, Cl-, and Br-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, or phenyl, which saturated monocyclic cycloalkyl, bridged cycloalkyl, or phenyl are optionally substituted with one haloC_{1-6}alkyl selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, or phenyl, which saturated monocyclic cycloalkyl, bridged cycloalkyl, or phenyl are optionally substituted with two haloC_{1-6}alkyl independently selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or

one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is $HOCH_2$-, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

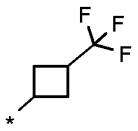
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which cycloalkyl is optionally substituted with one or two haloC_{1-6}alkyl independently selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one, two, or three substitutents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are

hydrogen, n is 0, and R^6 is cyclobutyl, which cyclobutyl is optionally substituted with one F- or CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 has the structure:



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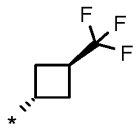
In particular, R^6 has the structure:



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In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is cyclobutyl, which cyclobutyl is optionally substituted with two F- or CF_3- as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is unsubstituted cyclobutyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is phenyl, which phenyl is optionally substituted with one, two, or three substituents independently selected from halogen or haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is phenyl, which phenyl is optionally substituted with one or two substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0 and R^6 is phenyl, which phenyl is optionally substituted with one or two substituents independently selected from Cl-, F-, CH_3-, and CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is phenyl, which phenyl is optionally substituted with one or two halogen independently selected from F-, and Cl-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is phenyl, which phenyl is optionally substituted with one or two halogen independently selected from F-, and Cl-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is phenyl, which phenyl is optionally substituted with one or two Cl-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is phenyl, which phenyl is optionally substituted with one Cl- and one F-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl selected from bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and adamantine, which bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, or adamantine are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and adamantine, which bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, or adamantine are optionally substituted with one F- or CF_3- as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and adamantine, which bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, or adamantine are optionally substituted with two F- or CF_3- as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is

bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and adamantine, which bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, or adamantine are optionally substituted with two F- or CF_3- as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is bicyclo[1.1.1]pentanyl, which bicyclo[1.1.1]pentanyl is optionally substituted with two F- or CF_3- as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, and n is 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 1, and R^4 and R^5 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 1, R^4 and R^5 are hydrogen, and R^6 is a selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10

membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is $HOCH_2$- or $HOCH_2CH_2$-, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which cycloalkyl is optionally substituted with one or two substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

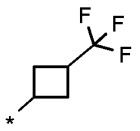
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which cycloalkyl is optionally substituted with one or two halogen independently selected from F-, Cl-, and Br-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which cycloalkyl is optionally substituted with one or two haloC_{1-6}alkyl independently selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one or two substituents independently selected from F- and CF_3-.

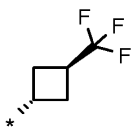
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexeyl are substituted with one or two substituents independently selected from F- or CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 has the structure:



.

In particular R^6 has the structure:



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In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is unsubstituted cyclobutyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is phenyl, which phenyl is optionally substituted with one or two substituents independently selected from halogen, $C_{1\text{-}6}$alkyl, and halo$C_{1\text{-}6}$alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is phenyl, which phenyl is optionally substituted with one or two halogen independently selected from F-, Cl-, and Br-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is phenyl, which phenyl is optionally substituted with one or two halogen independently selected from F-, Cl-, and Br-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is phenyl which phenyl is optionally substituted with one or two halo$C_{1\text{-}6}$alkyl independently selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

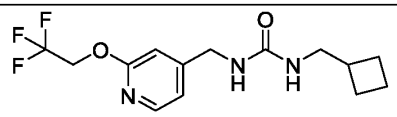
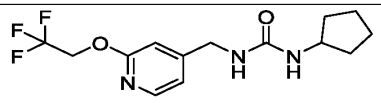
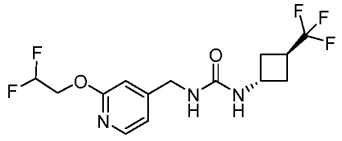
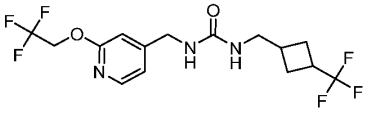
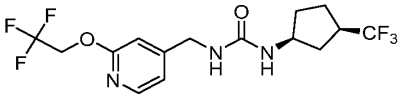
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is phenyl, which phenyl is optionally substituted with one or two substituents independently selected Cl-, F- and CF_3-.

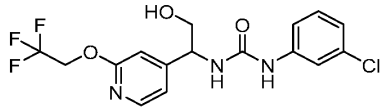
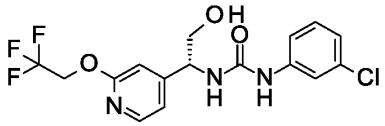
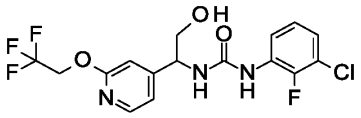
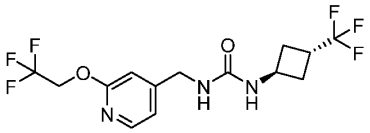
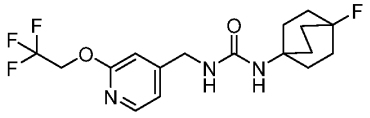
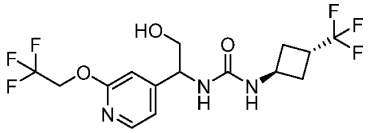
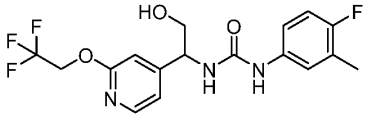
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n

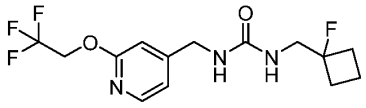
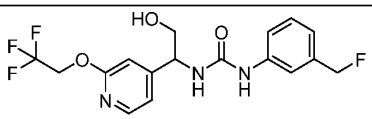
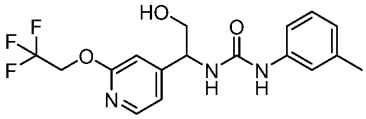
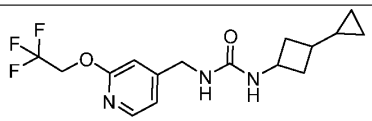
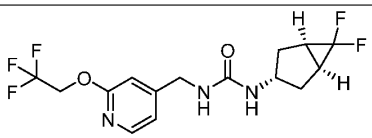
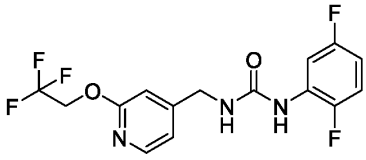
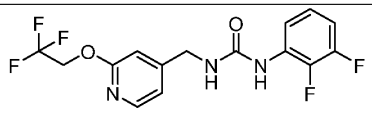
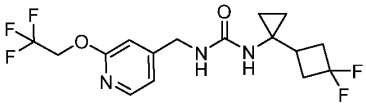
is 1, R^4 and R^5 are hydrogen, and R^6 is phenyl, which phenyl is optionally substituted with one or two Cl-.

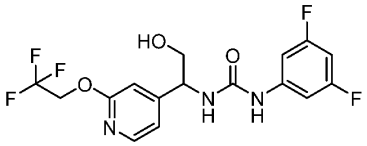
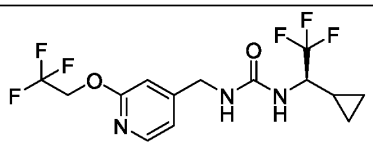
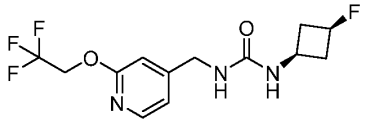
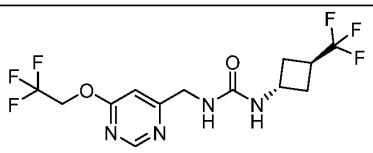
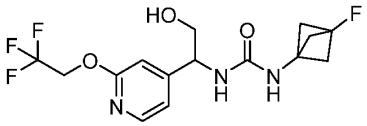
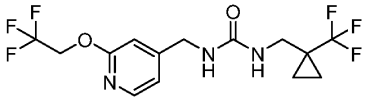
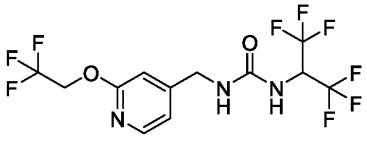
In some embodiments when R^1 is CF_3CH_2O- the substituent R^6 is not a tert-butyl or CF_3-.

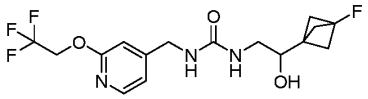
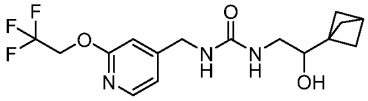
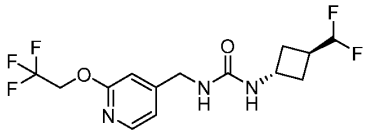
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2, R^3, n, R^4, R^5 and R^6 are as described herein, and non-limiting examples are selected from:

21	1-(cyclobutylmethyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
43	1-cyclopentyl-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
56	1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
71	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
79	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

92	1-(3-chlorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
150	1-(3-chloro-2-fluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
179	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
180	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
185	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
205	1-(4-fluoro-3-methylphenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

210	1-[(1-fluorocyclobutyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
232	1-[3-(fluoromethyl)phenyl]-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
233	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-(3-methylphenyl)urea	
235	1-(3-cyclopropylcyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
238	1-[(1R,3s,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
245	1-(2,5-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
248	1-(2,3-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
254	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

256	1-(3,5-difluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
269	1-((1s,3s)-3-fluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
279	1-[[6-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
283	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
284	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
285	1-(1,1,1,3,3,3-hexafluoropropan-2-yl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

290	1-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
292	1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
293	1-[(1r,3r)-3-(difluoromethyl)cyclobutyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, and R^2 and R^3 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, and n is 0.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, or haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or

three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen or haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a a saturated monocyclic 4-6 membered cycloalkyl optionally substituted with one or two halogen substituents independently selected from F-, Cl-, and Br-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl optionally substituted with one or two haloC_{1-6}alkyl independently selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl optionally substituted with one or two substituents independently selected from F- and CF_3- as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0 and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl which are substituted with one or two substituents independently selected from F- or CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0 and R^6 is cyclobutyl substituted with one CF_3- as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl optionally substituted with one, two, or three substituents independently selected from halogen or haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl optionally substituted with one or two halogen substituents independently selected from F-, Cl-, and Br-.

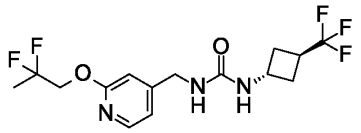
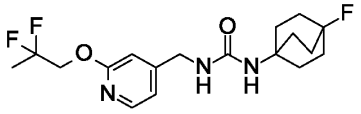
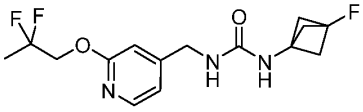
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl optionally substituted with one or two haloC_{1-6}alkyl independently selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl optionally substituted with one or two substituents independently selected from F- and CF_3- as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0 and R^6 is a 4-10 membered bridged cycloalkyl selected from bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and adamantine which bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, or adamantine are optionally substituted with one or two substituents independently selected from F- and CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2 and R^3 are hydrogen, n is 0 and R^6 is bicyclo[2.2.2]octanyl substituted with one F- as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is $CH_3CF_2CH_2O$-, R^2, R^3, n, R^4 and R^5 and R^6 are as described herein, and non-limiting examples have the structures:

121	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
122	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
201	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3CFHCH_2O-.

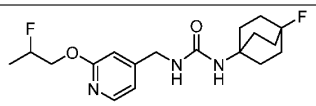
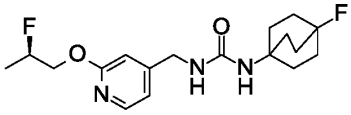
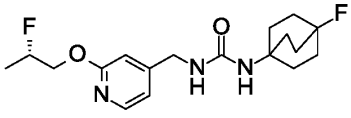
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3CFHCH_2O-, R^2 and R^3 are hydrogen.

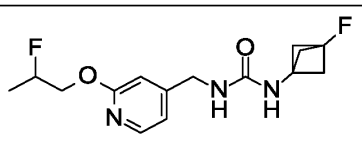
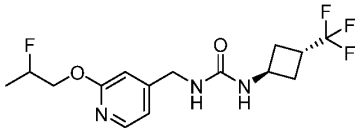
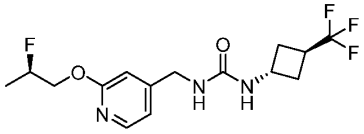
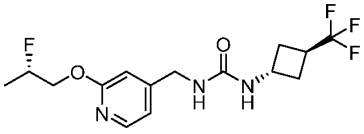
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3CFHCH_2O-, R^2 and R^3 are hydrogen, and n is 0.

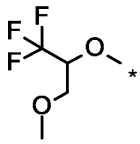
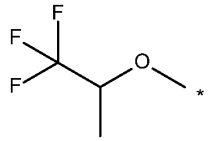
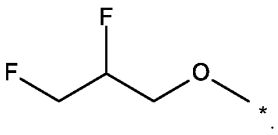
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3CFHCH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

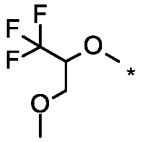
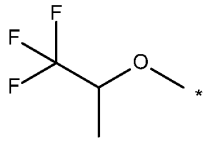
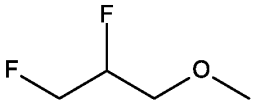
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3CFHCH_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one or two substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

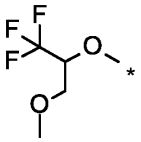
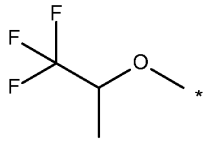
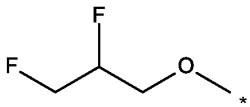
In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_3CFHCH_2O-, R^2, R^3, n, R^4, R^5, and R^6 are as described herein, and non-limiting examples are selected from:

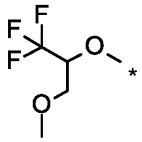
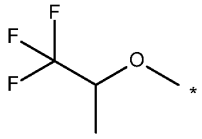
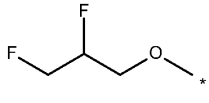
88	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	
151	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]urea	
156	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]urea	

160	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	
183	1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
199	1-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
202	1-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

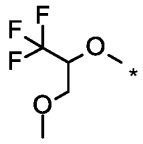
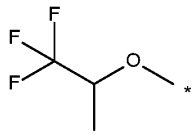
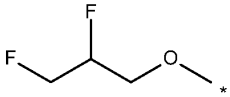
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CH_2FO-,  ,  ; and  .

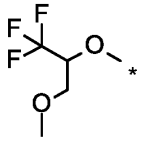
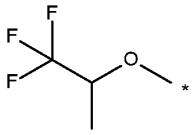
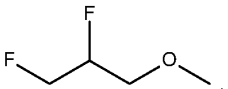
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CH_2FO-,  ,  ; and  , and R^2 and R^3 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CH_2FO-,  ,  and  and R^2 and R^3 are hydrogen, and n is 0.

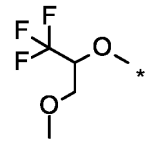
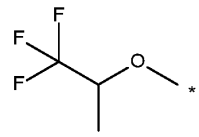
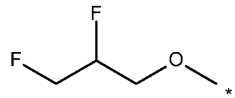
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2FO-,  ,  and  and R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently

selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

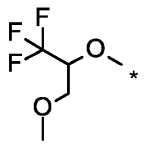
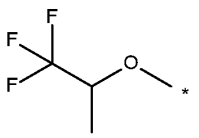
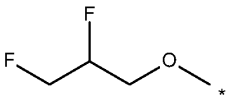
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2FO-,  ,  and  and R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a 4-10 membered bridged cycloalkyl, and phenyl, which bridged cycloalkyl, or phenyl are optionally substituted with one or two substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2FO-,  ,  and  and R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a 4-10 membered bridged cycloalkyl, and phenyl, which bridged cycloalkyl, or phenyl are optionally substituted with one or two halogen independently selected from Cl-, F-, and Br-.

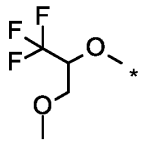
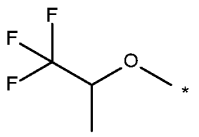
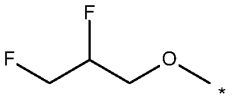
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2FO-,

 ,  and  and R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a 4-10 membered bridged cycloalkyl, and phenyl which bridged cycloalkyl or phenyl are optionally substituted with one or two haloC_{1-6}alkyl independently selected from $(CH_3)_2CF$-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

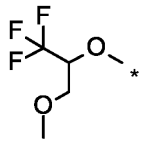
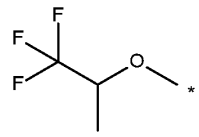
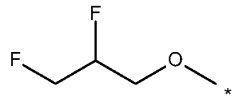
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2FO-,

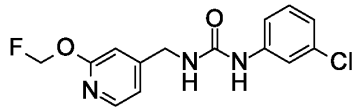
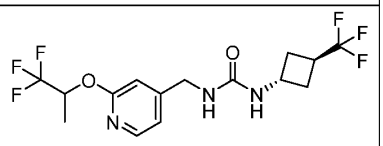
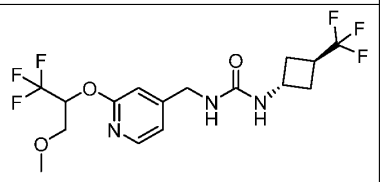
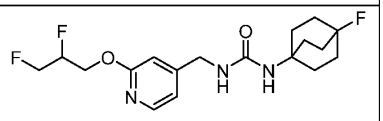
 ,  and  and R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from bicyclo[2.2.2]octanyl, bicyclo[1.1.1]pentanyl, and phenyl, which biyclo[2.2.2]octanyl, bicyclo[1.1.1]pentanyl, or phenyl are optionally substituted with one or two F- or CF_3- as described herein.

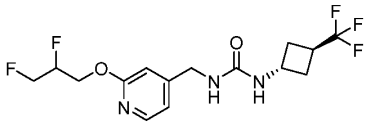
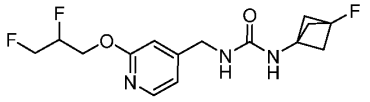
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2FO-,

 ,  and  and R^2 and R^3 are hydrogen, n is 0, and R^6 is phenyl optionally substituted with one Cl-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CH_2FO-,


,

and

and R^2, R^3, n, R^4, R^5, and R^6 are as described herein, and non-limiting examples are selected from:

164	1-(3-chlorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
221	1-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(1,1,1-trifluoropropan-2-yloxy)pyridin-4-yl]methyl]urea	
281	1-[[2-(1,1,1-trifluoro-3-methoxypropan-2-yl)oxypyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
213	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	

214	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
216	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, and R^6 is selected from is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, and R^6 is selected from:

$_6$alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) C_{1-6} alkyl; and

f) haloC_{1-6}alkyl;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, , heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, bicyclic edge-to-edge fused cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, and R^6 is selected from:

$_6$alkoxy, and R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

wherein the bicyclic edge-to-edge fused heterocycloalkyl; bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, and R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, and R^6 is selected from

dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxyl.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, and R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxy$C_{1\text{-}6}$alkyl, and R^6 is as described herein.

In some embodiments, R^1 is CHF_2O-, and one of R^2 and R^3 is hydrogen and the other is hydroxy$C_{1\text{-}6}$alkyl selected from $HOCH_2$-, $HOCH_2CH_2$-, $HOCH_2CH_2CH_2$-, and $HOCH_2CH_2CH_2CH_2$-.

In some preferred embodiments, R^1 is CHF_2O-, and one of R^2 and R^3 is hydrogen and the other is hydroxy$C_{1\text{-}6}$alkyl is $HOCH_2$- or $HOCH_2CH_2$- .

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxy$C_{1\text{-}6}$alkyl as described above, and n is 0, 1, or 2.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxy$C_{1\text{-}6}$alkyl as described above, and n is 0 or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl as described above, and n is 0.

In one particularily preferred embdiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other hydroxyC_{1-6}alkyl as described above, n is 0, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, or haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

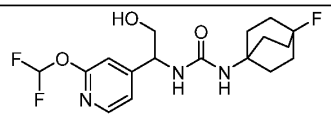
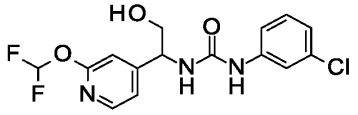
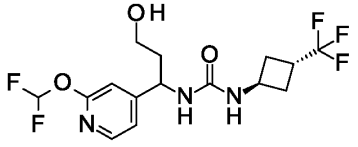
In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is $HOCH_2$- or $HOCH_2CH_2$- as described above, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, phenyl, a C_{1-6}alkyl, a haloC_{1-6}alkyl, and a 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, phenyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

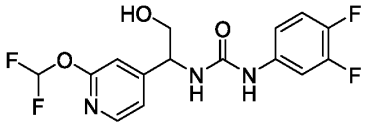
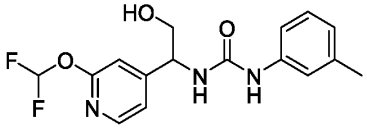
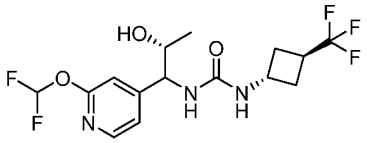
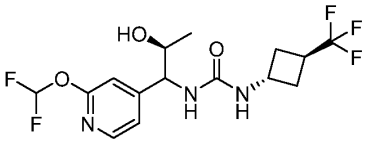
In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other is $HOCH_2$- or $HOCH_2CH_2$- as described above, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, phenyl, a

C_{1-6}alkyl, a haloC_{1-6}alkyl, and a 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, phenyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen and the other is $HOCH_2$- or $HOCH_2CH_2$- as described above, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, phenyl, a C_{1-6}alkyl, a haloC_{1-6}alkyl, or a 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, phenyl, or heteroaryl are optionally substituted with one, two, or three F-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2, R^3, n, R^4, R^5, and R^6 are as described herein, and non-limiting examples are:

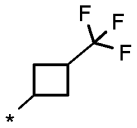
85	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
117	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-3-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea	
286	1-[(2R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
287	1-[(2S)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

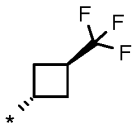
In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is as described herein and optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, ethyl, $(CH_3)_2CF$-, CF_3-, CH_3O-, tert-butyl, CN-, cyclopropyl, and hydroxy.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is as described herein which R^6 is optionally substituted with one, two, or three F- or CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 has the structure:



In particular R^6 has the structure:



In one particularly preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, and n is 1.

In one particularly preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is hydrogen or C_{1-6}alkyl, and R^5 is hydrogen.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is hydrogen or C_{1-6}alkyl, R^5 is hydrogen, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, or haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is C_{1-6}alkyl, R^5 is hydrogen, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, or haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted

with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is C_{1-6}alkyl, R^5 is hydrogen, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which saturated monocyclic cycloalkyl, or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is C_{1-6}alkyl, R^5 is hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl or a 4-10 membered bridged cycloalkyl, which saturated monocyclic cycloalkyl or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is C_{1-6}alkyl, R^5 is hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is C_{1-6}alkyl, R^5 is hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, and cyclohexyl are optionally substituted with one, two, or three substituents independently

selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is CH_3-, R^5 is hydrogen, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is CH_3-, R^5 is hydrogen, and R^6 is cyclobutyl or cyclopentyl which are unsubstituted.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is CH_3-, R^5 is hydrogen, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are optionally substituted with one CH_3O-, F-, or CF_3-.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is CH_3-, R^5 is hydrogen, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are optionally substituted with one F-, or CF_3-.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is CH_3-, R^5 is hydrogen, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are optionally substituted with one F-, or CF_3-.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3

are hydrogen, n is 1, R^4 is CH_3-, R^5 is hydrogen, and R^6 is unsubstituted cyclobutyl or unsubstituted cyclopentyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is C_{1-6}alkyl, R^5 is hydrogen, and R^6 is a 4-10 membered bridged cycloalkyl or a 7-10 membered bicyclic fused cycloalkyl, which bridged cycloalkyl or fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxylC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is C_{1-6}alkyl, R^5 is hydrogen, and R^6 is a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic fused cycloalkyl, which bridged cycloalkyl or fused cycloalkyl are selected from bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, and bicyclo[3.1.0]hexanyl, and which bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, or bicyclo[3.1.0]hexanyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

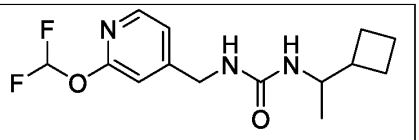
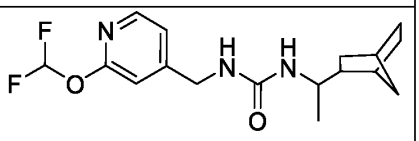
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is CH_3-, R^5 is hydrogen, and R^6 is a 4-10 membered bridged cycloalkyl or a 7-10 membered bicyclic fused cycloalkyl, which bridged cycloalkyl or fused cycloalkyl are selected from bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, and bicyclo[3.1.0]hexanyl, and which bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, or bicyclo[3.1.0]hexanyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

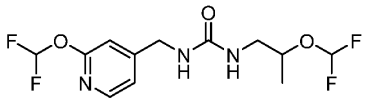
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is CH_3-, R^5 is hydrogen, and R^6 is a 4-10 membered bridged cycloalkyl or a 7-10 membered bicyclic fused cycloalkyl, which bridged cycloalkyl or fused cycloalkyl are selected from bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, and bicyclo[3.1.0]hexanyl, and which bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, or bicyclo[3.1.0]hexanyl are unsubstituted.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is CH_3-, R^5 is hydrogen, and R^6 is bicyclo[2.2.1]heptanyl, which bicyclo[2.2.1]heptanyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is CH_3-, R^5 is hydrogen, and R^6 is unsubstituted bicyclo[2.2.1]heptanyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2, R^3, n, R^4 is CH_3-, R^5 is hydrogen, and R^6 are as described herein, and non-limiting examples are selected from:

17	1-(1-cyclobutylethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
24	1-[1-(2-bicyclo[2.2.1]heptanyl)ethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

268	1-[2-(difluoromethoxy)propyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1 or 2, and R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, and R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl.

In some embodiments, the saturated monocyclic 3-5 membered cycloalkyl formed is unsubstituted.

In some embodiments, the saturated monocyclic 3-5 membered cycloalkyl formed is substituted with one, two, three, or four, preferably one or two, substituents independently selected from halogen, haloC_{1-6}alkyl, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and R^6 is selected from a C_{1-6} alkyl, and a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three F-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one or two CF_3- as described herein.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and R^6 is a C_{1-6}alkyl or a saturated monocyclic 4-6 membered cycloalkyl as described herein.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5, together with the one carbon atom to which they are attached, form a

saturated monocyclic 3-5 membered cycloalkyl, and R^6 is a C_{1-6}alkyl or a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, and cyclohexyl are optionally substituted as described herein.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and R^6 is unsubstituted cyclobutyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and R^6 is tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl, and R^6 is tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl, and R^6 is unsubstituted cyclobutyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and the second pair of R^4 and R^5 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a

saturated monocyclic 3-5 membered cycloalkyl and the second pair of R^4 and R^5 are hydrogen, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl and the second pair of R^4 and R^5 are hydrogen, and R^6 is selected from a C_{1-6} alkyl, and a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl and the second pair of R^4 and R^5 are hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three F-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl and the second pair of R^4 and R^5 are hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one or two CF_3- as described herein.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl and the second pair of R^4 and R^5 are hydrogen, and R^6 is a C_{1-6}alkyl or a saturated monocyclic 4-6 membered cycloalkyl as described herein.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl and the second pair of R^4 and R^5 are hydrogen, and R^6 is a C_{1-6}alkyl or a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, and cyclohexyl are optionally substituted as described herein.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl and the second pair of R^4 and R^5 are hydrogen, and R^6 is unsubstituted cyclobutyl.

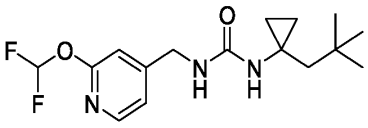
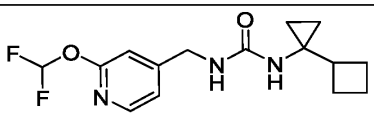
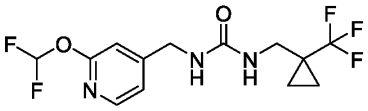
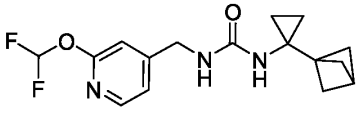
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl and the second pair of R^4 and R^5 are hydrogen, and R^6 is tert-butyl.

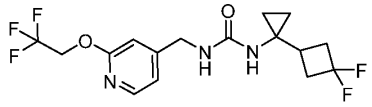
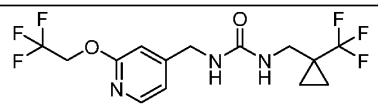
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a

saturated monocyclic 3-5 membered cycloalkyl and the second pair of R^4 and R^5 are hydrogen, and R^6 is tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl and the second pair of R^4 and R^5 are hydrogen, and R^6 is unsubstituted cyclobutyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, n is 1 or 2, R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, or are hydrogen as described herein, n, R^2, R^3 and R^6 are as described herein, and non-limiting examples are selected from:

44	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2-dimethylpropyl)cyclopropyl]urea	
50	1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
229	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
246	1-[1-(1-bicyclo[1.1.1]pentanyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

254	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
284	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1 or 2, R^4 and R^5 are hydrogen, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which saturated monocyclic cycloalkyl, or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which saturated monocyclic cycloalkyl, or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, C_{1-6}alkyl, haloC_{1-6}alkyl, and a 4-10 membered bridged cycloalkyl, which saturated monocyclic cycloalkyl or bridged cycloalkyl are optionally substituted with one, two, or

three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl and a 4-10 membered bridged cycloalkyl, which saturated monocyclic cycloalkyl or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is C_{1-6}alkyl or haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from bicyclo[2.2.1]heptanyl, tert-

butyl, cyclobutyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$- , cyclopentyl, and cyclohexyl, which bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, cyclopentyl, or cyclohexyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from bicyclo[2.2.1]heptanyl, tert-butyl, cyclobutyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, cyclopentyl, and cyclohexyl, which bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, cyclopentyl, or cyclohexyl are optionally substituted with one, two, or three substituents independently selected from halogen, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, cyclopentyl, cyclohexyl which bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, cyclopentyl, or cyclohexyl are optionally substituted with one, two, or three substituents independently selected from halogen, and haloC_{1-6}alkyl.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are unsubstituted.

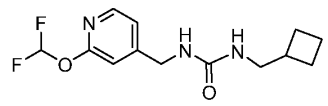
In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one CH_3O-, F-, or CF_3-.

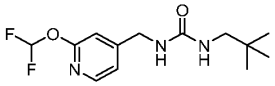
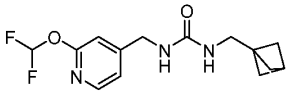
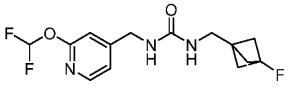
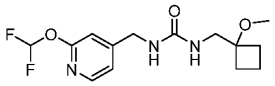
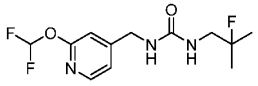
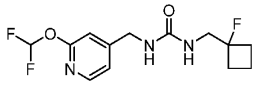
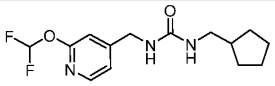
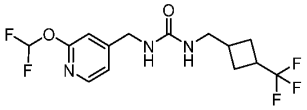
In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one F-, or CF_3-.

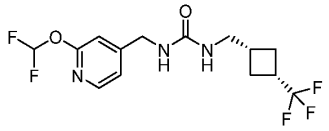
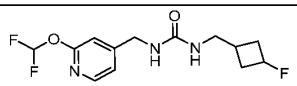
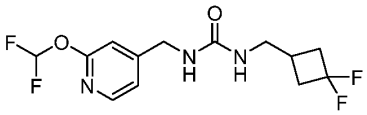
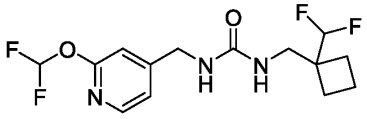
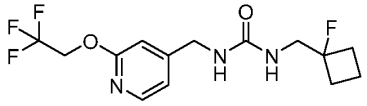
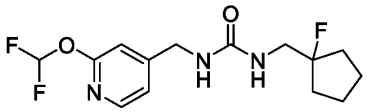
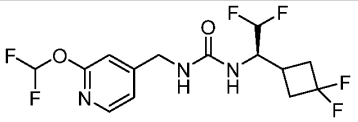
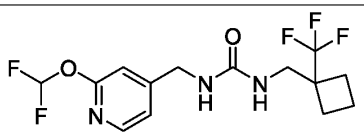
In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one F-, or CF_3-.

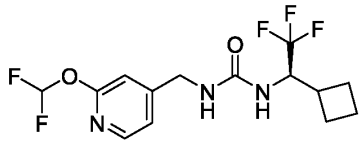
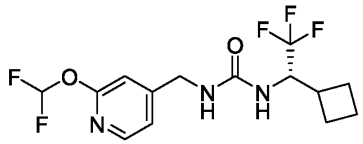
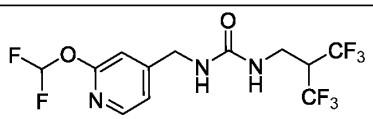
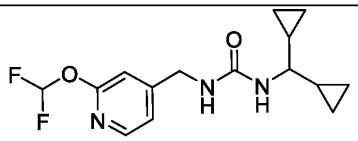
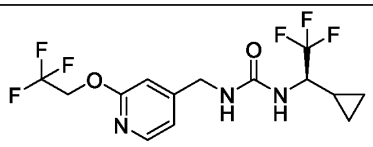
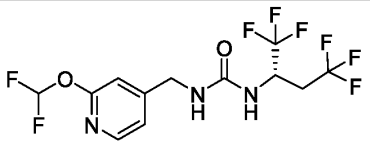
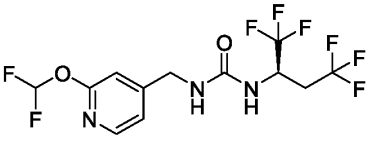
In one more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is unsubstituted cyclobutyl, cyclopentyl, cyclohexyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, n is 1, R^4 and R^5 are hydrogen, R^2, R^3 and R^6 are as described herein, and non-limiting examples are selected from:

13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

29	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,2-dimethylpropyl)urea	
31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
32	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea	
38	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-methoxycyclobutyl)methyl]urea	
39	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-fluoro-2-methylpropyl)urea	
40	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclobutyl)methyl]urea	
46	1-(cyclopentylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
62	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	

87	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(1r,3r)-(trifluoromethyl)cyclobutyl]methyl]urea	
89	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea	
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
191	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluoromethyl)cyclobutyl]methyl]urea	
210	1-[(1-fluorocyclobutyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
227	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclopentyl)methyl]urea	
230	1-[(1R)-1-(3,3-difluorocyclobutyl)-2,2-difluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
237	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-	

	(trifluoromethyl)cyclobutyl]methyl]urea	
241	1-[(1R)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
242	1-[(1S)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
252	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea	
253	1-(dicyclopropylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
273	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	
294	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is hydroxy, R^5 is hydrogen, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is hydroxy, R^5 is hydrogen, and R^6 is C_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is hydroxy, R^5 is hydrogen, and R^6 is C_{1-6}alkyl selected from selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, and tert-butyl.

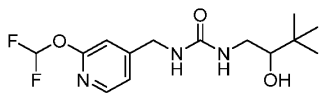
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is hydroxy, R^5 is hydrogen, and R^6 is tert-butyl.

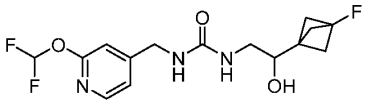
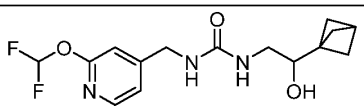
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is hydroxy, R^5 is hydrogen, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is hydroxy, R^5 is hydrogen, and R^6 is selected from bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered fused cycloalkyl, tert-butyl, $(CH_3)_2CF$-, 6 membered heteroaryl, wherein the bicyclic heterocyloalkyl, saturated monocylic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl.

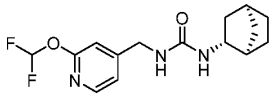
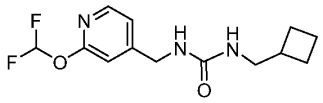
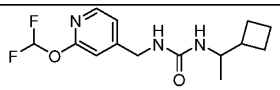
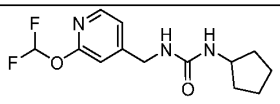
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is hydroxy, R^5 is hydrogen, and R^6 is selected from bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered fused cycloalkyl, and 6 membered heteroaryl, wherein the bicyclic heterocyloalkyl, saturated monocylic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl. Examples are described in this application.

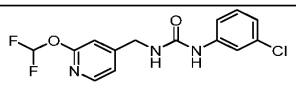
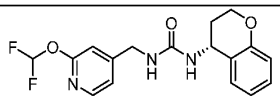
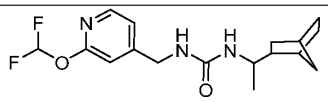
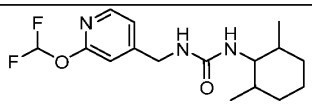
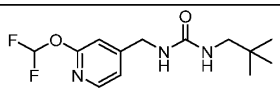
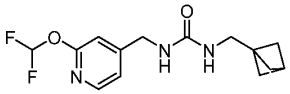
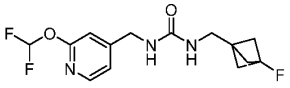
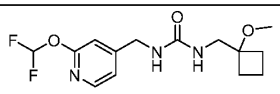
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, n is 1, R^4 is hydroxyl and R^5 is hydrogen, R^2, R^3 and R^6 are as described herein, and non-limiting example is:

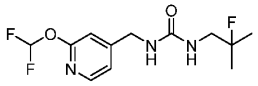
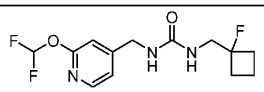
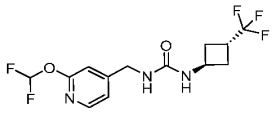
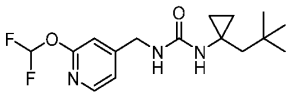
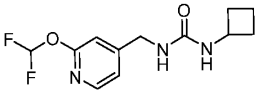
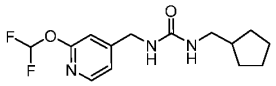
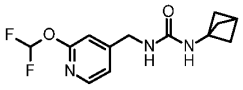
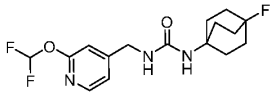
95	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea	

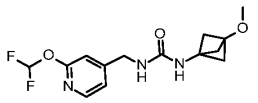
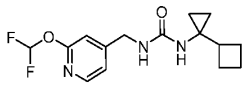
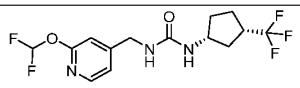
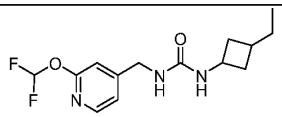
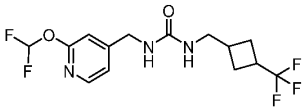
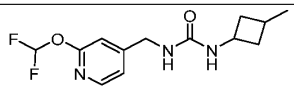
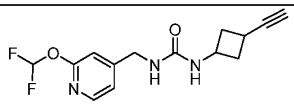
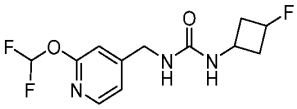
289	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]urea	
291	1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

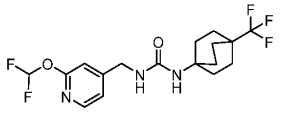
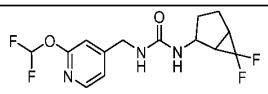
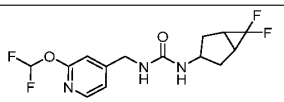
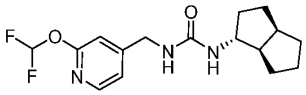
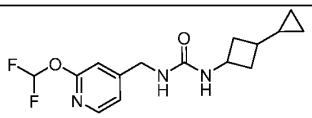
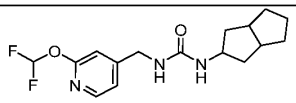
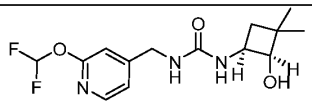
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2, R^3, n, R^4, R^5 and R^6 are as described herein, and non-limiting examples are selected from:

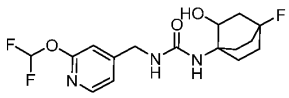
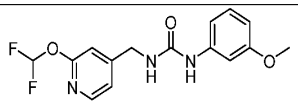
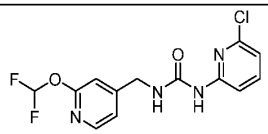
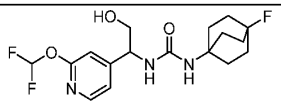
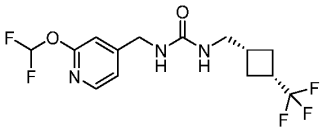
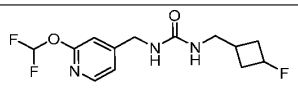
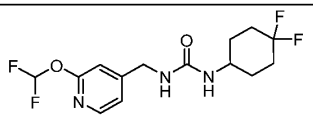
12	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
17	1-(1-cyclobutylethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
20	1-cyclopentyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

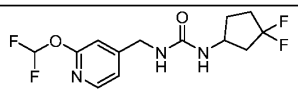
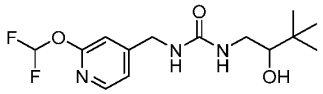
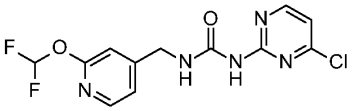
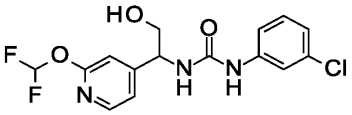
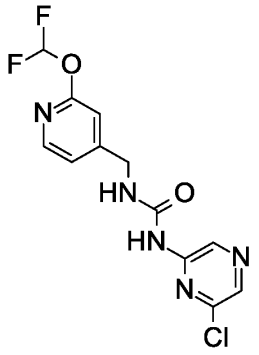
22	1-(3-chlorophenyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
23	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(4R)-3,4-dihydro-2H-chromen-4-yl]urea	
24	1-[1-(2-bicyclo[2.2.1]heptanyl)ethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
25	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,6-dimethylcyclohexyl)urea	
29	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,2-dimethylpropyl)urea	
31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
32	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea	
38	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-methoxycyclobutyl)methyl]urea	

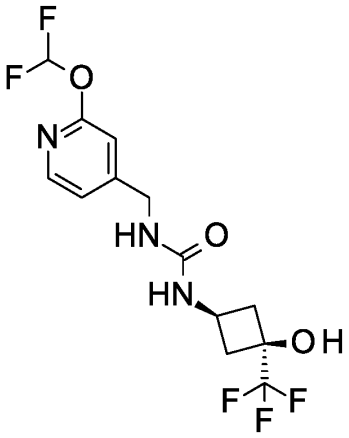
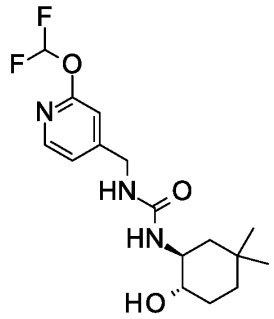
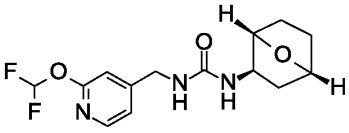
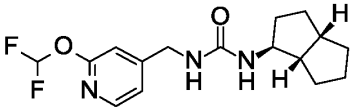
39	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-fluoro-2-methylpropyl)urea	
40	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclobutyl)methyl]urea	
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
44	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2-dimethylpropyl)cyclopropyl]urea	
45	1-cyclobutyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
46	1-(cyclopentylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
47	1-(1-bicyclo[1.1.1]pentanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	

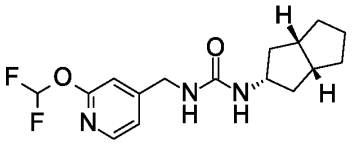
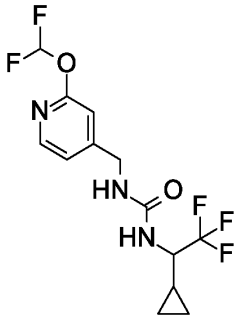
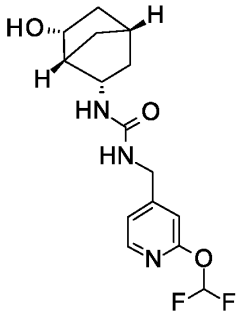
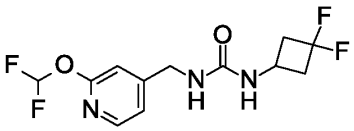
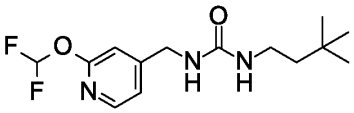
49	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxy-1-bicyclo[1.1.1]pentanyl)urea	
50	1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
59	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea	
60	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethylcyclobutyl)urea	
62	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
65	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylcyclobutyl)urea	
66	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethynylcyclobutyl)urea	
67	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-fluorocyclobutyl)urea	

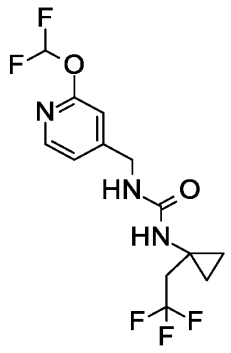
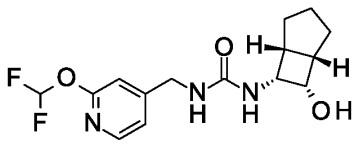
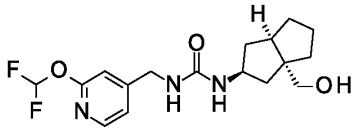
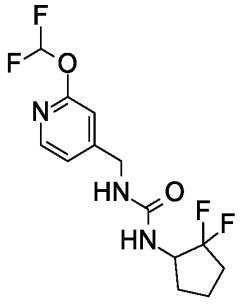
68	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[4-(trifluoromethyl)-1-bicyclo[2.2.2]octanyl]urea	
73	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]urea	
74	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
76	1-[(1R,3aR,6aR)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
77	1-(3-cyclopropylcyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
78	1-(1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
81	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]urea	

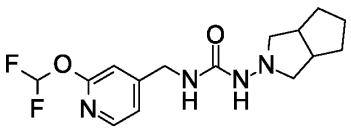
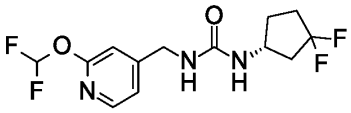
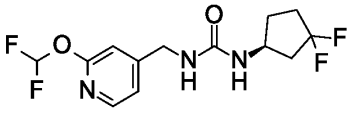
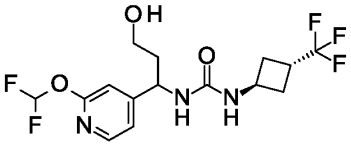
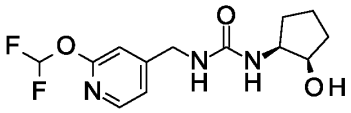
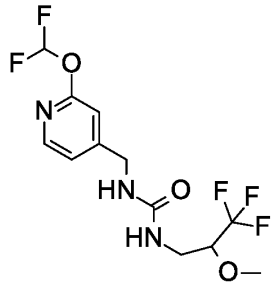
82	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-2-hydroxy-1-bicyclo[2.2.2]octanyl)urea	
83	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxyphenyl)urea	
84	1-(6-chloropyridin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
85	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
87	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(1r,3r)-(trifluoromethyl)cyclobutyl]methyl]urea	
89	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea	
90	1-(4,4-difluorocyclohexyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

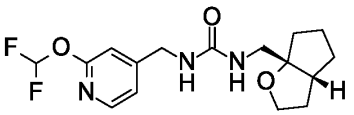
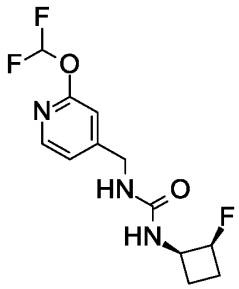
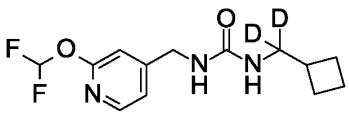
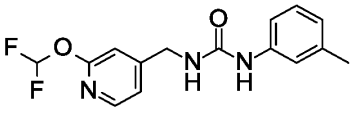
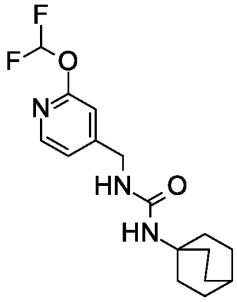
93	1-(3,3-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
95	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea	
96	1-(4-chloropyrimidin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
98	1-(6-chloropyrazin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

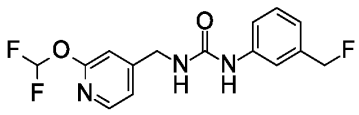
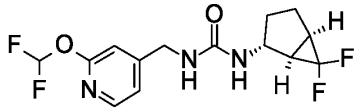
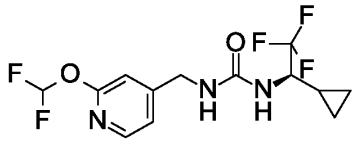
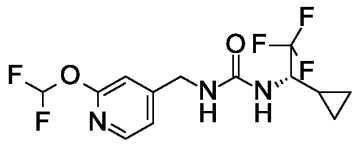
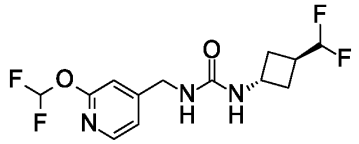
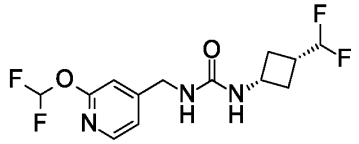
100	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-hydroxy-3-(trifluoromethyl)cyclobutyl]urea	
101	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-5,5-dimethylcyclohexyl]urea	
102	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S)-7-oxabicyclo[2.2.1]heptan-2-yl]urea	
103	1-[(1S,3aS,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

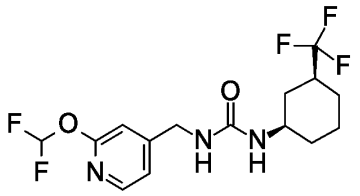
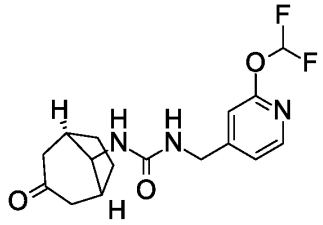
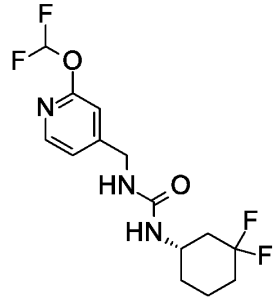
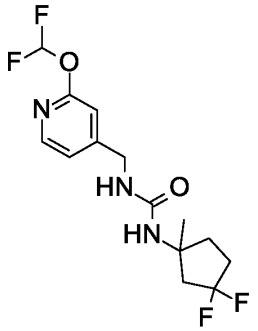
105	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3aR,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]urea	
106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
107	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S,6R)-6-hydroxy-2-bicyclo[2.2.1]heptanyl]urea	
108	1-(3,3-difluorocyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
109	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-dimethylbutyl)urea	

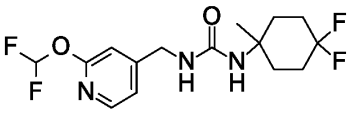
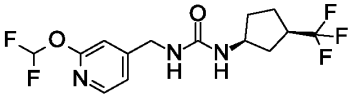
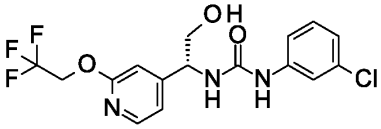
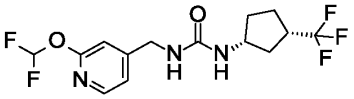
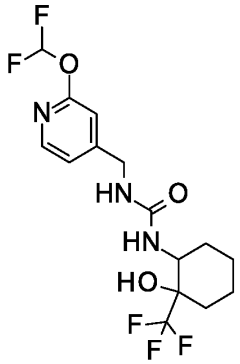
110	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2,2-trifluoroethyl)cyclopropyl]urea	
111	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6S,7R)-7-hydroxy-6-bicyclo[3.2.0]heptanyl]urea	
112	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(2R,3aS,6aS)-6a-(hydroxymethyl)-2,3,3a,4,5,6-hexahydro-1H-pentalen-2-yl]urea	
113	1-(2,2-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

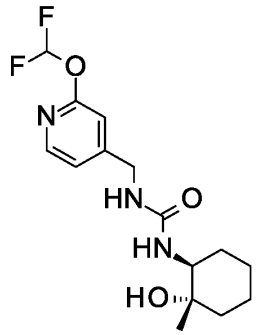
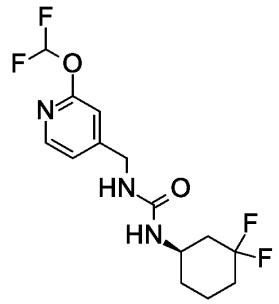
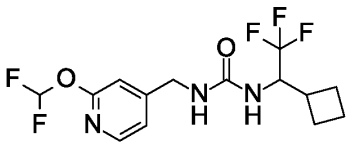
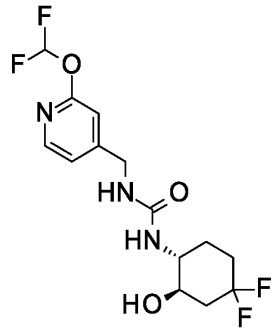
114	1-(3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
117	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-3-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
118	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxycyclopentyl]urea	
119	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3,3-trifluoro-2-methoxypropyl)urea	

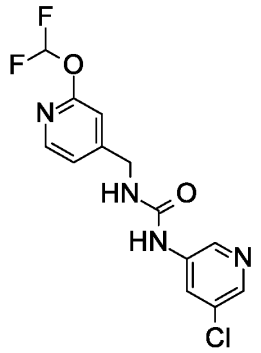
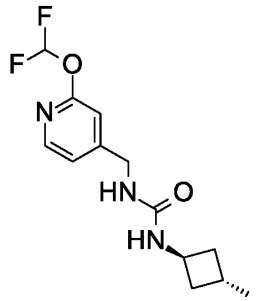
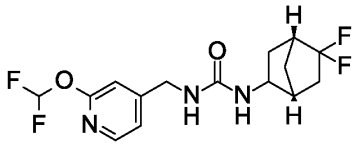
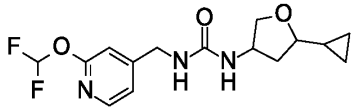
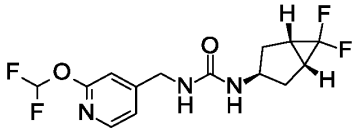
120	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[rac-(3aR,6aR)-2,3,3a,4,5,6-hexahydrocyclopenta[b]furan-6a-yl]methyl]urea	
123	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-fluorocyclobutyl]urea	
125	1-[cyclobutyl(dideuterio)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
126	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylphenyl)urea	
131	1-(1-bicyclo[2.2.2]octanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

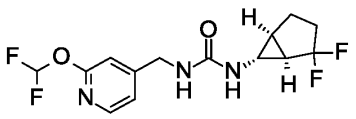
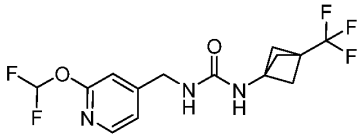
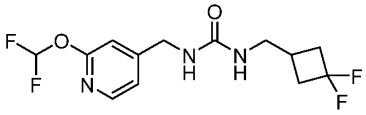
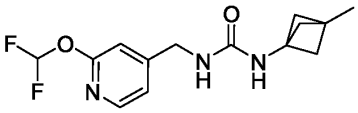
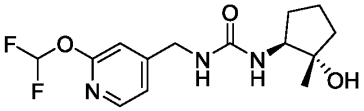
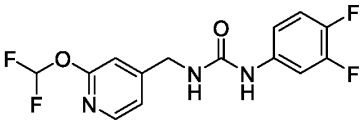
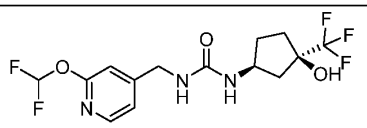
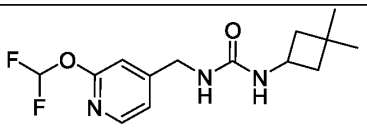
132	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(fluoromethyl)phenyl]urea	
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
135	1-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
136	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(difluoromethyl)cyclobutyl]urea	
137	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(difluoromethyl)cyclobutyl]urea	

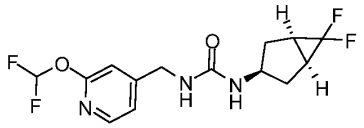
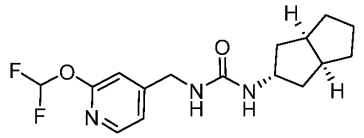
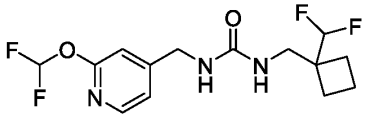
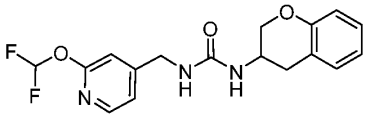
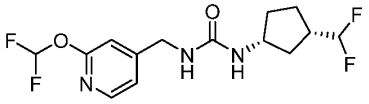
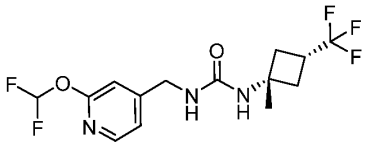
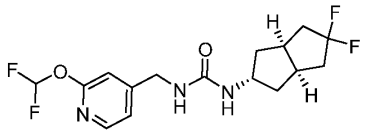
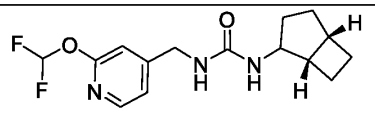
138	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	
139	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3-oxo-8-bicyclo[3.2.1]octanyl]urea	
140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
142	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-difluoro-1-methylcyclopentyl)urea	

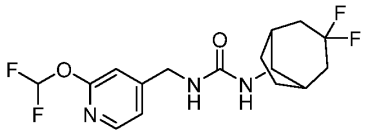
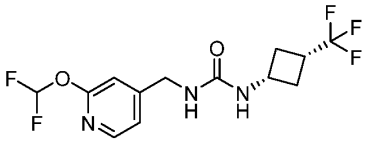
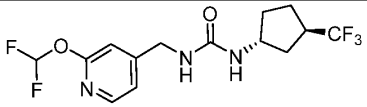
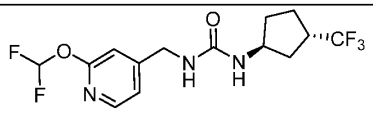
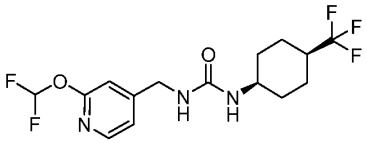
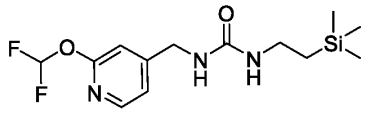
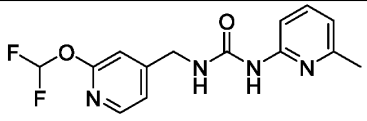
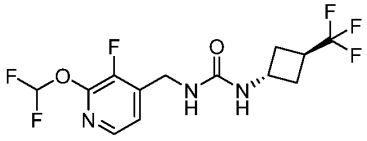
143	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4,4-difluoro-1-methylcyclohexyl)urea	
144	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3R)-3-(trifluoromethyl)cyclopentyl]urea	
145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
146	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea	
147	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-hydroxy-2-(trifluoromethyl)cyclohexyl]urea	

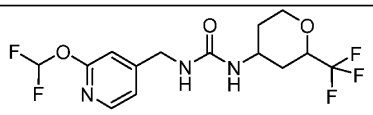
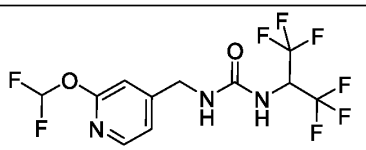
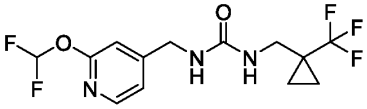
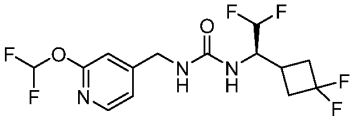
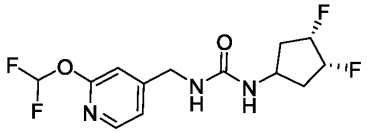
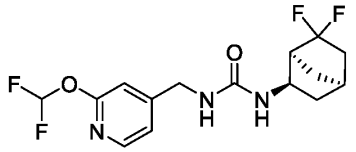
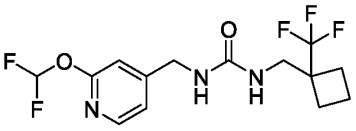
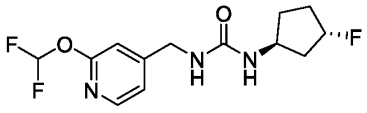
148	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-2-methylcyclohexyl]urea	
149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
152	1-(1-cyclobutyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
154	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-4,4-difluoro-2-hydroxycyclohexyl]urea	

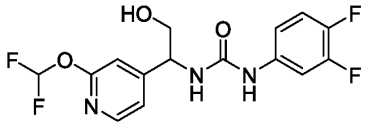
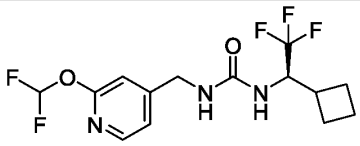
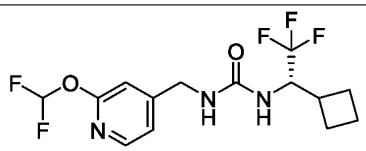
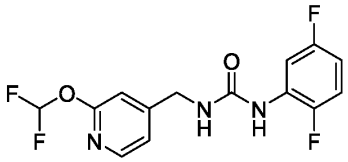
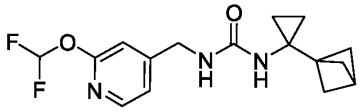
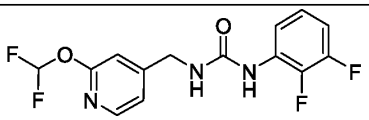
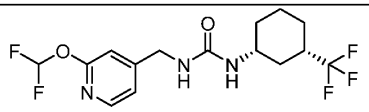
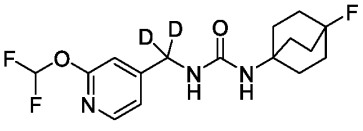
161	1-(5-chloropyridin-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
163	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1r,3r)-3-methylcyclobutyl)urea	
165	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,4R)-5,5-difluoro-2-bicyclo[2.2.1]heptanyl]urea	
166	1-(5-cyclopropyloxolan-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
169	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	

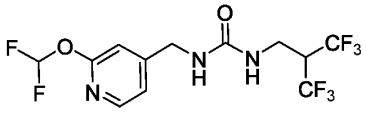
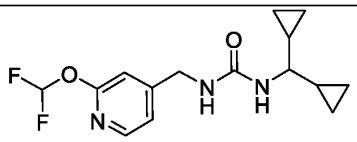
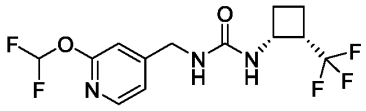
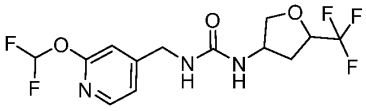
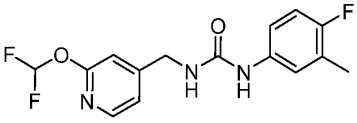
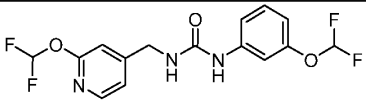
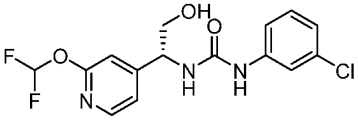
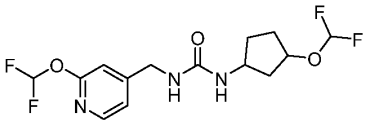
170	1-[(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
178	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
182	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methyl-1-bicyclo[1.1.1]pentanyl)urea	
184	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,2S)-2-hydroxy-2-methylcyclopentyl]urea	
186	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-difluorophenyl)urea	
187	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-hydroxy-3-(trifluoromethyl)cyclopentyl]urea	
188	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-dimethylcyclobutyl)urea	

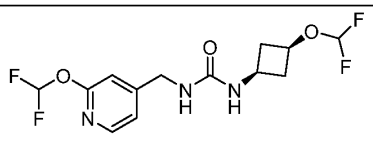
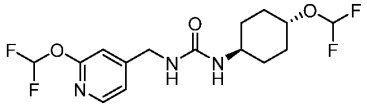
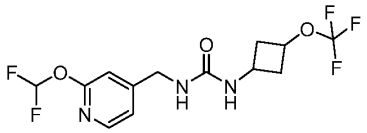
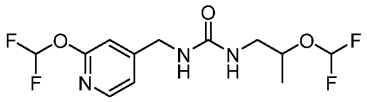
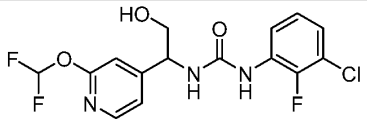
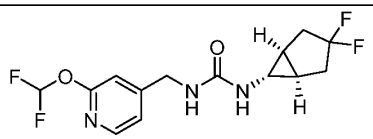
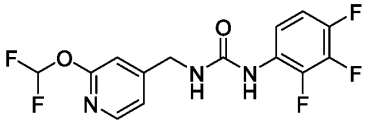
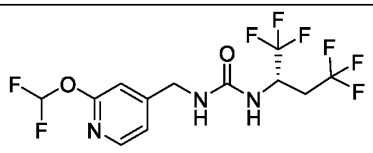
189	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3r,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
190	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2s,3aR,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]urea	
191	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluoromethyl)cyclobutyl]methyl]urea	
192	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-dihydro-2H-chromen-3-yl)urea	
193	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(difluoromethyl)cyclopentyl]urea	
194	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-1-methyl-3-(trifluoromethyl)cyclobutyl]urea	
195	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2r,3aR,6aS)-5,5-difluoro-2,3,3a,4,6,6a-hexahydro-1H-pentalen-2-yl]urea	
196	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5R)-2-bicyclo[3.2.0]heptanyl]urea	

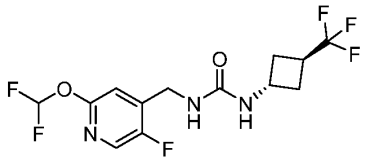
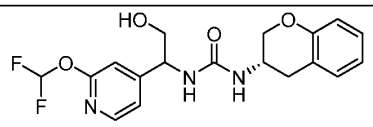
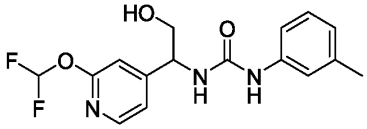
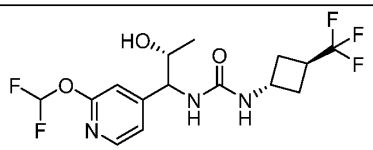
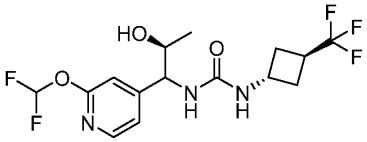
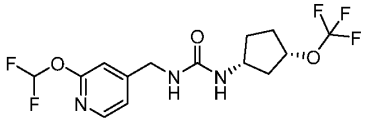
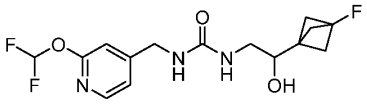
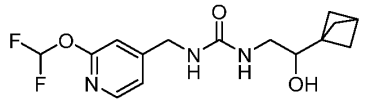
197	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3,3-difluoro-8-bicyclo[3.2.1]octanyl]urea	
198	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(trifluoromethyl)cyclobutyl]urea	
206	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3R)-3-(trifluoromethyl)cyclopentyl]urea	
207	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-(trifluoromethyl)cyclopentyl]urea	
211	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,4s)-4-(trifluoromethyl)cyclohexyl]urea	
212	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-trimethylsilylethyl)urea	
218	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(6-methylpyridin-2-yl)urea	
219	1-[[2-(difluoromethoxy)-3-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

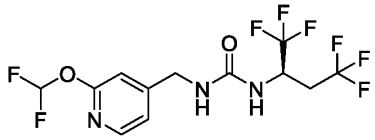
226	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(trifluoromethyl)oxan-4-yl]urea	
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea	
229	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
230	1-[(1R)-1-(3,3-difluorocyclobutyl)-2,2-difluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
234	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(3R,4S)-3,4-difluorocyclopentyl]urea	
236	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S)-6,6-difluoro-2-bicyclo[2.2.1]heptanyl]urea	
237	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclobutyl]methyl]urea	
239	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-fluorocyclopentyl]urea	

240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
241	1-[(1R)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
242	1-[(1S)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
244	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,5-difluorophenyl)urea	
246	1-[1-(1-bicyclo[1.1.1]pentanyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
247	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3-difluorophenyl)urea	
250	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	
251	1-[dideuterio-[2-(difluoromethoxy)pyridin-4-	

	yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
252	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea	
253	1-(dicyclopropylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
255	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-(trifluoromethyl)cyclobutyl]urea	
258	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[5-(trifluoromethyl)oxolan-3-yl]urea	
261	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-3-methylphenyl)urea	
262	1-[3-(difluoromethoxy)phenyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
263	rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
264	1-[3-(difluoromethoxy)cyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

265	1-[(1s,3s)-3-(difluoromethoxy)cyclobutyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
266	1-[(1r,4r)-4-(difluoromethoxy)cyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
267	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethoxy)cyclobutyl]urea	
268	1-[2-(difluoromethoxy)propyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
270	1-(3-chloro-2-fluorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
271	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-3,3-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
272	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3,4-trifluorophenyl)urea	
273	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	

277	1-[[2-(difluoromethoxy)-5-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
278	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(3S)-3,4-dihydro-2H-chromen-3-yl]urea	
280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea	
286	1-[(2R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
287	1-[(2S)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
288	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethoxy)cyclopentyl]urea	
289	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]urea	
291	1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-	

	(difluoromethoxy)pyridin-4-yl]methyl]urea	
294	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, and R^2 and R^3 are hydrogen.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, and n is 1.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl,

cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one or two halogen independently selected from F-, Cl-, and Br.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, which saturated monocyclic cycloalkyl is optionally substituted with one or two haloC_{1-6}alkyl independently selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl which are optionally substituted with one or two substituents independently selected from F- and CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, and cyclohexyl are optionally substituted with one or two F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with two F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one F-.

In one preferred emodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are optionally substituted with one or two F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are optionally substituted with two F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are optionally substituted with one F-.

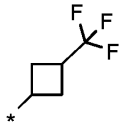
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclobutyl optionally substituted with one or two F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclobutyl optionally substituted with two F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclobutyl optionally substituted with one F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclobutyl optionally substituted with one CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 has the structure:



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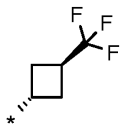
In particular R^6 has the structure:



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In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are

hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, and cyclohexyl are unsubstituted.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are unsubstituted.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is unsubstituted cyclobutyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is unsubstituted cyclopentyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is unsubstituted cyclohexyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is cyclopentyl optionally substituted with one or two F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is cyclopentyl optionally substituted with two F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are

hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is cyclopentyl optionally substituted with one F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is cyclopentyl optionally substituted with one CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is cyclohexyl optionally substituted with one or two substituents independently selected from F- or CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is cyclohexyl optionally substituted with one or two F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is cyclohexyl optionally substituted with one F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is cyclohexyl optionally substituted with one CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 are hydrogen, and R^6 is selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, and cyclohexyl are unsubstituted.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are unsubstituted.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, and R^6 is unsubstituted cyclobutyl.

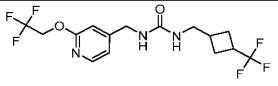
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, and R^6 is unsubstituted cyclopentyl.

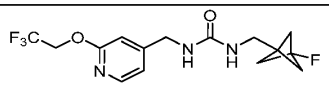
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, and R^6 is unsubstituted cyclopentyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, and R^6 is unsubstituted cyclohexyl.

In some embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, wherein R^4 and R^5 are as described herein, preferably both are hydrogen.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CF_3CH_2O-, R^2, R^3, n, R^4, R^5 and R^6 are as described herein, and a non-limting example has the structure:

71	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[3-	

	(trifluoromethyl)cyclobutyl]methyl]urea	
75	1-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, one or both R^2 and R^3 are hydrogen or one of R^2 and R^3 is hydrogen and the other one is hydroxyC_{1-6}alkyl, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl, a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, C_{1-6}alkyl, haloC_{1-6}alkyl, and 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl, comprising one aliphatic and one aromatic ring, wherein one ring comprises an O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, C_{1-6}alkyl, haloC_{1-6}alkyl, and 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl, phenyl, or heteroaryl are optionally

substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl, comprising one aliphatic and one aromatic ring, wherein one ring comprises an O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, and 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl phenyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl, comprising one aliphatic and one aromatic ring, wherein one ring comprises an O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, and 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, fused cycloalkyl, phenyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl, comprising one aliphatic and one aromatic ring, wherein one ring comprises an O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, C_{1-6}alkyl,

haloC$_{1-6}$alkyl, and 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl, phenyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl, comprising one aliphatic and one aromatic ring, wherein one ring comprises an O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, phenyl, a 7-10 membered a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, and 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl, phenyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl, comprising one aliphatic and one aromatic ring, wherein one ring comprises an O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, and 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, fused cycloalkyl, phenyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl, comprising one aliphatic and one aromatic ring, wherein one ring comprises an O-atom, a

saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, and 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, fused cycloalkyl, phenyl or heteroaryl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl, comprising one aliphatic and one aromatic ring, wherein one ring comprises an O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, and 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, fused cycloalkyl, phenyl, or heteroaryl are optionally substituted with one substituent independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl, comprising one aliphatic and one aromatic ring, wherein one ring comprises an O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, and 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, fused cycloalkyl, phenyl, or heteroaryl are optionally substituted with two substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are

hydrogen, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl, comprising one aliphatic and one aromatic ring, wherein one ring comprises an O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, and 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, fused cycloalkyl, phenyl, or heteroaryl are optionally substituted with F-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl, comprising one aliphatic and one aromatic ring, wherein one ring comprises an O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, and 6 membered heteroaryl, which fused heterocyloalkyl, saturated monocyclic cycloalkyl, bridged cycloalkyl, fused cycloalkyl, phenyl or heteroaryl are unsubstituted.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a bicyclo[2.2.1]heptanyl, cyclopentyl, phenyl, dihydrochromenyl, tert-butyl, cyclohexyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrimidinyl, pyridinyl, and pyrazinyl, which bicyclo[2.2.1]heptanyl, cyclopentyl, phenyl, dihydrochromenyl, cyclohexyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[1.1.1]pentanyl, cyclopentyl, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrimidinyl, pyridinyl, or pyrazinyl are optionally substituted with one, two, or three substituents independently selected from halogen, $C_{1\text{-}6}$alkyl, $C_{3\text{-}6}$cycloalkyl, $C_{1\text{-}6}$ alkoxy, cyano, oxo, hydroxy, hydroxy$C_{1\text{-}6}$alkyl and halo$C_{1\text{-}6}$alkyl.

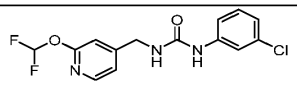
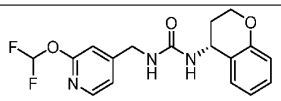
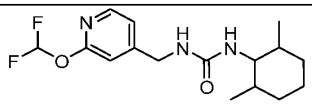
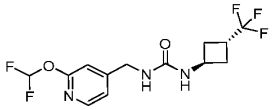
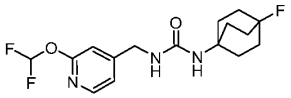
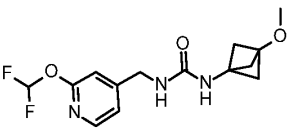
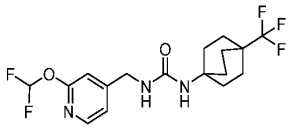
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 is hydrogen, R^3 is hydrogen, n is 0, and R^6 is selected from a bicyclo[2.2.1]heptanyl, cyclopentyl, phenyl, dihydrochromenyl, tert-butyl, cyclohexyl, bicyclo[2.2.2]octanyl, bicyclo[1.1.1]pentanyl,

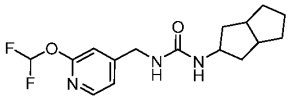
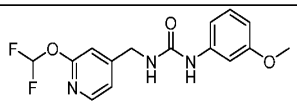
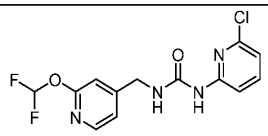
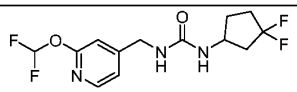
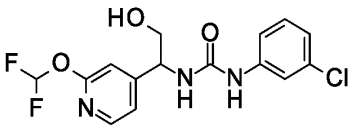
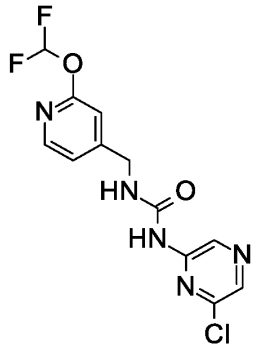
$(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrazinyl, pyrimidinyl, and pyridinyl, which bicyclo[2.2.1]heptanyl, cyclopentyl, phenyl, dihydrochromenyl, cyclohexyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[1.1.1]pentanyl, cyclopentyl, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

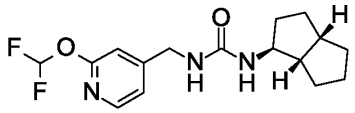
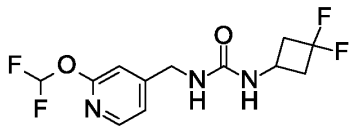
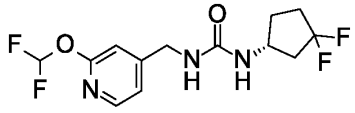
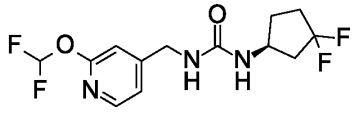
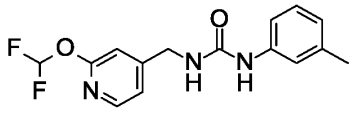
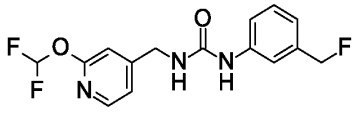
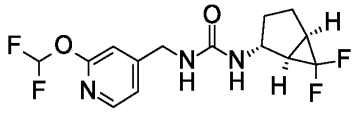
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is selected from a bicyclo[2.2.1]heptanyl, cyclopentyl, phenyl, dihydrochromenyl, tert-butyl, cyclohexyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrimidinyl , pyrazinyl, and pyrimidinyl, which bicyclo[2.2.1]heptanyl, cyclopentyl, phenyl, dihydrochromenyl, cyclohexyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[1.1.1]pentanyl, cyclopentyl, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from halogen, $C_{1\text{-}6}$alkyl, $C_{3\text{-}6}$cycloalkyl, $C_{1\text{-}6}$ alkoxy, cyano, hydroxy, and halo$C_{1\text{-}6}$alkyl.

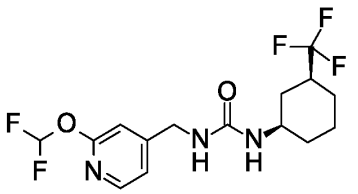
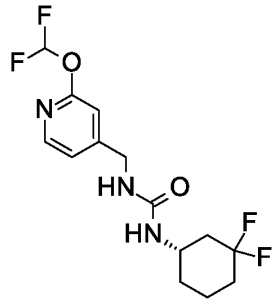
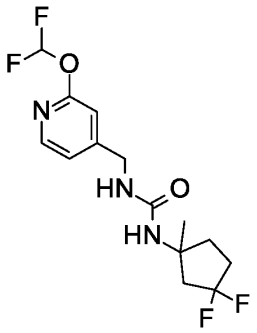
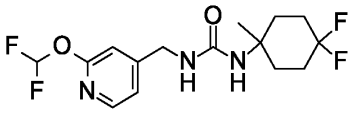
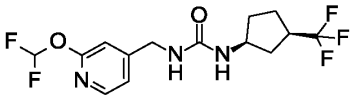
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 is hydrogen, R^3 is hydrogen, n is 0, and R^6 is selected from a bicyclo[2.2.1]heptanyl, cyclopentyl, phenyl, dihydrochromenyl, cyclohexyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[1.1.1]pentanyl, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrazinyl, pyrimidinyl, and pyridinyl, which bicyclo[2.2.1]heptanyl, cyclopentyl, phenyl, dihydrochromenyl, cyclohexyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[1.1.1]pentanyl, cyclopentyl, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

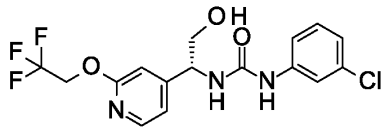
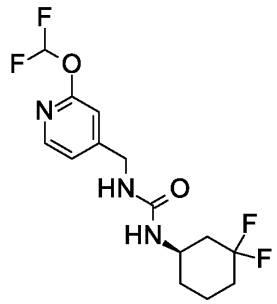
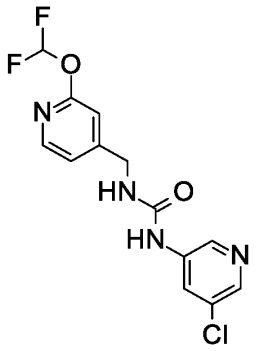
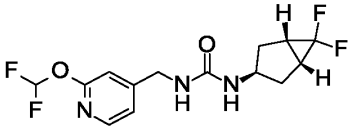
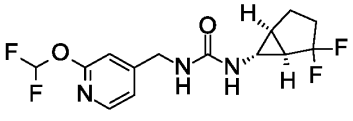
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2, R^3, n is 0, and R^6 are as described herein, and non-limiting examples are selected from:

22	1-(3-chlorophenyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
23	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(4R)-3,4-dihydro-2H-chromen-4-yl]urea	
25	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,6-dimethylcyclohexyl)urea	
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
49	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxy-1-bicyclo[1.1.1]pentanyl)urea	
68	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[4-(trifluoromethyl)-1-bicyclo[2.2.2]octanyl]urea	

78	1-(1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
83	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxyphenyl)urea	
84	1-(6-chloropyridin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
93	1-(3,3-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
98	1-(6-chloropyrazin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

103	1-[(1S,3aS,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
108	1-(3,3-difluorocyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
126	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylphenyl)urea	
132	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(fluoromethyl)phenyl]urea	
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

138	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	
140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
142	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-difluoro-1-methylcyclopentyl)urea	
143	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4,4-difluoro-1-methylcyclohexyl)urea	
144	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3R)-3-(trifluoromethyl)cyclopentyl]urea	

145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
161	1-(5-chloropyridin-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
169	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
170	1-[(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-	

	(difluoromethoxy)pyridin-4-yl]methyl]urea	

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 is hydrogen, R^3 is hydrogen, and n is 1.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy, and R^5 is hydrogen.

In some preferred embodiments, R^4 and R^5 are both hydrogen.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, C_{1-6}alkyl, and a saturated monocyclic 3-5 membered cycloalkyl, and R^5 is hydrogen,

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, C_{1-6}alkyl, and a saturated monocyclic 3-5 membered cycloalkyl, R^5 is hydrogen, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; which saturated monocyclic cycloalkyl, or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, C_{1-6}alkyl, and a saturated monocyclic 3-

5 membered cycloalkyl, R^5 is hydrogen, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which saturated monocyclic cycloalkyl, or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, $(CH_3)_2CF$-, CF_3-, CH_3O-, tert-butyl, CN-, cyclopropyl, and hydroxy.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, C_{1-6}alkyl, and a saturated monocyclic 3-5 membered cycloalkyl, R^5 is hydrogen, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, and a 4-10 membered bridged cycloalkyl, which saturated monocyclic cycloalkyl, or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, C_{1-6}alkyl, and a saturated monocyclic 3-5 membered cycloalkyl, R^5 is hydrogen, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, and a 4-10 membered bridged cycloalkyl which saturated monocyclic cycloalkyl, or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, C_{1-6}alkyl, and a saturated monocyclic 3-5 membered cycloalkyl, R^5 is hydrogen, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which saturated monocyclic cycloalkyl, or bridged cycloalkyl are unsubstituted.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, C_{1-6}alkyl, and a saturated monocyclic 3-5 membered cycloalkyl, R^5 is hydrogen, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, and a 4-10 membered bridged cycloalkyl, which saturated monocyclic cycloalkyl, or bridged cycloalkyl are unsubstituted.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, CH_3-, and cyclopropyl, R^5 is hydrogen, and R^6 is selected from bicyclo[2.2.1]heptanyl, tert-butyl, cyclobutyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, CF_3-, and cyclopentyl, which bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, or cyclopentyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, CH_3-, and cyclopropyl, R^5 is hydrogen, and R^6 is selected from cyclobutyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, and CF_3-, which cyclobutyl, or bicyclo[1.1.1]pentanyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, CH_3-, and cyclopropyl, R^5 is hydrogen, and R^6 is selected from bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, CF_3-, and cyclopentyl, which bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, or cyclopentyl are optionally substituted with one, two, or three substituents independently selected

from halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, CH_3-, and cyclopropyl, R^5 is hydrogen, and R^6 is selected from bicyclo[2.2.1]heptanyl, tert-butyl, cyclobutyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, CF_3-, and cyclopentyl, which bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, or cyclopentyl are unsubstituted.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, CH_3-, and cyclopropyl, R^5 is hydrogen, and R^6 is selected from bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, CF_3-, and cyclopentyl, which bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, or cyclopentyl are unsubstituted.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, CH_3-, and cyclopropyl, R^5 is hydrogen, and R^6 is selected from bicyclo[2.2.1]heptanyl, tert-butyl, cyclobutyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, CF_3-, and cyclopentyl, which bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, or cyclopentyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, $(CH_3)_2CF$-, CF_3-, CH_3O-, tert-butyl, CN-, cyclopropyl, and hydroxy.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, hydroxy, CH_3-, and cyclopropyl, R^5 is hydrogen, and R^6 is selected from bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, CF_3-, and cyclopentyl, which bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, or

cyclopentyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, $(CH_3)_2CF$-, CF_3-, CH_3O-, tert-butyl, CN-, cyclopropyl, and hydroxy.

In one preferred embodiment, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, CH_3- and cyclopropyl, R^5 is hydrogen, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, CH_3-, and cyclopropyl, R^5 is hydrogen, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are unsubstituted.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, CH_3- and cyclopropyl, R^5 is hydrogen, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are substituted with one, two, threem or four substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, CH_3- and cyclopropyl, R^5 is hydrogen, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are optionally substituted with one or two halogen selected from F-, Cl-, and Br-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, CH_3-, and cyclopropyl, R^5 is hydrogen, and R^6 is

cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are optionally substituted with one haloC_{1-6}alkyl selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, CH_3-, and cyclopropyl, R^5 is hydrogen, and R^6 is cyclobutyl or cyclopentyl, which cyclobutyl or cyclopentyl are optionally substituted with one or two F-, or CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 is selected from hydrogen, CH_3-, and cyclopropyl, R^5 is hydrogen, and R^6 is selected from bicyclo[2.2.1]heptanyl, tert-butyl) cyclobutyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, CF_3-, and cyclopentyl, which bicyclo[2.2.1]heptanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, or cyclopentyl, are optionally substituted with one, two, or three substituents independently selected from F-, CH_3O-, $(CH_3)_2CF$-, or CF_3-.

In some preferred embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^4 is cycloalkyl, e.g. cyclopropyl, this cycloalkyl or cyclopropyl is optionally substituted with one, two, three, or four substituents independently selected from halogen, haloC_{1-6}alkyl, and hydroxy, in particular the cycloalkyl or cyclopropyl are unsubstituted as described herein, and R^5 is hydrogen.

In some preferred embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^4 is cycloalkyl, e.g. cyclopropyl, this cycloalkyl or cyclopropyl is optionally substituted with one, two, three, or four substituents independently selected from halogen, haloC_{1-6}alkyl, and hydroxy, in particular the cycloalkyl or cyclopropyl is unsubstituted as described herein, and R^5 is hydrogen, and R^6 is as described herein.

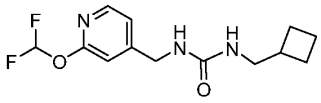
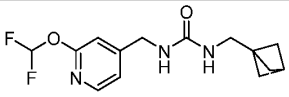
In some preferred embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^4 is cycloalkyl, e.g.

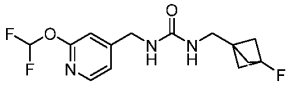
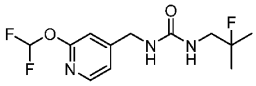
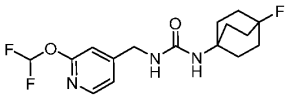
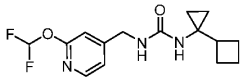
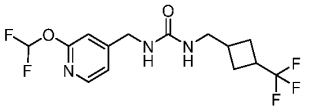
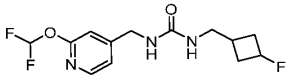
cyclopropyl, this cycloalkyl or cyclopropyl is optionally substituted with one, two, three, or four substituents independently selected from halogen, haloC_{1-6}alkyl, and hydroxy, in particular the cycloalkyl or cyclopropyl is unsubstituted as described herein, R^5 is hydrogen, and R^6 is haloC_{1-6}alkyl.

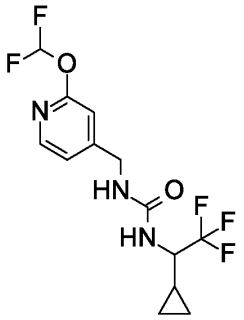
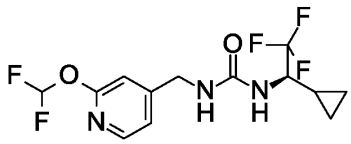
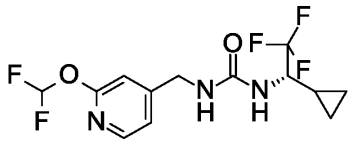
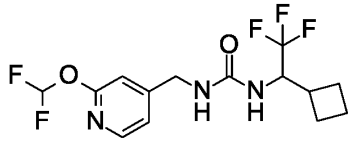
In some preferred embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^4 is cycloalkyl, e.g. cyclopropyl, this cycloalkyl or cyclopropyl is optionally substituted with one, two, three, or four substituents independently selected from halogen, haloC_{1-6}alkyl, and hydroxy, in particular the cycloalkyl or cyclopropyl is unsubstituted as described herein, R^5 is hydrogen, and R^6 is CF_3-.

In some preferred embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^4 and R^5 together with the one carbon atom they are attached to, form 3-5 membered saturated monocyclic cycloalkyl as described herein.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, n is 1, R^2, R^3, R^4, R^5 and R^6 are as described herein, and the non-limiting examples are selected from:

13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

32	1-[[2-(difluoomethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea	
39	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-fluoro-2-methylpropyl)urea	
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
50	1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
62	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
89	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea	

106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
135	1-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
152	1-(1-cyclobutyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, and n is 0 or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2

and R^3 are hydrogen, n is 0 or 1, and R^6 is a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, haloC_{1-6}alkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, which bridged cycloalkyl, saturated monocyclic cycloalkyl, phenyl, fused heterocycloalkyl, or fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, haloC_{1-6}alkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, which bridged cycloalkyl, saturated monocyclic cycloalkyl, phenyl, fused heterocycloalkyl, or fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, haloC_{1-6}alkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, which bridged cycloalkyl, saturated monocyclic cycloalkyl, phenyl, fused heterocycloalkyl, or fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2

and R^3 are hydrogen, n is 0 or 1, and R^6 is a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, haloC_{1-6}alkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, which bridged cycloalkyl, saturated monocyclic cycloalkyl, phenyl, fused heterocycloalkyl, or fused cycloalkyl are optionally substituted with one, two, or three halogen.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, haloC_{1-6}alkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, which bridged cycloalkyl, saturated monocyclic cycloalkyl, phenyl, fused heterocycloalkyl, or fused cycloalkyl are optionally substituted with one, two, or three halogen selected from F-, Cl-, or Br-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, haloC_{1-6}alkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, which bridged cycloalkyl, saturated monocyclic cycloalkyl, phenyl, fused heterocycloalkyl, or fused cycloalkyl are optionally substituted with one, two, or three haloC_{1-6}alkyl.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused

heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, haloC_{1-6}alkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, which bridged cycloalkyl, heterocycloalkyl, saturated monocyclic cycloalkyl, phenyl, fused heterocycloalkyl, or fused cycloalkyl are optionally substituted with one, two, or three haloC_{1-6}alkyl selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, or CHF_2.

In one particularly preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, and n is 0 or 1, and R^6 is a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, haloC_{1-6}alkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, which bridged cycloalkyl, saturated monocyclic cycloalkyl, phenyl, fused heterocycloalkyl, or fused cycloalkyl are optionally substituted with two F-.

In one particularly preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, and n is 0 or 1, and R^6 is a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, haloC_{1-6}alkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, which bridged cycloalkyl, saturated monocyclic cycloalkyl, phenyl, fused heterocycloalkyl, or fused cycloalkyl are optionally substituted with one F-.

In one particularly preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, and n is 0 or 1, and R^6 is a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, haloC_{1-6}alkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising

two aliphatic rings, which bridged cycloalkyl, saturated monocyclic cycloalkyl, phenyl, fused heterocycloalkyl, or fused cycloalkyl are optionally substituted with one CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a saturated monocyclic cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one, two, or three substituents independently selected from F-, CF_3- and cyclopropyl.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a saturated monocyclic cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are unsubstituted.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclobutyl which is optionally substituted with one, two, or three substituents independently selected from F- or CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0, and R^6 is cyclobutyl which is optionally substituted with one or two substituents independently selected from F- or CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclopentyl which is optionally substituted with one, two, or three substituents independently selected from F- or CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclopentyl which is optionally substituted with one or two substituents independently selected from F- or CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclohexyl which is optionally substituted with one, two, or three substituents independently selected from F- or CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is cyclohexyl which is optionally substituted with one or two substituents independently selected from F- or CF_3-.

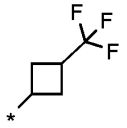
In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, and n is 0 or 1, and R^6 is a 4-6 membered saturated monocyclic cycloalkyl, which cycloalkyl is optionally substituted with one CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, and n is 0 or 1, and R^6 is a 4-6 membered saturated monocyclic cycloalkyl, which cycloalkyl is optionally substituted with one or two F-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, and n is 0 or 1, and R^6 is a 4-6 membered saturated monocyclic cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, and cyclohexyl is optionally substituted with one or two F-.

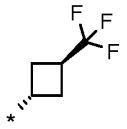
In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, and n is 0 or 1, and R^6 is a 4-6 membered saturated monocyclic cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, and cyclohexyl is optionally substituted with one CF_3-.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 has the structure:



.

In particular R^6 has the structure:



.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is unsubstituted cyclobutyl.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom which is optionally substituted with one, two, or three substituents independently selected from F- or CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom which are unsubstituted.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a 7-10 membered bridged cycloalkyl which is optionally substituted with one, two, or three substituents independently selected from F- or CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a 7-10 membered bridged cycloalkyl which is unsubstituted.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings which is optionally substituted with one, two, or three substituents independently selected from F- or CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is a 7-10 membered bicyclic edge-to-edge fused cycloalkyl selected from bicyclo[3.1.0]hexanyl, octahydropentalenyl, bicyclo[3.2.0]heptanyl, bicyclo[3.2.1]octanyl, bicyclo[3.2.2]octanyl, and hexahydropentalenyl which are optionally substituted with one, two, or three substituents independently selected from F- or CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 , and R^6 is a 7-10 membered bicyclic edge-to-edge fused cycloalkyl

selected from bicyclo[3.1.0]hexanyl, octahydropentalenyl, bicyclo[3.2.0]heptanyl, bicyclo[3.2.1]octanyl, bicyclo[3.2.2]octanyl, and hexahydropentalenyl which are optionally substituted with one, two, or three substituents independently selected from F- or CF_3-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 1, R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl as described herein.

In some particularily preferred embodiments, R^6 is optionally substituted with two F-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, and R^6 is phenyl which is optionally substituted with one, two, or three substituents independently selected from Cl-, CH_3-, F- and CF_3-.

In some particularily preffered embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^4 is cycloalkyl, e.g. cyclopropyl, this cycloalkyl or cyclopropyl is optionally substituted with one, two, three, or four substituents independently selected from halogen, haloC_{1-6}alkyl, and hydroxy, in particular the cycloalkyl or cyclopropyl is unsubstituted as described herein, and R^5 is hydrogen.

In some particularily preferred embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^4 is cycloalkyl, e.g. cyclopropyl, this cycloalkyl or cyclopropyl is optionally substituted with one, two, three, or four substituents independently selected from halogen, haloC_{1-6}alkyl, and hydroxy, in particular the cycloalkyl or cyclopropyl is unsubstituted as described herein, and R^5 is hydrogen, and R^6 is as described herein.

In some particularily preferred embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^4 is cycloalkyl,

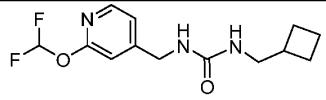
e.g. cyclopropyl, this cycloalkyl or cyclopropyl is optionally substituted with one, two, three, or four substituents independently selected from halogen, haloC_{1-6}alkyl, and hydroxy, in particular the cycloalkyl or cyclopropyl is unsubstituted as described herein, R^5 is hydrogen, and R^6 is haloC_{1-6}alkyl.

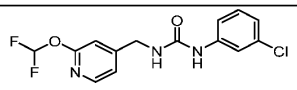
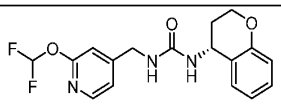
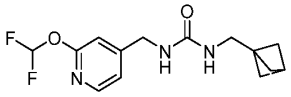
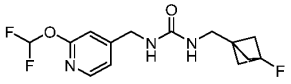
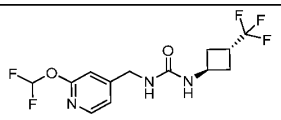
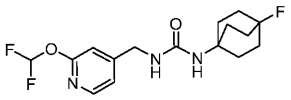
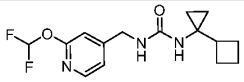
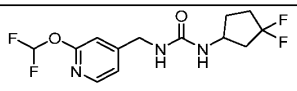
In some particularily preferred embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^4 is cycloalkyl, e.g. cyclopropyl, this cycloalkyl or cyclopropyl is optionally substituted with one, two, three, or four substituents independently selected from halogen, haloC_{1-6}alkyl, and hydroxy, in particular the cycloalkyl or cyclopropyl is unsubstituted as described herein, R^5 is hydrogen, and R^6 is CF_3-.

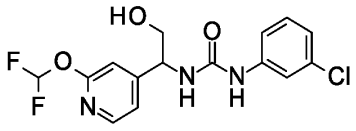
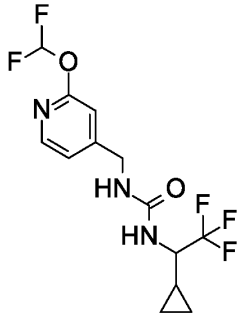
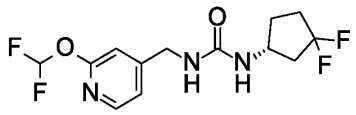
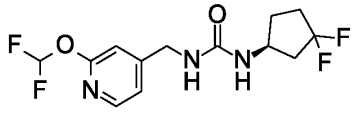
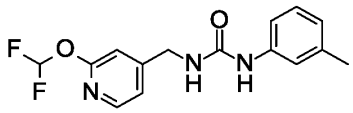
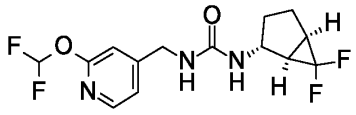
In some particularily preferred embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1, R^2, and R^3 are as described herein, R^4 and R^5 are (i) both hydrogen, or (ii) one of R^4 and R^5 is hydrogen the other one is selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and hydroxy, and R^6 is as described herein.

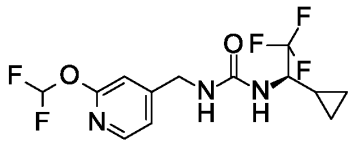
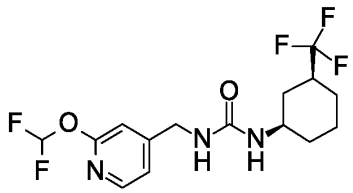
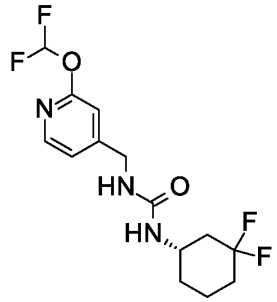
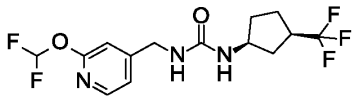
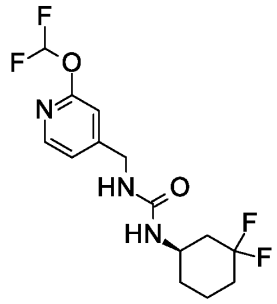
In some particularily preferred embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1, R^2, and R^3 are as described herein, R^4 and R^5 are both hydrogen, and R^6 is as described herein.

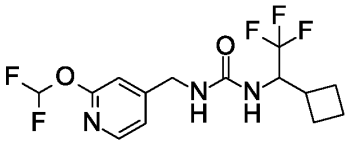
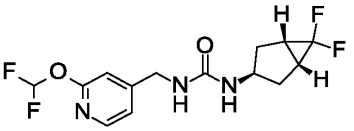
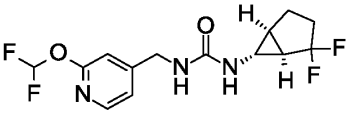
In one particularily particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, n is 0 or 1, R^2, R^3, and R^6 are as described herein, and non-limiting examples are selected from:

13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

22	1-(3-chlorophenyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
23	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(4R)-3,4-dihydro-2H-chromen-4-yl]urea	
31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
32	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea	
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
50	1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
93	1-(3,3-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
126	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylphenyl)urea	
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
138	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	
140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
144	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3R)-3-(trifluoromethyl)cyclopentyl]urea	
149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

152	1-(1-cyclobutyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
169	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
170	1-[(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are both hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is hydrogen and the other one is hydrogen or hydroxyC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is hydrogen and the other one is hydrogen or hydroxyC_{1-6}alkyl selected from $HOCH_2$-, $HOCH_2CH_2$-, $HOCH_2CH_2CH_2$- and $HOCH_2CH_2CH_2CH_2$-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is hydrogen and the other one is hydrogen, $HOCH_2$- or $HOCH_2CH_2$-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is hydrogen and the other one is $HOCH_2$- or $HOCH_2CH_2$-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy and one of R^2 and R^3 is hydrogen and the other one is hydroxyC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy selected from CHF_2O-, CH_2FO-, CF_3CH_2O-, CF_2HCH_2O-, $CH_3CF_2CH_2O$-, and CH_3CFHCH_2O-, and one of R^2 and R^3 is hydrogen and the other one is hydroxyC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, and R^3 is hydroxyC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, and R^3 is hydroxyC_{1-6}alkyl selected from $HOCH_2$-, $HOCH_2CH_2$-, $HOCH_2CH_2CH_2$- and $HOCH_2CH_2CH_2CH_2$-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, and R^3 is $HOCH_2$- or $HOCH_2CH_2$-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, and R^3 is $HOCH_2$-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, and R^3 is $HOCH_2CH_2$-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- or $HOCH_2CH_2$-, and n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- or $HOCH_2CH_2$-, and n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is selected from a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl, and phenyl, which bridged

cycloalkyl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one, two, or three substituents inpendently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- $HOCH_2CH_2$-, n is 0, and R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and adamantine, which bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and adamantine are optionally substituted with one, two, or three substituents inpendently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is phenyl, which which phenyl is optionally substituted with one, two, or three substituents independently selected from halogen, hydroxy, or haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantine, and phenyl, which bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantine, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, hydroxy, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen,

R^3 is $HOCH_2$- or $HOCH_2CH_2$- and n is 0, and R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantine, and phenyl, which bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantine, or phenyl are optionally substituted with one or two substituents independently selected from hydroxy, halogen, and halo$C_{1\text{-}6}$alkyl.

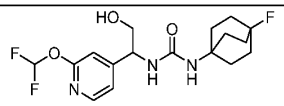
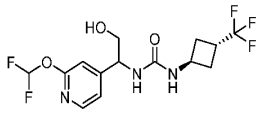
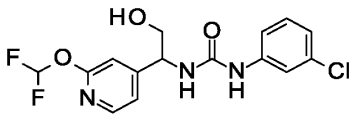
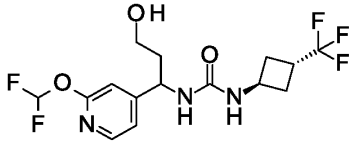
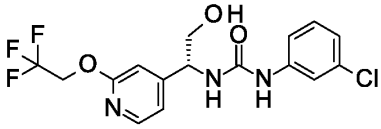
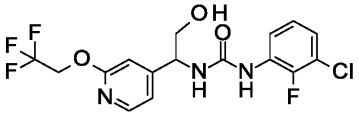
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantine, and phenyl, which bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantine, or phenyl are optionally substituted with one or two substituents independently selected from hydroxy, Cl-, F-, Br- and CF_3-.

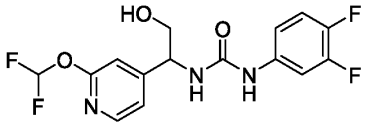
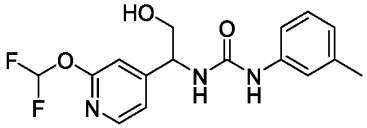
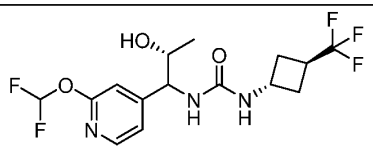
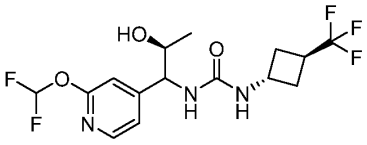
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is phenyl, which which phenyl is optionally substituted with two halogen selected from Cl-, F- or Br-.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is selected from bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantine, and phenyl, which bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, adamantine, or phenyl are optionally substituted with one Cl-, F- and CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 is hydrogen, R^3 is $HOCH_2$- or $HOCH_2CH_2$-, n is 0, and R^6 is a saturated monocylic 4-6 memberd cycloalkyl selected from cyclobutyl, cyclopentyl and cyclohexyl; which cyclobutyl, cyclopentyl or cyclohexyl are optionally substituted with one Cl-, F- and CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate, or pharmaceutically acceptable salt thereof, wherein R^1 is haloC_{1-6}alkoxy, R^2 is hydrogen, R^3 is hydroxyC_{1-6}alkyl, n and R^6 is as described herein, and non-limiting examples are selected from:

85	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
91	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
117	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-3-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
150	1-(3-chloro-2-fluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea	
286	1-[(2R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
287	1-[(2S)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

In the below embodiments, "saturated monocyclic 3-5 membered cycloalkyl formed" means an unsubstituted cycloalkyl or a cycloalkyl which is substituted as described herein. In particular, the cycloalkyl is unsubstitued.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3, together with the one carbon atom to which they are attached, form cyclopropyl with the structure:

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3, together with the one carbon atom to which they are attached, form cyclopropyl as described above, and n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3, together with the one carbon atom to which they are attached, form cyclopropyl as described above, and n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3, together with the one carbon atom to which they are attached, form cyclopropyl as described above, n is 0 or 1, R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxyl as described herein, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3, together with the one carbon atom to which they are attached, form cyclopropyl as described above, n is 0 or 1, R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxyl as described herein, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3, together with the

one carbon atom to which they are attached, form cyclopropyl as described above, n is 0 or 1, R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxyl as described herein, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one or two F-.

In some particularily preferred embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1, R^2, and R^3 are as described herein, R^4 and R^5 are (i) both hydrogen, or (ii) one of R^4 and R^5 is hydrogen the other one is selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and hydroxyl as described herein, and R^6 is as described herein.

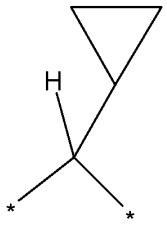
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein wherein R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and R^1, R^2, R^4, R^5, n, and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is hydrogen and the other one is hydrogen or a saturated monocyclic 3-5 membered cycloalkyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is hydrogen and the other one is hydrogen or a saturated monocyclic 3-5 membered cycloalkyl selected from cyclopropyl, cyclobutyl, and cyclopentyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is hydrogen and the other one is hydrogen or cyclopropyl.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is hydrogen and the other one is hydrogen or cyclopropyl attached to the molecule as follows:



In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen and R^3 is a saturated monocyclic 3-5 membered cycloalkyl, selected from cyclopropyl, cyclobutyl, and cyclopentyl, and n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^2 is hydrogen and R^3 is a saturated monocyclic cycloalkyl, and n is 0 or 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 is hydrogen and R^3 is cyclopropyl as described above, n is 0 or 1, R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxyl as described herein, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, hydroxy, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 is hydrogen and R^3 is cyclopropyl as

described above, n is 0 or 1, R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl as described herein, and R^6 is selected from a 4-10 membered cycloalkyl and haloC_{1-6}alkyl, wherein the cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, hydroxy, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 is hydrogen and R^3 is cyclopropyl as described above, n is 0 or 1, R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 is hydrogen and R^3 is cyclopropyl as described above, n is 0 or 1, R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl as described herein, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cycloalkyl is unsubstituted.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 is hydrogen and R^3 is cyclopropyl as described above, n is 0 or 1, R^4 and R^5 are independently selected from hydrogen and C_{1-6}alkyl as described herein, and R^6 haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 is hydrogen and R^3 is cyclopropyl as described above, n is 0 or 1, R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl, and R^6 haloC_{1-6}alkyl is selected from $(CH_3)_2FC$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In the above embodiments, "saturated monocyclic 3-5 membered cycloalkyl formed" means an unsubstituted cycloalkyl or a cycloalkyl which is substituted as described herein. In particular, the cycloalkyl is unsubstitued.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 is hydrogen and R^3 is cyclopropyl as described above, n is 0 or 1, R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl, and R^6 haloC_{1-6}alkyl is CF_3- as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, 1, 2, or 3.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, 1, or 2.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, or 1.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1.

In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, which heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl; R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl, or R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl; R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy, and hydroxy, or R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl; and R^6 is selected from a 5-12 membered

heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl, and n is 2.

In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein n is 2 and R^1 is a 5 membered heteroaryl as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, R^1 is a 5-membered heteroaryl, R^2 and R^3 are hydrogen, both pairs of R^4 and R^5 are hydrogen, and R^6 is a 4-10 membered cycloalkyl, which cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, R^1 is a 5 membered heteroaryl, R^2 and R^3 are hydrogen, both pairs of R^4 and R^5 are hydrogen, and R^6 is an unsubstituted monocyclic 6 membered cycloalkenyl group with one non-aromatic double bond.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, R^1 is a 5 membered heteroaryl, R^2 and R^3 are hydrogen, both pairs R^4 and R^5 are hydrogen, and R^6 is an unsubstituted monocyclic 6 membered cycloalkenyl group with one non-aromatic double bond, which cycloalkenyl group is selected from cyclobutenyl, cyclopentenyl, and cyclohexenyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, R^1 is unsubstituted pyrazolyl, R^2 and R^3 are hydrogen, both pairs of R^4 and R^5 are hydrogen, and R^6 is an unsubstituted cyclohexenyl group with one non-aromatic double bond.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, R^1 is a haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, the first pair of R^4 and R^5 are both hydrogen and in the second pair of R^4 and R^5 one is hydrogen and the other one is hydroxy, and R^6 is C_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, R^1 is a CHF_2O-, R^2 and R^3 are hydrogen, acceptable salt thereof, wherein n is 2, R^1 is a haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, the first pair of R^4 and R^5 are both hydrogen and in the second pair of R^4 and R^5 one is hydrogen and the other one is hydroxy, and R^6 is C_{1-6}alkyl selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl), n-butyl, sec-butyl, and tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, R^1 is a CHF_2O-, heteroaryl, R^2 and R^3 are hydrogen, acceptable salt thereof, wherein n is 2, R^1 is a haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, the first pair of R^4 and R^5 are both hydrogen and in the second pair of R^4 and R^5 one is hydrogen and the other one is hydroxy, and R^6 is tert-butyl.

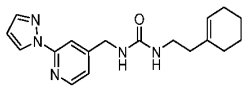
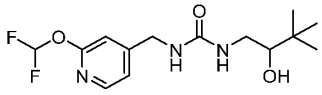
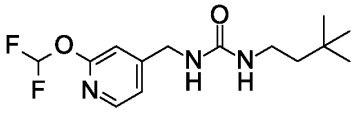
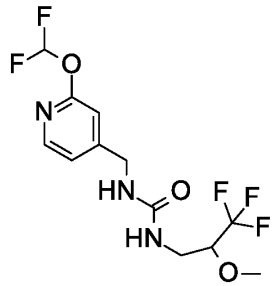
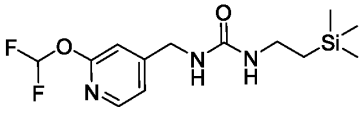
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, R^1 is a CHF_2O-, heteroaryl, R^2 and R^3 are hydrogen, acceptable salt thereof, wherein n is 2, R^1 is a haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, R^4 and R^5 are hydrogen, and R^6 is tert-butyl.

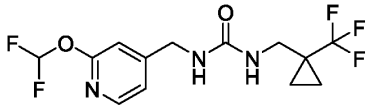
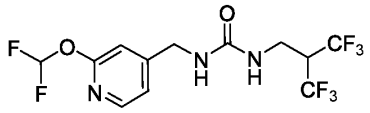
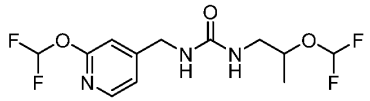
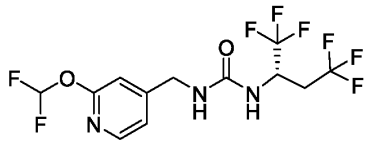
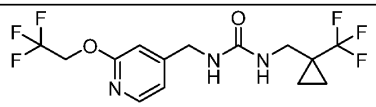
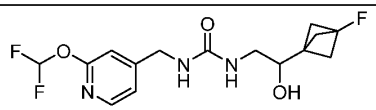
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, R^1 is a CHF_2O-, R^2 and R^3 are hydrogen, acceptable salt thereof, wherein n is 2, R^1 is a haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen, the first pair of R^4 and R^5 are both hydrogen and in the second pair of R^4 and R^5 one is hydrogen and the other one is C_{1-6}alkoxy as described herein, and R^6 is haloC_{1-6}alkyl as described herein.

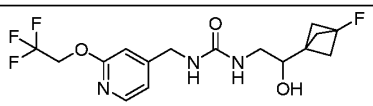
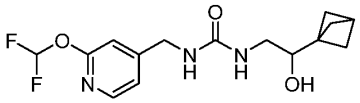
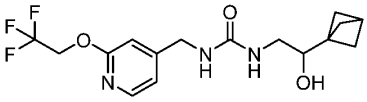
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, R^1 is a CHF_2O-, R^2 and R^3 are hydrogen, acceptable salt thereof, wherein n is 2, R^1 is a haloC_{1-6}alkoxy, R^2 and R^3 are hydrogen,

the first pair of R^4 and R^5 are both hydrogen and in the second pair of R^4 and R^5 one is hydrogen and the other one is CH_3O-, and R^6 is CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, R^1, R^2, R^3, R^4, R^5 and R^6 are as described herein, and non-limiting examples have the structure:

10	1-[2-(cyclohexen-1-yl)ethyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
95	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea	
109	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-dimethylbutyl)urea	
119	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3,3-trifluoro-2-methoxypropyl)urea	
212	1-[[2-(difluoromethoxy)pyridin-4-	

	yl]methyl]-3-(2-trimethylsilylethyl)urea	
229	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
252	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea	
268	1-[2-(difluoromethoxy)propyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
273	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	
284	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
289	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]urea	

290	1-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
291	1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
292	1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

In one embodiment, the invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein n is 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, which heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl; R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl, or R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl; R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy, and hydroxy, or R^4 and R^5, together with the one carbon atom to which they are attached, form a

saturated monocyclic 3-5 membered cycloalkyl; R^6 is a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, or haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and n is 1.

In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from haloC_{1-6}alkoxy, haloC_{1-6}alkyl, and a 5 membered heteroaryl, which heteroaryl is optionally substituted as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from haloC_{1-6}alkoxy, haloC_{1-6}alkyl, and a 5 membered heteroaryl, which heteroaryl is optionally substituted as described herein, and R^2 and R^3 are hydrogen.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from haloC_{1-6}alkoxy, haloC_{1-6}alkyl, and 5 membered heteroaryl, which heteroaryl is optionally substituted as described herein, R^2 and R^3 are hydrogen, and one of R^4 and R^5 is hydrogen and the other one is C_{1-6}alkyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from haloC_{1-6}alkoxy, haloC_{1-6}alkyl, and 5 membered heteroaryl, which heteroaryl is optionally substituted as described herein, R^2 and R^3 are hydrogen, and one of R^4 and R^5 is hydrogen and the other one is C_{1-6}alkyl selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, and tert-butyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from haloC_{1-6}alkoxy, haloC_{1-6}alkyl, and 5 membered heteroaryl which heteroaryl is optionally substituted as described herein, R^2 and R^3 are hydrogen, and one of R^4 and R^5 is hydrogen and the other one is CH_3-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from haloC_{1-6}alkoxy, haloC_{1-6}alkyl, and 5 membered heteroaryl, which heteroaryl is optionally substituted as described herein, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is C_{1-6}alkyl, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which saturated monocylic cycloalkyl or bridged are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, hydroxy, and haloC_{1-6}alkyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from haloC_{1-6}alkoxy, haloC_{1-6}alkyl, and 5 membered heteroaryl, which heteroaryl is optionally substituted as described herein, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is C_{1-6}alkyl, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which saturated monocylic cycloalkyl or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is haloC_{1-6}alkoxy, haloC_{1-6}alkyl, or 5 membered heteroaryl, which heteroaryl is optionally substituted as described herein, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is CH_3-, and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which saturated monocylic cycloalkyl or bridged cycloalkyl are optionally substituted with one, two, or three substituents independently selected from F-, CF_3-, and CH_3O-.

In one embodient, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from CF_3CH_2O-, CHF_2O-, and imidazolyl, which imidazolyl is optionally substituted as described herein, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is CH_3-, and R^6 is selected from cyclobutyl, bicyclo[2.2.1]heptanyl, tert-butyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, and

cyclopentyl, which cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, and cyclopentyl are optionally substituted with one substituent selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-.

In one embodient, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from CF_3CH_2O-, CHF_2O-, and imidazolyl, which imidazolyl is optionally substituted with one or two CF_3-, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is CH_3-, and R^6 is selected from cyclobutyl, bicyclo[2.2.1]heptanyl, tert-butyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, and cyclopentyl, which cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, and cyclopentyl are optionally substituted with one substituent selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-.

In one embodient, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from CF_3CH_2O-, CHF_2O-, and imidazolyl, which imidazolyl is optionally substituted with one CF_3-, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is CH_3-, and R^6 is selected from cyclobutyl, bicyclo[2.2.1]heptanyl, tert-butyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, and cyclopentyl, which cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, and cyclopentyl are optionally substituted with one substituent selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-.

In one embodient, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from CF_3CH_2O-, CHF_2O-, and imidazolyl, which imidazolyl is optionally substituted as described herein, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is CH_3-, and R^6 is selected from cyclobutyl, bicyclo[2.2.1]heptanyl, tert-butyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, or cyclopentyl, which cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, and cyclopentyl are optionally substituted with one substituent selected from F-, CF_3-, and CH_3O-.

In one embodient, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from CF_3CH_2O-, CHF_2O-,

and imidazolyl, which imidazolyl is optionally substituted with one or two CF_3-, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is CH_3-, and R^6 is selected from cyclobutyl, bicyclo[2.2.1]heptanyl, tert-butyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, and cyclopentyl, which cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, or cyclopentyl are optionally substituted with one substituent selected from F-, CF_3-, and CH_3O-.

In one embodient, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from CF_3CH_2O-, CHF_2O-, and imidazolyl, which imidazolyl is optionally substituted with one CF_3-, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is CH_3-, and R^6 is selected from cyclobutyl, bicyclo[2.2.1]heptanyl, tert-butyl, bicyclo[1.1.1]pentanyl, $(CH_3)_2CF$-, and cyclopentyl, which cyclobutyl, bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, or cyclopentyl are optionally substituted with one substituent selected from F-, CF_3-, and CH_3O-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from CF_3CH_2O-, CHF_2O-, and imidazolyl, which imidazolyl is optionally substituted as described herein, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is CH_3-, and R^6 is cyclobutyl, which cyclobutyl is optionally substituted with one substituent selected from F-, CF_3-, and CH_3O-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from CF_3CH_2O-, CHF_2O-, and imidazolyl, which imidazolyl is optionally substituted with one or two CF_3-, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is CH_3-, and R^6 is cyclobutyl, which cyclobutyl is optionally substituted with one substituent selected from F-, CF_3-, and CH_3O-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from CF_3CH_2O-, CHF_2O-, and imidazolyl, which imidazolyl is optionally substituted with one CF_3-, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is CH_3-, and R^6 is cyclobutyl, which cyclobutyl is optionally substituted with one substituent selected from F-, CF_3-, and CH_3O-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from CF_3CH_2O-, CHF_2HO-, and imidazolyl, which imidazolyl is substituted with one CF_3-, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is CH_3-, and R^6 is unsubstituted cyclobutyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from CF_3CH_2O-, CHF_2O-, and imidazolyl, which imidazolyl is substituted with one CF_3-, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is CH_3-, and R^6 is unsubstituted cyclobutyl.

In one preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is CHF_2O-, R^2 and R^3 are hydrogen, R^4 and R^5 are hydrogen, and R^6 is cyclobutyl optionally substituted with one substituent selected from F-, CF_3-, and CH_3O-.

In one preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is CHF_2O-, R^2 and R^3 are hydrogen, R^4 and R^5 are hydrogen, and R^6 is unsubstituted cyclobutyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is CHF_2O-, R^2 and R^3 are hydrogen, R^4 is hydrogen, R^5 is a $C_{1\text{-}6}$alkyl, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, or a 4-10 membered bridged cycloalkyl as described herein.

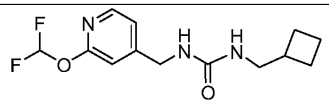
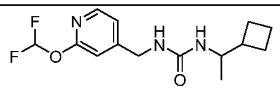
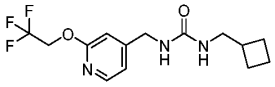
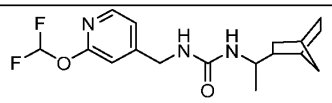
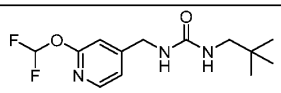
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is CHF_2O-, R^2 and R^3 are hydrogen, R^4 is hydrogen, R^5 is CH_3-, and R^6 is an unsubstituted saturated monocyclic 4-6 membered cycloalkyl, or an unsubstituted 4-10 membered bridged cycloalkyl as described herein.

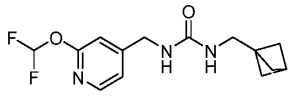
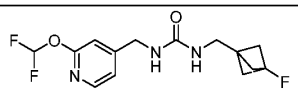
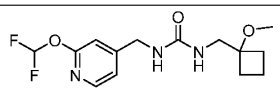
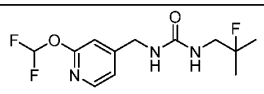
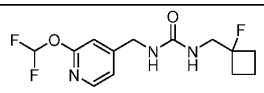
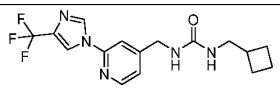
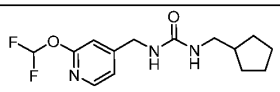
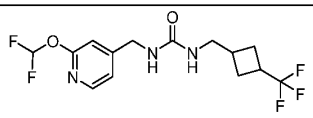
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is CHF_2O-, R^2 and R^3 are hydrogen,

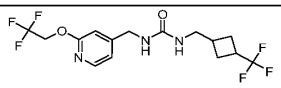
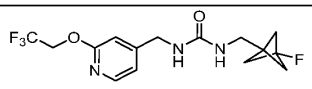
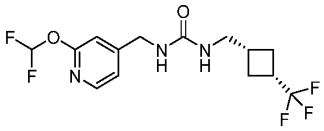
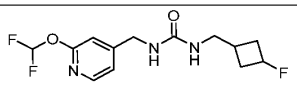
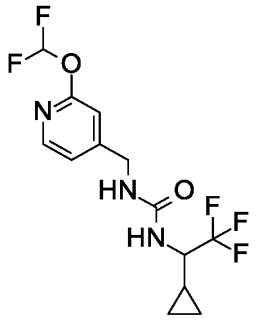
R^4 is hydrogen, R^5 is CH_3-, and R^6 is an unsubstituted cyclobutyl or an unsubstituted bicyclo[2.2.1]heptanyl as described herein.

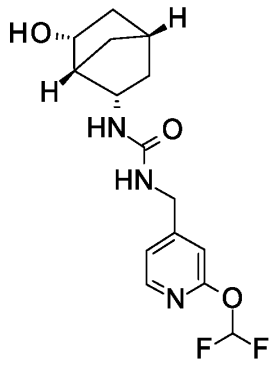
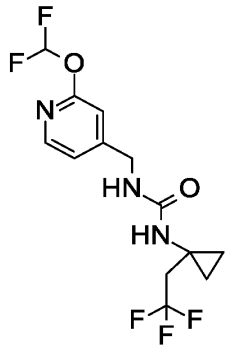
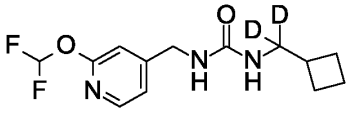
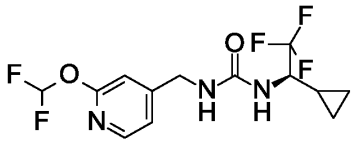
In one embodient, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from CF_3CH_2O-, CHF_2O-, and imidazolyl, which imidazolyl is optionally substituted as described herein, R^2 and R^3 are hydrogen, one of R^4 and R^5 is hydrogen and the other one is cyclopropyl as described herein, and R^6 is C_{1-6}alkyl as described herein, in particular tert-butyl.

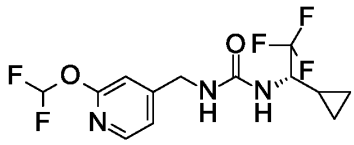
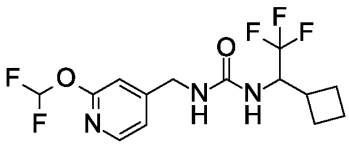
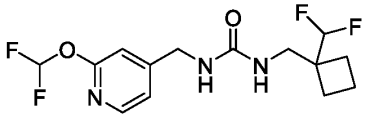
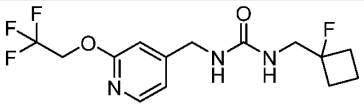
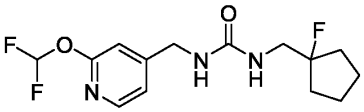
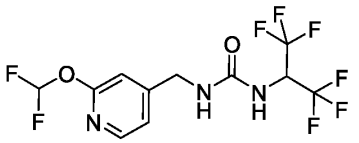
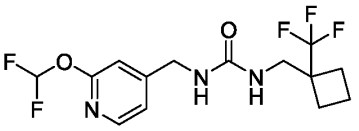
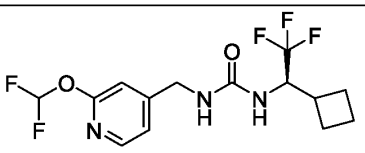
In one preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1, R^2, R^3, R^4, R^5, and R^6 are as described herein, and the non-limiting examples are selected from:

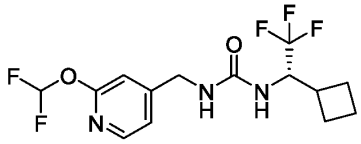
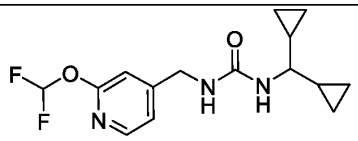
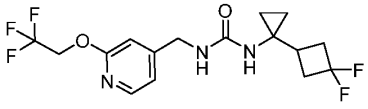
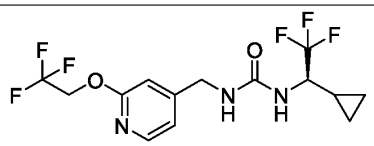
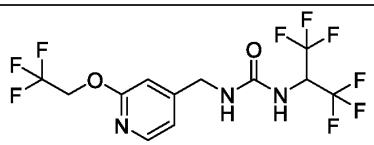
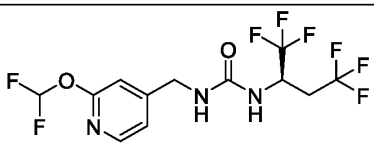
13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
17	1-(1-cyclobutylethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
21	1-(cyclobutylmethyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
24	1-[1-(2-bicyclo[2.2.1]heptanyl)ethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
29	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,2-dimethylpropyl)urea	

31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
32	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea	
38	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-methoxycyclobutyl)methyl]urea	
39	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-fluoro-2-methylpropyl)urea	
40	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclobutyl)methyl]urea	
41	1-(cyclobutylmethyl)-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	
46	1-(cyclopentylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
62	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	

71	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
75	1-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
87	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(1r,3r)-(trifluoromethyl)cyclobutyl]methyl]urea	
89	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea	
106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

107	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S,6R)-6-hydroxy-2-bicyclo[2.2.1]heptanyl]urea	
110	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2,2-trifluoroethyl)cyclopropyl]urea	
125	1-[cyclobutyl(dideuterio)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

135	1-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
152	1-(1-cyclobutyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
191	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluoromethyl)cyclobutyl]methyl]urea	
210	1-[(1-fluorocyclobutyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
227	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclopentyl)methyl]urea	
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea	
237	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclobutyl]methyl]urea	
241	1-[(1R)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-	

	(difluoromethoxy)pyridin-4-yl]methyl]urea	
242	1-[(1S)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
253	1-(dicyclopropylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
254	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
285	1-(1,1,1,3,3,3-hexafluoropropan-2-yl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
294	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, which heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl; R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl, or R^2 and R^3, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl; R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy, and hydroxy, or R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl; R^6 is a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, or haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and n is 0.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, and tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one haloC_{1-6}alkyl selected from $(CH_3)_2CF$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is a 5 membered heteroaryl as described herein optionally substituted with one CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are unsubstituted.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl as described herein, and one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered

heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl as described herein, and one of R^2 and R^3 is hydrogen and the other is hydroxyC_{1-6}alkyl selected from $HOCH_2$-, $HOCH_2CH_2$-, $HOCH_2CH_2CH_2$- and $HOCH_2CH_2CH_2CH_2$-.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC1-6alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl as described herein and one of R^2 and R^3 is hydrogen and the other is $HOCH_2$-.

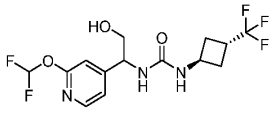
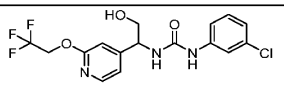
In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl as described herein, one of R^2 and R^3 is hydrogen and the other is $HOCH_2$- and R^6 is a saturated monocyclic 4-6 membered cycloalkyl or phenyl, which cycloalkyl or phenyl are optionally substituted with one, two, or three halogen or haloC_{1-6}alkyl.

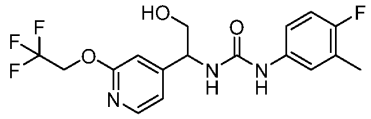
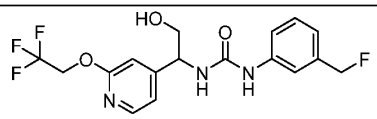
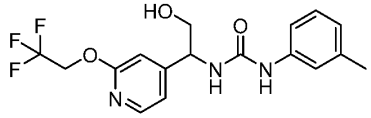
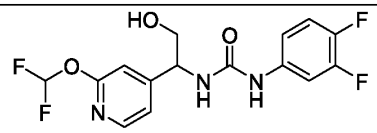
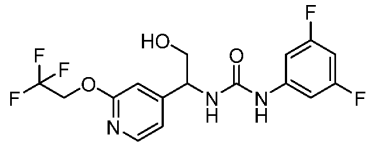
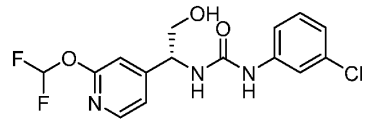
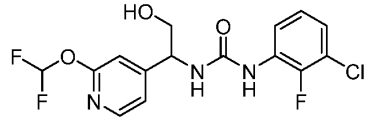
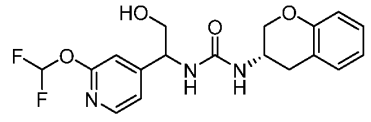
In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC1-6alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl as described herein, one of R^2 and R^3 is hydrogen and the other is $HOCH_2$-, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl or phenyl, which cycloalkyl or phenyl are optionally substituted with one, two, or three F-, Cl-, or CF_3-.

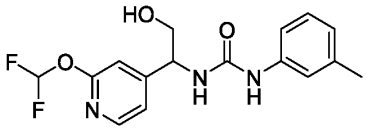
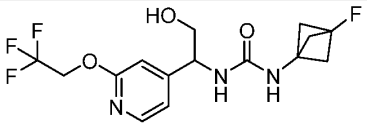
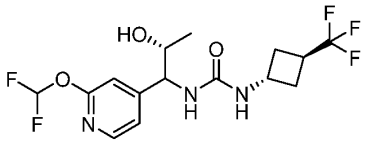
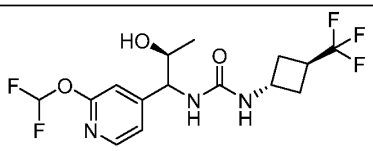
In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC1-6alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl as described herein, one of R^2 and R^3 is hydrogen and the other is $HOCH_2$-, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl or phenyl, which cycloalkyl or phenyl are optionally substituted with one or two F-, Cl-, or CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl as described herein, one of R^2 and R^3 is hydrogen and the other is $HOCH_2$-, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl or phenyl, which cycloalkyl or phenyl are optionally substituted with one F-, Cl-, or CF_3-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1, R^2, R^3, R^4, R^5, and R^6 are as described herein, and the non-limiting examples are selected from:

91	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[3-(trifluoromethyl)cyclobutyl] urea	
92	1-(3-chlorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

205	1-(4-fluoro-3-methylphenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
232	1-[3-(fluoromethyl)phenyl]-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
233	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-(3-methylphenyl)urea	
240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
256	1-(3,5-difluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
263	rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
270	1-(3-chloro-2-fluorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
278	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(3S)-3,4-dihydro-2H-chromen-3-yl]urea	

280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea	
283	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
286	1-[(2R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
287	1-[(2S)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

In some embodiments, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are both hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from C_{1-6} alkyl and haloC_{1-6}alkyl as described herein, and R^2 and R^3 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered

heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl as described herein, and R^2 and R^3 are hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl as described herein, R^2 and R^3 are hydrogen, and R^6 is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, a saturated monocyclic 4-6 membered cycloalkyl, phenyl, a 4-10 membered bridged cycloalkyl, and 6 membered heteroaryl, which fused heterocycloalkyl, saturated monocylic cycloalkyl, phenyl, bridged cycloalkyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from 5 membered heteroaryl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocycloalkyl, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy, which heterocycloalkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, or heteroaryl are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl as described herein, R^2 and R^3 are hydrogen, and R^6 is selected from a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and 6 membered heteroaryl, which fused heterocycloalkyl, saturated monocylic cycloalkyl, phenyl, bridged cycloalkyl, or heteroaryl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from unsubstituted pyrazinyl, cyano, CHF_2O-, CH_3O-, unsubstituted oxetanyl, imidazolyl substituted with one CF_3-, unsubstituted oxazolyl, Br-, CH_3CF_2-, CHF_2-, CF_3-, CF_3CH_2O-, unsubstituted cyclopropylmethoxyl, unsubstituted cyclobutylmethoxyl, CH_3F_2CO-, CH_3F_2C-, cyanomethoxy, and CF_3CH_2-, R^2 and R^3 are hydrogen, and R^6 is selected from cyclopentyl, phenyl, bicyclo[2.2.1]heptanyl, cyclohexyl, phenyl, dihydrochromenyl, cyclobutyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrazinyl, pyrimidinyl, and pyridinyl, which cyclopentyl, phenyl, bicyclo[2.2.1]heptanyl, cyclohexyl, phenyl, dihydrochromenyl, cyclobutyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from unsubstituted pyrazolyl, cyano, CHF_2O-, CH_3O-, unsubstituted oxetanyl, imidazolyl substituted with one CF_3-, unsubstituted oxazolyl, Br-, CH_3CF_2-, CHF_2-, CF_3-, CF_3CH_2O-, unsubstituted cyclopropylmethoxyl, unsubstituted cyclobutylmethoxyl, CH_3F_2CO-, CH_3F_2C-, cyanomethoxy, and CF_3CH_2-, R^2 and R^3 are hydrogen, and R^6 is selected from cyclopentyl, bicyclo[2.2.1]heptanyl, cyclohexyl, phenyl, dihydrochromenyl, cyclobutyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrazinyl, pyrimidinyl, and pyridinyl, which cyclopentyl, bicyclo[2.2.1]heptanyl, cyclohexyl, phenyl, dihydrochromenyl, cyclobutyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one or two substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxyl.

In one preferred embodiment, the invention provides a compound of formula (I) or solvate or pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is selected from unsubstituted pyrazolyl and CHF_2O-, R^2 and R^3 are hydrogen, and R^6 is selected from cyclobutyl, cyclopentyl,

and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one, two, or three independently selected F-, or CF_3-.

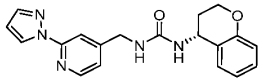
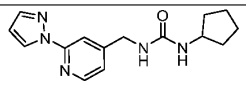
In one preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is unsubstituted pyrazolyl or CF_2HO-, R^2 and R^3 are hydrogen, and R^6 is cyclobutyl, cyclopentyl, or cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one or two F-, or CF_3-.

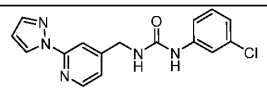
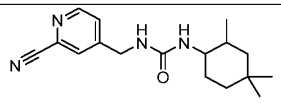
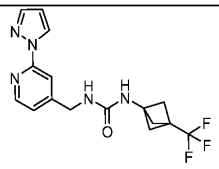
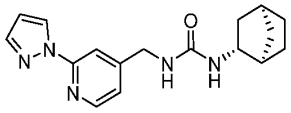
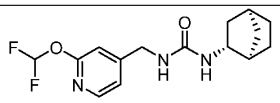
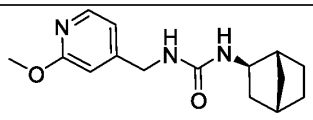
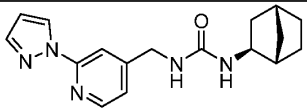
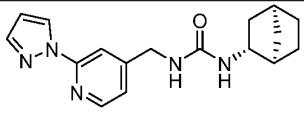
In one particularily preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is CHF_2O-, R^2 and R^3 are hydrogen, and R^6 is unsubstituted cyclobutyl.

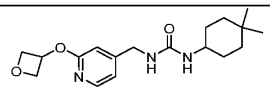
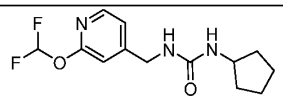
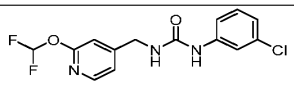
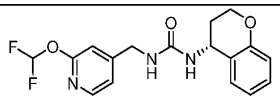
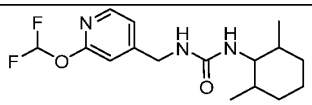
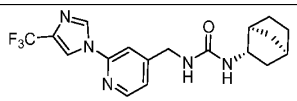
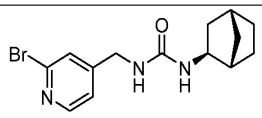
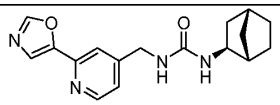
In one particularily preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is CHF_2O-, R^2 and R^3 are hydrogen, and R^6 is cyclobutyl, which cyclobutyl optionally substituted with one, two, or three F- or CF_3-.

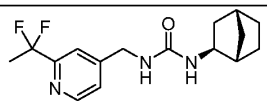
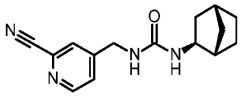
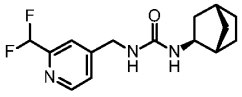
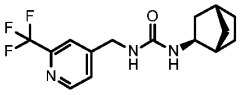
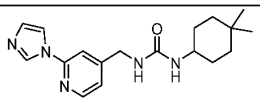
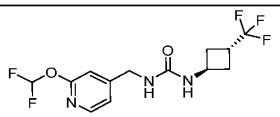
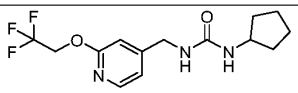
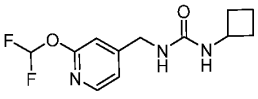
In one particularily preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0, R^1 is CHF_2O-, R^2 and R^3 are hydrogen, and R^6 is cyclobutyl, which cyclobutyl is optionally substituted with one or two F- or CF_3-.

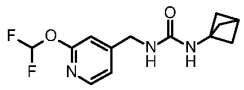
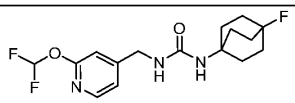
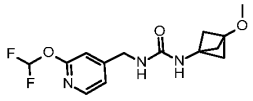
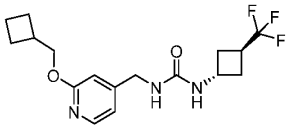
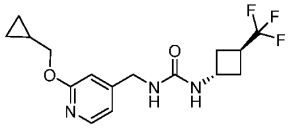
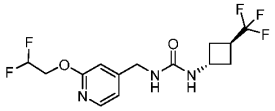
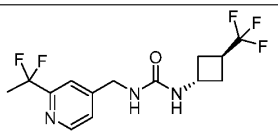
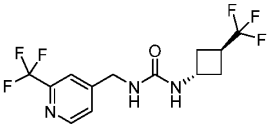
In one preferred embodiment, the invention provides a compound of formula (I), or a solvate wherein n is 0, R^1, R^2, R^3, R^4, R^5 and R^6 are as described herein, and the non-limiting examples are selected from:

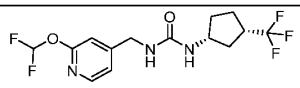
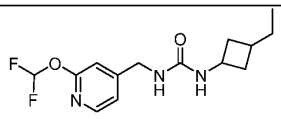
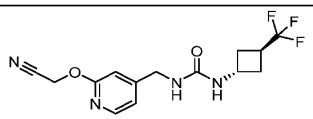
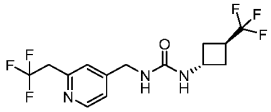
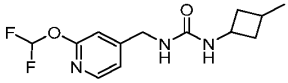
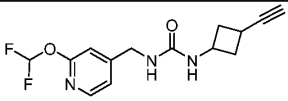
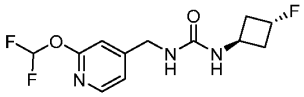
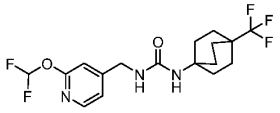
1	1-[(4R)-3,4-dihydro-2H-chromen-4-yl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
2	1-cyclopentyl-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	

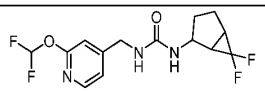
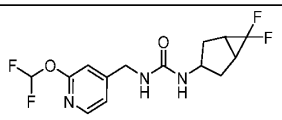
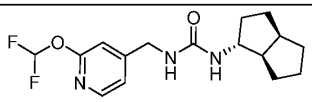
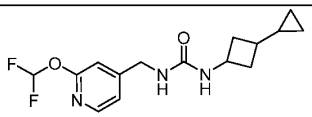
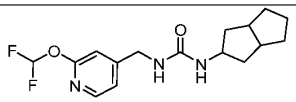
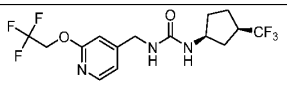
4	1-(3-chlorophenyl)-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
5	1-[(2-cyanopyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	
6	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
7	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
12	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
14	1-[(2-methoxypyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
15	1-[(1S,2S,4R)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
16	1-[(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	

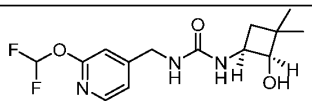
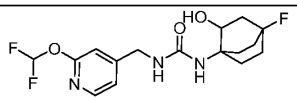
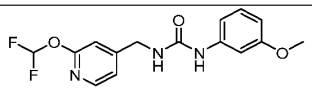
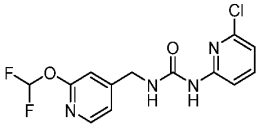
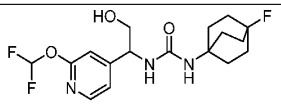
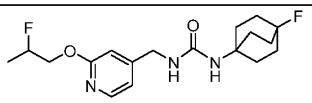
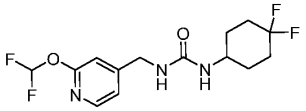
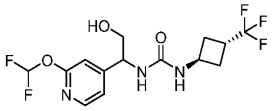
18	1-(4,4-dimethylcyclohexyl)-3-[[2-(oxetan-3-yloxy)pyridin-4-yl]methyl]urea	
20	1-cyclopentyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
22	1-(3-chlorophenyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
23	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(4R)-3,4-dihydro-2H-chromen-4-yl]urea	
25	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,6-dimethylcyclohexyl)urea	
26	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	
27	1-[(2-bromopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
28	1-[[2-(1,3-oxazol-5-yl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	

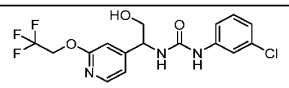
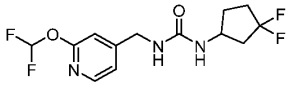
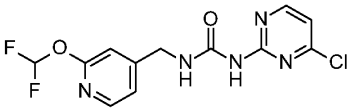
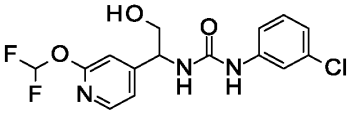
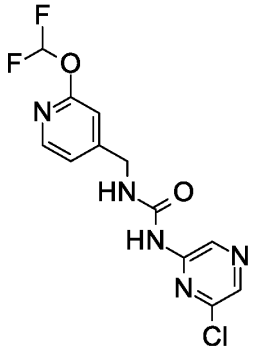
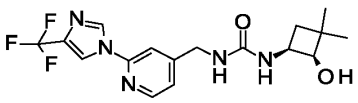
33	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
34	1-[(2-cyanopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
35	1-[[2-(difluoromethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
36	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	
37	1-(4,4-dimethylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea	
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
43	1-cyclopentyl-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
45	1-cyclobutyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

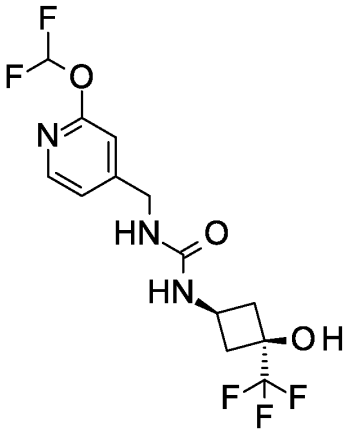
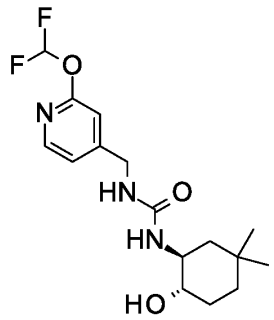
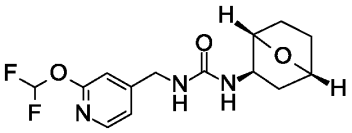
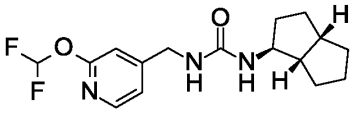
47	1-(1-bicyclo[1.1.1]pentanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
49	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxy-1-bicyclo[1.1.1]pentanyl)urea	
54	1-[[2-(cyclobutylmethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
55	1-[[2-(cyclopropylmethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
56	1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
57	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
58	1-[3-(trifluoromethyl)cyclobutyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	

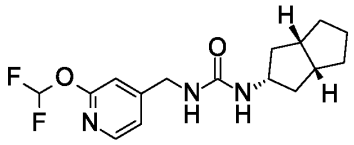
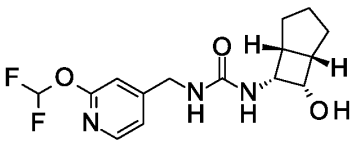
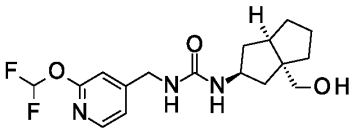
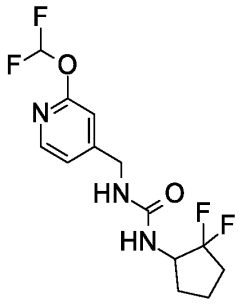
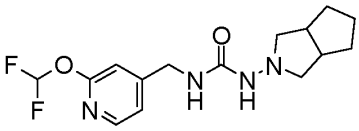
59	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea	
60	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethylcyclobutyl)urea	
63	1-[[2-(cyanomethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
64	1-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
65	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylcyclobutyl)urea	
66	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethynylcyclobutyl)urea	
67	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1*r*,3*r*)-3-fluorocyclobutyl)urea	
68	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[4-(trifluoromethyl)-1-bicyclo[2.2.2]octanyl]urea	

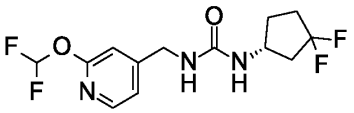
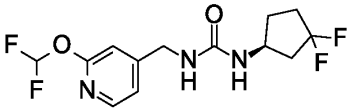
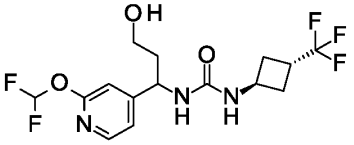
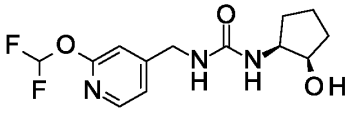
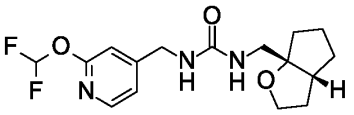
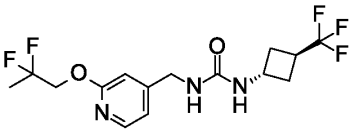
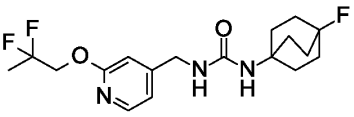
73	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]urea	
74	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
76	1-[(1R,3aR,6aR)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
77	1-(3-cyclopropylcyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
78	1-(1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
79	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

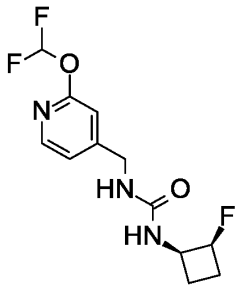
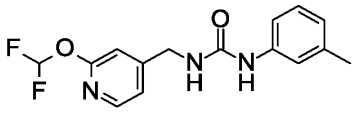
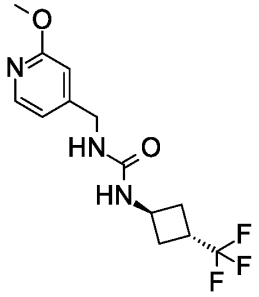
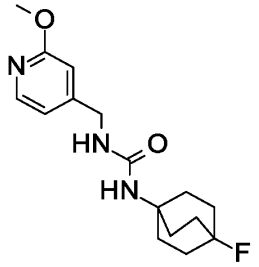
81	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]urea	
82	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-2-hydroxy-1-bicyclo[2.2.2]octanyl)urea	
83	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxyphenyl)urea	
84	1-(6-chloropyridin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
85	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
88	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	
90	1-(4,4-difluorocyclohexyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
91	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	

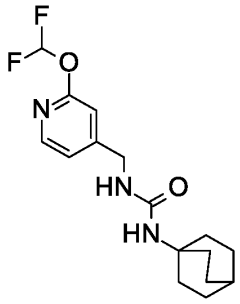
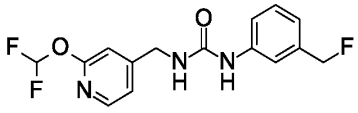
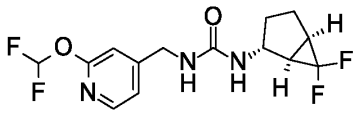
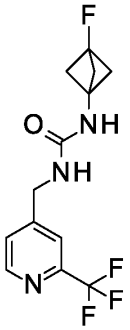
92	1-(3-chlorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
93	1-(3,3-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
96	1-(4-chloropyrimidin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
98	1-(6-chloropyrazin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
99	1-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	

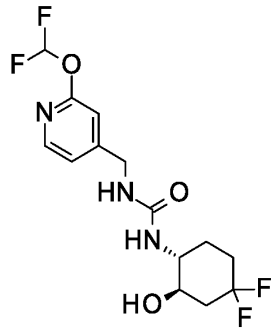
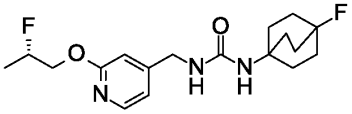
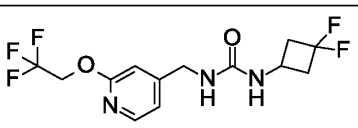
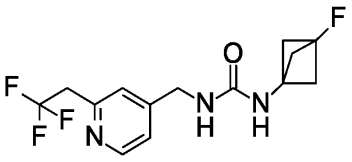
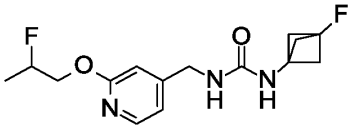
100	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-hydroxy-3-(trifluoromethyl)cyclobutyl]urea	
101	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-5,5-dimethylcyclohexyl]urea	
102	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S)-7-oxabicyclo[2.2.1]heptan-2-yl]urea	
103	1-[(1S,3aS,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

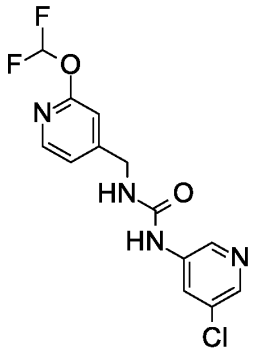
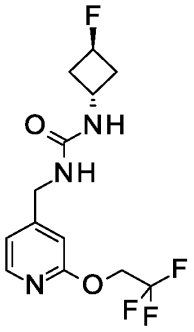
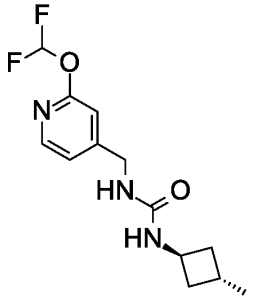
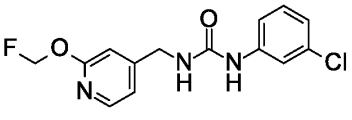
105	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3aR,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]urea	
111	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6S,7R)-7-hydroxy-6-bicyclo[3.2.0]heptanyl]urea	
112	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(2R,3aS,6aS)-6a-(hydroxymethyl)-2,3,3a,4,5,6-hexahydro-1H-pentalen-2-yl]urea	
113	1-(2,2-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
114	1-(3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

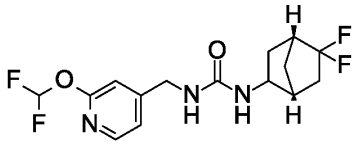
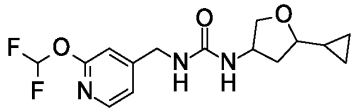
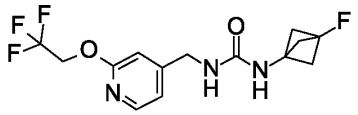
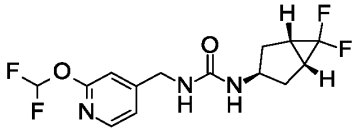
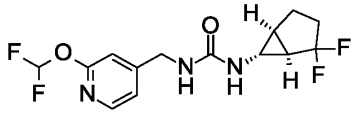
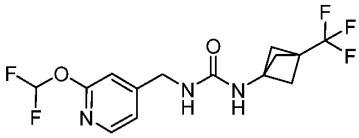
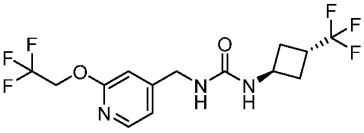
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
117	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-3-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
118	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxycyclopentyl]urea	
120	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[rac-(3aR,6aR)-2,3,3a,4,5,6-hexahydrocyclopenta[b]furan-6a-yl]methyl]urea	
121	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
122	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	

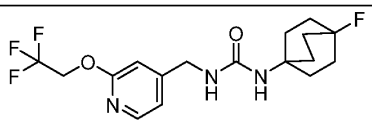
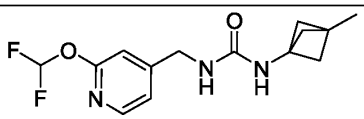
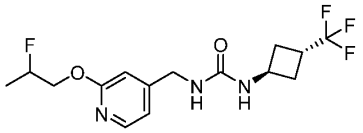
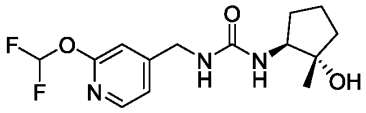
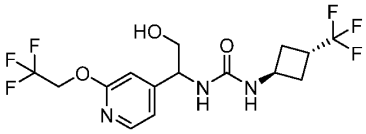
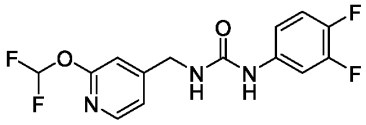
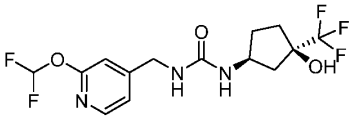
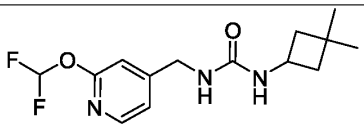
123	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-fluorocyclobutyl]urea	
126	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylphenyl)urea	
128	1-[(2-methoxypyridin-4-yl)methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
129	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[(2-methoxypyridin-4-yl)methyl]urea	

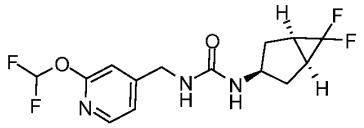
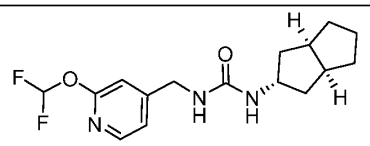
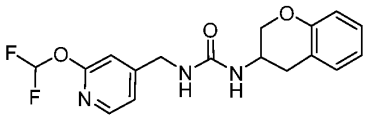
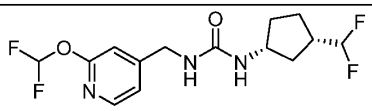
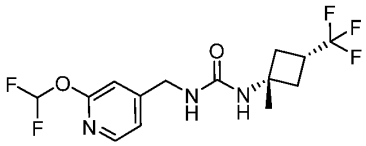
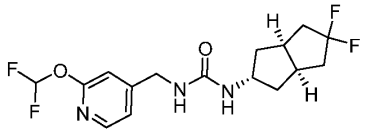
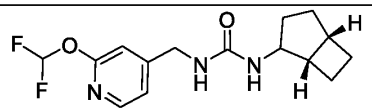
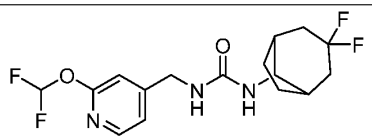
131	1-(1-bicyclo[2.2.2]octanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
132	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(fluoromethyl)phenyl]urea	
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
153	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	

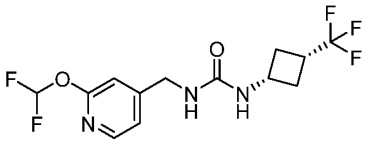
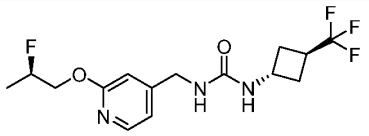
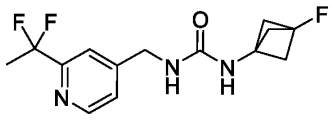
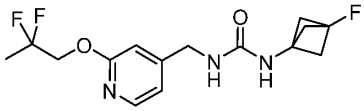
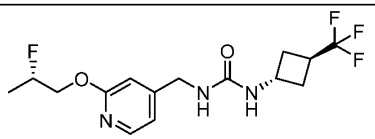
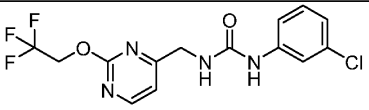
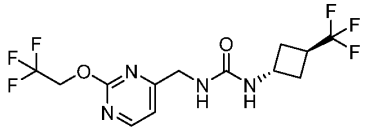
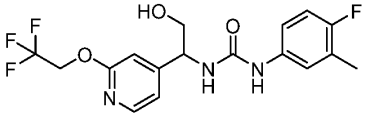
154	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-4,4-difluoro-2-hydroxycyclohexyl]urea	
156	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]urea	
157	1-(3,3-difluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
159	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
160	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	

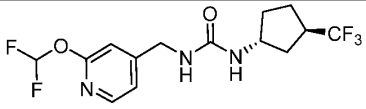
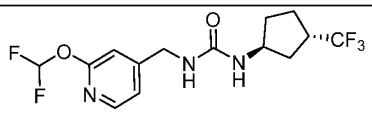
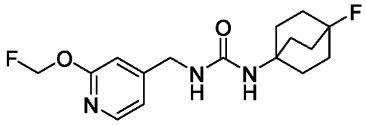
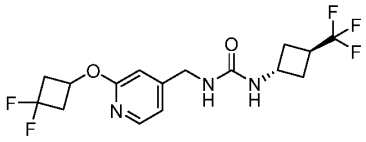
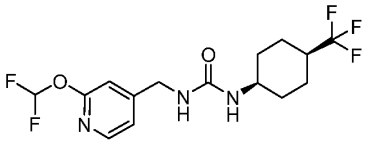
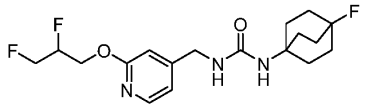
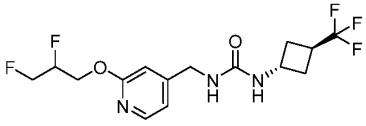
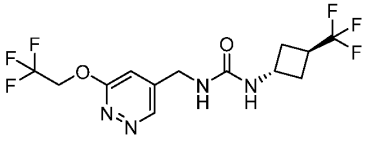
161	1-(5-chloropyridin-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
162	1-((1r,3r)-3-fluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
163	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1r,3r)-3-methylcyclobutyl)urea	
164	1-(3-chlorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	

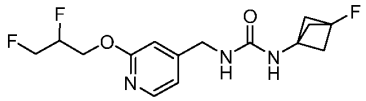
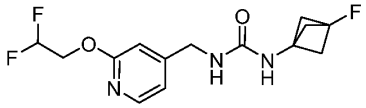
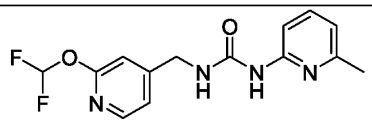
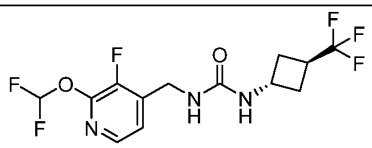
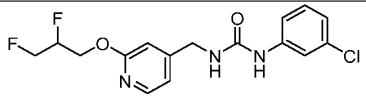
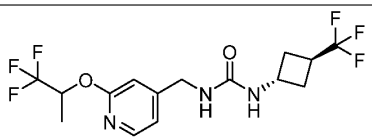
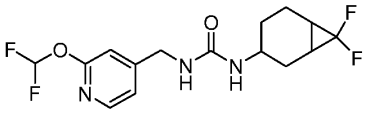
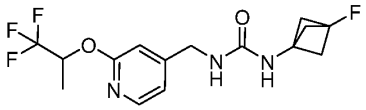
165	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,4R)-5,5-difluoro-2-bicyclo[2.2.1]heptanyl]urea	
166	1-(5-cyclopropyloxolan-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
168	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
169	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
170	1-[(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
178	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
179	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

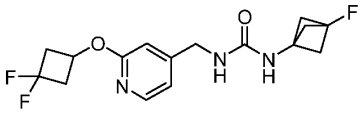
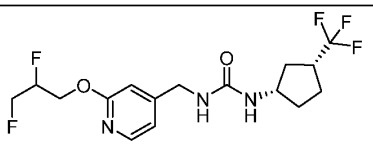
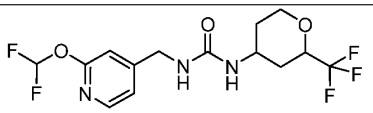
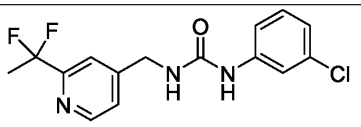
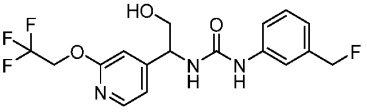
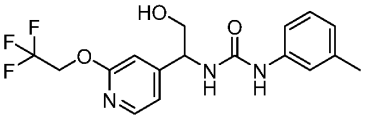
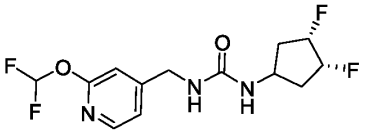
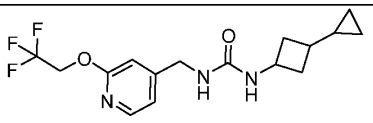
180	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
182	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methyl-1-bicyclo[1.1.1]pentanyl)urea	
183	1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
184	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,2S)-2-hydroxy-2-methylcyclopentyl]urea	
185	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
186	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-difluorophenyl)urea	
187	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-hydroxy-3-(trifluoromethyl)cyclopentyl]urea	
188	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-dimethylcyclobutyl)urea	

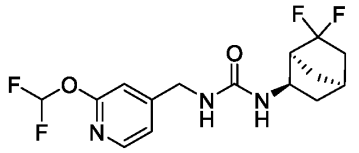
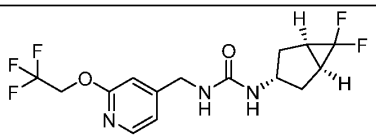
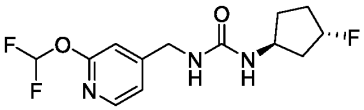
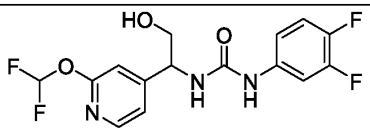
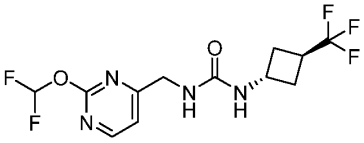
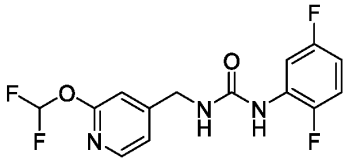
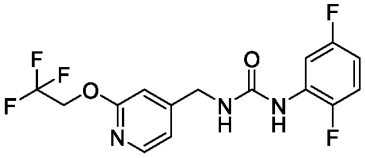
189	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3r,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
190	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2s,3aR,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]urea	
192	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-dihydro-2H-chromen-3-yl)urea	
193	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(difluoromethyl)cyclopentyl]urea	
194	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-1-methyl-3-(trifluoromethyl)cyclobutyl]urea	
195	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2r,3aR,6aS)-5,5-difluoro-2,3,3a,4,6,6a-hexahydro-1H-pentalen-2-yl]urea	
196	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5R)-2-bicyclo[3.2.0]heptanyl]urea	
197	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3,3-difluoro-8-bicyclo[3.2.1]octanyl]urea	

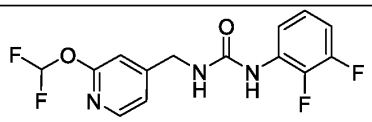
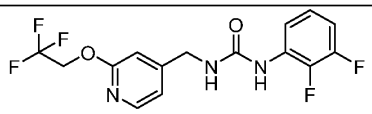
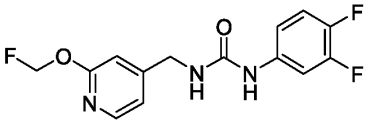
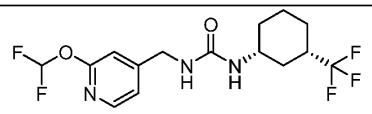
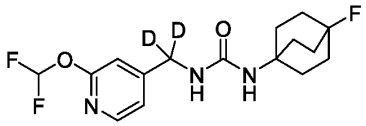
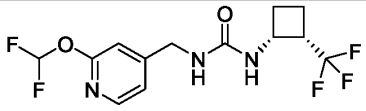
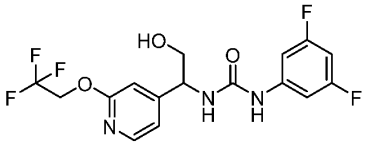
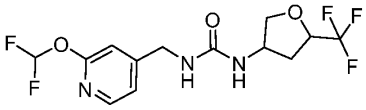
198	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(trifluoromethyl)cyclobutyl]urea	
199	1-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
200	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
201	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
202	1-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
203	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]urea	
204	1-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
205	1-(4-fluoro-3-methylphenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

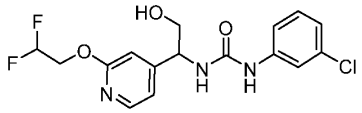
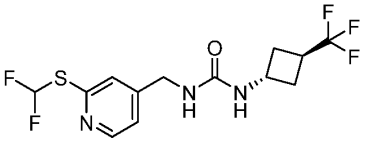
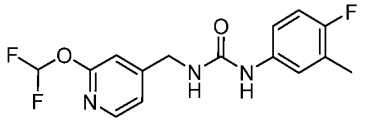
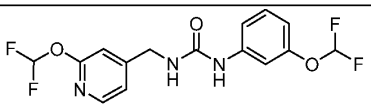
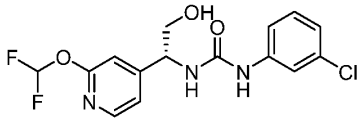
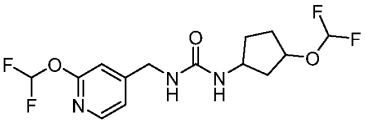
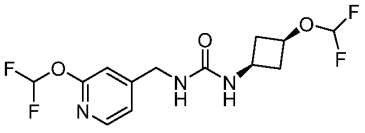
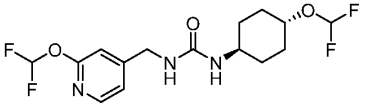
206	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3R)-3-(trifluoromethyl)cyclopentyl]urea	
207	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-(trifluoromethyl)cyclopentyl]urea	
208	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
209	1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
211	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,4s)-4-(trifluoromethyl)cyclohexyl]urea	
213	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
214	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
215	1-[[6-(2,2,2-trifluoroethoxy)pyridazin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

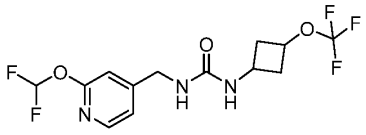
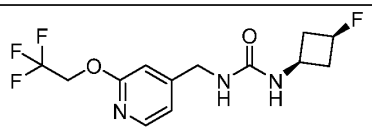
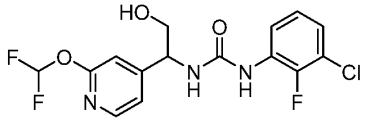
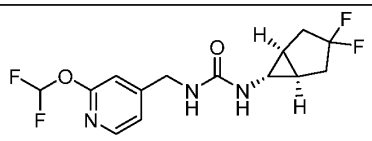
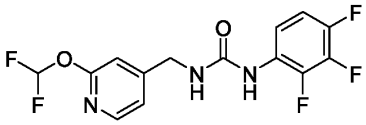
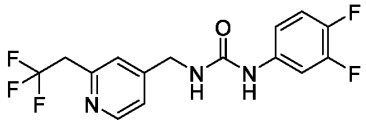
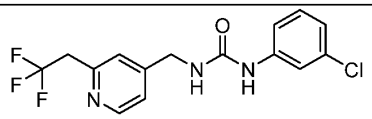
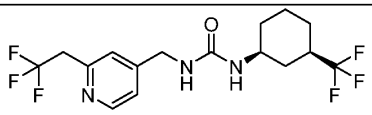
216	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
217	1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
218	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(6-methylpyridin-2-yl)urea	
219	1-[[2-(difluoromethoxy)-3-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
220	1-(3-chlorophenyl)-3-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]urea	
221	1-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(1,1,1-trifluoropropan-2-yloxy)pyridin-4-yl]methyl]urea	
222	1-(7,7-difluoro-3-bicyclo[4.1.0]heptanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
223	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(1,1,1-trifluoropropan-2-yloxy)pyridin-4-yl]methyl]urea	

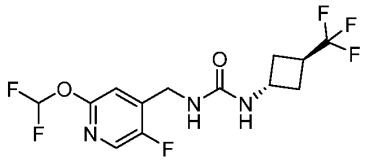
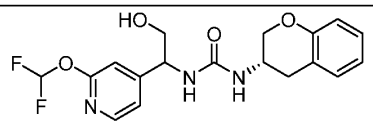
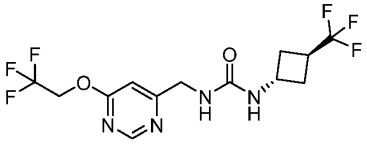
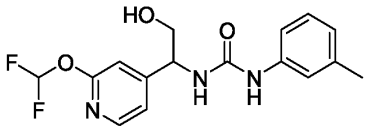
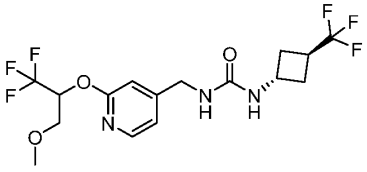
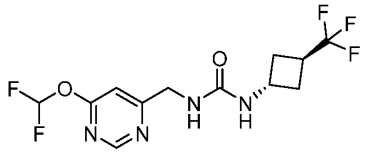
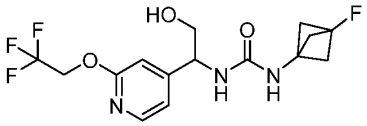
224	1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
225	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea	
226	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(trifluoromethyl)oxan-4-yl]urea	
231	1-(3-chlorophenyl)-3-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]urea	
232	1-[3-(fluoromethyl)phenyl]-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
233	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-(3-methylphenyl)urea	
234	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(3R,4S)-3,4-difluorocyclopentyl]urea	
235	1-(3-cyclopropylcyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

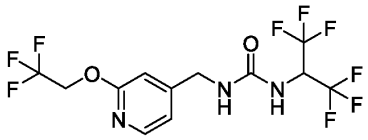
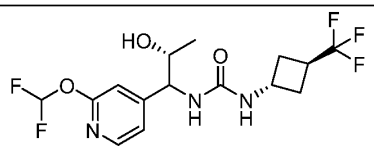
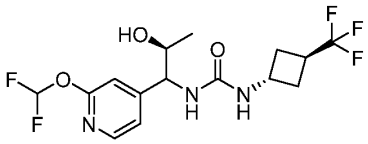
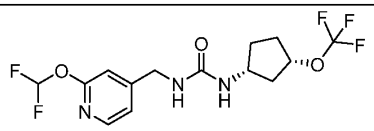
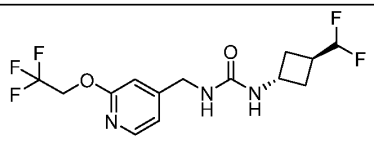
236	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S)-6,6-difluoro-2-bicyclo[2.2.1]heptanyl]urea	
238	1-[(1R,3s,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
239	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-fluorocyclopentyl]urea	
240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
243	1-[[2-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
244	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,5-difluorophenyl)urea	
245	1-(2,5-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

247	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3-difluorophenyl)urea	
248	1-(2,3-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
249	1-(3,4-difluorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
250	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	
251	1-[dideuterio-[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
255	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-(trifluoromethyl)cyclobutyl]urea	
256	1-(3,5-difluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
258	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[5-(trifluoromethyl)oxolan-3-yl]urea	

259	1-(3-chlorophenyl)-3-[1-[2-(2,2-difluoroethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
260	1-[[2-(difluoromethylsulfanyl)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
261	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-3-methylphenyl)urea	
262	1-[3-(difluoromethoxy)phenyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
263	rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
264	1-[3-(difluoromethoxy)cyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
265	1-[(1s,3s)-3-(difluoromethoxy)cyclobutyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
266	1-[(1r,4r)-4-(difluoromethoxy)cyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

267	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethoxy)cyclobutyl]urea	
269	1-((1s,3s)-3-fluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
270	1-(3-chloro-2-fluorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
271	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-3,3-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
272	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3,4-trifluorophenyl)urea	
274	1-(3,4-difluorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
275	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
276	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	

277	1-[[2-(difluoromethoxy)-5-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
27g8	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(3S)-3,4-dihydro-2H-chromen-3-yl]urea	
279	1-[[6-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea	
281	1-[[*2-(1,1,1-trifluoro-3-methoxypropan-2-yl)*oxypyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
282	1-[[6-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
283	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

285	1-(1,1,1,3,3,3-hexafluoropropan-2-yl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
286	1-[(2R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
287	1-[(2S)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
288	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethoxy)cyclopentyl]urea	
293	1-[(1r,3r)-3-(difluoromethyl)cyclobutyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

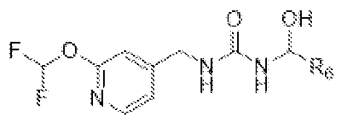
In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, a saturated monocyclic 3-5 membered cycloalkyl, hydroxyC_{1-6}alkyl, and hydroxy; or R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl.

In the specified embodiments, "saturated monocyclic 3-5 membered cycloalkyl formed" means an unsubstituted cycloalkyl or a cycloalkyl which is substituted as described herein. In particular, the cycloalkyl is unsubstitued.

The aforementioned embodiment can be combined with any embodiment in this application as described herein.

If n is 2 or 3, there can different pairs of R^4 and R^5. For example if n is 2, the are two pairs of R^4 and R^5. If n is 3, there are three pairs of R^4 and R^5. The respective pairs can be identical or different. E.g. if n is 2, the first pair of R^4 and R^5 can be both hydrogen, while in the second pair one of R^4 and R^5 is hydrogen and the other one is hydroxyC_{1-6}alkyl or a saturated monocyclic cycloalkyl.

If n is 1, R^4 or R^5 are not hydroxy. For example, if n is 1, the compound cannot be:



, or a similar compound of formula (I) with different R^1, R^2 and R^3.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2, and R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic cycloalkyl, and hydroxyC_{1-6}alkyl; or R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically a acceptable salt thereof, wherein n is 1 or 2, and R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and hydroxyC_{1-6}alkyl, wherein the cycloalkyl is optionally substituted as described herein.

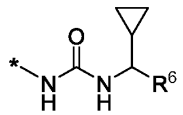
In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2, and one of R^4 or R^5 is hydrogen and the other one is a satuared monocyclic 3-5 membered cycloalkyl which is selected from cyclopropyl, cyclobutyl or cyclopentyl, which cycloalkyl is optionally substituted with one, two,

or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 2 and in the first pair of R^4 and R^5 both are hydrogen and in the second pair of R^4 and R^5 one is hydrogen and the other one is a saturated monocyclic 3-5 membered cycloalkyl, which is selected from cyclopropyl, cyclobutyl or cyclopentyl, and which cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, , the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 2 and in the first pair of R^4 and R^5 both are hydrogen and in the second pair of R^4 and R^5 one is hydrogen and the other one is selected from unsubstituted cyclopropyl, cyclobutyl, or cyclopentyl.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1 and one of R^4 or R^5 is a saturated monocyclic 3-5 membered cycloalkyl, this cycloalkyl is attached to the compound as shown in the following structure:



In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are both hydrogen, n is 1, one of R^4 and R^5 is hydrogen and the other is a saturated 3-5 membered cycloalkyl, which cycloalkyl is selected from unsubsituted cyclopropyl, cyclobutyl or cyclopentyl and R^6 is as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^2 and R^3 are both hydrogen, n is 1, one of R^4 and R^5 is hydrogen and the other is a saturated 3-5 membered cycloalkyl, which cycloalkyl is

selected from unsubsituted cyclopropyl, cyclobutyl or cyclopentyl and R^6 is selected from a saturated monocyclic cycloalkyl, and haloC_{1-6}alkyl, which cylcoalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, hydroxy, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3 are both hydrogen, n is 1, one of R^4 and R^5 is hydrogen and the other is a saturated 3-5 membered cycloalkyl, which cycloalkyl is selected from unsubsituted cyclopropyl, cyclobutyl or cyclopentyl and R^6 is a saturated monocyclic cycloalkyl, which cycloalkyl is selected from unsubstituted cyclopropyl, cyclobutyl, and cyclopentyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3 are both hydrogen, n is 1, one of R^4 and R^5 is hydrogen and the other is a saturated 3-5 membered cycloalkyl, which cycloalkyl is selected from unsubsituted cyclopropyl and unsubstituted cyclobutyl, and R^6 is a saturated monocyclic cycloalkyl, which cycloalkyl is selected from unsubsituted cyclopropyl, cyclobutyl. and cyclopentyl.

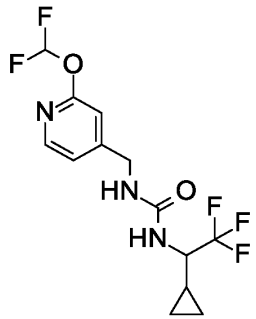
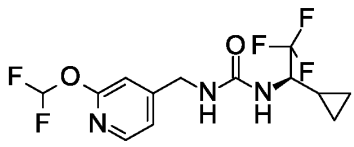
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3 are both hydrogen, n is 1, one of R^4 and R^5 is hydrogen and the other is a saturated 3-5 membered cycloalkyl, which cycloalkyl is selected from cyclopropyl, cyclobutyl, and cyclopentyl which are unsubstituted, and R^6 is haloC_{1-6}alkyl selected from $(CH_3)_2FC$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

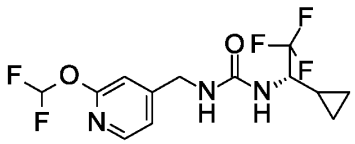
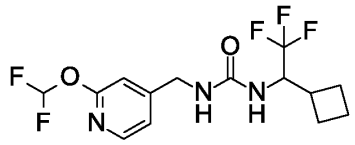
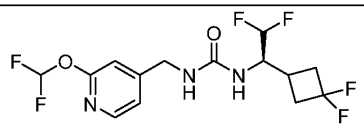
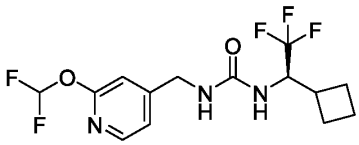
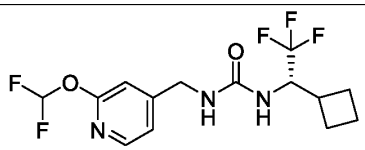
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3 are both hydrogen, n is 1, one of R^4 and R^5 is hydrogen and the other is a saturated 3-5 membered cycloalkyl, which cycloalkyl is selected from unsubsituted cyclopropyl, and cyclobutyl which are unsubstituted, and R^6 is haloC_{1-6}alkyl selected from $(CH_3)_2FC$-, CF_3CH_2-, CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

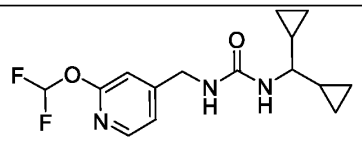
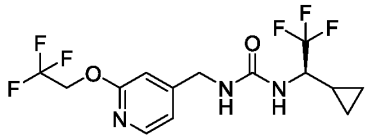
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3 are both hydrogen and R^3 is cyclopropyl as described above, n is 1, one of R^4 and R^5 is hydrogen and the other is a saturated 3-5 membered cycloalkyl, which cycloalkyl is selected from cyclopropyl, cyclobutyl, and cyclopentyl which are unsubstituted, and R^6 is CF_3- as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^2 and R^3 are both hydrogen, n is 1, one of R^4 and R^5 is hydrogen and the other is a saturated 3-5 membered cycloalkyl, which cycloalkyl is selected from cyclopropyl, cyclobutyl, cyclopentyl which are unsubstituted, and R^6 is CF_3- as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^1, R^2, n and R^6 are as described herein, and one of R^4 and R^5 is hydrogen and the other is a saturated monocylic cycloalkyl, and non-limiting exampes are selected from:

106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

135	1-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
152	1-(1-cyclobutyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
230	1-[(1R)-1-(3,3-difluorocyclobutyl)-2,2-difluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
241	1-[(1R)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
242	1-[(1S)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

253	1-(dicyclopropylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1 and R^4 or R^5 are both hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 2 and R^4 or R^5 are both hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^4 or R^5 are both hydrogen, and R^1, R^2, R^3 and R^6 are as described herein.

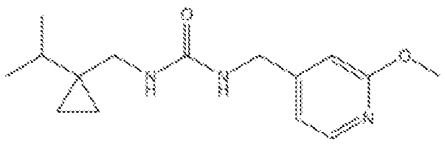
In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, R^4 or R^5 are all hydrogen, and R^1, R^2, R^3 and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 2, the individual pairs of R^4 or R^5, and R^1, R^2, R^3 and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl.

In the specified embodiments, "saturated monocyclic 3-5 membered cycloalkyl formed" means an unsubstituted cycloalkyl or a cycloalkyl which is substituted as described herein. In particular, the cycloalkyl is unsubstitued.

In some embodiments, wherein R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, the compound of formula (I) is not:



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In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2, R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl, R^2 and R^3 are hydrogen, and R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2, R^1 is selected from is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl, R^2 and R^3 are hydrogen, and R^4 and R^5,

together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate, or a pharmaceutically acceptable salt thereof, wherein, n is 1 or 2 and R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl with the structure:

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2, R^1 is selected from is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl, R^2 and R^3 are hydrogen, and R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl with the structure:

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2, R^1 is selected from is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl, R^2 and R^3 are hydrogen, and R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl with the structure:

and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, hydroxy, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1 or 2, R^1 is selected from R^1 is selected from is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl, R^2 and R^3 are hydrogen, and R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl with the structure:

and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, hydroxy, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are

optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl, R^2 and R^3 are hydrogen, and R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl with the structure:

and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl, R^2 and R^3 are hydrogen, and R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl with the structure:

and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from is selected from a 4-

6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl, R^2 and R^3 are hydrogen, and R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl with the structure:

and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three F- or CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl, R^2 and R^3 are hydrogen, and R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl with the structure:

and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one or two CF_3-.

In one embodiment, the present invention provides a compound of formula (I), or solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, R^1 is selected from is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl, R^2 and R^3 are hydrogen, and R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl with the structure:

and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, C_{1-6}alkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one or two F-

In some of the embodiments when n is 2, one pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl and the other pair of R^4 and R^5 are selected from hydrogen, C_{1-6}alkyl and hydroxy.

In some of the embodiments when n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl and in the other pair of R^4 and R^5 both are hydrogen.

In some of the embodiments, wherein n is 2, the first pair of pair of R^4 and R^5, together with the one carbon atom to which they are attached, form cycloalkyl as described herein, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, C_{1-6}alkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one or two F-.

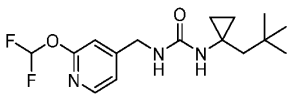
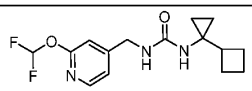
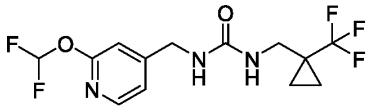
In some of the embodiments when n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl and in the

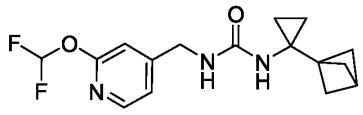
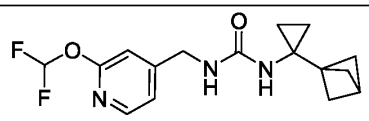
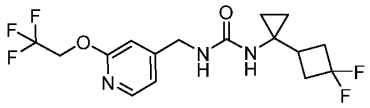
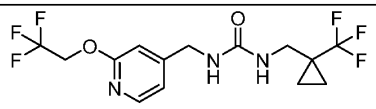
other pair of R^4 and R^5 both are hydrogen, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, C_{1-6}alkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one or two F-.

In some of the embodiments, wherein n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form cycloalkyl as described herein, R^6 is C_{1-6}alkyl as described herein.

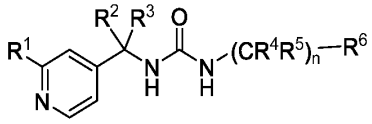
In so-me of the embodiments, wherein n is 2, the first pair of R^4 and R^5, together with the one carbon atom to which they are attached, form cycloalkyl as described herein, R^6 is CH_3- or tert-butyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein, R^1, R^2, n and R^6 are as described herein, and R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl, and non-limiting exampes are selected from:

44	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2-dimethylpropyl)cyclopropyl]urea	
50	1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
229	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	

246	1-[1-(1-bicyclo[1.1.1]pentanyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
246	1-[1-(1-bicyclo[1.1.1]pentanyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
254	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
284	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	

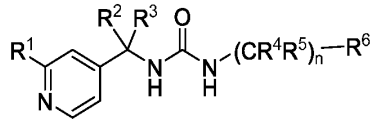
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof



(I)

wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, or haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl

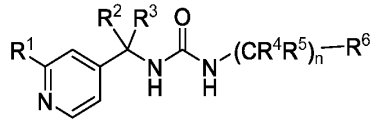
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof



(I)

wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, or haloC_{1-6}alkyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof



(I)

wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from;

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

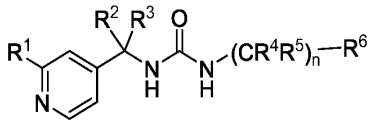
c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl; and

e) haloC_{1-6}alkyl;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, bicyclic edge-to-edge fused cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof



(I)

wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from;

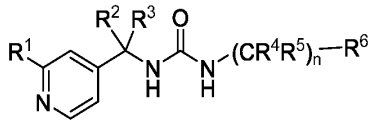
a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

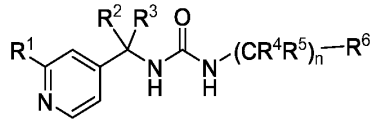
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof



(I)

wherein wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, CF_3-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

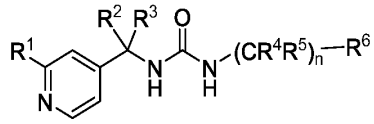
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof



(I)

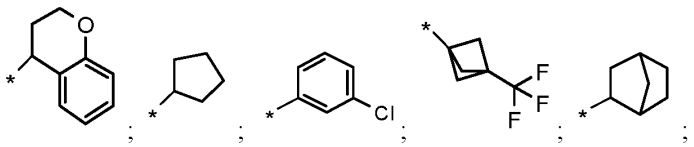
wherein wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

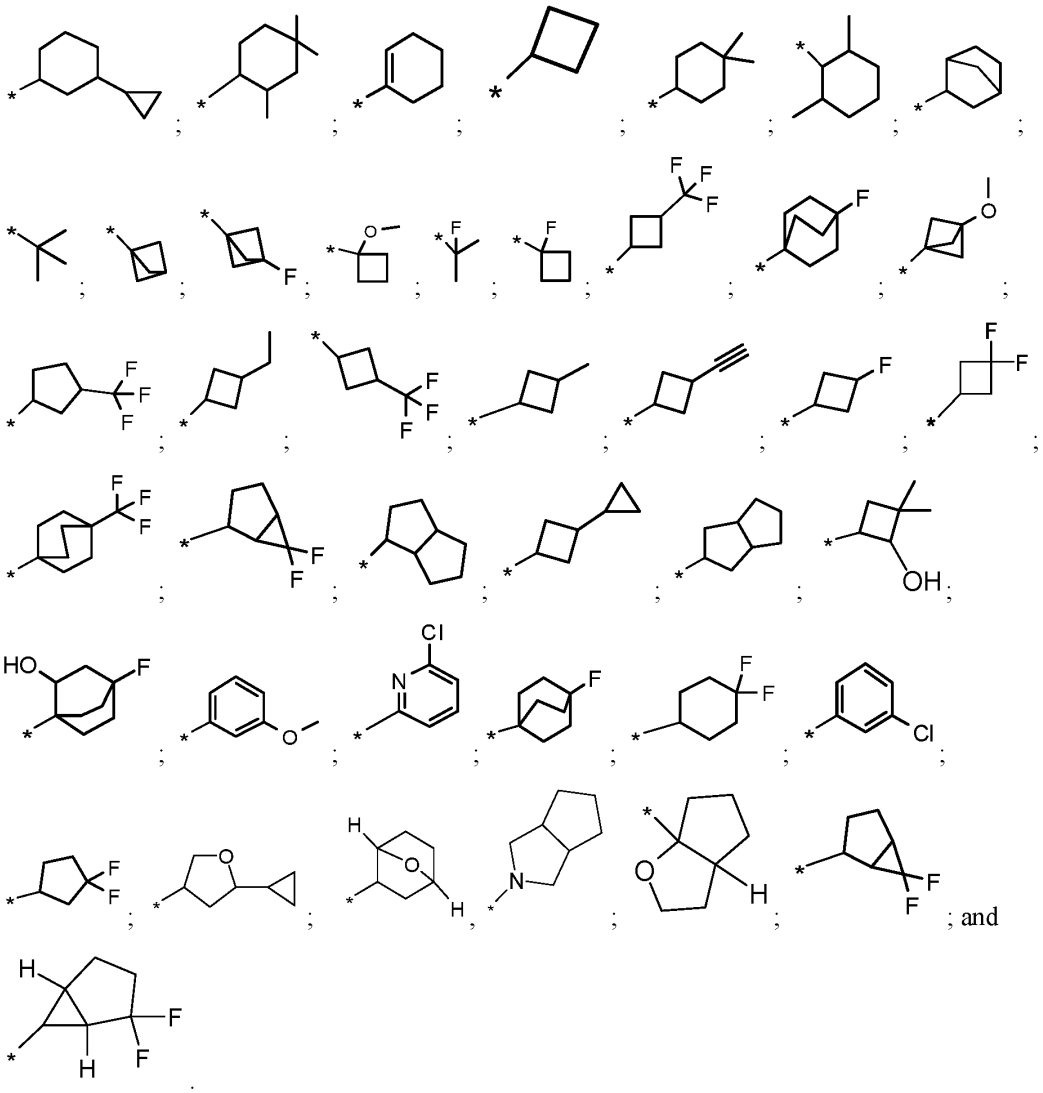
In one preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof



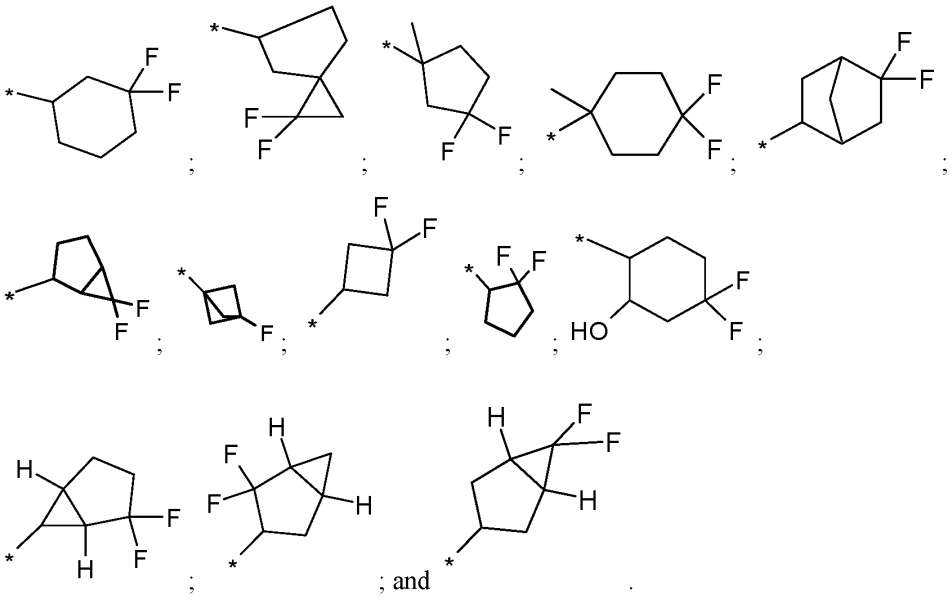
(I)

wherein wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from:



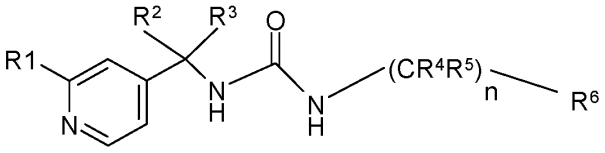


In some particularily preferred embodiments R^6 is selected from:



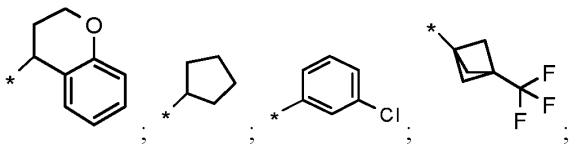
In the above embodiments of R^6, all stereoisomeric, diastereomeric and enantiomeric structures are incorporated.

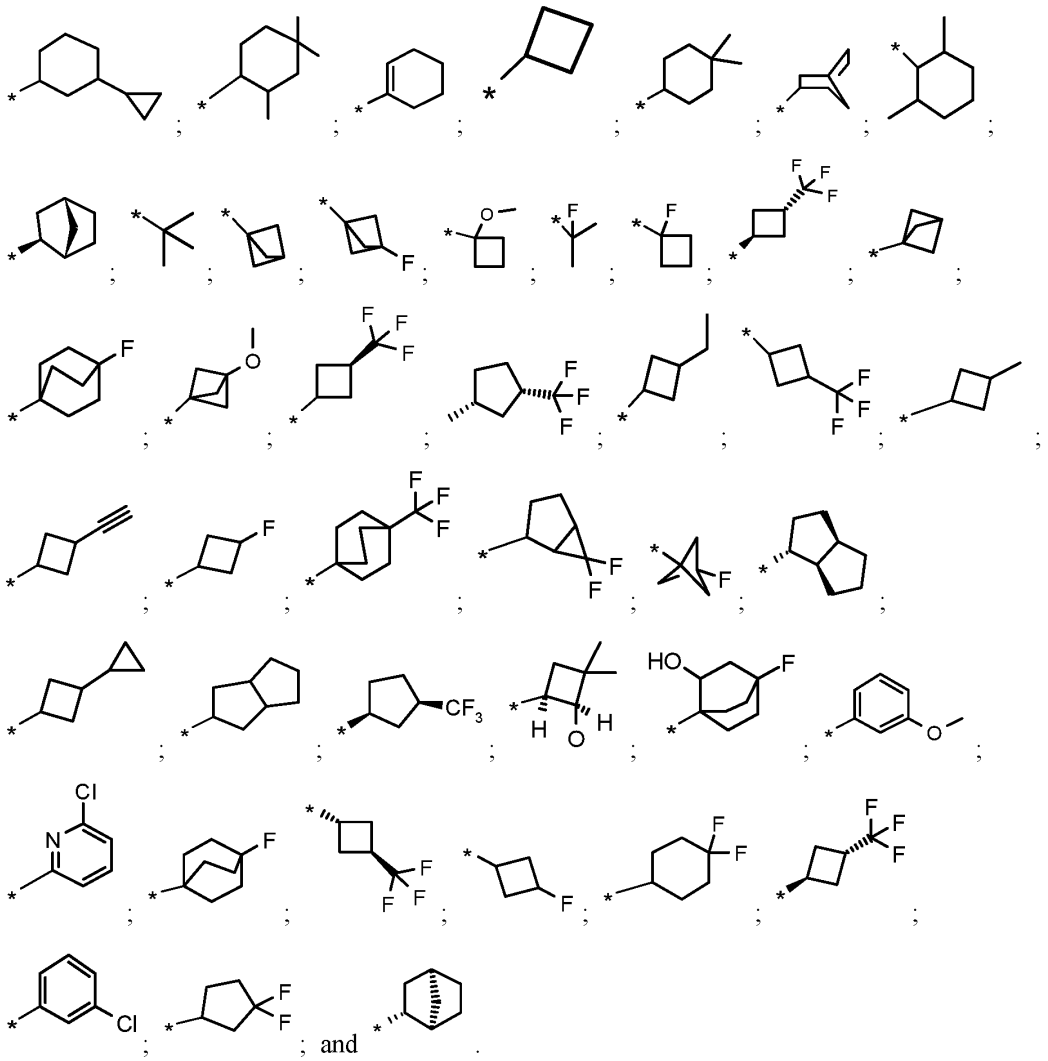
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof



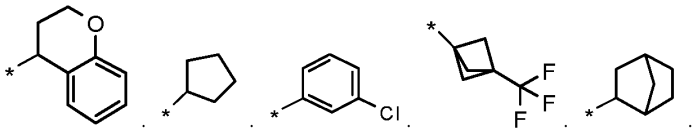
(I)

wherein wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from

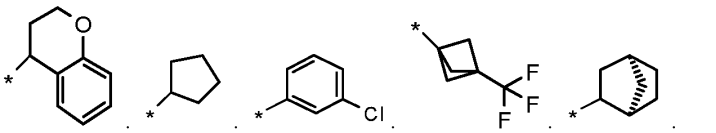




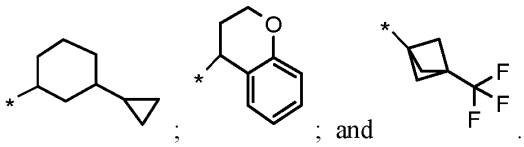
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein and R^6 is selected from:


; and .

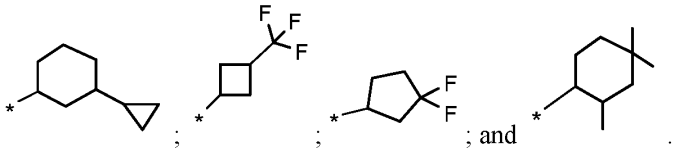
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from:


and .

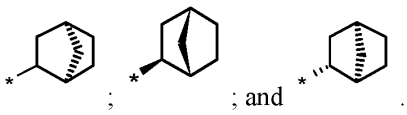
In one preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from:


; and .

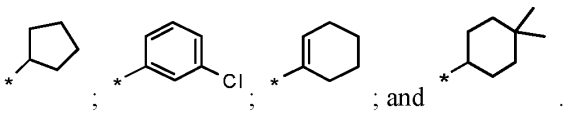
In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from:



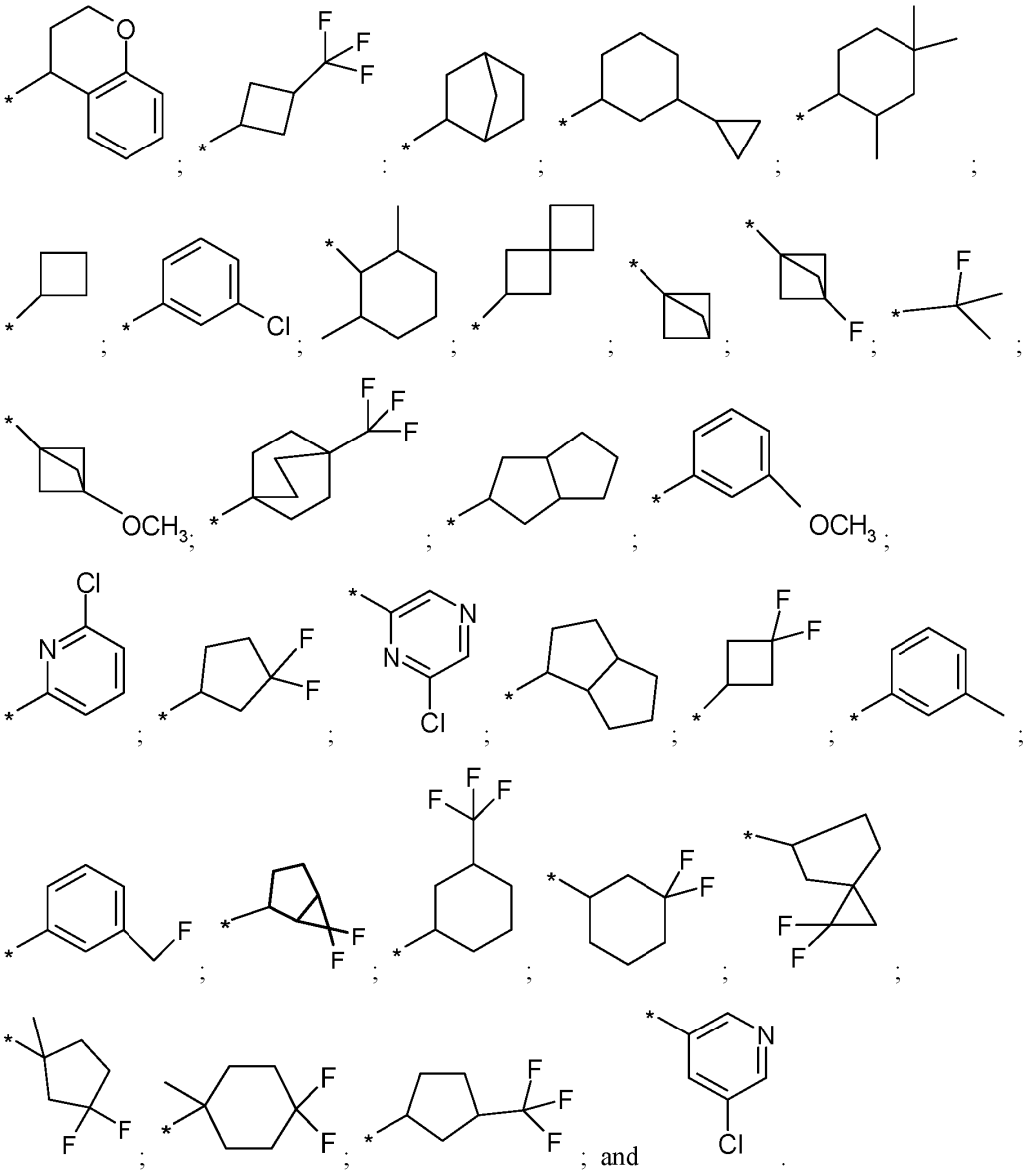
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from:



In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is selected from:

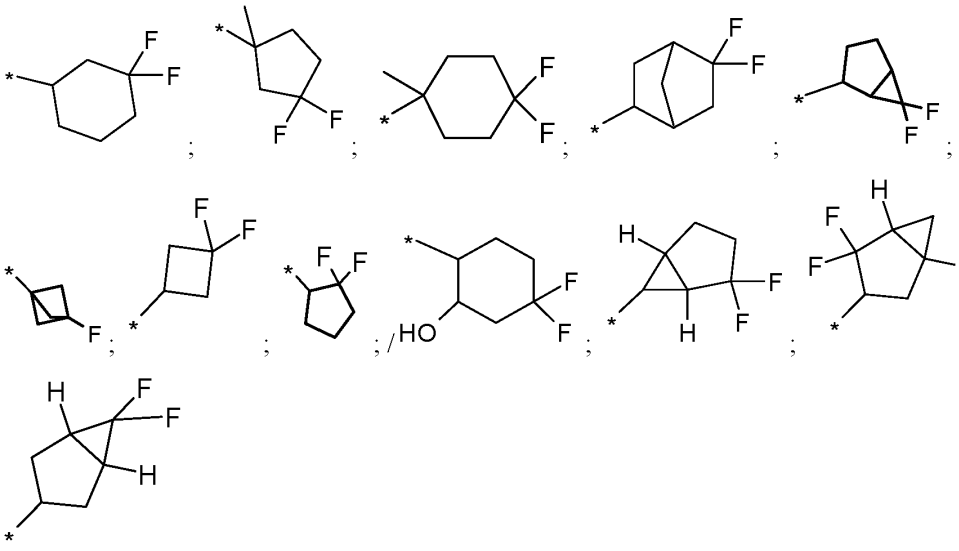


In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, wherein R^6 is selected from a 5-12 membered heterocycloalkyl, 6 membered heteroaryl, 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl having the structures:



In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, wherein R^6 is selected from a 5-12 membered heterocycloalkyl, 6 membered heteroaryl, 4-

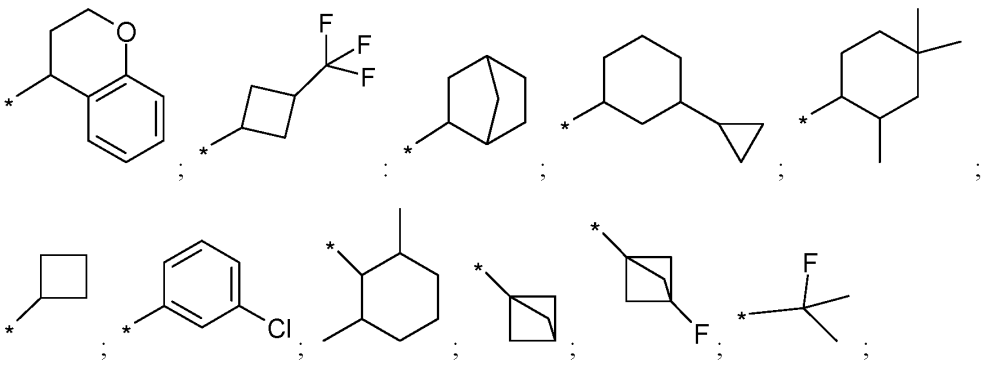
10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl having the structures:

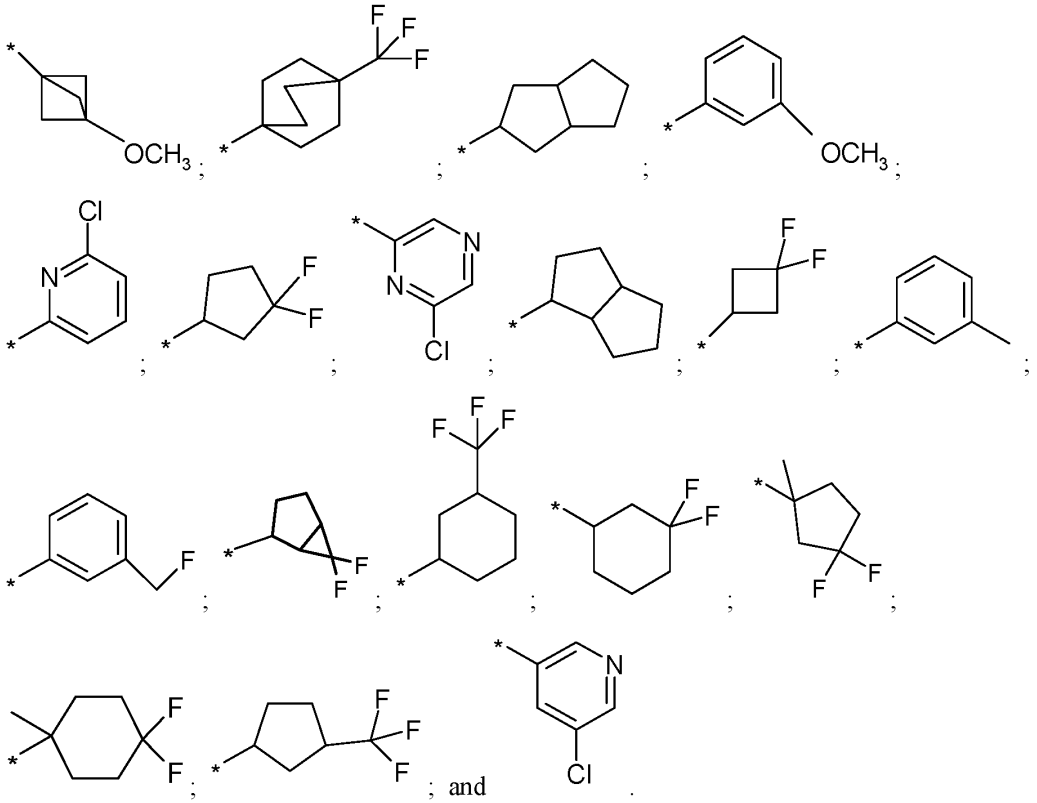


; and

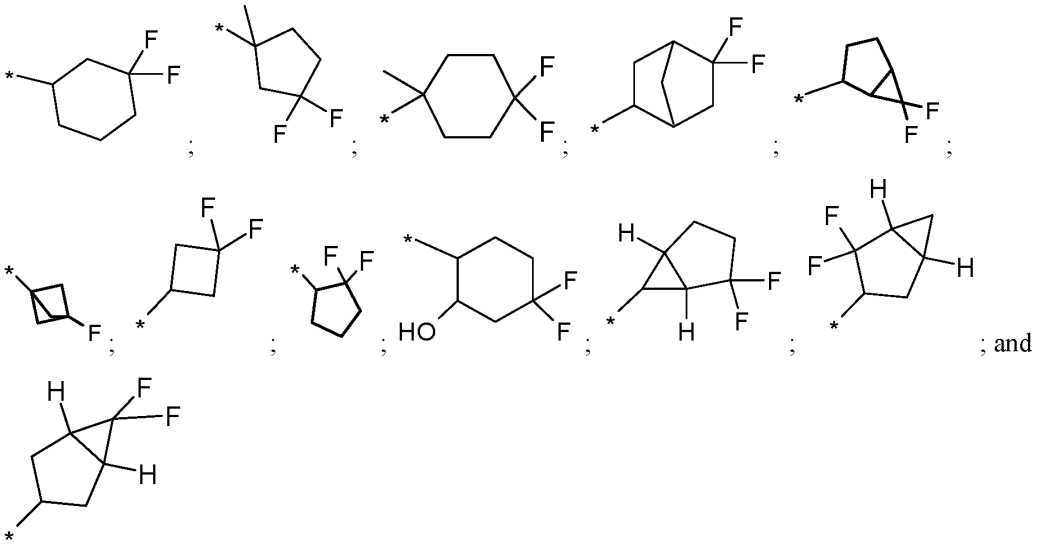
.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, wherein R^6 is selected from a 5-12 membered heterocycloalkyl, 6 membered heteroaryl, 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl having the structures:

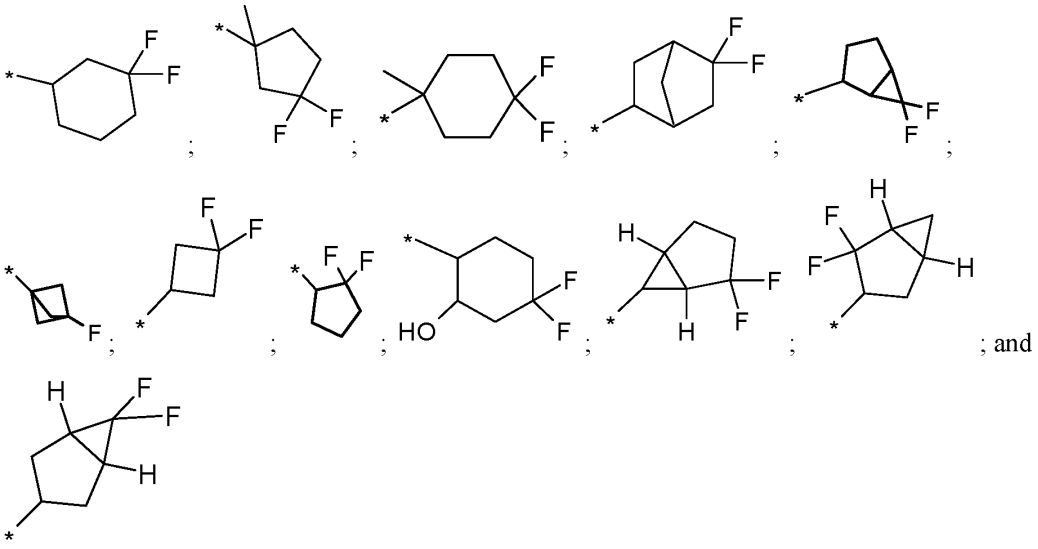




In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, wherein R^6 is selected from a 5-12 membered heterocycloalkyl, 6 membered heteroaryl, 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl having the structures:



In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, wherein R^6 is selected from a 5-12 membered heterocycloalkyl, 6 membered heteroaryl, 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl having the structures:



In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 4-10 membered cycloalkyl which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 4-10 membered cycloalkyl which is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, ethyl, $(CH_3)_2CF$-, CF_3-, CH_3O-, tert-butyl, CN-, cyclopropyl, and hydroxyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, which saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three

substituents independently selected from Cl-, F-, CH_3-, ethyl, $(CH_3)_2CF$-, CF_3-, CH_3O-, tert-butyl, CN-, cyclopropyl, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a saturated monocyclic 4-6 membered cycloalkyl optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, ethyl, $(CH_3)_2CF$-, CHF_2-, CF_3-. CH_3O-, tert-butyl, CN-, cyclopropyl, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, ethyl, $(CH_3)_2CF$-, CHF_2-, CF_3-, CH_3O-, tert-butyl, CN-, cyclopropyl, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one hydroxy and one or two substituents independently selected from F-, CH_3-, and CF_3-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one $C_{1\text{-}6}$alkyl and one or two substituents independently selected from F-, CH_3-, and CF_3-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one, two, or three substituents independently selected from F-, cyclopropyl, and CF_3-.

In one preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl, or cyclohexyl are optionally substituted with one or two substituents independently selected from F-, cyclopropyl, and CF_3-.

In one preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is cyclobutyl which is optionally substituted with one or two substituents independently selected from F-, cyclopropyl, and CF_3-.

In one particularily preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is cyclopentyl which is optionally substituted with one or two substituents independently selected from F-, cyclopropyl, and CF_3-.

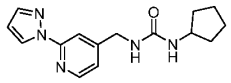
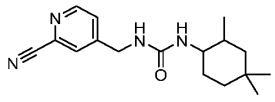
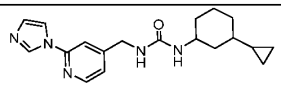
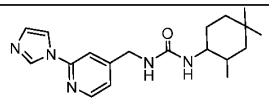
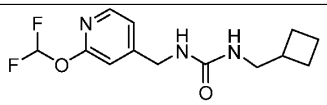
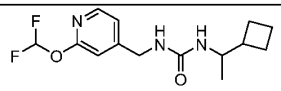
In one particularily preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is cyclohexyl which is optionally substituted with one or two substituents independently selected from F-, cyclopropyl, and CF_3-.

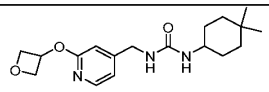
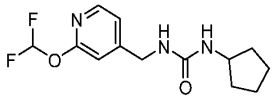
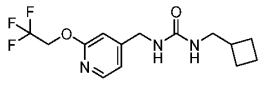
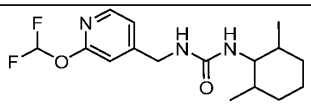
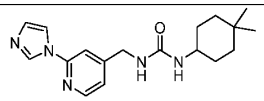
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a saturated monocyclic 4-6 membered cycloalkyl selected from unsubstituted cyclobutyl, unsubstituted cyclopentyl, and unsubstituted cyclohexyl.

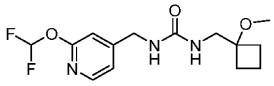
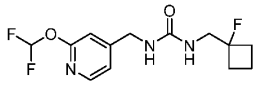
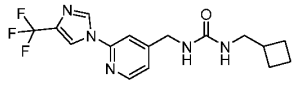
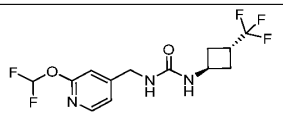
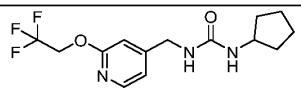
In all of the herein embodiments of R^6 as a saturated monocyclic 4-6 membered cycloalkyl, R^1, R^2, R^3, R^4, R^5 and n are as described herein, i.e. including any combination of R^1, R^2, R^3, R^4, R^5 and n as described herein.

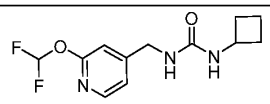
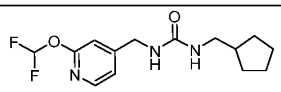
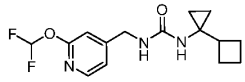
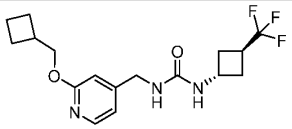
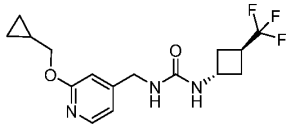
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a saturated monocyclic 4-6 membered

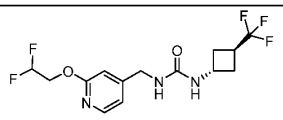
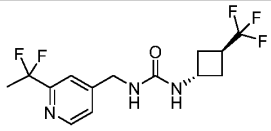
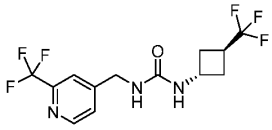
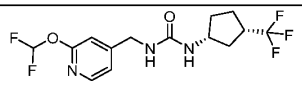
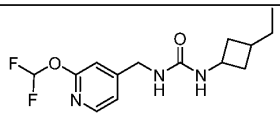
cycloalkyl, R^1, R^2, R^3, R^4, R^5 and n are as described herein, and the non-limiting examples are selected from:

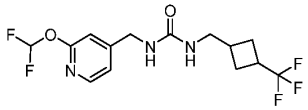
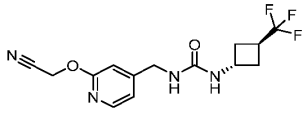
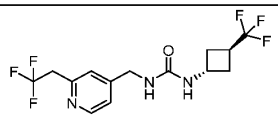
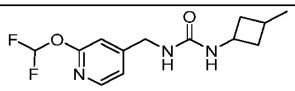
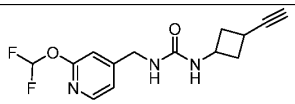
2	1-cyclopentyl-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
5	1-[(2-cyanopyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	
8	1-(3-cyclopropylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea	
9	1-[(2-imidazol-1-ylpyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	
13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
17	1-(1-cyclobutylethyl)-3-[[2-	

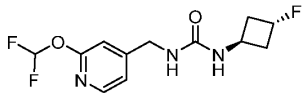
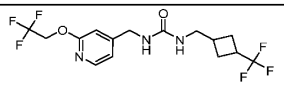
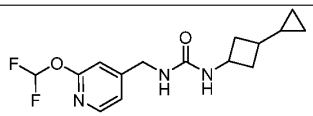
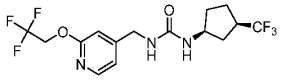
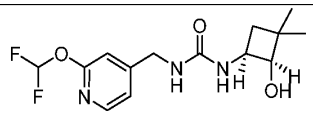
	(difluoromethoxy)pyridin-4-yl]methyl]urea	
18	1-(4,4-dimethylcyclohexyl)-3-[[2-(oxetan-3-yloxy)pyridin-4-yl]methyl]urea	
20	1-cyclopentyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
21	1-(cyclobutylmethyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
25	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,6-dimethylcyclohexyl)urea	
37	1-(4,4-dimethylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea	

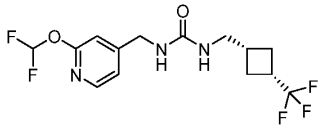
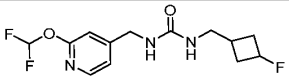
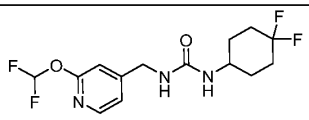
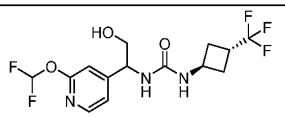
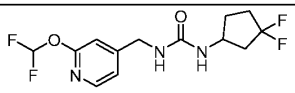
38	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-methoxycyclobutyl)methyl]urea	
40	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclobutyl)methyl]urea	
41	1-(cyclobutylmethyl)-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
43	1-cyclopentyl-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

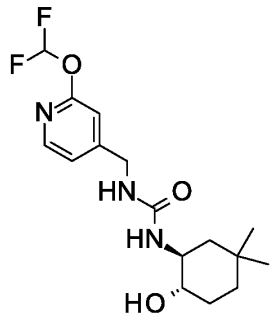
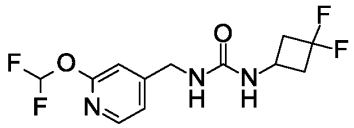
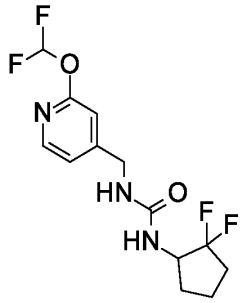
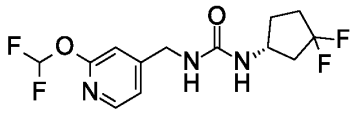
45	1-cyclobutyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
46	1-(cyclopentylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
50	1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
54	1-[[2-(cyclobutylmethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
55	1-[[2-(cyclopropylmethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	

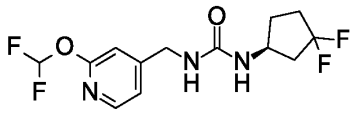
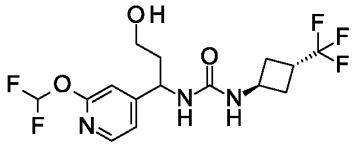
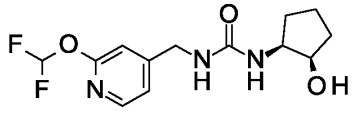
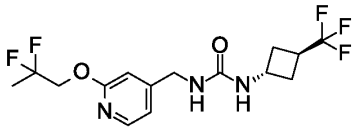
56	1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
57	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
58	1-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	
59	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea	
60	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethylcyclobutyl)urea	

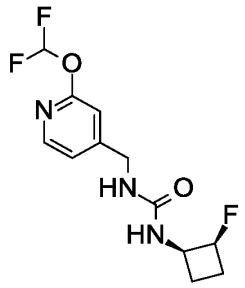
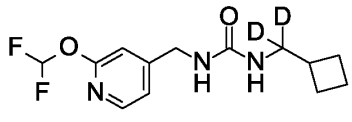
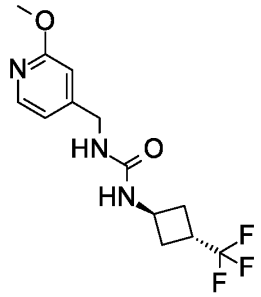
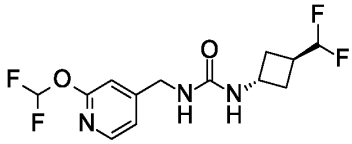
62	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
63	1-[[2-(cyanomethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
64	1-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
65	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylcyclobutyl)urea	
66	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethynylcyclobutyl)urea	

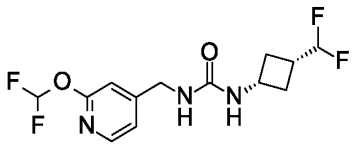
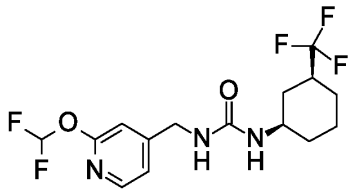
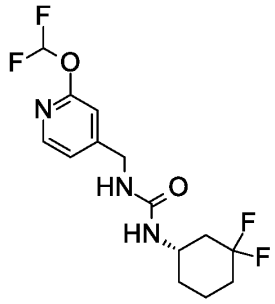
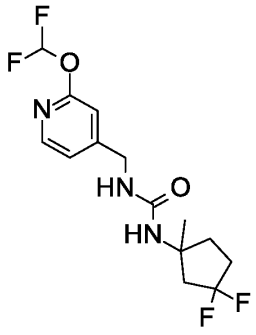
67	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1*r*,3*r*)-3-fluorocyclobutyl)urea	
71	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
77	1-(3-cyclopropylcyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
79	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
81	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]urea	

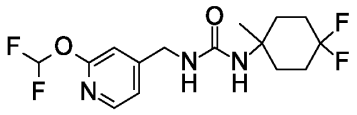
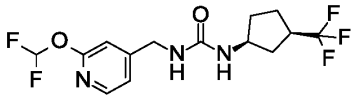
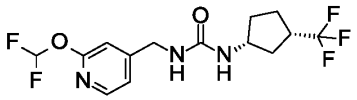
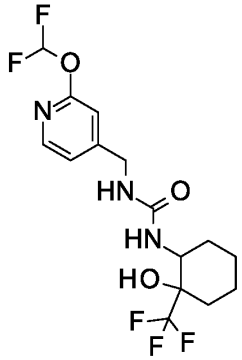
87	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(1r,3r)-(trifluoromethyl)cyclobutyl]methyl]urea	
89	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea	
90	1-(4,4-difluorocyclohexyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
91	**1**-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
93	1-(3,3-difluorocyclopentyl)-3-[[2-	

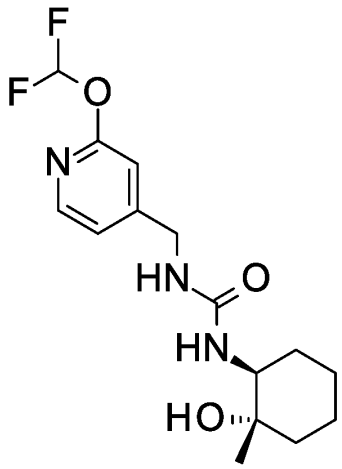
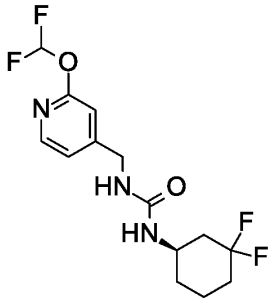
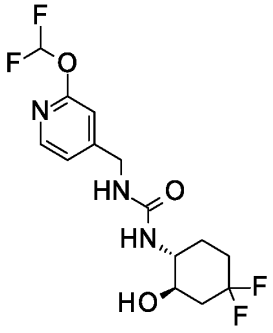
	(difluoromethoxy)pyridin-4-yl]methyl]urea	
101	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-5,5-dimethylcyclohexyl]urea	
108	1-(3,3-difluorocyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
113	1-(2,2-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-	

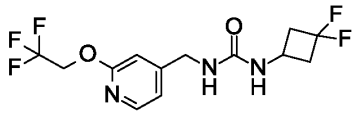
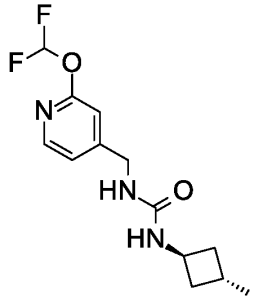
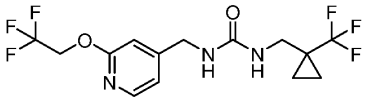
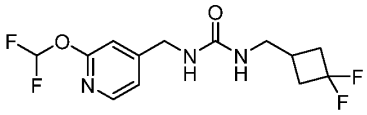
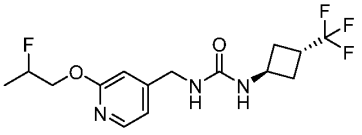
	(difluoromethoxy)pyridin-4-yl]methyl]urea	
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
117	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-3-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
118	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxycyclopentyl]urea	
121	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

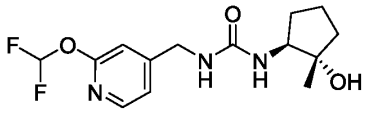
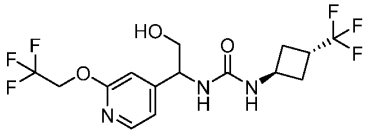
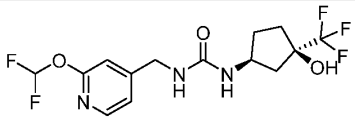
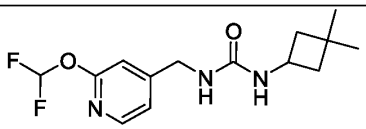
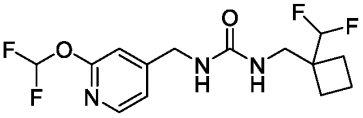
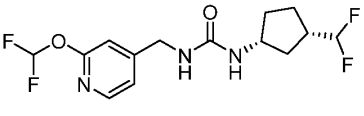
123	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-fluorocyclobutyl]urea	
125	1-[cyclobutyl(dideuterio)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
128	1-[(2-methoxypyridin-4-yl)methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
136	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(difluoromethyl)cyclobutyl]urea	

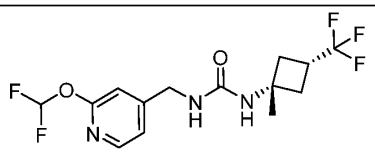
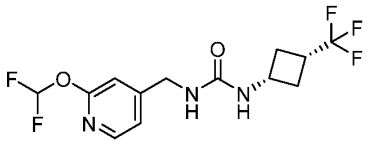
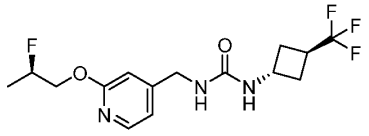
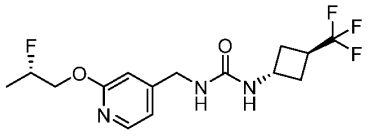
137	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(difluoromethyl)cyclobutyl]urea	
138	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	
140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
142	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-difluoro-1-methylcyclopentyl)urea	

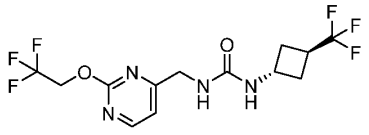
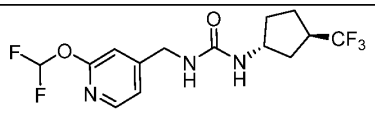
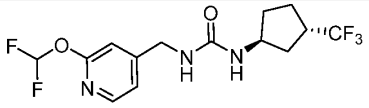
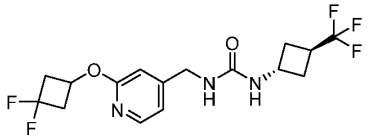
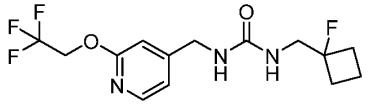
143	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4,4-difluoro-1-methylcyclohexyl)urea	
144	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3R)-3-(trifluoromethyl)cyclopentyl]urea	
146	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea	
147	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-hydroxy-2-(trifluoromethyl)cyclohexyl]urea	

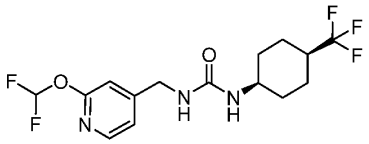
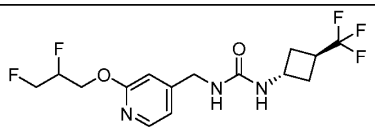
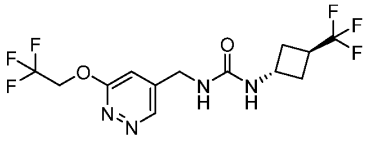
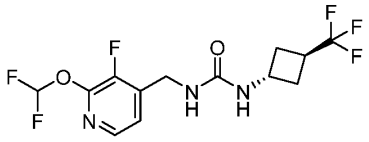
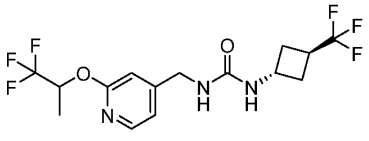
148	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-2-methylcyclohexyl]urea	
149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
154	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-4,4-difluoro-2-hydroxycyclohexyl]urea	

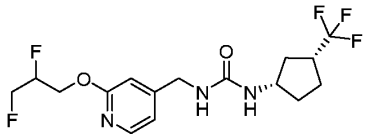
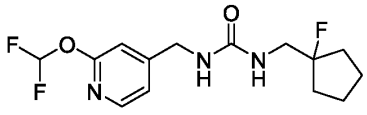
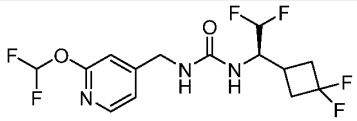
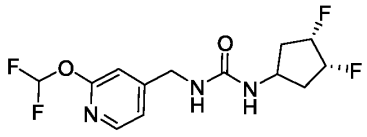
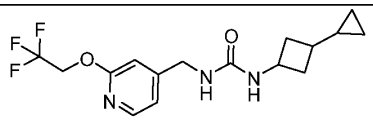
157	1-(3,3-difluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
163	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1r,3r)-3-methylcyclobutyl)urea	
284	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
183	1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

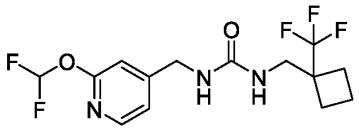
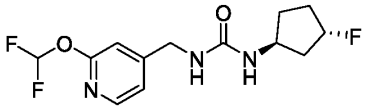
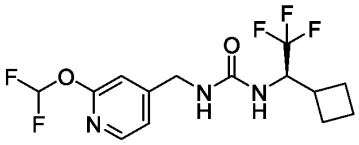
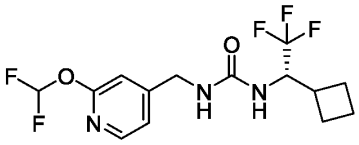
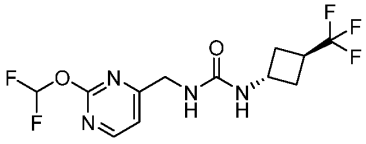
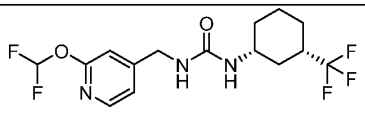
184	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,2S)-2-hydroxy-2-methylcyclopentyl]urea	
185	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
187	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-hydroxy-3-(trifluoromethyl)cyclopentyl]urea	
188	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-dimethylcyclobutyl)urea	
191	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluoromethyl)cyclobutyl]methyl]urea	
193	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-	

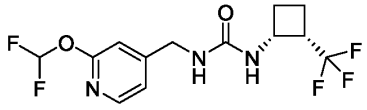
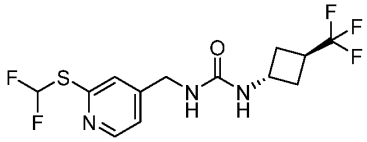
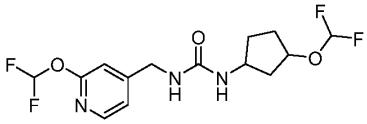
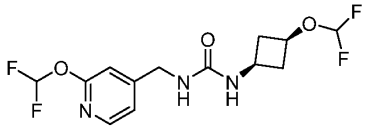
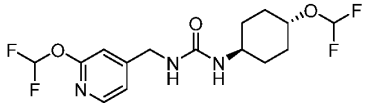
	(1R,3S)-3-(difluoromethyl)cyclopentyl]urea	
194	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-1-methyl-3-(trifluoromethyl)cyclobutyl]urea	
198	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(trifluoromethyl)cyclobutyl]urea	
199	1-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
202	1-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

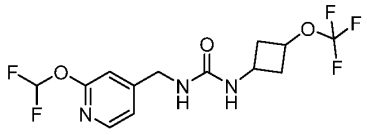
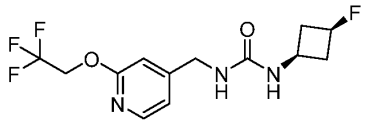
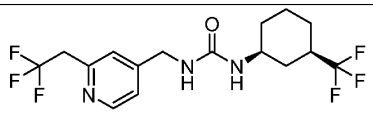
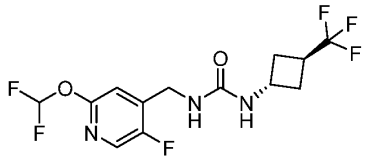
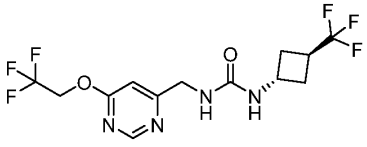
204	1-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
206	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3R)-3-(trifluoromethyl)cyclopentyl]urea	
207	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-(trifluoromethyl)cyclopentyl]urea	
209	1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
210	1-[(1-fluorocyclobutyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

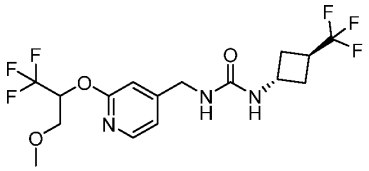
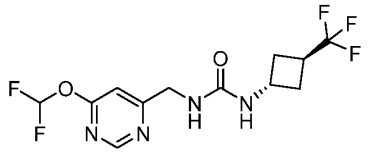
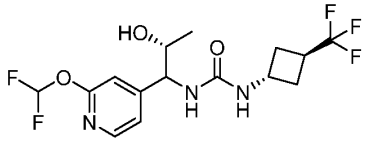
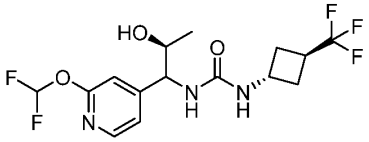
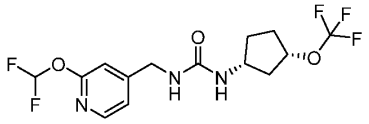
211	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,4s)-4-(trifluoromethyl)cyclohexyl]urea	
214	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
215	1-[[6-(2,2,2-trifluoroethoxy)pyridazin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
219	1-[[2-(difluoromethoxy)-3-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
221	1-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(1,1,1-trifluoropropan-2-yloxy)pyridin-4-yl]methyl]urea	

225	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea	
227	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclopentyl)methyl]urea	
230	1-[(1R)-1-(3,3-difluorocyclobutyl)-2,2-difluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
234	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(3R,4S)-3,4-difluorocyclopentyl]urea	
235	1-(3-cyclopropylcyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

237	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclobutyl]methyl]urea	
239	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-fluorocyclopentyl]urea	
241	1-[(1R)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
242	1-[(1S)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
243	1-[[2-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
250	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-	

	(trifluoromethyl)cyclohexyl]urea	
255	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-(trifluoromethyl)cyclobutyl]urea	
260	1-[[2-(difluoromethylsulfanyl)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
264	1-[3-(difluoromethoxy)cyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
265	1-[(1s,3s)-3-(difluoromethoxy)cyclobutyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
266	1-[(1r,4r)-4-(difluoromethoxy)cyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

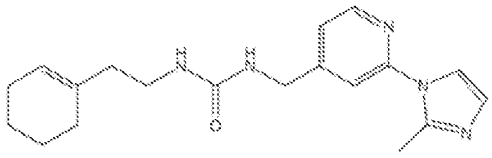
267	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethoxy)cyclobutyl]urea	
269	1-((1s,3s)-3-fluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
276	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
277	1-[[2-(difluoromethoxy)-5-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
279	1-[[6-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

281	1-[[*2-(1,1,1-trifluoro-3-methoxypropan-2-yl)*oxypyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
282	1-[[6-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
286	1-[(2R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
287	1-[(2S)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
288	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-	

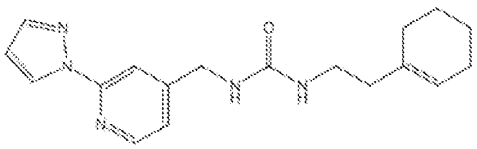
	(trifluoromethoxy)cyclopentyl]urea	
293	1-[(1r,3r)-3-(difluoromethyl)cyclobutyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered cycloalkenyl, which is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

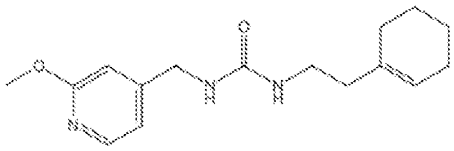
In some embodiments, wherein R^6 is a 6 membered cycloalkenyl, the compound of formula (I) is not:



;



; or



In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered cycloalkenyl, which is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, ethyl, $(CH_3)_2CF$-, CHF_2-, CF_3-, CH_3O-, tert-butyl, CN-, cyclopropyl, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered cycloalkenyl selected from cyclobutenyl, cyclopentenyl, and cyclohexenyl, which cyclobutenyl, cyclopentenyl, or cyclohexenyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, ethyl, $(CH_3)_2CF$-, CHF_2-, CF_3-, CH_3O-, tert-butyl, CN-, cyclopropyl, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered cycloalkenyl selected from cyclobutenyl, cyclopentenyl, and cyclohexenyl, which cyclobutenyl, cyclopentenyl, or cyclohexenyl are optionally substituted with one, two, or three substituents independently selected from from F-, cyclopropyl, and CF_3-.

In one preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered cycloalkenyl selected from cyclobutenyl, cyclopentenyl, and cyclohexenyl, which cyclobutenyl, cyclopentenyl, or cyclohexenyl are optionally substituted with one or two substituents independently selected from F-, cyclopropyl, and CF_3-.

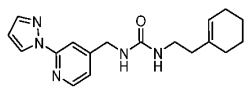
In one preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered cycloalkenyl

selected from cyclobutenyl, cyclopentenyl, and cyclohexenyl, which cyclobutenyl, cyclopentenyl, or cyclohexenyl are unsubstituted.

In one preferred embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is unsubstituted cyclohexenyl.

In all of the herein embodiments of R^6 as a 6 membered cycloalkenyl, R^1, R^2, R^3, R^4, R^5 and n are as described herein, i.e. including any combination of R^1, R^2, R^3, R^4, R^5 and n as described herein.

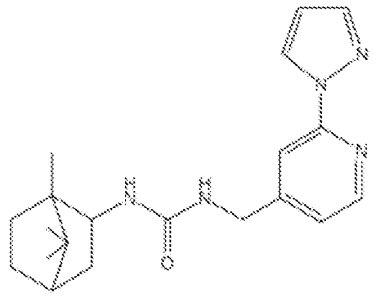
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is a 6 membered cycloalkenyl and the non-limiting example has the structure:

10	1-[2-(cyclohexen-1-yl)ethyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	

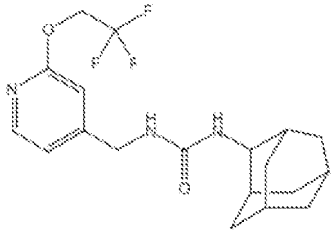
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In some embodiments, wherein R^6 is a 4-10 membered bridged cycloalkyl as described herein, R^1 is not C_{1-6}alkoxy.

In some embodiments, wherein R^6 is a 4-10 membered bridged cycloalkyl as described herein, the compound of formula (I) is not:



; or



.

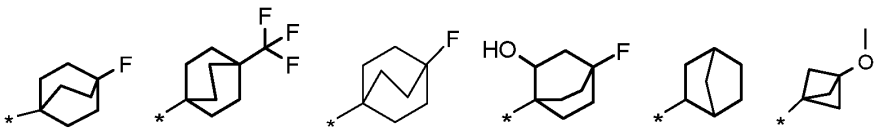
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 4-10 membered bridged cycloalkyl, which bridged cycloalkyl is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

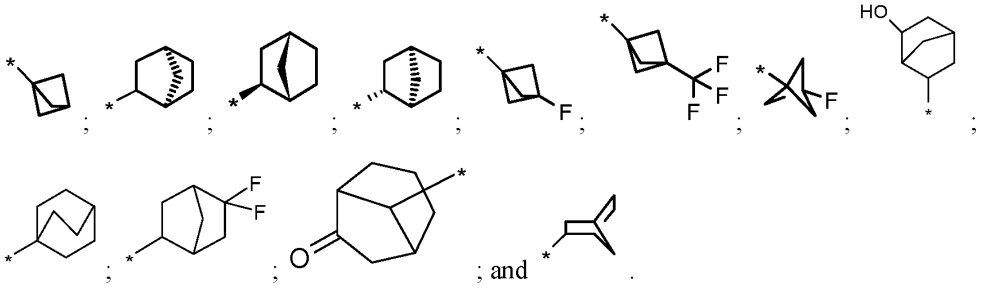
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 4-10 membered bridged cycloalkyl, selected from bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, and bicyclo[3.1.0]hexanyl, which bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, or bicyclo[3.1.0]hexanyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 4-10 membered bridged cycloalkyl, selected from bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, and bicyclo[3.1.0]hexanyl, which bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, or bicyclo[3.1.0]hexanyl are optionally substituted with one, two, or three substituents independently selected from F-, cyclopropyl, and CF_3-.

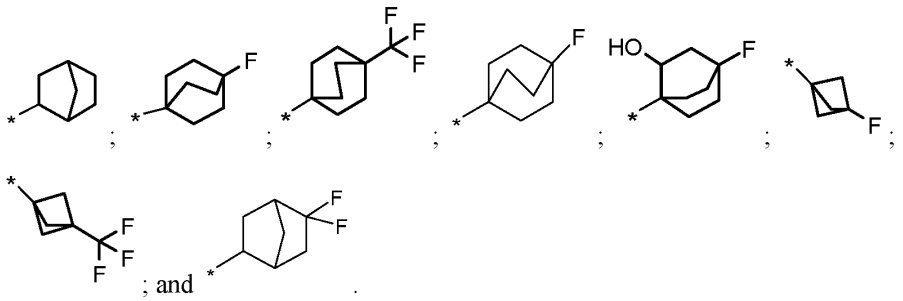
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 4-10 membered bridged cycloalkyl, selected from bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, and bicyclo[3.1.0]hexanyl; wherein the bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, octahydropentalen (bicylo[3.3.0]octanyl), or bicyclo[3.1.0]hexanyl are optionally substituted with one or two substituents independently selected from F-, cyclopropyl, and CF_3-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 4-10 membered bridged cycloalkyl, selected from bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, or bicyclo[3.1.0]hexanyl, which bicyclo[2.2.1]heptanyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.2]octanyl, and bicyclo[3.1.0]hexanyl are unsubstituted.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 4-10 membered bridged cycloalkyl, selected from 

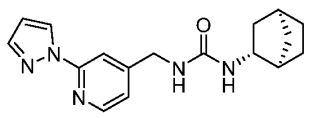


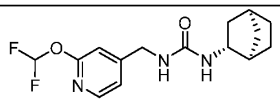
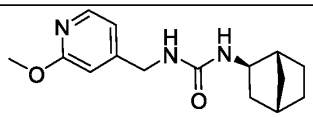
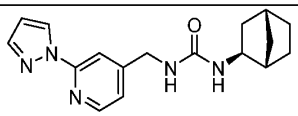
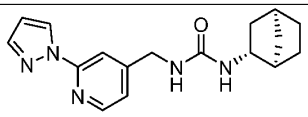
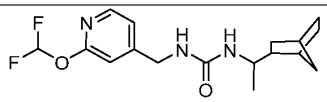
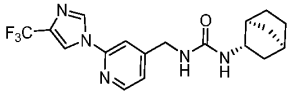
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 4-10 membered bridged cycloalkyl, selected from:

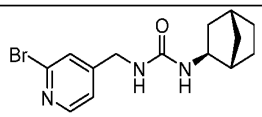
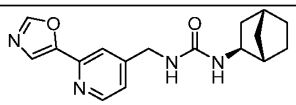
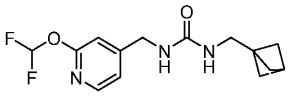
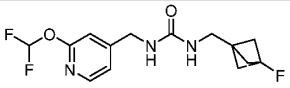
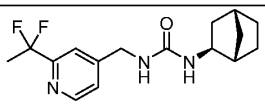
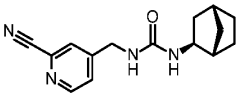


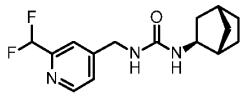
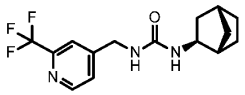
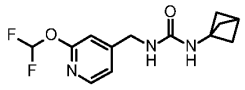
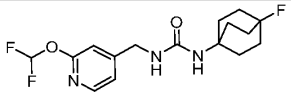
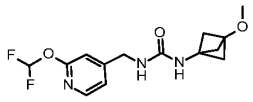
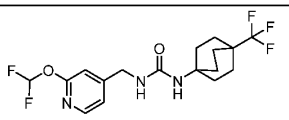
In all of the herein embodiments of R^6 as a 4-10 membered bridged cycloalkyl, R^1, R^2, R^3, R^4, R^5 and n are as described herein, i.e. including any combination of R^1, R^2, R^3, R^4, R^5 and n are as described herein.

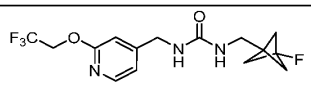
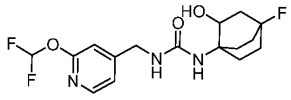
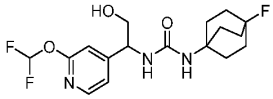
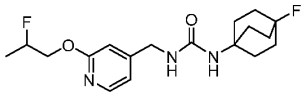
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is a 4-10 membered bridged cycloalkyl and non-limiting examples are selected from:

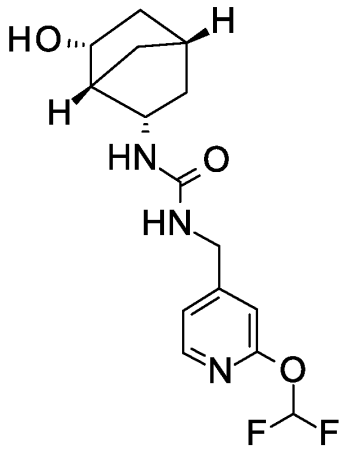
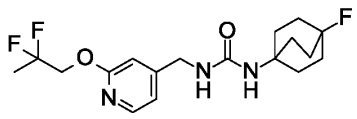
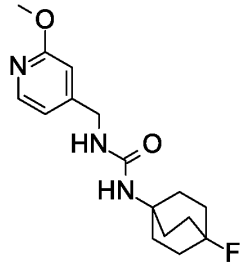
7	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	

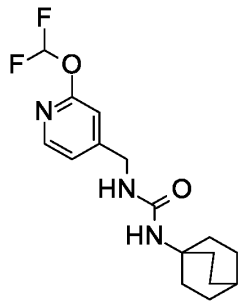
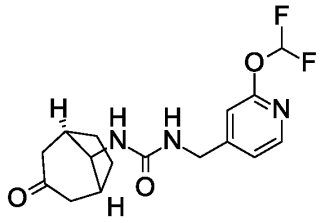
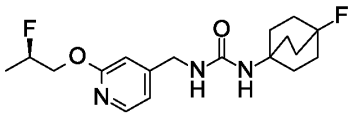
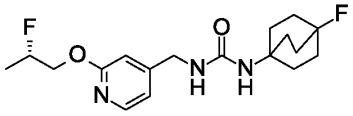
12	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
14	1-[(2-methoxypyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
15	1-[(1S,2S,4R)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
16	1-[(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
24	1-[1-(2-bicyclo[2.2.1]heptanyl)ethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
26	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	

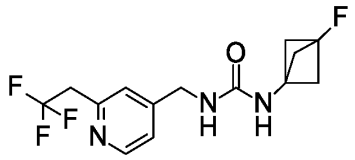
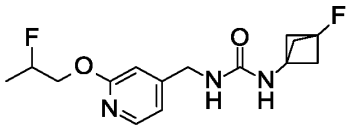
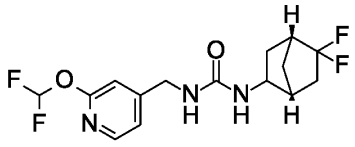
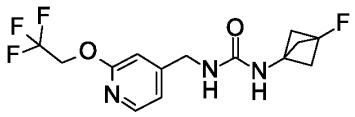
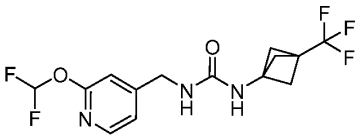
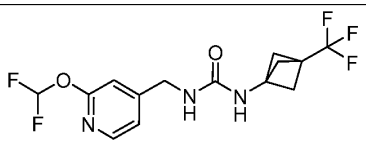
27	1-[(2-bromopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
28	1-[[2-(1,3-oxazol-5-yl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
32	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea	
33	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
34	1-[(2-cyanopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	

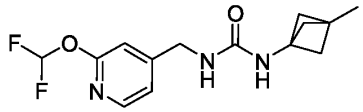
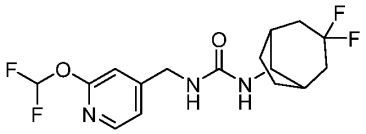
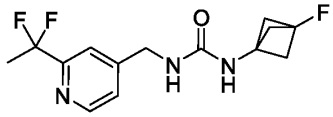
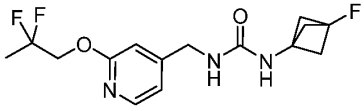
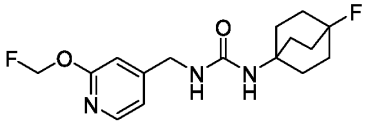
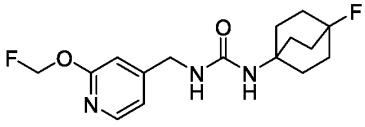
35	1-[[2-(difluoromethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
36	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	
47	1-(1-bicyclo[1.1.1]pentanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
49	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxy-1-bicyclo[1.1.1]pentanyl)urea	
68	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[4-(trifluoromethyl)-1-bicyclo[2.2.2]octanyl]urea	

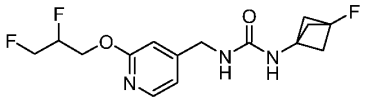
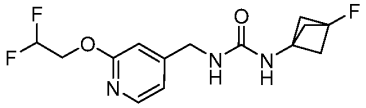
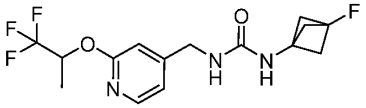
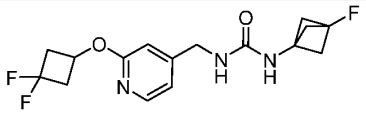
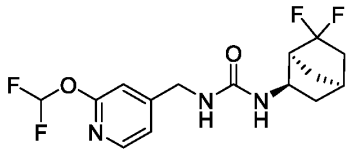
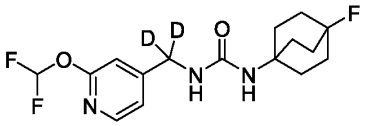
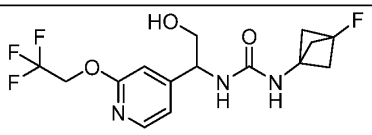
75	1-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
82	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-2-hydroxy-1-bicyclo[2.2.2]octanyl)urea	
85	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
88	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	

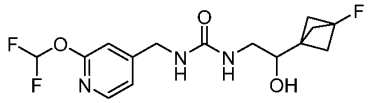
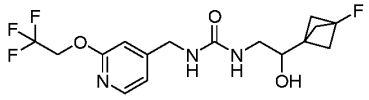
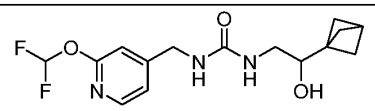
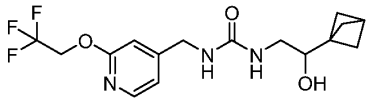
107	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S,6R)-6-hydroxy-2-bicyclo[2.2.1]heptanyl]urea	
122	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
129	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[(2-methoxypyridin-4-yl)methyl]urea	

131	1-(1-bicyclo[2.2.2]octanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
139	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3-oxo-8-bicyclo[3.2.1]octanyl]urea	
151	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]urea	
156	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]urea	

159	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
160	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	
165	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,4R)-5,5-difluoro-2-bicyclo[2.2.1]heptanyl]urea	
168	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
178	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
178	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-	

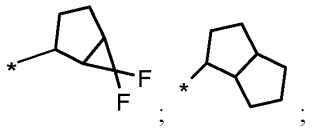
	(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
182	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methyl-1-bicyclo[1.1.1]pentanyl)urea	
197	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3,3-difluoro-8-bicyclo[3.2.1]octanyl]urea	
200	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
201	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
208	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
208	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	

216	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
217	1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
223	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(1,1,1-trifluoropropan-2-yloxy)pyridin-4-yl]methyl]urea	
224	1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
236	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S)-6,6-difluoro-2-bicyclo[2.2.1]heptanyl]urea	
251	1-[dideuterio-[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
283	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[2-hydroxy-1-[2-(2,2,2-	

	trifluoroethoxy)pyridin-4-yl]ethyl]urea	
289	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]urea	
290	1-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
291	1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
292	1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, which 7-10 membered fused cycloalkyl is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings selected from:



which 7-10 membered fused cycloalkyl is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF^3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings selected from bicyclo[3.1.0]hexanyl, bicyclo[3.2.0]heptanyl, hexahydro-1H-pentalenyl, cyclopenta[c]pyrrol-2-yl, and octahydropentalenyl, which bicyclo[3.1.0]hexanyl, bicyclo[3.2.0]heptanyl, hexahydro-1H-pentalenyl, cyclopenta[c]pyrrol-2-yl, or octahydropentalenyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

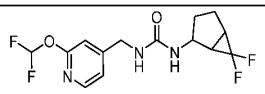
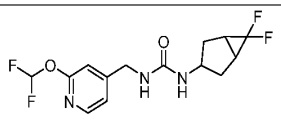
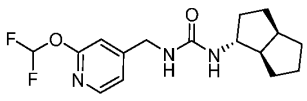
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings selected from bicyclo[3.1.0]hexanyl, bicyclo[3.2.0]heptanyl, hexahydro-1H-pentalenyl, cyclopenta[c]pyrrol-2-yl, and octahydropentalenyl, which bicyclo[3.1.0]hexanyl, bicyclo[3.2.0]heptanyl, hexahydro-1H-pentalenyl, cyclopenta[c]pyrrol-2-yl, or octahydropentalenyl are optionally substituted with one or two substituents independently selected from F-, cyclopropyl, and CF_3-.

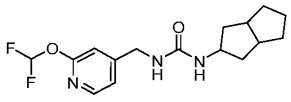
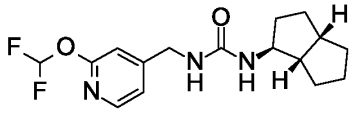
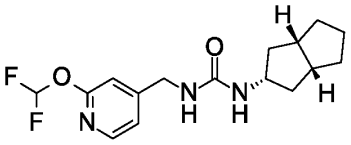
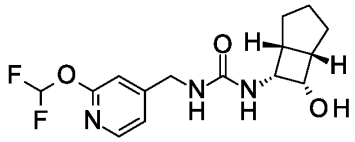
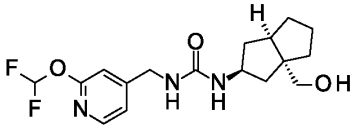
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings selected from bicyclo[3.1.0]hexanyl,

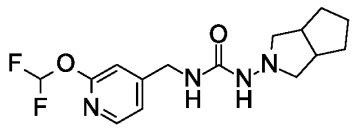
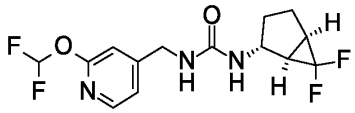
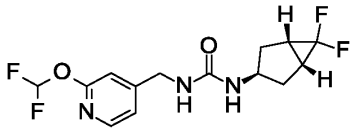
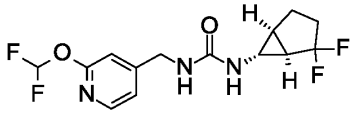
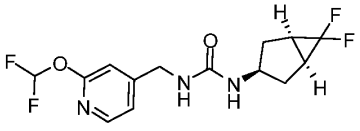
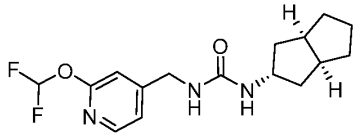
bicyclo[3.2.0]heptanyl, hexahydro-1H-pentalenyl, cyclopenta[c]pyrrol-2-yl, and octahydropentalenyl, which bicyclo[3.1.0]hexanyl, bicyclo[3.2.0]heptanyl, hexahydro-1H-pentalenyl, cyclopenta[c]pyrrol-2-yl, or octahydropentalenyl are unsubstituted.

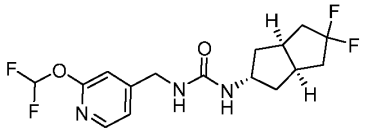
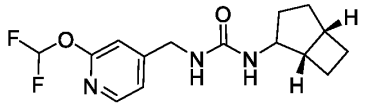
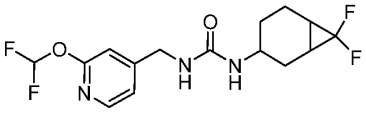
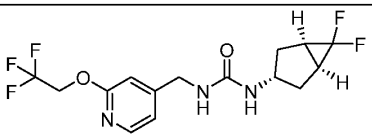
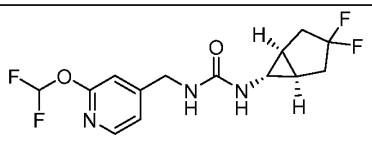
In all of the herein embodiments of R^6 as a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, R^1, R^2, R^3, R^4, R^5 and n are as described herein, i.e. including any combination of R^1, R^2, R^3, R^4, R^5 and n are as described herein.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as describd herein and R^6 is a 7-10 membered fused cycloalkyl; and non-limiting examples are selected from:

73	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]urea	
74	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
76	1-[(1R,3aR,6aR)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

78	1-(1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
103	1-[(1S,3aS,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
105	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3aR,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]urea	
111	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6S,7R)-7-hydroxy-6-bicyclo[3.2.0]heptanyl]urea	
112	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(2R,3aS,6aS)-6a-(hydroxymethyl)-2,3,3a,4,5,6-hexahydro-1H-pentalen-2-yl]urea	

114	1-(3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
169	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
170	1-[(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
189	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3r,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
190	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2s,3aR,6aS)-	

	1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]urea	
195	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2r,3aR,6aS)-5,5-difluoro-2,3,3a,4,6,6a-hexahydro-1H-pentalen-2-yl]urea	
196	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5R)-2-bicyclo[3.2.0]heptanyl]urea	
222	1-(7,7-difluoro-3-bicyclo[4.1.0]heptanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
238	1-[(1R,3s,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
271	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-3,3-difluoro-6-bicyclo[3.1.0]hexanyl]urea	

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered heteroaryl, which heteroaryl

is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered heteroaryl, heteroaryl is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered heteroaryl selected from pyridinyl, pyrimidinyl, and pyrazinyl, which pyridinyl, pyrimidinyl, or pyrazinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered heteroaryl selected from pyridinyl, pyrimidinyl, and pyrazinyl, which pyridinyl, pyrimidinyl, or pyrazinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, cyclopropyl, and CF_3-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered heteroaryl selected from pryridinyl, pyrimidinyl, and pyrazinyl, which pyridinyl, pyrimidinyl, or pyrazinyl are optionally substituted with one Cl-, F-, cyclopropyl, and CF_3-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered heteroaryl selected from pyridinyl, pyrimidinyl, and pyrazinyl, which pyridinyl, pyrimidinyl, or pyrazinyl are optionally substituted with one Cl-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 6 membered heteroaryl, which 6

membered heteroaryl selected from pyridinyl, pyrimidinyl, and pyrazinyl which are optionally substituted with one or two Cl-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from unsubstituted pyridinyl, unsubstituted pyrimidinyl, and unsubstituted pyrazinyl.

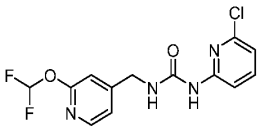
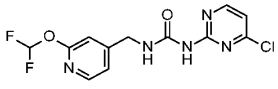
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is unsubstituted pyridinyl.

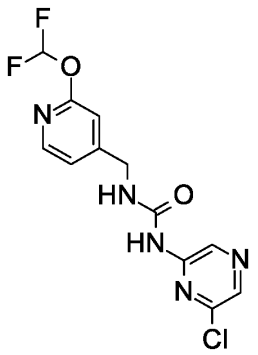
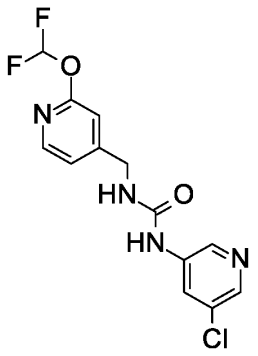
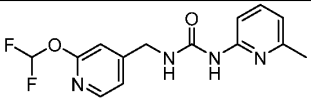
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is unsubstituted pyrimidinyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is unsubstituted pyrazinyl.

In all of the herein embodiments of R^6 as a 6 membered heteroaryl, R^1, R^2, R^3, R^4, R^5 and n are as described herein, i.e. including any combination of R^1, R^2, R^3, R^4, R^5 and n as described herein.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is a 6 membered heteroaryl as described herein, and wherein a non-limiting example is:

84	1-(6-chloropyridin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
96	1-(4-chloropyrimidin-2-yl)-3-[[2-	

	(difluoromethoxy)pyridin-4-yl]methyl]urea	
98	1-(6-chloropyrazin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
161	1-(5-chloropyridin-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
218	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(6-methylpyridin-2-yl)urea	

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is phenyl, which phenyl is optionally

substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In some embodiments of the invention, wherein R^6 is optionally substituted phenyl as described herein, R^1 is not 5 membered heteroaryl.

In some embodiments of the invention, wherein R^6 is optionally substituted phenyl as described herein, R^1 is not C_{1-6}alkoxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is phenyl, which phenyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is phenyl, which phenyl is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is phenyl, which phenyl is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CHF_2-, cyclopropyl, and CF_3-.

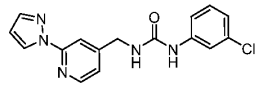
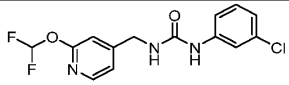
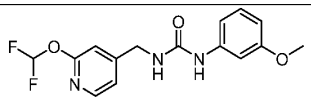
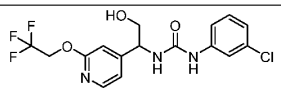
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is phenyl, which optionally substituted with onem two, or three substituents independentyl selected from Cl-, F-, CH_3O-, CHF_2-, and CF_3-.

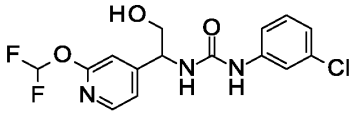
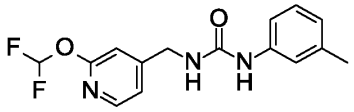
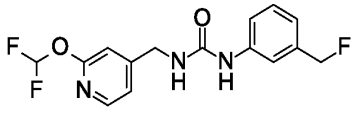
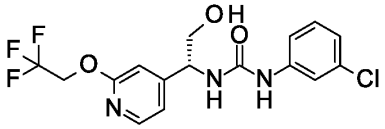
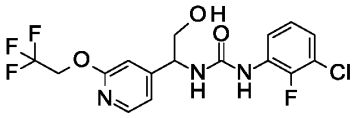
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is phenyl, which is optionally substituted with one Cl- or CH_3O-.

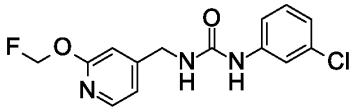
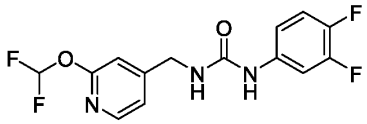
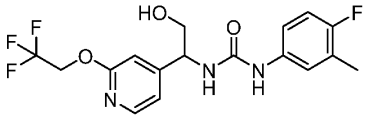
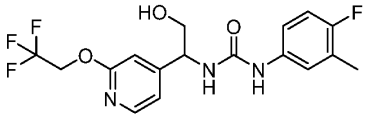
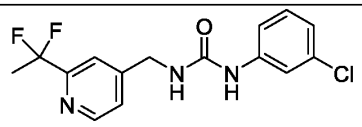
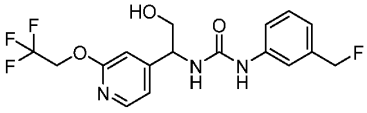
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is unsubstituted phenyl.

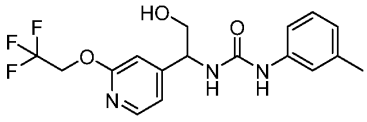
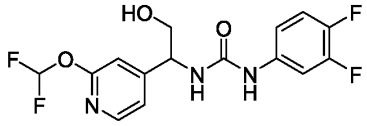
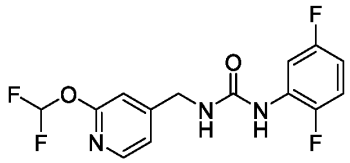
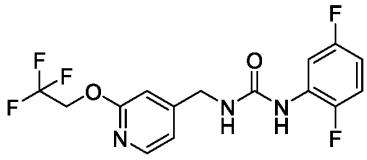
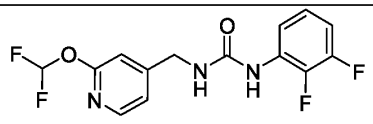
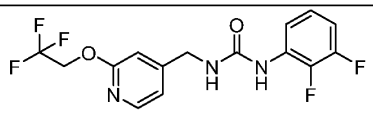
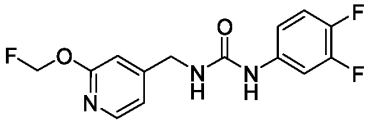
In all of the herein embodiments of R^6 is phenyl, R^1, R^2, R^3, R^4, R^5 and n are as described herein, i.e. including any combination of R^1, R^2, R^3, R^4, R^5 and n as described herein.

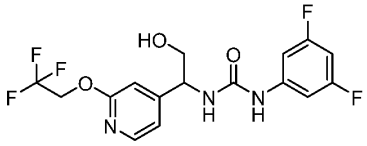
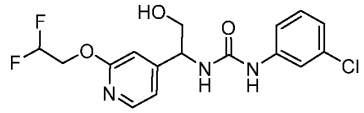
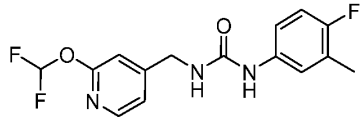
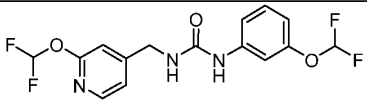
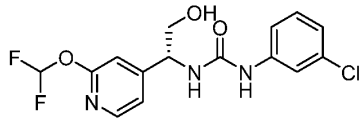
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is phenyl and R^1, R^2, R^3, n, R^4 and R^5 are as described herein, and non-limiting examples are selected from:

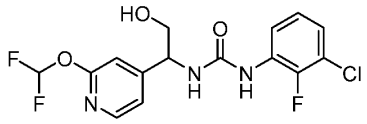
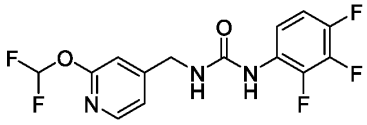
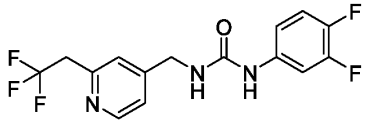
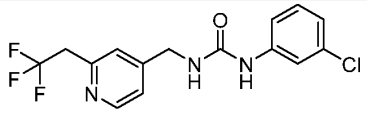
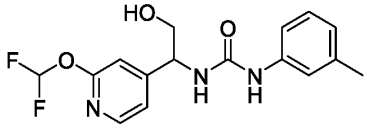
4	1-(3-chlorophenyl)-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
22	1-(3-chlorophenyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
83	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxyphenyl)urea	
92	1-(3-chlorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
126	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylphenyl)urea	
132	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(fluoromethyl)phenyl]urea	
145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
150	1-(3-chloro-2-fluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

164	1-(3-chlorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
186	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-difluorophenyl)urea	
205	1-(4-fluoro-3-methylphenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
205	1-(4-fluoro-3-methylphenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
231	1-(3-chlorophenyl)-3-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]urea	
232	1-[3-(fluoromethyl)phenyl]-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

233	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-(3-methylphenyl)urea	
240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
244	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,5-difluorophenyl)urea	
245	1-(2,5-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
247	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3-difluorophenyl)urea	
248	1-(2,3-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
249	1-(3,4-difluorophenyl)-3-[[2-	

	(fluoromethoxy)pyridin-4-yl]methyl]urea	
256	1-(3,5-difluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
259	1-(3-chlorophenyl)-3-[1-[2-(2,2-difluoroethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
261	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-3-methylphenyl)urea	
262	1-[3-(difluoromethoxy)phenyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
263	rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	

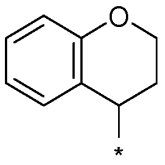
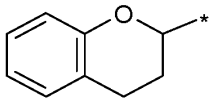
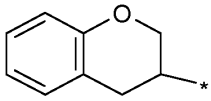
270	1-(3-chloro-2-fluorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
272	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3,4-trifluorophenyl)urea	
274	1-(3,4-difluorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
275	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea	

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 5-12 membered heterocycloalkyl; which 5-12 membered heterocycloalkyl is optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 5-12 membered heterocycloalkyl; which 5-12 membered heterocycloalkyl is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CHF_2-. CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In some embodiments, wherein R^6 is a 5-12 membered heterocycloalkyl the compound of formula (I) is not:

In some embodiments of the compound of formula (I) is not a chromen


; 
; or 
, which can be unsubstituted or the aromatic ring is substituted with one halogen, alkoxy, or hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 5-12 membered heterocycloalkyl, which heterocycloalkyl is a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom; which fused heterocycloalkyl, or bridged heterocycloalkyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a

7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom; which fused heterocycloalkyl, or bridged heterocycloalkyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, cyclopropyl, and CF_3-.

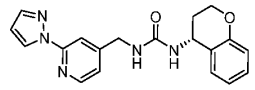
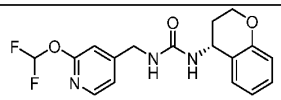
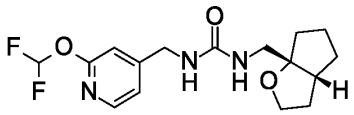
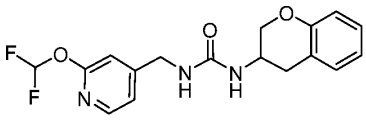
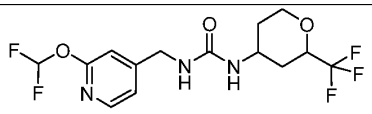
In one embodiment, the inve§ntion provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom; which fused heterocycloalkyl, or bridged heterocycloalkyl are unsubstitued.

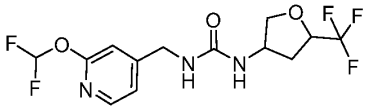
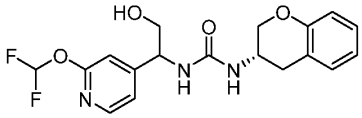
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom; which fused heterocycloalkyl, or bridged heterocycloalkyl are selected from dihydrochromenyl, and hexahydrocyclopenta[b]furanyl which are optionally substituted with one or two Cl-, F-, CH_3O-, and CF_3- .

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from dihydrochromenyl, and hexahydrocyclopenta[b]furanyl which are unsubstituted.

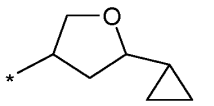
In all of the herein embodiments of R^6 as a 5-12 membered heterocycloalkyl, R^1, R^2, R^3, R^4, R^5 and n are as described herein, i.e. including any combination of R^1, R^2, R^3, R^4, R^5 and n are as described herein.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein , and R^6 is 5-12 membered heterocycloalkyl, and non-limiting examples are selected from:

1	1-[(4R)-3,4-dihydro-2H-chromen-4-yl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
23	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(4R)-3,4-dihydro-2H-chromen-4-yl]urea	
120	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[rac-(3aR,6aR)-2,3,3a,4,5,6-hexahydrocyclopenta[b]furan-6a-yl]methyl]urea	
192	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-dihydro-2H-chromen-3-yl)urea	
226	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-	

	(trifluoromethyl)oxan-4-yl]urea	
258	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[5-(trifluoromethyl)oxolan-3-yl]urea	
278	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(3S)-3,4-dihydro-2H-chromen-3-yl]urea	

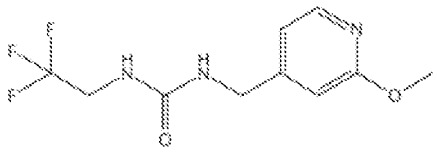
In some preferred embodiments, R^6 is



In some of the aforementioned embodiments, the O-atom is at a different position.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a haloC_{1-6}alkyl.

In some embodiments, wherein R^6 is a haloC_{1-6}alkyl and the compound of formula (I) is not:



In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a haloC_{1-6}alkyl. Halogen atoms may be fluoro (F), chloro (Cl) or bromo (Br). More preferably, haloC_{1-6}alkyl is substituted with fluoro (F).

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a haloC_{1-6}alkyl selected from CH_3CF_2-, CF_3-, CH_2F-, and CHF_2-.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is CHF_2-.

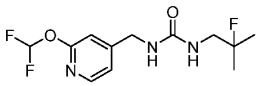
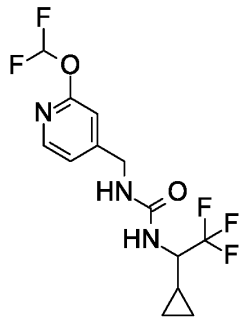
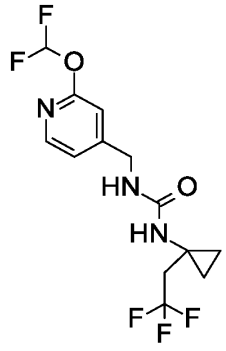
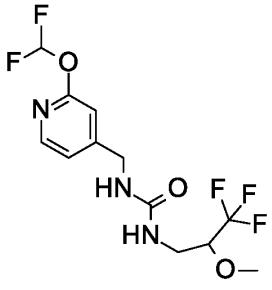
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is CH_2F-.

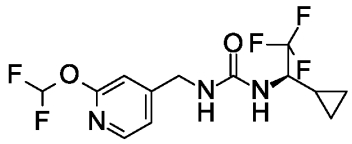
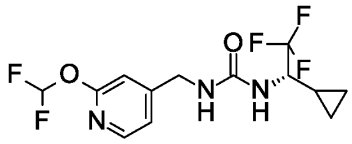
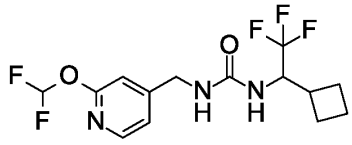
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is CF_3-.

In some embodidments, wherein R^6 is CF_3- is not CF_3CH_2O-

In all of the herein embodiments of R^6 as a haloC_{1-6}alkyl, R^1, R^2, R^3, R^4, R^5 and n are as described herein, i.e. including any combination of R^1, R^2, R^3, R^4, R^5 and n are as described herein.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is a haloC_{1-6}alkyl, and a non-limiting example has the structure:

39	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-fluoro-2-methylpropyl)urea	
106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
110	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2,2-trifluoroethyl)cyclopropyl]urea	
119	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3,3-trifluoro-2-methoxypropyl)urea	

134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
135	1-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
152	1-(1-cyclobutyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a C_{1-6}alkyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a C_{1-6}alkyl selected from CH_3-, ethyl, propyl, 2-propyl (isopropyl), n-butyl, iso-butyl, sec-butyl, and tert-butyl.

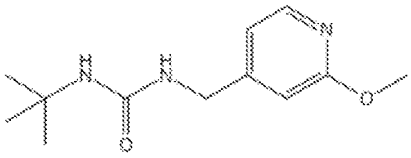
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a C_{1-6}alkyl selected from CH_3- and tert-butyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is a C_{1-6}alkyl, which C_{1-6}alkyl is CH_3-.

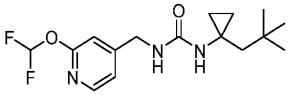
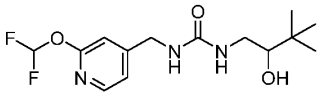
In all of the herein embodiments of R^6 as a C_{1-6}alkyl, R^1, R^2, R^3, R^4, R^5 and n are as described herein, i.e. including any combination of R^1, R^2, R^3, R^4, R^5 and n are as described herein.

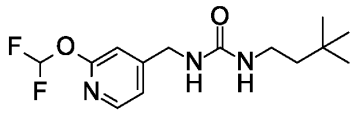
In some embodiments, when R^6 is tert-butyl, R^1 is not CF_3CH_2O-.

In some other embodiments, the compound of formula (I) is not:



In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5 and n are as described herein, and R^6 is a C_{1-6}alkyl, and non-limiting examples have the structures:

29	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,2-dimethylpropyl)urea	
44	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2-dimethylpropyl)cyclopropyl]urea	
95	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea	

109	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-dimethylbutyl)urea	

Additional Options for Variables

In all aspects, embodiments, claims and chemical formulae described herein, various lists of options are provided for the variables R^1, R^4, R^5 and R^6. In additional, distinct, aspects, embodiments and chemical formulae, these lists of options for R^1, R^4, R^5 and R^6 may each independently be expanded to include additional options in one or more of the lists associated with a given aspect, embodiment, or formula as provided below. These additional options may be included independently of the additional options for other variables in a formula, e.g. the additional options for one variable, such as R^6, may be included in a given Formula independently, without requiring inclusion of the additional options for any of the other variables in the molecule; and similarly for any and all of the other variables.

Throughout this specification, this has the effect of providing additional aspects, embodiments, claims and formulae in which the definitions of one or more of the variables R^1, R^4, R^5 and R^6 are expanded to encompass the following additional options.

In particular, these additional options are applicable to each of formulae (I'), (I*), (I**), (I),(II), (III), (IV) etc.

Additional Options for R^1

In addition to the options defined herein for R^1 in any of the various lists, including in the most general lists and in narrower lists, such as preferred, more preferred, and most preferred lists, the options for R^1 may also include:

halo$C_{1\text{-}6}$ alkylthio, 4-6 membered cycloalkyloxy, and halo$C_{1\text{-}6}$alkoxy substituted with $C_{1\text{-}6}$alkoxy; wherein the 4-6 membered cycloalkyloxy is optionally substituted with one, two, or three substituents independently selected from halogen.

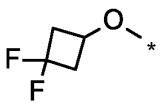
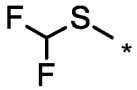
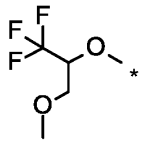
Particular preferences for the additional options for R^1 are selected from:

4-6 membered cycloalkyloxy substituted with one, two, or three substituents independently selected from F and Cl; haloC_{1-6}alkylthio wherein the halo is selected from F and Cl; and haloC_{1-6}alkoxy substituted with C_{1-6}alkoxy wherein the halo is selected from F and Cl.

Further preferences for the additional options for R^1 are selected from:

Cyclobutyloxy substituted with two substituents independently selected from F and Cl, preferably F; halomethylthio wherein the halo is selected from F and Cl, preferably F; and halopropoxy substituted with methoxy wherein the halo is selected from F and Cl, preferably F.

Specific additional options for R^1 are selected from:

Additional Options for R^4 and R^5

In addition to the options defined herein for R^4 and R^5 in any of the various lists, including in the most general lists and in narrower lists, such as preferred, more preferred, and most preferred lists, the options for R^4 and R^5 may also include:

haloC_{1-6}alkyl

Particular preferences for the additional options for R^4 and R^5 are selected from:

haloC_{1-6}alkyl wherein the halo is selected from F and Cl, preferably F

Further preferences for the additional options for R^4 and R^5 are selected from:

haloC_{1-3}alkyl wherein the halo is selected from F and Cl, preferably F

Specific additional options for R^4 and R^5 are selected from:

CF_3, CHF_2, and CH_2F; in particular CF_3, and CHF_2,

Additional Options for R^6

In addition to the options defined herein for R^6 in any of the various lists, including in the most general lists and in narrower lists, such as preferred, more preferred, and most preferred lists, the options for R^6 may also include:

3 membered cycloalkyl, haloC_{1-6}alkoxy, Si(C_{1-6}alkyl)$_3$; and

5-12 membered heterocycloalkyl, 6 membered heteroaryl, 3-10 membered cycloalkyl, or phenyl, each of which is substituted with one, two, or three substituents independently selected from: halogen, haloC_{1-6}alkoxy and C_{2-6} alkynyl.

Particular preferences for the additional options for R^6 are selected from:

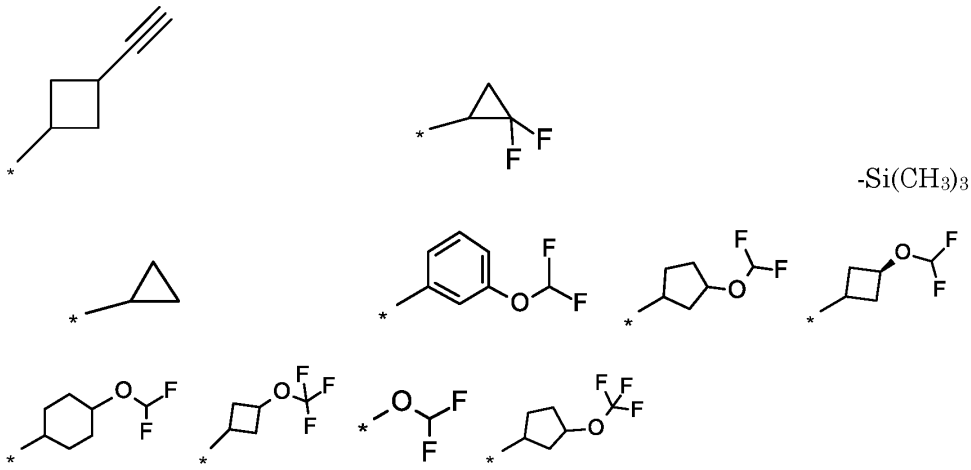
4-6 membered cycloalkyl substituted with one C_{2-6} alkynyl; 3 membered cycloalkyl; 3-6 membered cycloalkyl substituted with one, two, or three halogen atoms selected from F and Cl; Si(C_{1-6}alkyl)$_3$; phenyl substituted with one, two, or three haloC_{1-6}alkoxy wherein the halo is selected from F and Cl; 3-10 membered cycloalkyl substituted with one, two, or three haloC_{1-6}alkoxy wherein the halo is selected from F and Cl; and haloC_{1-6}alkoxy wherein the halo is selected from F and Cl.

Further preferences for the additional options for R^6 are selected from:

4-6 membered cycloalkyl substituted with one C_{2-6} alkynyl; cyclopropyl; cyclopropyl substituted with one, two, or three F atoms; Si(C_{1-3}alkyl)$_3$; phenyl substituted with one, two, or

three haloC_{1-3}alkoxy wherein the halo is F; 3-10 membered cycloalkyl substituted with one, two, or three haloC_{1-3}alkoxy wherein the halo is F; and haloC_{1-3}alkoxy wherein the halo is F.

Specific additional options for R^6 are selected from:



Preferences and Embodiments Involving Additional Options

While the above-mentioned additional options for variables are applicable to any and all aspects, embodiments and formulae herein, the following represent specifically envisaged embodiments.

In some embodiments the additional options for R^1, R^4, R^5 and R^6 are associated with formula I'.

In some embodiments the additional options for R^1, R^4, R^5 and R^6 are associated with formula I.

In some embodiments the present invention relates to compounds and compositions including formula I as defined herein, with the following additional options for R^1, R^4, R^5 and R^6 are associated with formula I:

Each R^4 and R^5 is independently selected from H and haloC_{1-6}alkyl; in combination with

R^1 being selected from haloC_{1-6}alkoxy;

R^2 and R^3 being H;

R^6 being selected from haloC_{1-6}alkyl, and 4-10 membered cycloalkyl substituted with one, two or three halogen atoms; and

n is 1.

In some embodiments the present invention relates to compounds and compositions including formula I as defined herein, with the following additional options for R^1, R^4, R^5 and R^6 are associated with formula I:

R^6 is selected from $Si(C_{1-6}alkyl)_3$, 3 membered cycloalkyl, 3-10 membered cycloalkyl substituted with one, two, or three substituents independently selected from: halogen, and haloC_{1-6}alkoxy; in combination with

R^1 being selected from haloC_{1-6}alkoxy;

R^2 and R^3 being H;

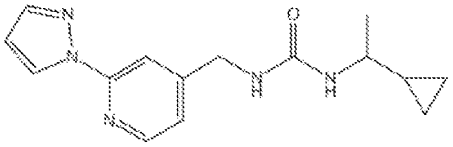
each R^4 and R^5 being independently selected from H and monocyclic 3-5 membered cycloalkyl; and

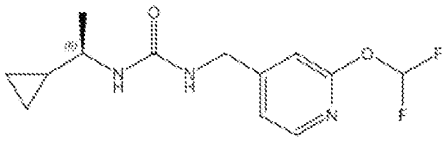
n is 0 or 1.

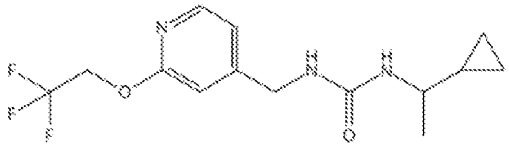
Additional Exclusions

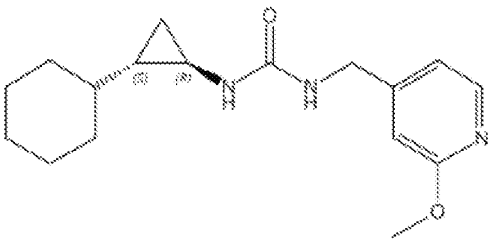
In relation to aspects, embodiments associated with formula (I') as described herein; or when the lists of options for variables associated with aspects, embodiments, claims and chemical formulae described herein are expanded to include any or all of the additional options described above, the relevant aspect or embodiment may also exclude specific compounds as follows.

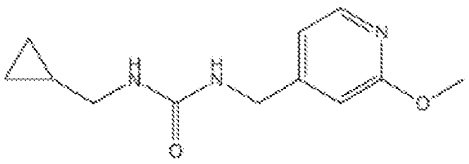
In certain aspects and embodiments, the invention excludes the following compounds.

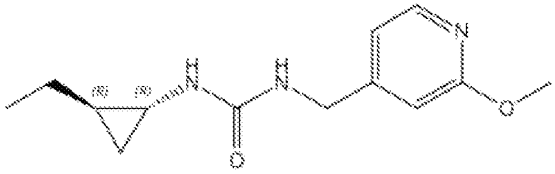


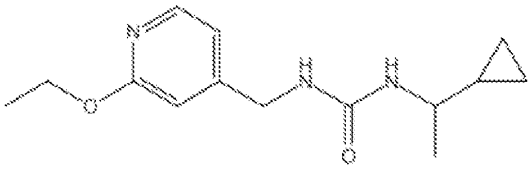


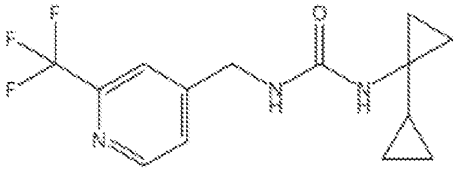


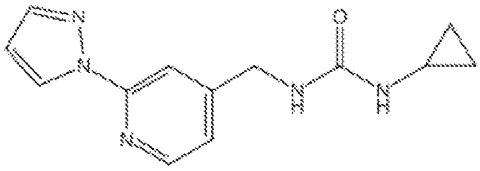












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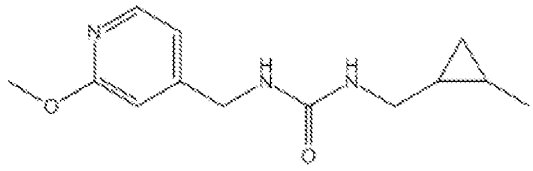

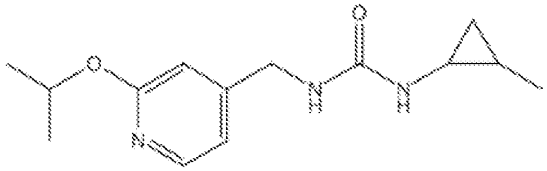

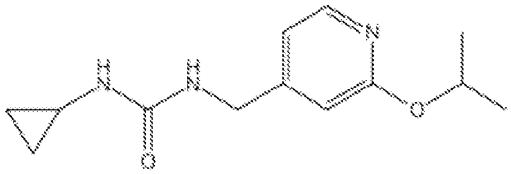

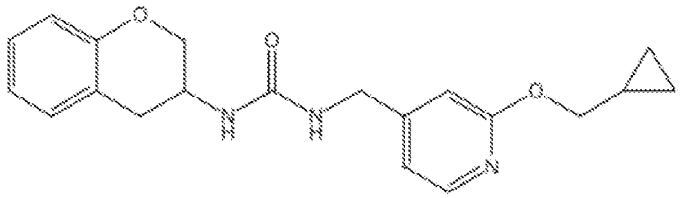

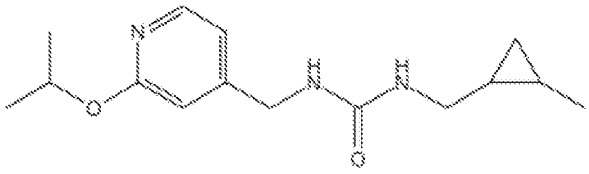

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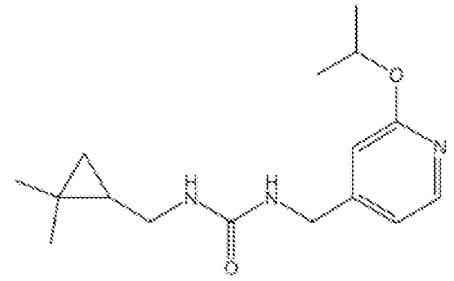
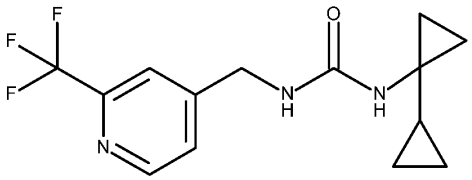


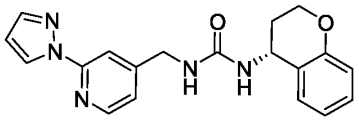
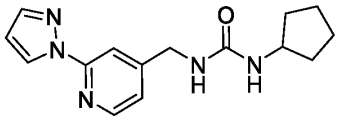
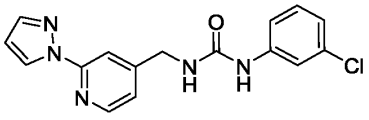


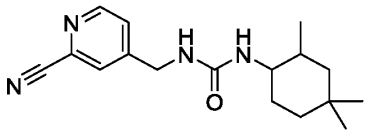
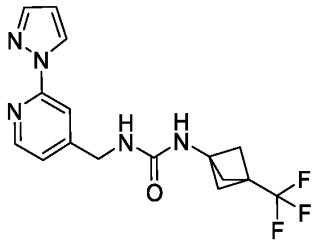
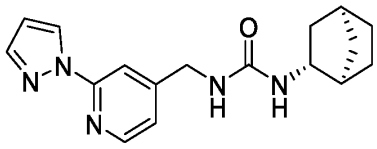
In some aspects and embodiments, the invention excludes these compounds alone, whereas in some aspects and embodiments, the invention excludes these compounds in addition to those listed as excluded elsewhere herein.

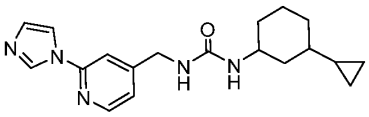
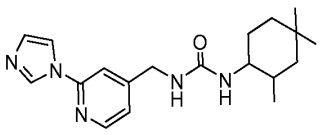
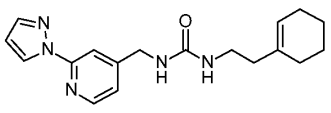
Exemplary formula (I) or formula (I') compounds in Table 1 were made, characterized, and tested for activation of Kv7.2 (EC_{50} less than 10 micromolar, μM) and Kv7.2 activation max % according to the methods of this invention, and have the following structures and corresponding names (OpenEye Lexichem, Version 1.2.0, OpenEye Scientific Software, Santa Fe, NM, USA; https://www.eyesopen.com/lexichem-tk).

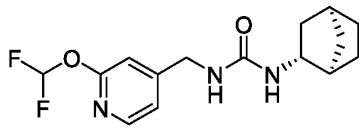
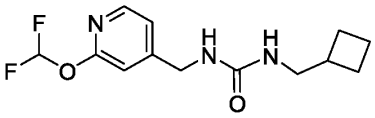
In some embodiments, the compound is selected from Table 1, or a solvate or a pharmaceutically acceptable salt thereof:

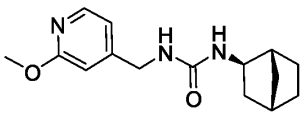
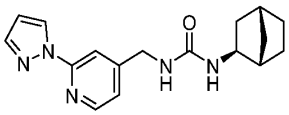
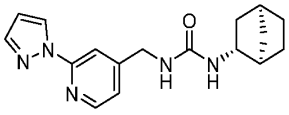
Table 1

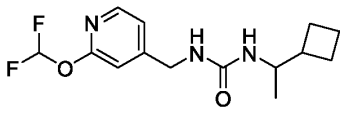
Example	Name	Structure	Kv7.2 EC_{50} (μM)	Kv7.2 max (%)
1	1-[(4R)-3,4-dihydro-2H-chromen-4-yl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea		2.42	54
2	1-cyclopentyl-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea		4.40	74
4	1-(3-chlorophenyl)-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea		0.43	60

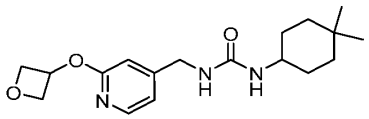
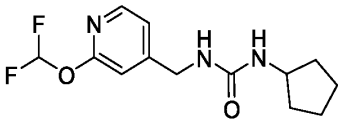
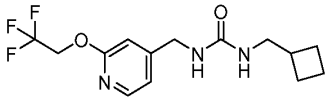
Example	Name	Structure	Kv7.2 EC_{50} (μM)	Kv7.2 max (%)
5	1-[(2-cyanopyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea		3.69	60
6	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea		1.14	58
7	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-		0.59	101

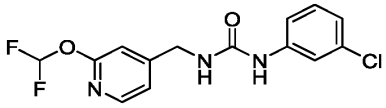
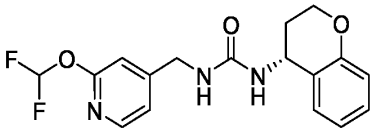
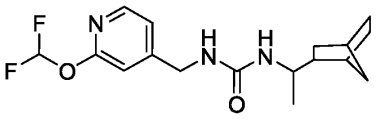
Example	Name	Structure	Kv7.2 EC_{50} (μM)	Kv7.2 max (%)
	bicyclo[2.2.1]heptanyl]urea			
8	1-(3-cyclopropylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea		1.52	52
9	1-[(2-imidazol-1-ylpyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea		0.70	53
10	1-[2-(cyclohexen-1-yl)ethyl]-3-[(2-pyrazol-1-		1.39	54

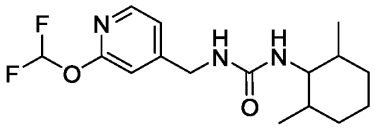
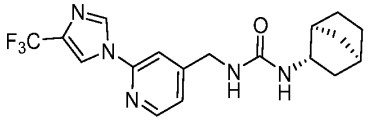
Example	Name	Structure	Kv7.2 EC_{50} (μM)	Kv7.2 max (%)
	ylpyridin-4-yl)methyl]urea			
12	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea		0.09	81
13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.33	56

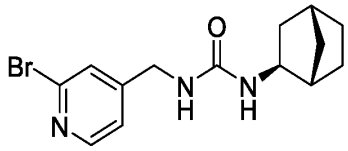
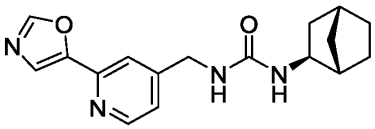
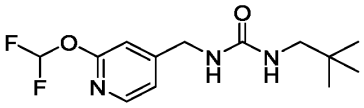
Example	Name	Structure	Kv7.2 EC_{50} (μM)	Kv7.2 max (%)
14	1-[(2-methoxypyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea		1.84	86
15	1-[(1S,2S,4R)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea		0.38	78
16	1-[(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-		0.39	73

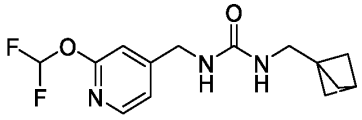
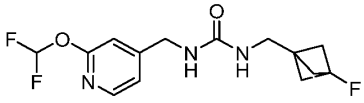
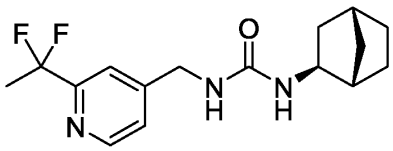
Example	Name	Structure	Kv7.2 EC_{50} (μM)	Kv7.2 max (%)
	3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea			
17	1-(1-cyclobutylethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.51	51

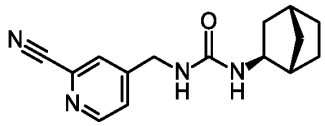
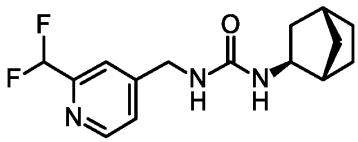
18	1-(4,4-dimethylcyclohexyl)-3-[[2-(oxetan-3-yloxy)pyridin-4-yl]methyl]urea		0.27	71
20	1-cyclopentyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.39	57
21	1-(cyclobutylmethyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.19	52

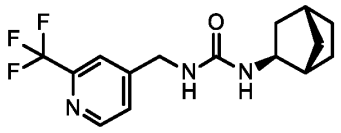
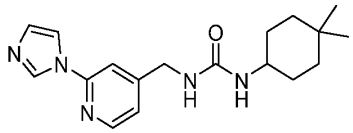
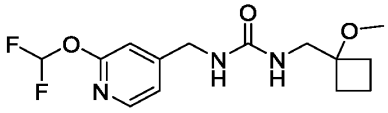
22	1-(3-chlorophenyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.03	41
23	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(4R)-3,4-dihydro-2H-chromen-4-yl]urea		0.13	52
24	1-[1-(2-bicyclo[2.2.1]heptanyl)ethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.02	76

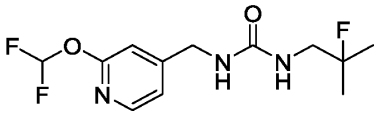
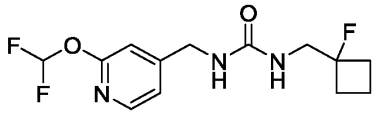
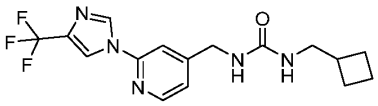
25	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,6-dimethylcyclohexyl)urea		0.03	75
26	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea		0.38	65

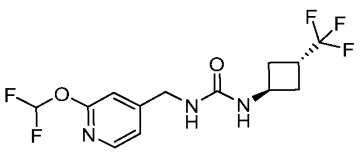
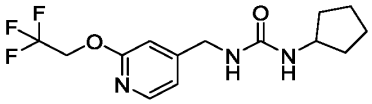
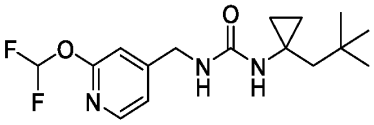
27	1-[(2-bromopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea		2.69	76
28	1-[[2-(1,3-oxazol-5-yl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea		8.28	76
29	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,2-dimethylpropyl)urea		0.57	63

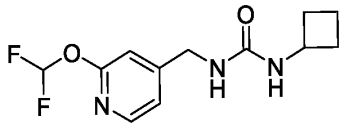
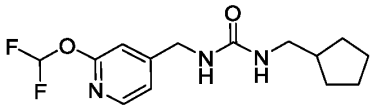
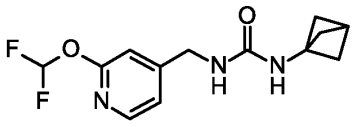
31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.42	57
32	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea		0.83	42
33	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea		0.26	80

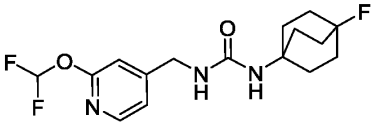
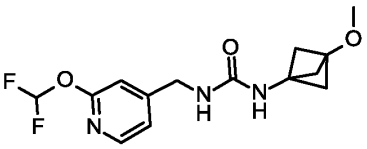
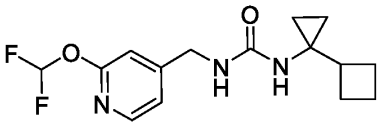
34	1-[(2-cyanopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea		2.77	49
35	1-[[2-(difluoromethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea		1.14	67

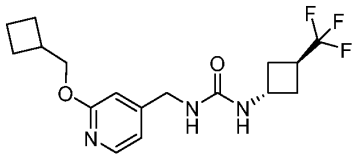
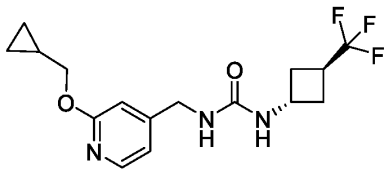
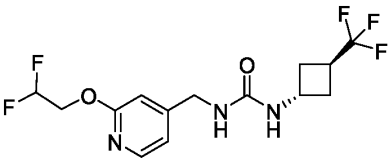
36	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea		0.54	64
37	1-(4,4-dimethylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea		1.31	59
38	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-methoxycyclobutyl)methyl]urea		3.73	73

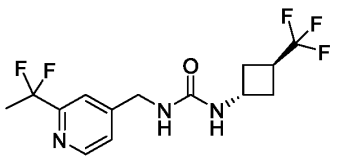
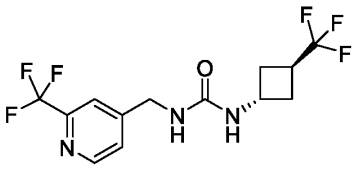
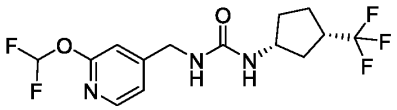
39	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-fluoro-2-methylpropyl)urea		1.95	55
40	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclobutyl)methyl]urea		0.64	58
41	1-(cyclobutylmethyl)-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea		1.13	40

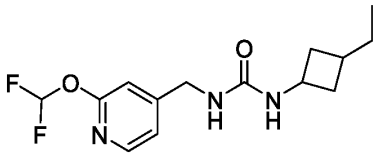
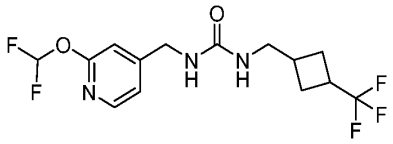
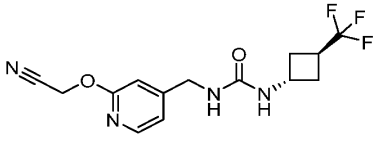
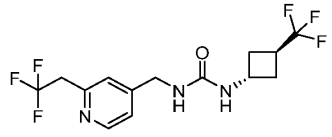
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.07	58
43	1-cyclopentyl-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.14	75
44	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2-dimethylpropyl)cyclopropyl]urea		0.48	75

45	1-cyclobutyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		1.23	62
46	1-(cyclopentylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.21	64
47	1-(1-bicyclo[1.1.1]pentanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		1.51	65

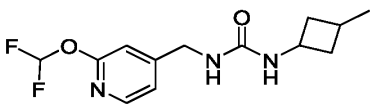
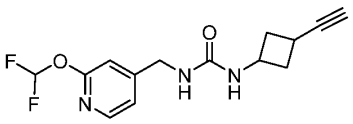
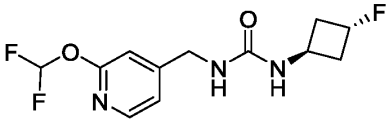
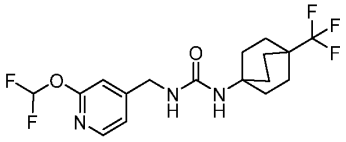
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea		0.16	54
49	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxy-1-bicyclo[1.1.1]pentanyl)urea		1.83	48
50	1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.30	56

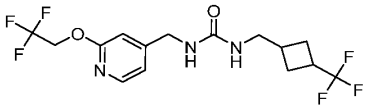
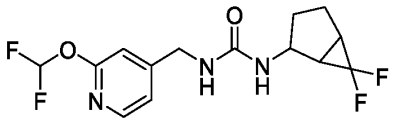
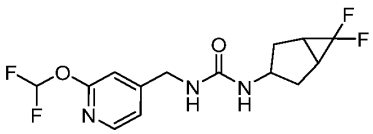
54	1-[[2-(cyclobutylmethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea		0.15	62
55	1-[[2-(cyclopropylmethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea		0.30	51
56	1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea		0.34	56

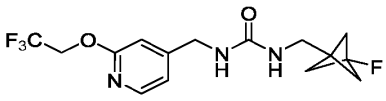
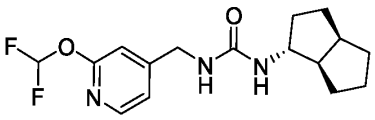
57	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea		0.61	60
58	1-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea		0.34	42
59	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea		0.11	65

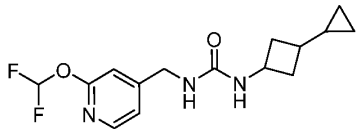
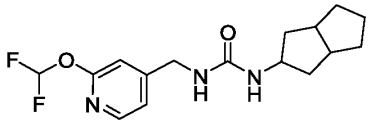
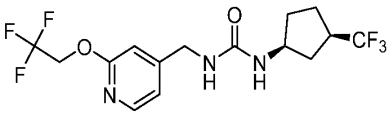
60	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethylcyclobutyl)urea		0.14	77
62	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea		0.75	43
63	1-[[2-(cyanomethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea		0.25	66
64	1-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-		0.34	70

	(trifluoromethyl)cyclobutyl]urea			

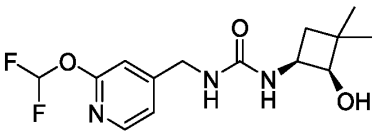
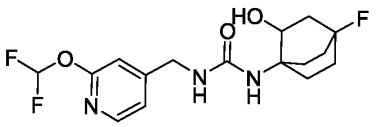
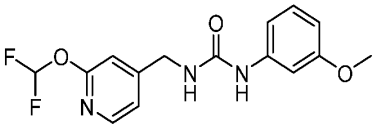
65	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylcyclobutyl)urea		0.45	76
66	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethynylcyclobutyl)urea		0.53	56
67	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1*r*,3*r*)-3-fluorocyclobutyl)urea		1.87	52
68	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[4-(trifluoromethyl)-1-		2.55	66

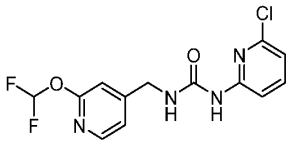
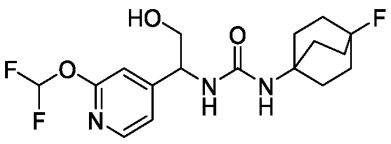
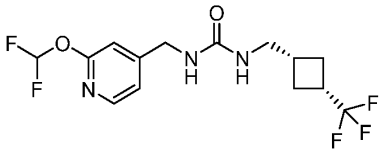
	bicyclo[2.2.2]octanyl]urea			
71	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea		0.23	53
73	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]urea		0.25	49
74	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-		0.17	58

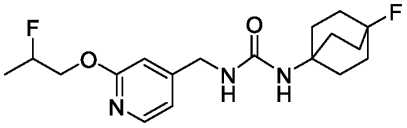
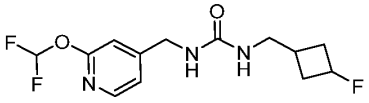
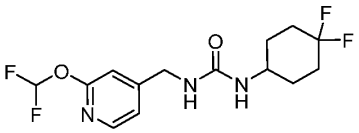
	bicyclo[3.1.0]hexanyl]urea			
75	1-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.60	40
76	1-[(1R,3aR,6aR)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.02	79

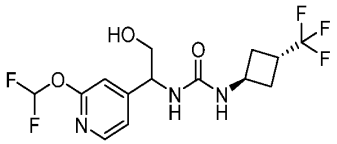
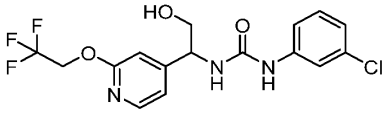
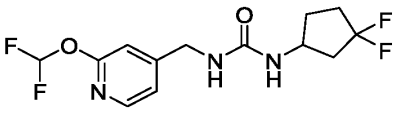
77	1-(3-cyclopropylcyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.09	62
78	1-(1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.02	62
79	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-		0.10	55

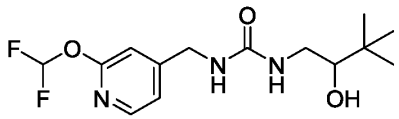
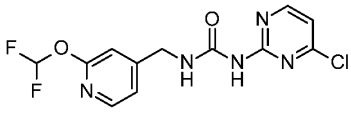
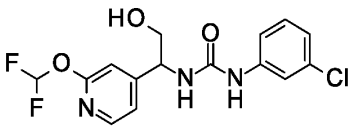
	yl]methyl]ure a			

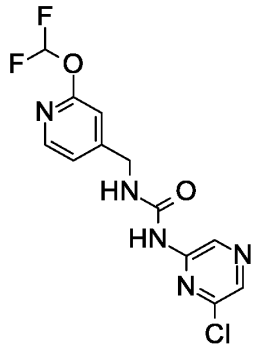
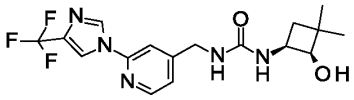
81	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]urea		1.36	73
82	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-2-hydroxy-1-bicyclo[2.2.2]octanyl)urea		1.03	48
83	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxyphenyl)urea		2.47	45

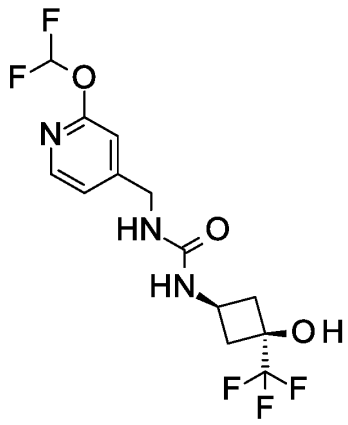
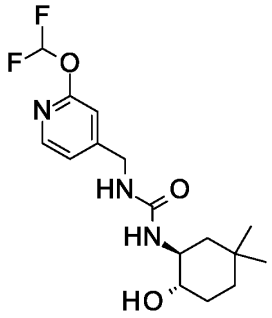
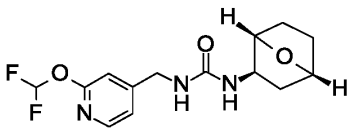
84	1-(6-chloropyridin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.21	42
85	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea		0.42	74
87	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(1r,3r)-(trifluoromethyl)cyclobutyl]methyl]urea		0.85	40

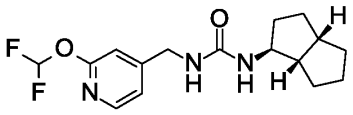
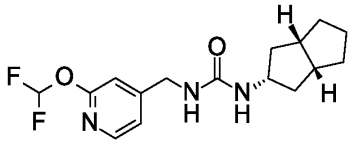
88	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea		0.44	43
89	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea		1.04	46
90	1-(4,4-difluorocyclohexyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.18	62

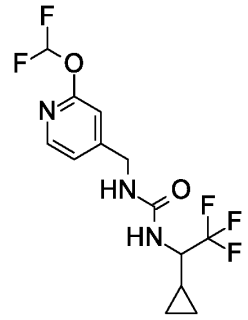
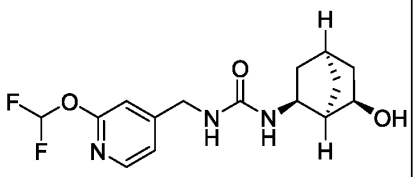
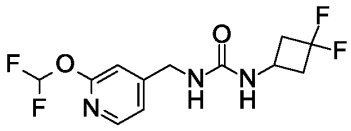
91	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea		1.26	82
92	1-(3-chlorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea		0.18	64
93	1-(3,3-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.45	56

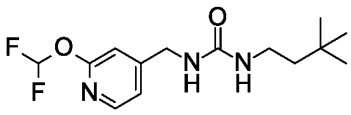
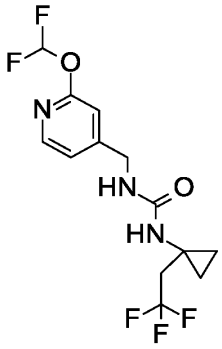
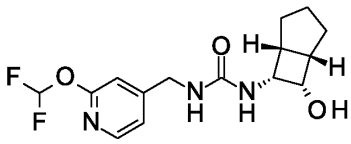
95	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea		1.16	43
96	1-(4-chloropyrimidin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		7.22	85
97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea		0.08	55

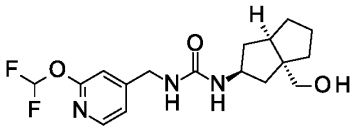
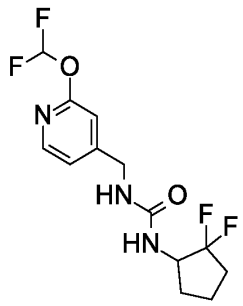
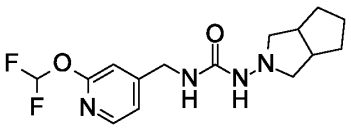
98	1-(6-chloropyrazin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.81	48
99	1-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea		6.51	44

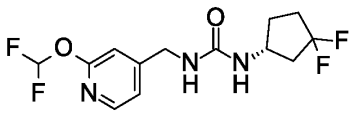
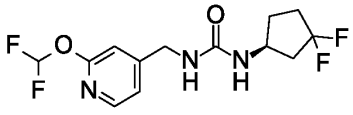
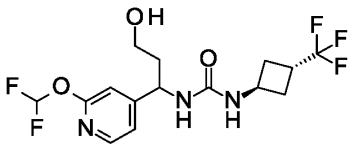
100	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-hydroxy-3-(trifluoromethyl)cyclobutyl]urea		3.66	40
101	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-5,5-dimethylcyclohexyl]urea		1.20	72
102	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S)-7-oxabicyclo[2.		5.86	71

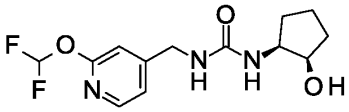
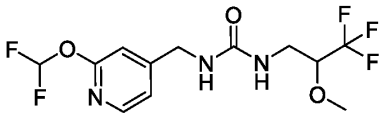
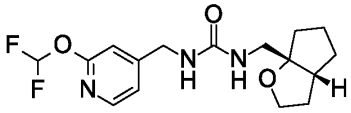
	2.1]heptan-2-yl]urea			
103	1-[(1S,3aS,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.03	71
105	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3aR,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]urea		0.04	78

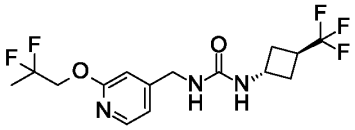
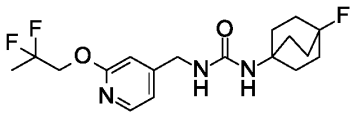
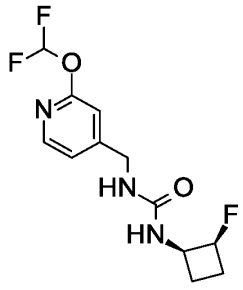
106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.82	47
107	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S,6R)-6-hydroxy-2-bicyclo[2.2.1]heptanyl]urea		1.70	95
108	1-(3,3-difluorocyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-		2.08	51

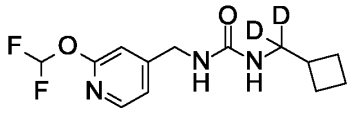
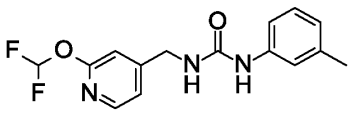
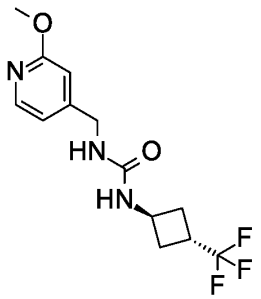
	yl]methyl]urea			
109	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-dimethylbutyl)urea		0.30	51
110	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2,2-trifluoroethyl)cyclopropyl]urea		1.23	40
111	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6S,7R)-7-hydroxy-6-bicyclo[3.2.0		2.78	63

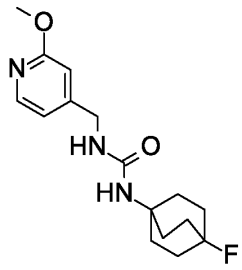
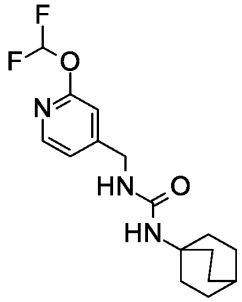
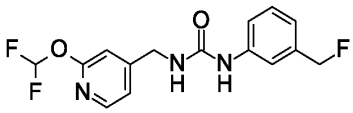
	]heptanyl]urea			
112	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(2R,3aS,6aS)-6a-(hydroxymethyl)-2,3,3a,4,5,6-hexahydro-1H-pentalen-2-yl]urea		4.91	49
113	1-(2,2-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		3.49	77
114	1-(3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]		7.43	68

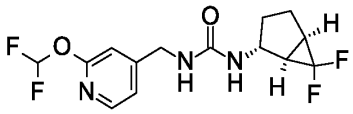
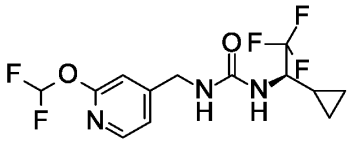
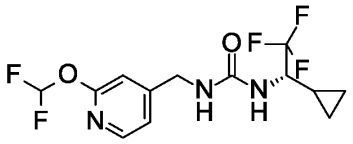
	pyrrol-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea			
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.33	48
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.32	58
117	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-3-hydroxyprop		1.90	94

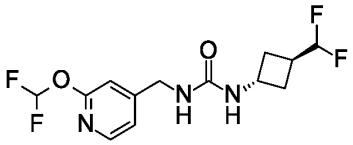
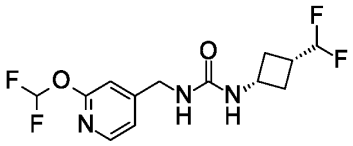
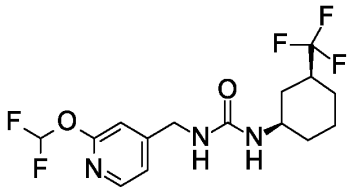
	yl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea			
118	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxycyclopentyl]urea		7.87	63
119	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3,3-trifluoro-2-methoxypropyl)urea		1.60	41
120	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[rac-(3aR,6aR)-2,3,3a,4,5,6-		3.45	53

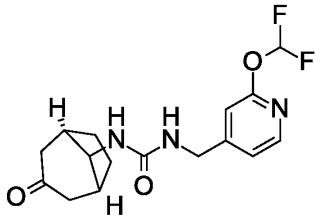
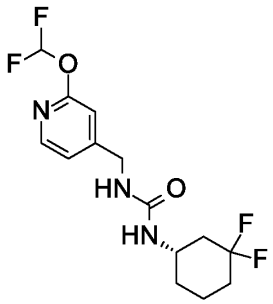
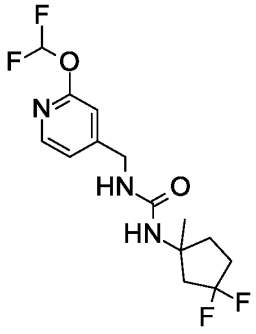
	hexahydrocyclopenta[b]furan-6a-yl]methyl]urea			
121	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.12	62
122	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea		0.19	61
123	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-		4.16	40

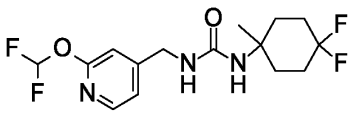
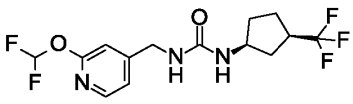
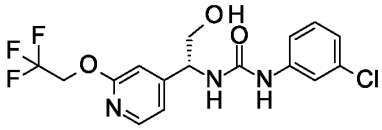
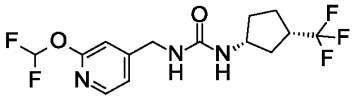
	fluorocyclobutyl]urea			
125	1-[cyclobutyl(dideuterio)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.75	62
126	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylphenyl)urea		0.65	50
128	1-[(2-methoxypyridin-4-yl)methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		5.36	75

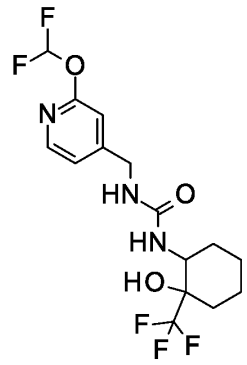
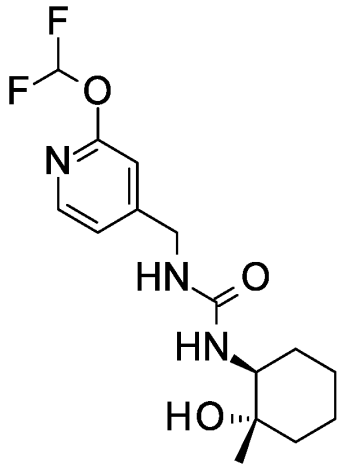
129	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[(2-methoxypyridin-4-yl)methyl]urea		4.97	53
131	1-(1-bicyclo[2.2.2]octanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.17	61
132	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(fluoromethyl)phenyl]urea		1.07	43

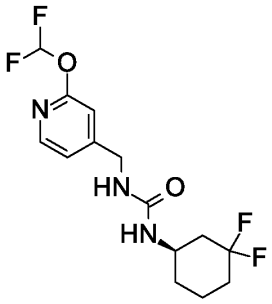
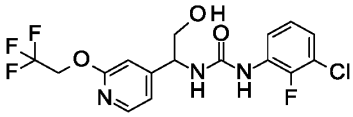
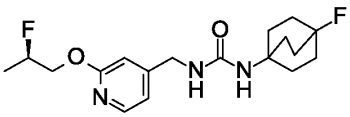
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.60	62
134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.55	43
135	1-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluorometh		1.11	68

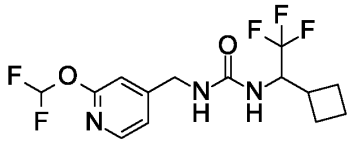
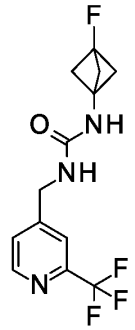
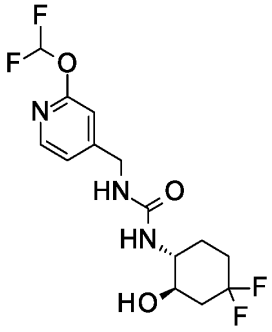
	oxy)pyridin-4-yl]methyl]urea			
136	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(difluoromethyl)cyclobutyl]urea		0.28	50
137	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(difluoromethyl)cyclobutyl]urea		2.41	48
138	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromet		0.10	40

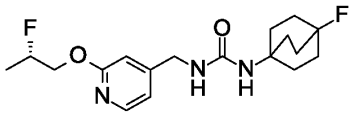
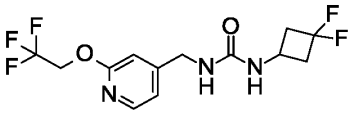
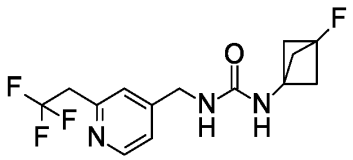
	hyl)cyclohexyl]urea			
139	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3-oxo-8-bicyclo[3.2.1]octanyl]urea		5.25	61
140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.10	42
142	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-difluoro-1-methylcyclopentyl)urea		1.03	40

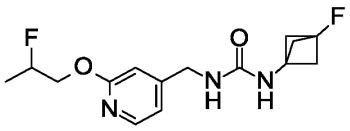
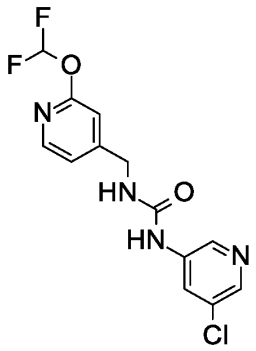
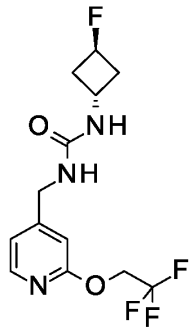
143	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4,4-difluoro-1-methylcyclohexyl)urea		1.05	40
144	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3R)-3-(trifluoromethyl)cyclopentyl]urea		0.22	48
145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea		0.08	58
146	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-		0.16	68

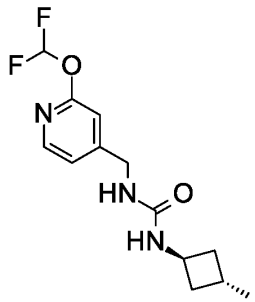
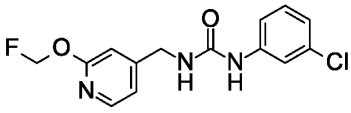
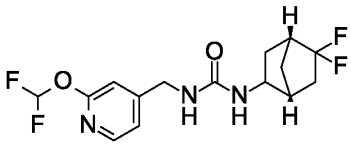
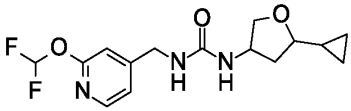
	3-[(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea			
147	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-hydroxy-2-(trifluoromethyl)cyclohexyl]urea		0.54	56
148	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-2-methylcyclohexyl]urea		5.07	64

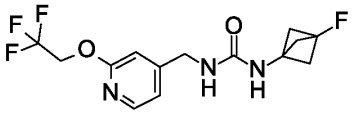
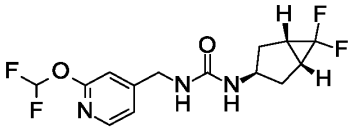
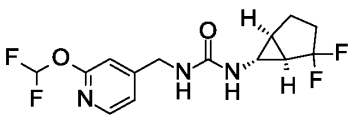
149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.24	43
150	1-(3-chloro-2-fluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea		0.08	73
151	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]urea		0.65	42

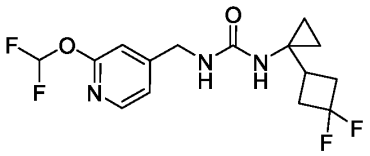
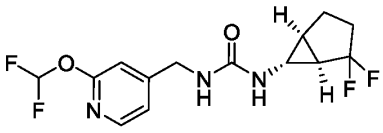
152	1-(1-cyclobutyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.14	64
153	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea		7.27	41
154	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-4,4-difluoro-2-		2.13	60

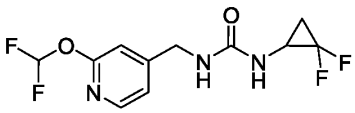
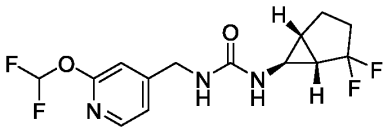
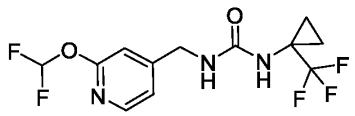
	hydroxycyclohexyl]urea			
156	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]urea		0.56	50
157	1-(3,3-difluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.38	50
159	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-		5.18	67

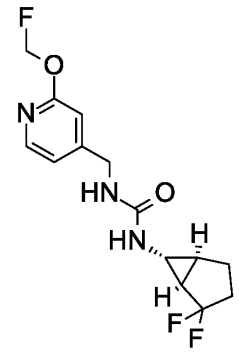
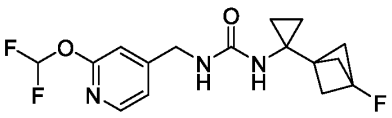
	yl]methyl]urea			
160	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea		6.31	61
161	1-(5-chloropyridin-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		1.05	43
162	1-((1r,3r)-3-fluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.19	50

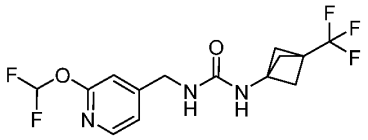
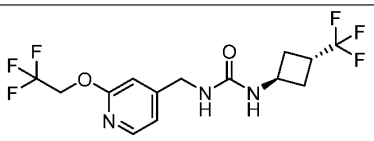
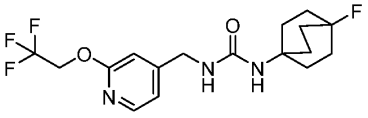
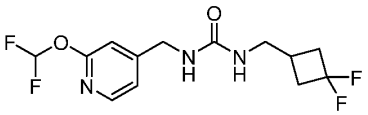
163	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1r,3r)-3-methylcyclobutyl)urea		0.24	83
164	1-(3-chlorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea		1.72	78
165	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,4R)-5,5-difluoro-2-bicyclo[2.2.1]heptanyl]urea		0.25	94
166	1-(5-cyclopropyloxolan-3-yl)-		3.33	66

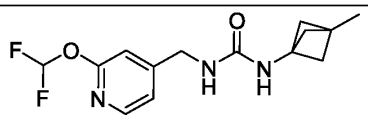
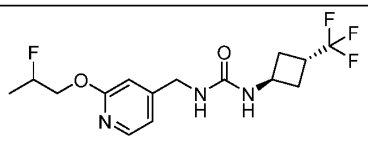
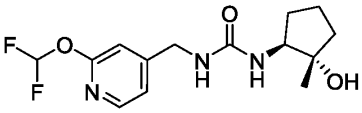
	3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea			
168	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.21	59
169	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea		0.34	69
170	1-[(1R,5S,6R)-2,2-difluoro-6-		0.08	59

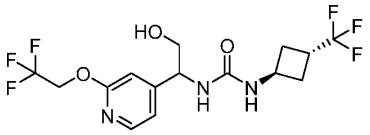
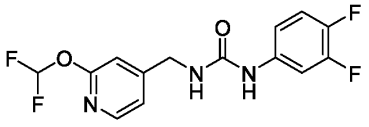
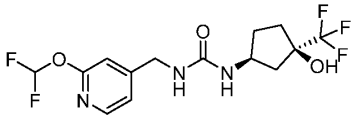
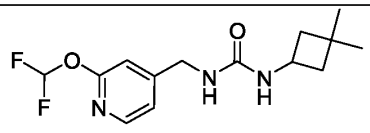
	bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea			
171	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.36	48
172	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]urea		0.46	66

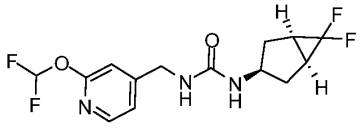
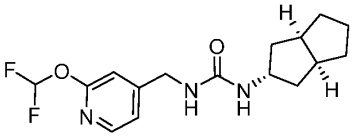
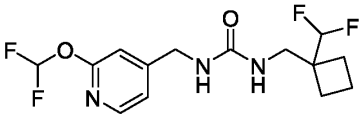
173	1-(2,2-difluorocyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		4.40	57
174	1-[(1S,5R,6S)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.20	51
175	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(trifluoromet		8.30	50

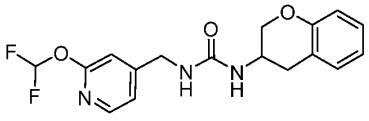
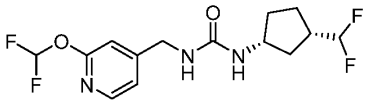
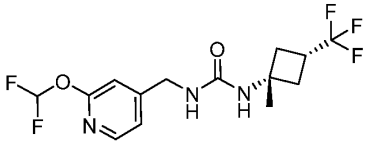
	hyl)cyclopropyl]urea			
176	1-[[2-(fluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]urea		0.89	62
177	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)cyclopropyl]urea		1.40	43
Example	**Name**	**Structure**	**Kv7.2 EC_{50} (μM)**	**Kv7.2 max (%)**

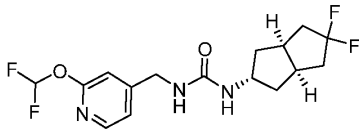
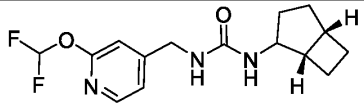
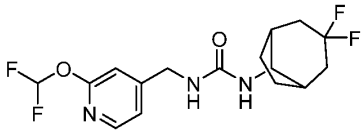
178	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea		1.86	62
179	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.02	48
180	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.31	72
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluorometh		0.66	41

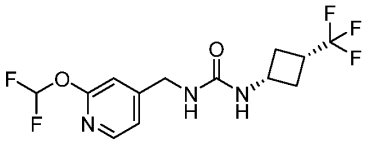
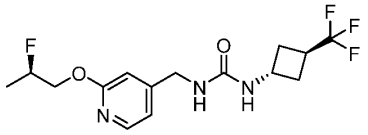
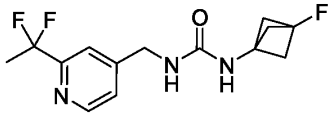
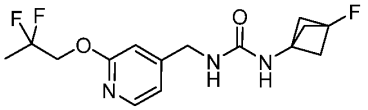
	oxy)pyridin-4-yl]methyl]urea			
182	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methyl-1-bicyclo[1.1.1]pentanyl)urea		0.09	63
183	1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.26	58
184	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,2S)-2-hydroxy-2-methylcyclopentyl]urea		1.81	55

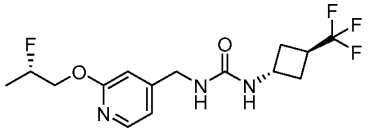
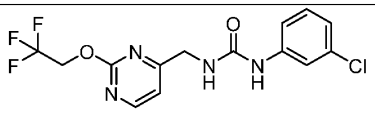
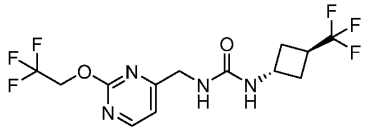
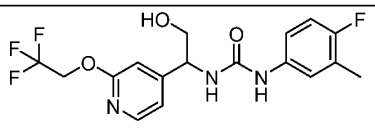
185	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.38	84
186	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-difluorophenyl)urea		0.55	62
187	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-hydroxy-3-(trifluoromethyl)cyclopentyl]urea		1.14	40
188	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-		0.05	82

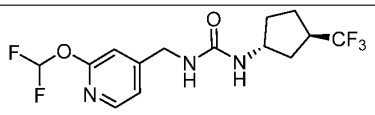
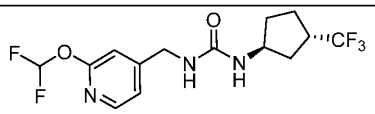
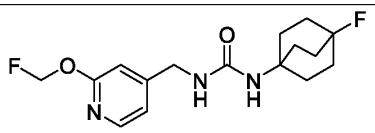
	dimethylcyclobutyl)urea			
189	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3r,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea		0.13	74
190	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2s,3aR,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]urea		0.03	85
191	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluorometh		0.45	68

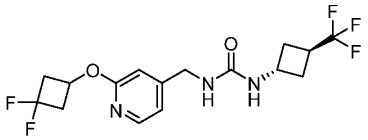
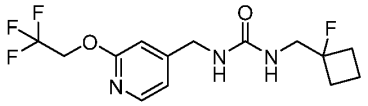
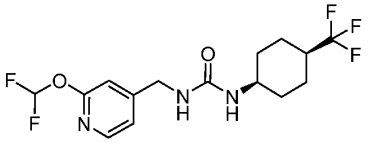
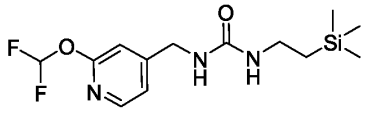
	yl)cyclobutyl]methyl]urea			
192	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-dihydro-2H-chromen-3-yl)urea		0.24	51
193	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(difluoromethyl)cyclopentyl]urea		0.22	48
194	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-1-methyl-3-(trifluoromethyl)cyclobutyl]urea		1.54	40

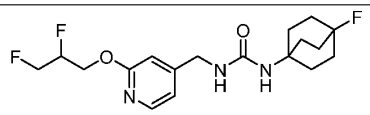
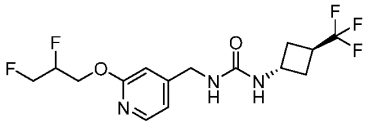
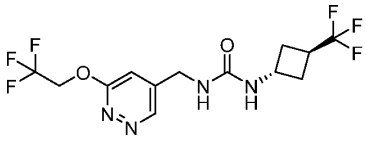
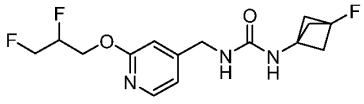
195	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2r,3aR,6aS)-5,5-difluoro-2,3,3a,4,6,6a-hexahydro-1H-pentalen-2-yl]urea		0.29	51
196	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5R)-2-bicyclo[3.2.0]heptanyl]urea		0.07	75
197	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3,3-difluoro-8-bicyclo[3.2.1]octanyl]urea		0.50	54

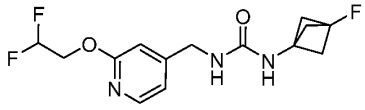
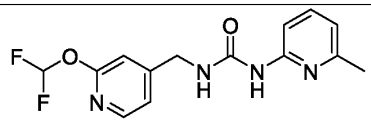
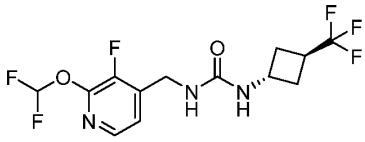
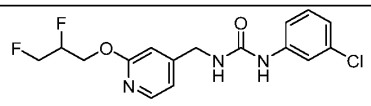
198	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(trifluoromethyl)cyclobutyl]urea		0.40	65
199	1-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.29	52
200	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea		4.93	54
201	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1		0.21	60

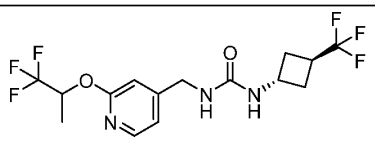
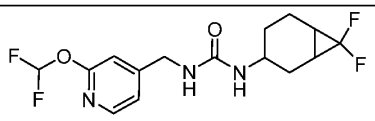
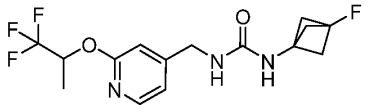
	]pentanyl)urea			
202	1-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.26	57
203	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]urea		0.21	42
204	1-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.34	45
205	1-(4-fluoro-3-methylphenyl)-3-[2-		0.24	64

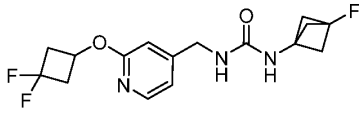
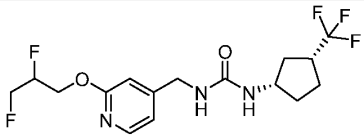
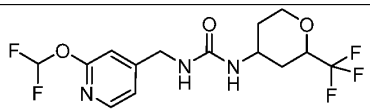
	hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea			
206	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3R)-3-(trifluoromethyl)cyclopentyl]urea		0.49	75
207	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-(trifluoromethyl)cyclopentyl]urea		0.23	58
208	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea		0.47	58

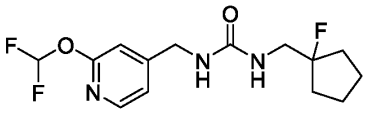
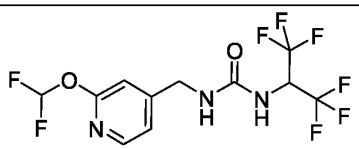
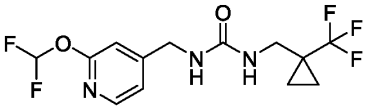
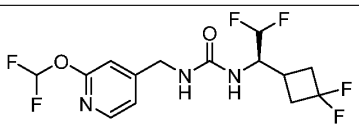
209	1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.49	71
210	1-[(1-fluorocyclobutyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.16	48
211	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,4s)-4-(trifluoromethyl)cyclohexyl]urea		0.32	61
212	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-		0.40	82

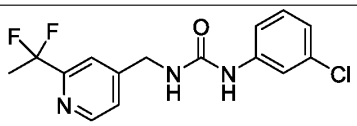
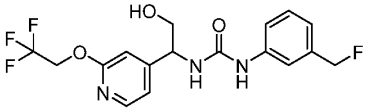
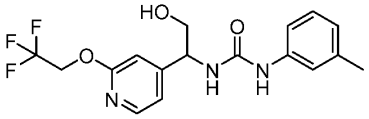
	trimethylsilylethyl)urea			
213	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea		0.34	47
214	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.50	54
215	1-[[6-(2,2,2-trifluoroethoxy)pyridazin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		6.83	40
216	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1		1.47	50

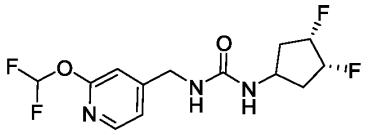
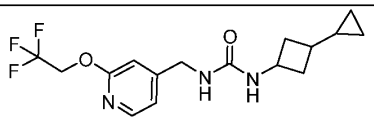
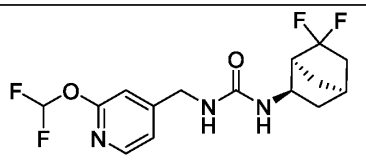
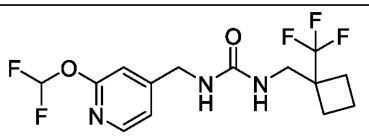
	]pentanyl)urea			
217	1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea		0.31	43
218	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(6-methylpyridin-2-yl)urea		1.49	54
219	1-[[2-(difluoromethoxy)-3-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.38	48
220	1-(3-chlorophenyl)-3-[[2-(2,3-difluoropropo		0.46	48

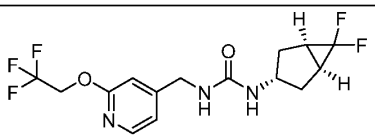
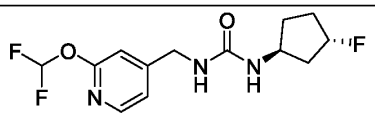
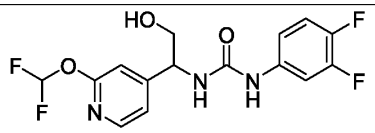
	xy)pyridin-4-yl]methyl]urea			
221	1-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(1,1,1-trifluoropropan-2-yloxy)pyridin-4-yl]methyl]urea		0.07	78
222	1-(7,7-difluoro-3-bicyclo[4.1.0]heptanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.18	76
223	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(1,1,1-trifluoropropan-2-yloxy)pyridin		0.21	66

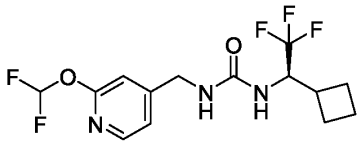
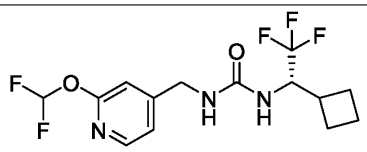
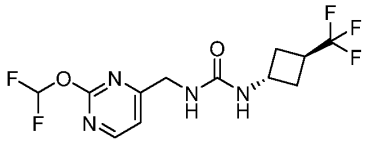
	-4-yl]methyl]urea			
224	1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea		0.54	40
225	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea		0.31	52
226	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(trifluoromethyl)oxan-4-yl]urea		2.45	40

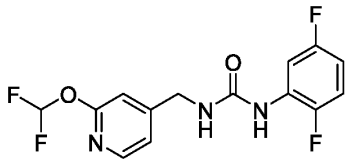
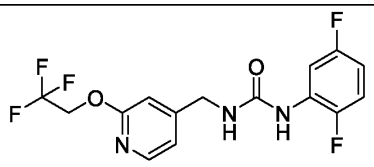
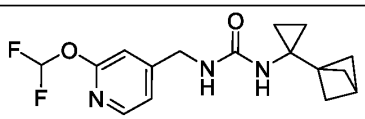
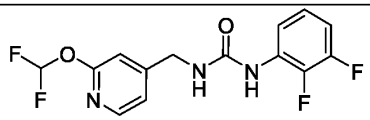
227	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclopentyl)methyl]urea		0.41	49
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea		0.26	58
229	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea		0.60	49
230	1-[(1R)-1-(3,3-difluorocyclobutyl)-2,2-difluoroethyl]-3-[[2-		1.09	55

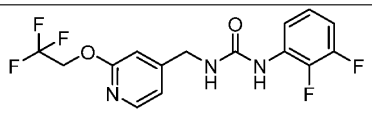
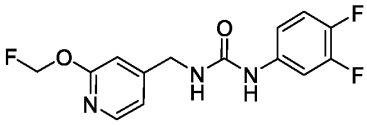
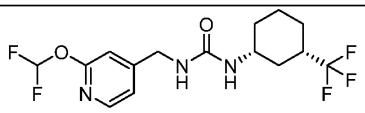
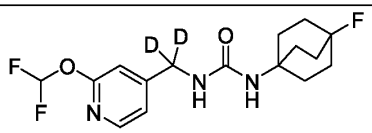
	(difluoromethoxy)pyridin-4-yl]methyl]urea			
231	1-(3-chlorophenyl)-3-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]urea		0.80	51
232	1-[3-(fluoromethyl)phenyl]-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea		0.25	47
233	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-(3-methylphenyl)urea		0.13	68

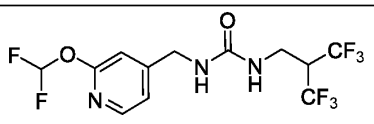
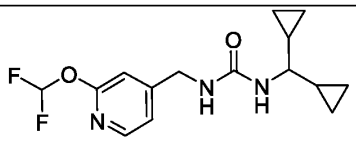
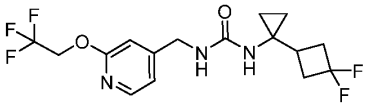
234	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(3R,4S)-3,4-difluorocyclopentyl]urea		4.27	56
235	1-(3-cyclopropylcyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.08	88
236	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S)-6,6-difluoro-2-bicyclo[2.2.1]heptanyl]urea		0.46	87
237	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-		0.16	54

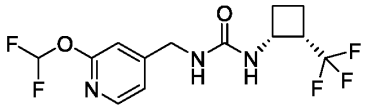
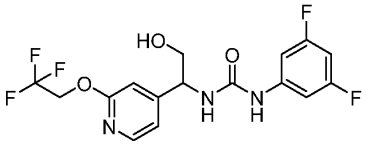
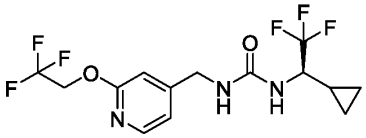
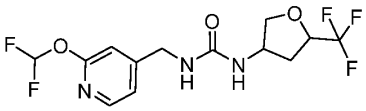
	(trifluoromethyl)cyclobutyl]methyl]urea			
238	1-[(1R,3s,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.06	79
239	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-fluorocyclopentyl]urea		0.44	57
240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea		0.30	55

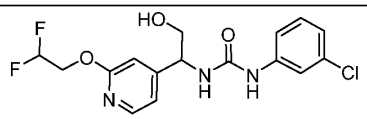
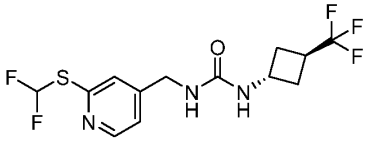
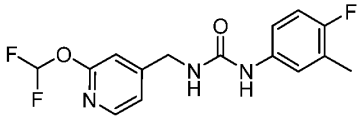
241	1-[(1R)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.07	68
242	1-[(1S)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.75	51
243	1-[[2-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.76	42

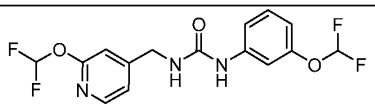
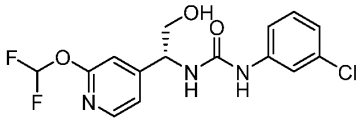
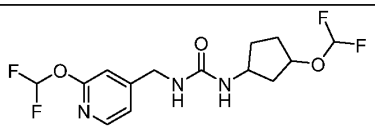
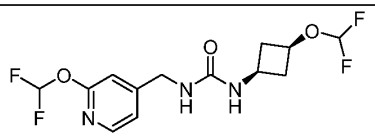
244	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,5-difluorophenyl)urea		0.25	50
245	1-(2,5-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.05	54
246	1-[1-(1-bicyclo[1.1.1]pentanyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.54	60
247	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3-		0.09	53

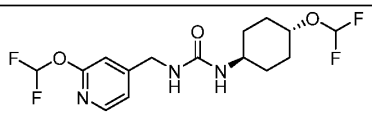
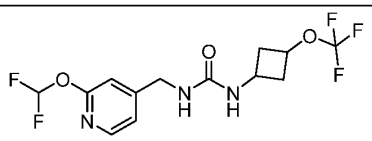
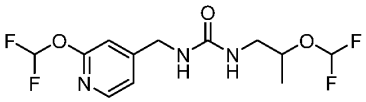
	difluorophenyl)urea			
248	1-(2,3-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.14	62
249	1-(3,4-difluorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea		0.26	43
250	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea		0.12	75
251	1-[dideuterio-[2-(difluoromethoxy)pyridin-4-yl]methyl]-		0.13	60

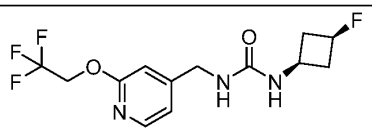
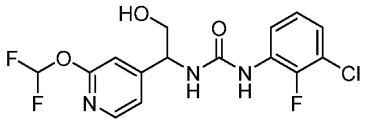
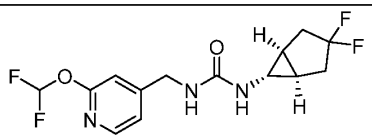
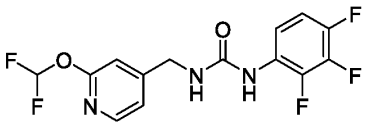
	3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea			
252	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea		0.72	73
253	1-(dicyclopropylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.32	70
254	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		1.01	40

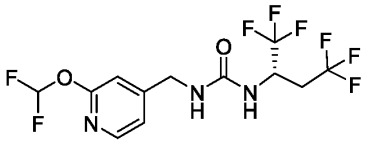
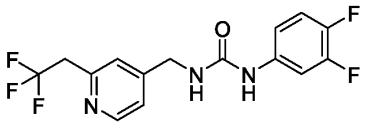
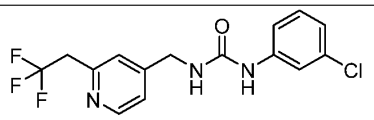
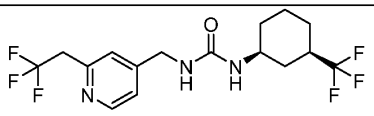
255	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-(trifluoromethyl)cyclobutyl]urea		2.57	78
256	1-(3,5-difluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea		0.03	84
257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.24	61
258	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[5-		0.50	53

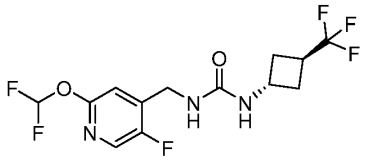
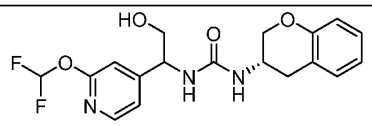
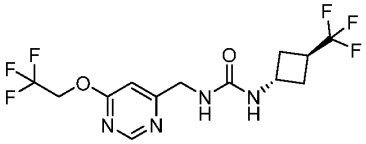
	(trifluoromethyl)oxolan-3-yl]urea			
259	1-(3-chlorophenyl)-3-[1-[2-(2,2-difluoroethoxy)pyridin-4-yl]-2-hydroxyethyl]urea		0.24	63
260	1-[[2-(difluoromethylsulfanyl)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.37	51
261	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-3-methylphenyl)urea		0.07	40

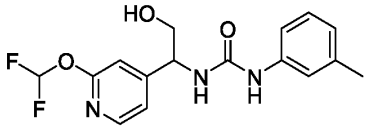
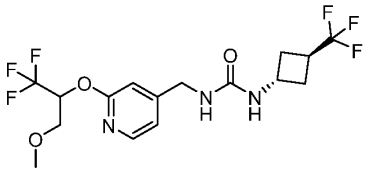
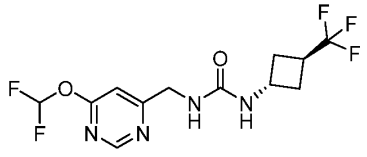
262	1-[3-(difluoromethoxy)phenyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		3.51	65
263	rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea		0.31	73
264	1-[3-(difluoromethoxy)cyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.43	49
265	1-[(1s,3s)-3-(difluoromethoxy)cyclobutyl]-3-[[2-(difluorometh		0.47	47

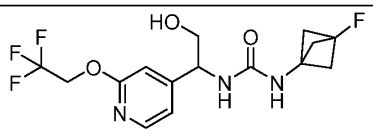
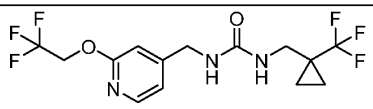
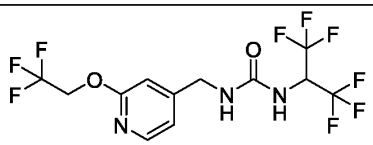
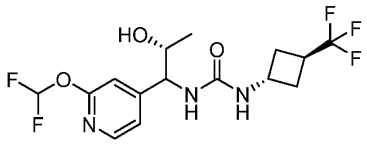
	oxy)pyridin-4-yl]methyl]urea			
266	1-[(1r,4r)-4-(difluoromethoxy)cyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.30	49
267	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethoxy)cyclobutyl]urea		0.29	51
268	1-[2-(difluoromethoxy)propyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		1.88	39

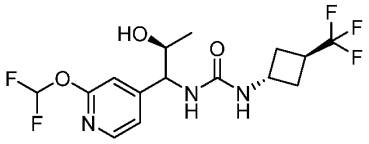
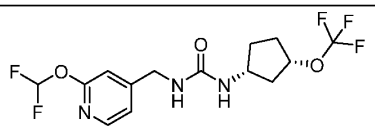
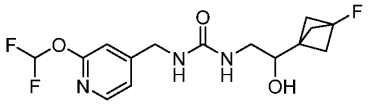
269	1-((1s,3s)-3-fluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.35	46
270	1-(3-chloro-2-fluorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea		0.17	65
271	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-3,3-difluoro-6-bicyclo[3.1.0]hexanyl]urea		0.34	42
272	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3,4-		0.91	44

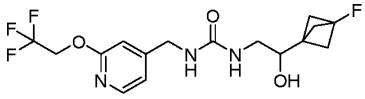
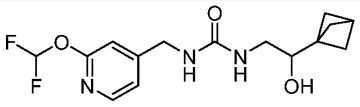
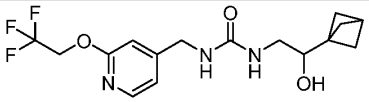
	trifluorophenyl)urea			
273	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea		0.89	48
274	1-(3,4-difluorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea		0.36	48
275	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea		0.55	59
276	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]-3-[[2-		0.54	62

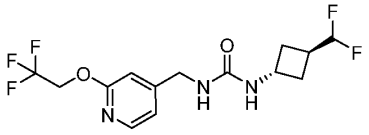
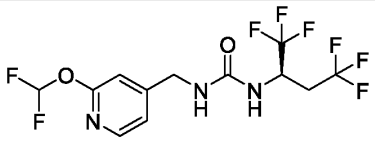
	(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea			
277	1-[[2-(difluoromethoxy)-5-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.33	58
278	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(3S)-3,4-dihydro-2H-chromen-3-yl]urea		0.43	52
279	1-[[6-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromet		0.17	75

	hyl)cyclobutyl]urea			
280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea		0.25	67
281	1-[[2-(1,1,1-trifluoro-3-methoxypropan-2-yl)oxypyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea		0.20	59
282	1-[[6-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.09	78

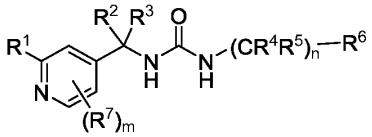
283	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea		0.49	68
284	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea		0.99	82
285	1-(1,1,1,3,3,3-hexafluoropropan-2-yl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.38	87
286	1-[(2R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyprop		0.55	66

	yl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea			
287	1-[(2S)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea		0.74	96
288	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethoxy)cyclopentyl]urea		0.25	68
289	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-		0.98	40

	hydroxyethyl]urea			
290	1-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.89	81
291	1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea		0.46	64
292	1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-		0.62	62

	yl]methyl]urea			
293	1-[(1r,3r)-3-(difluoromethyl)cyclobutyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea		0.61	93
294	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea			

In one embodiment, the present invention provides a compound of formula (I*), or a solvate or a pharmaceutically acceptable salt thereof:



(I*)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

R^7 is halogen, and

m is 0, 1, 2, or 3.

In one embodiment, the present invention provides a compound of formula (I*), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^7 is F- or Cl-.

In one embodiment, the present invention provides a compound of formula (I*), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^7 is F-.

In one embodiment, the present invention provides a compound of formula (I*), or a solvate or a pharmaceutically acceptable salt thereof, wherein m is 1 or 2.

In one embodiment, the present invention provides a compound of formula (I*), or a solvate or a pharmaceutically acceptable salt thereof, wherein m is 0.

In one preferred embodiment, the present invention provides a compound of formula (I*), or a solvate pharmaceutically acceptable salt thereof, wherein m is 1.

In one embodiment, the present invention provides a compound of formula (I*), or a solvate or a pharmaceutically acceptable salt thereof, wherein m is 2.

In one embodiment, the present invention provides a compound of formula (I*), or a or a solvate or a pharmaceutically acceptable salt thereof, wherein m is 3.

In one embodiment, the present invention provides a compound of formula (I*), or a pharmaceutically acceptable salt thereof, wherein m is 1 and R^7 is F-.

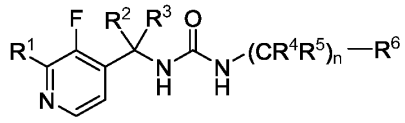
In one preferred embodiment, the present invention provides a compound of formula (I*), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0 or 1, m is 1, and R^7 is F-.

In one embodiment, the present invention provides a compound of formula (I*), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, n, and R^6 are as described herein, m is 1 and R^7 is F-.

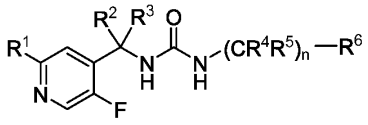
In one embodiment, the present invention provides a compound of formula (I*), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, and R^6 are as described herein, n is 0 or 1, m is 1 and R^7 is F-.

In one embodiment, the present invention provides a compound of formula (I*), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^7 is in ortho- or meta-position of the N-atom in the pyridine ring of formula (I*).

In one embodiment, the present invention provides a compound of formula (I*), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^7 is in meta-position of the N-atom in the pyridine ring of formula (I) and the compound has the formula (I**):



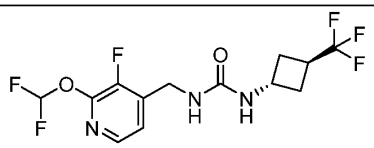
or

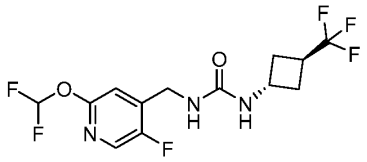


both (I**)

In all of the herein embodiments selected from any of formulae (I*) and (I**), or a solvate or a pharmaceutically acceptable salt thereof, R^1, R^2, R^3, R^4, R^5, n and R^6 are as described herein, i.e. including any combination of R^1, R^2, R^3, R^4, R^5, n and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I*) or (I**), or a pharmaceutically acceptable salt thereof, wherein R^7 is F and a non-limiting example is:

219	1-[[2-(difluoromethoxy)-3-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

277	1-[[2-(difluoromethoxy)-5-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

The halogen atoms can be introduced into the molecule by any method known to the skilled person.

The F- atoms can be introduced into the molecule by any method known to the skilled person.

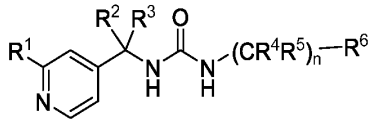
The compounds were characterized as described herein.

In some embodiments of the invention, one or more hydrogen atoms is (are) replaced by a deuterium. It has been surprisingly found that deuteration of the compounds of the present invention offer the advantage of retaining the pharmacological profile of their hydrogen counterparts while positively impacting their metabolic outcome. Selective replacement of one or more hydrogen with deuterium, in the compounds of the present invention, improves the pharmaceutical profile of compounds of this invention, e.g. by reducing the amount of undesired metabolites when compared to its all hydrogen counterparts and by lowering rates of metabolim, and hence increasing half-life.

Methods for incorporation of deuterium into compounds are well established. Using metabolic studies established in the art, the compound of the present invention can be tested to identify sites for selective placement of a deuterium isotope, which isotope will not be metabolized or be metabolized at a lower rate. Moreover, these studies identify sites of metabolism as the location where a deuterium atom would be placed.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one or more of the hydrogen atoms attached to the compound of formula (I), or a solvate or a pharmaceutically acceptable salt are replaced with deuterium.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof



(I)

wherein one or more of R^2, R^3, R^4, or R^5 is (are) deuterium and the others are as described herein, and R^6 is selected from;

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

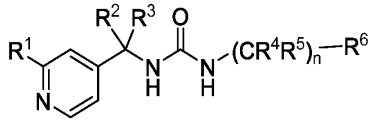
d) phenyl; or

e) haloC_{1-6}alkyl;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, , heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, bicyclic edge-to-edge fused

cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof



(I)

wherein one or more of R^2, R^3, R^4, or R^5 is (are) deuterium and the others are as described herein, and R^6 is selected from;

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

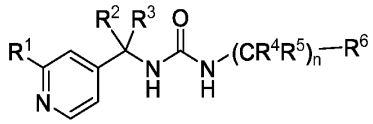
b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

wherein the bicyclic edge-to-edge fused heterocycloalkyl, bridged heterocycloalkyl, heteroaryl, saturated monocyclic cycloalkyl, cycloalkenyl, bridged cycloalkyl, or bicyclic edge-to-edge fused cycloalkyl are optionally substituted with one, two, or three substituents independently selected

from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl

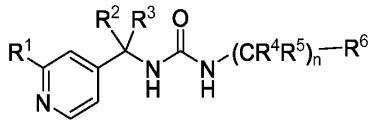
In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof



(I)

wherein one or more of R^2, R^3, R^4, or R^5 is (are) deuterium and the others are as described herein, and R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof



(I)

wherein one or more of R^2, R^3, R^4, or R^5 is (are) deuterium and the others are as described herein, and R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl,

oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6} alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one or both of R^2 and R^3 is (are) deuterium.

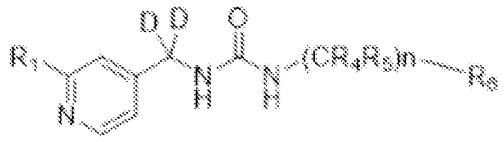
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein both of R^2 and R^3 are deuterium.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein both of R^2 and R^3 are deuterium, R^1 is haloC_{1-6}alkoxy and R^4, R^5, n, and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein both of R^2 and R^3 are deuterium, R^1 is haloC_{1-6}alkoxy selected from CHF_2O-, CF_3CH_2O-, CF_2HCH_2O-, $CH_3CF_2CH_2O$-, and CH_3CFHCH_2O- and R^4, R^5, n, and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein both of R^2 and R^3 are deuterium, R^1 is CHF_2O- or CF_3CH_2O-, and R^4, R^5, n, and R^6 are as described herein.

In one preferred embodiment, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein both of R^2 and R^3 are deuterium, R^1, R^4, R^5, n, and R^6 are as described herein and a non-limiting example with formula (II) is:



(II)

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is deuterium and the other one is as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is deuterium and the other one is as described herein, R^1, R^4, R^5, n, and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is deuterium and the other one is as described herein, R^1 is halo$C_{1\text{-}6}$alkoxy and R^4, R^5, n, and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is deuterium and the other one is as described herein, R^1 is halo$C_{1\text{-}6}$alkoxy selected from CHF_2O-, CF_3CH_2O-, CF_2HCH_2O-, $CH_3CF_2CH_2O$-, and CH_3CFHCH_2O-, R^4, R^5, n, and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is deuterium and the other one is as described herein, R^1 is CHF_2O- or CF_3CH_2O-, and R^4, R^5, n, and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, and one of R^4 and R^5 is deuterium and the other one is as described herein or both of R^4 and R^5.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, and both of R^4 and R^5 are deuterium.

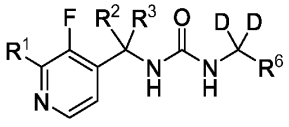
In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein wherein n is 1, and both of R^4 and R^5 are deuterium, R^1 is halo$C_{1\text{-}6}$alkoxy and R^2, R^3, and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, and both of R^4 and R^5 are deuterium, R^1 is halo$C_{1\text{-}6}$alkoxy selected from CHF_2O-, CF_3CH_2O-, CF_2HCH_2O-, $CH_3CF_2CH_2O$-, and CH_3CFHCH_2O-, R^2, R^3, and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1, and both of R^4 and R^5 are deuterium, R^1 is CHF_2O- or CF_3CH_2O-, and R^2, R^3, and R^6 are as described herein.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1 and both of R^4 and R^5 are deuterium and R^1 is CHF_2O-, and R^2, R^3, and R^6 are as described herein.

In one preferred embodiment, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein n is 1 and both of R^2 and R^3 are deuterium, R^1, R^4, R^5, and R^6 are as described herein and a non-limiting example with formula (III) is:



(III)

In one embodiment, the present invention provides a compound of formula (III), or a solvate or a pharmaceutically acceptable salt thereof, wherein both of R^4 and R^5 are deuterium and R^1 is CHF_2O-, R^2 and R^3 are hydrogen, n, and R^6 are as described herein

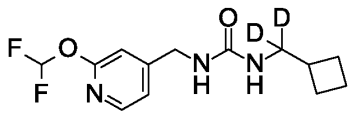
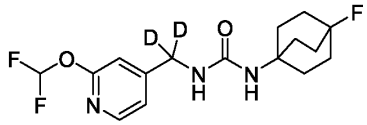
In one embodiment, the present invention provides a compound of formula (III), or a solvate or a pharmaceutically acceptable salt thereof, wherein both of R^4 and R^5 are deuterium and R^1 is CHF_2- or CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, and R^6 is as described herein.

In one embodiment, the present invention provides a compound of formula (III), or a solvate or a pharmaceutically acceptable salt thereof, wherein both of R^4 and R^5 are deuterium and R^1, R^2, R^3 are as described herein, n is 1, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (III), or a solvate or a pharmaceutically acceptable salt thereof, wherein both of R^4 and R^5 are deuterium and R^1, R^2, R^3 are as described herein, n is 1, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

In one embodiment, the present invention provides a compound of formula (III), or a solvate or a pharmaceutically acceptable salt thereof, wherein both of R^4 and R^5 are deuterium and R^1, R^2, R^3 are as described herein, n is 1, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are unsubstituted.

In one embodiment, the present invention provides a compound of formula (III), or a pharmaceutically acceptable salt thereof, wherein n is 1, both of R^4 and R^5 are deuterium and a non-limiting example is:

125	1-[cyclobutyl(dideuterio)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
251	1-[dideuterio-[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2 or 3 and only in one pair R^4 and R^5 both are deuterium, while the other pair(s) of R^4 and R^5 are as described herein.

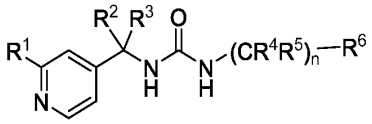
In embodiments, when n is 2 or 3, one pair of R^4 and R^5 are deuterium and the other pair(s) of R^4 and R^5 is (are) hydrogen.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 2 or 3 and only in first pair R^4 and R^5 both are deuterium, while the other pair(s) of R^4 and R^5 are as described herein.

Compounds having one or more of the following combinations of features are found to display particularly beneficial Kv7.2 EC_{50} values and/or Kv7.3_7.5/Kv7.2 selectivity ratios.

Compounds having one or more of the following combinations of features are found to display particulary beneficial Kv7.2 EC_{50} values and/or Kv7.3_7.5/Kv7.2 selectivity ratios in the range of: EC_{50}<3μM, Select.>10x, EC_{50}<1μM, Select.>30x or EC_{50}<1μM, Select.>30x with a favorable pharmacogical profile.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is haloC_{1-6}alkoxy or 5 membered heteroaryl, wherein the heteroaryl is optionally with one, two, or three substituents independently seletected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl;

R^2 and R^3 are hydrogen;

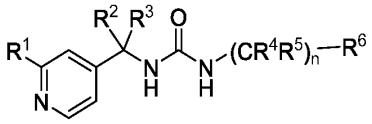
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached form unsubstituted cyclopropyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, 6 membered heteroaryl, 4-10 membered cycloalkyl, and phenyl, wherein the 5-12 membered heterocycloalkyl, 6 membered heteroaryl, 4-10 membered cycloalkyl, and phenyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is haloC_{1-6}alkoxy or 5 membered heteroaryl, wherein the heteroaryl is optionally substituted with one, two, or three substituents independently seletected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl;

R^2 and R^3 are hydrogen;

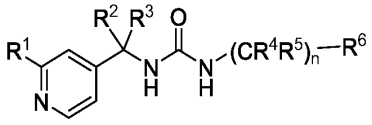
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached form unsubstituted cyclopropyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, 6 membered heteroaryl, and 4-10 membered cycloalkyl, wherein the 5-12 membered heterocycloalkyl, 6 membered heteroaryl, and 4-10 membered cycloalkyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, CF_3CH_2O-, pyrazolyl, and imidazolyl; wherein the pyrazolyl and imidazolyl are unsubstituted or substituted with one CF_3-;

R^2 and R^3 are hydrogen;

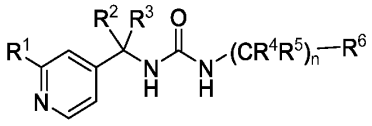
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached form unsubstituted cyclopropyl;

R^6 is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings; a 7-10 membered bridged heterocycloalkyl; a saturated monocyclic 4-6 membered cycloalkyl; phenyl; a 7-10 membered bridged cycloalkyl; a 7-10 membered fused cycloalkyl; tert-butyl; cycloalkyl; $(CH_3)_2CF$-; pyrazinyl, pyrimidinyl, and pyridinyl, wherein the bicyclic fused heterocyloalkyls, bridged heterocycloalkyl, saturated monocylic cycloalkyl, bridged cycloalkyl, phenyl, fused cycloalkyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, CF_3CH_2O-, pyrazolyl, and imidazolyl; wherein the pyrazolyl and imidazolyl are unsubstituted or substituted with one CF_3-;

R^2 and R^3 are hydrogen;

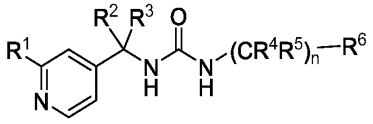
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, , bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, CF_3CH_2O-, pyrazolyl, and imidazolyl; wherein the pyrazolyl and imidazolyl are unsubstituted or substituted with one CF_3-;

R^2 and R^3 are hydrogen;

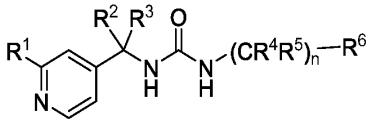
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, CF_3CH_2O-, pyrazolyl, and imidazolyl; wherein the pyrazolyl and imidazolyl are unsubstituted or substituted with one CF_3-;

R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen; or

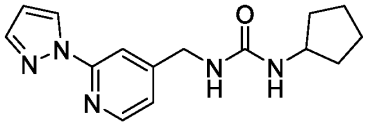
R^4 and R^5, together with the one carbon atom to which they are attached form unsubstituted cyclopropyl;

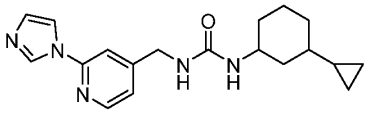
R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and

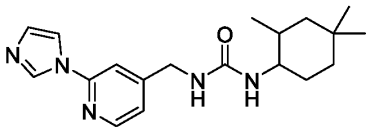
pyridinyl, wherein the dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1;

provided that

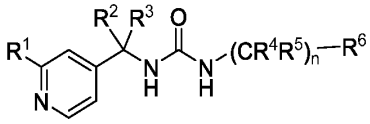

;


; and


;

are excluded.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:


(I)

wherein:

R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, CF_3CH_2O-, pyrazolyl, and imidazolyl; wherein the pyrazolyl and imidazolyl are unsubstituted or substituted with one CF_3-;

R^2 and R^3 are hydrogen;

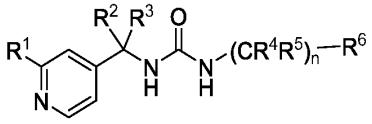
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, CF_3CH_2O-, pyrazolyl, and imidazolyl; wherein the pyrazolyl and imidazolyl are unsubstituted or substituted with one CF_3-;

R^2 and R^3 are hydrogen;

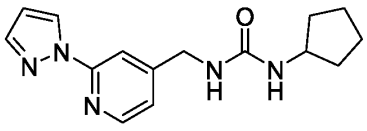
R^4 and R^5 are hydrogen; or

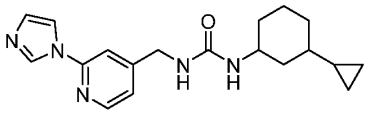
R^4 and R^5, together with the one carbon atom to which they are attached form unsubstituted cyclopropyl;

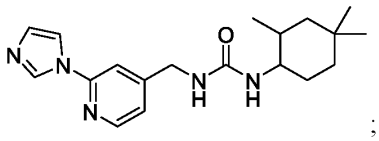
R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1;

provided that


;

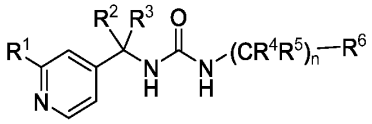

; and



;

are excluded.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, or CF_3CH_2O-;

R^2 and R^3 are hydrogen;

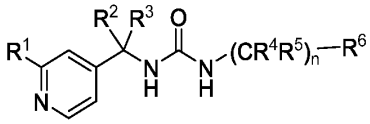
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, CF_3CH_2O-, pyrazolyl, and imidazolyl; wherein the pyrazolyl and imidazolyl are unsubstituted or substituted with one CF_3-;

R^2 and R^3 are hydrogen;

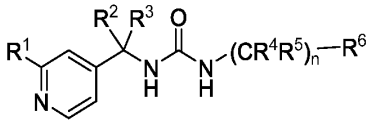
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1.

In one particularly preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, and CF_3CH_2O-;

R^2 and R^3 are hydrogen;

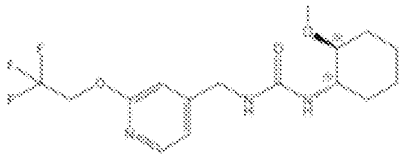
R^4 and R^5 are hydrogen; or

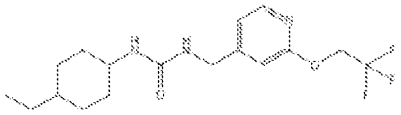
R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1;

provided that





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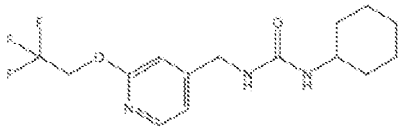

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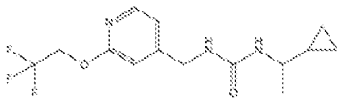

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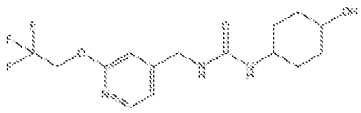

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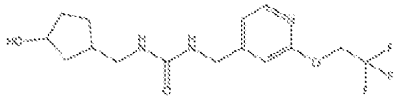

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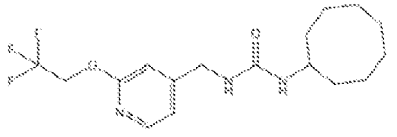

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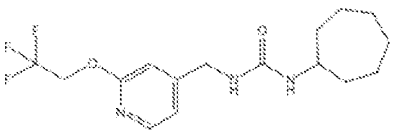
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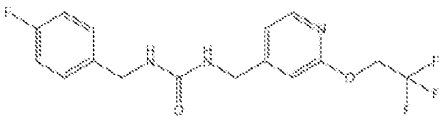
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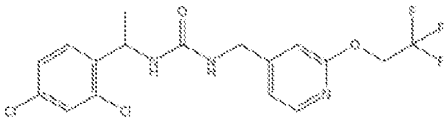
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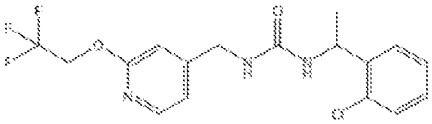
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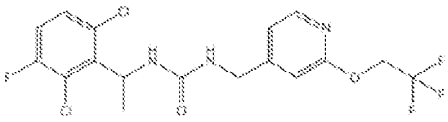
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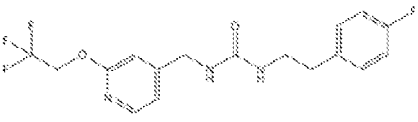
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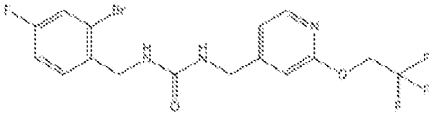
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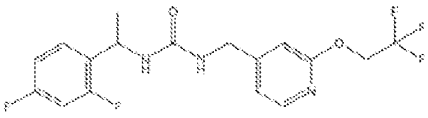
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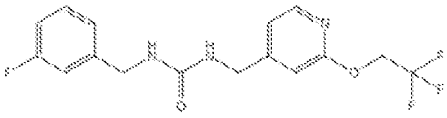
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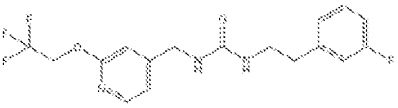
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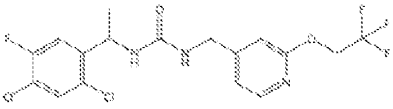
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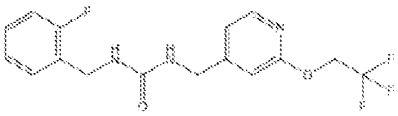
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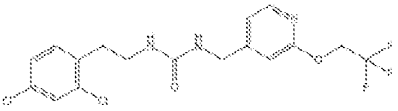
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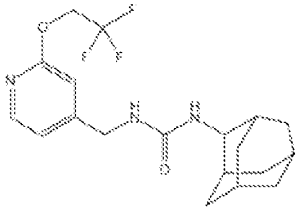
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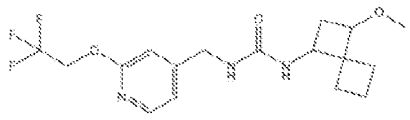
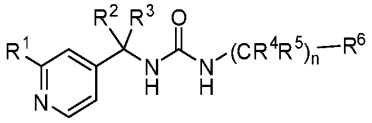


are excluded.

In one particularly preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, and CF_3CH_2O-;

R^2 and R^3 are hydrogen;

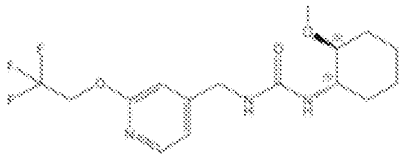
R^4 and R^5 are hydrogen; or

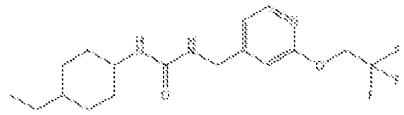
R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1;

provided that





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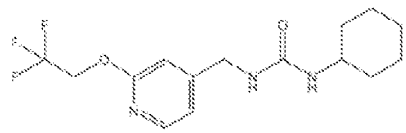

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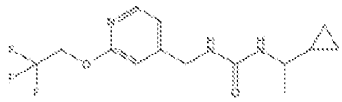

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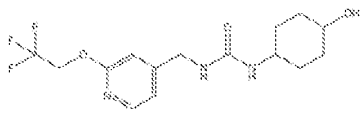

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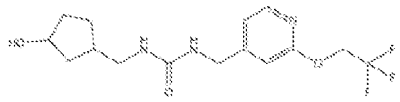

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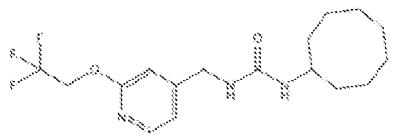

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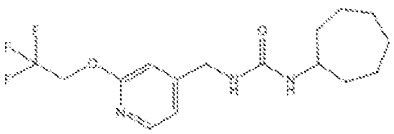

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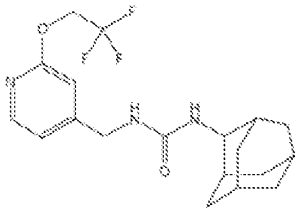

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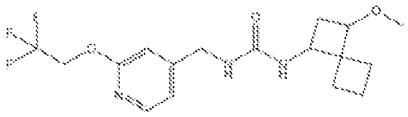
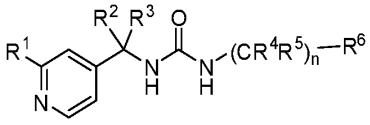


are excluded.

In one particularly preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is CHF_2O- or imidazolyl which is optionally substituted with one CF_3-;

R^2 and R^3 are hydrogen;

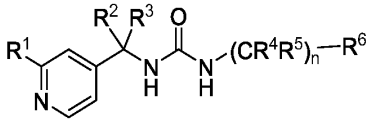
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is CHF_2O- or unsubstituted imidazolyl;

R^2 and R^3 are hydrogen;

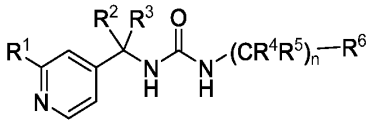
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is CHF_2O- or unsubstituted imidazolyl;

R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen; or

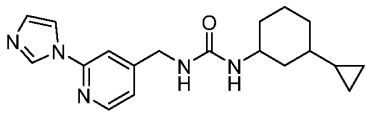
R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

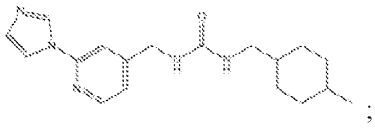
R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the

dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1;

provided that


; and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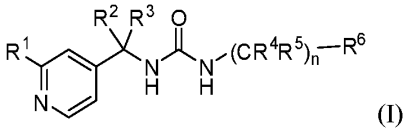
are excluded.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:


(I)

wherein:

R^1 is CHF_2O-;

R^2 and R^3 are hydrogen;

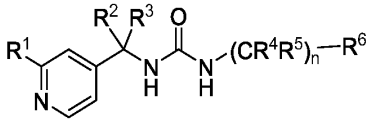
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is CHF_2O-;

R^2 and R^3 are hydrogen;

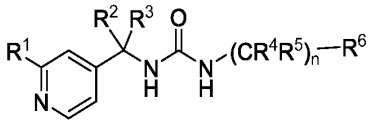
R^4 and R^5 are hydrogen; or

R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from F- and CF_3-; and

n is 0, or 1.

In one particularily preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is unsubstituted imidazolyl or imidazolyl substituted with one substituent selected from CH_3CF_2-, CF_3-, CH_2F, and CHF_2-;

R^2 and R^3 are hydrogen;

R^4 and R^5 are hydrogen; or

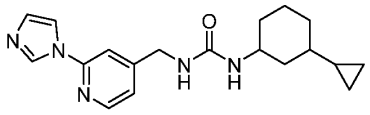
R^4 and R^5, together with the one carbon atom to which they are attached, form unsubstituted cyclopropyl;

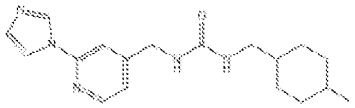
R^6 is selected from dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl,

hexahydrocyclopenta[b]furanyl, pyranzinyl, pyrimidinyl, and pyridinyl, wherein the dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, or pyridinyl are optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, cyclopropyl, CF_3-, and CH_3O-; and

n is 0, or 1;

provided that


; and


;

are excluded.

Measurements have shown that compounds of formula (I) or formula (I'), or solvates or pharmaceutical salts therof, have favorable pharmacological properties as described herein if the Kv7.2 EC_{50} <3μM and selectivity ratio Kv7.3_7.5/Kv7.2 >10x.

Measurements have also shown that compounds of formula (I) or formula (I'), or solvates or pharmaceutical salts therof, have favorable pharmacological properties as described herein, and are therefore preferred, if they demonstrate one or more of the following properties:Kv7.3_7.5/Kv7.2 selectivity ratio >10x; and/or

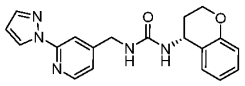
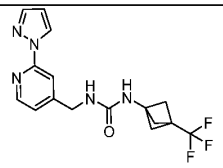
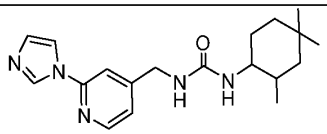
human liver microsomal clearance rate <20 ul/min/mg; and/or

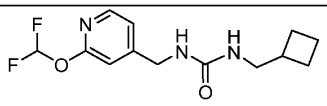
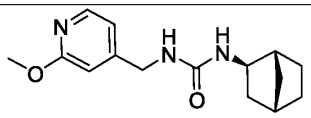
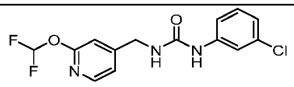
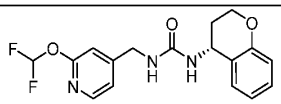
Kv4/Kv2 selectivity >10x.

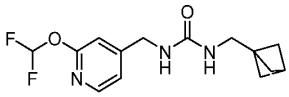
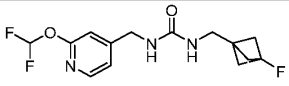
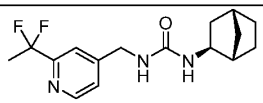
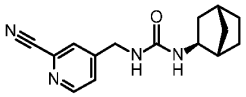
Compounds having one or more of the following combinations of features are found to display particulary beneficial Kv7.2 EC_{50} values and/or Kv7.3_7.5/Kv7.2 selectivity ratios in the range of: EC_{50}<3μM, Select.>10x (Table 2 and Table 5), EC_{50}<1μM, Select.>30x (Table 3 and Table 6) or EC_{50}<1μM, Select.>30x with a favorable metabolic clearance (Table 4 and Table 7).

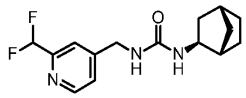
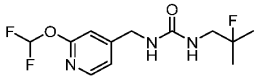
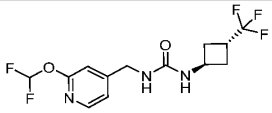
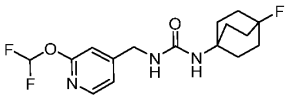
In one preferred embodiment, the compounds of formula (I) or formula (I') are selected from Table 2 (Kv7.2 EC_{50}<3μM and Kv35/Kv2 selectivity >10X).

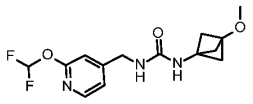
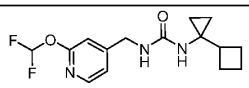
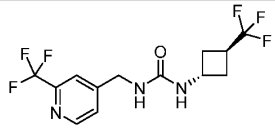
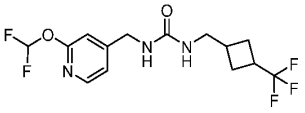
Table 2

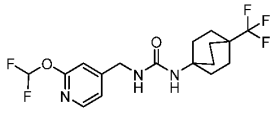
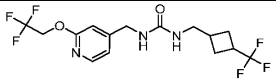
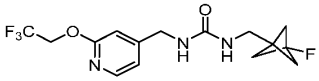
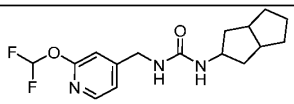
1	1-[(4R)-3,4-dihydro-2H-chromen-4-yl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
6	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
9	1-[(2-imidazol-1-ylpyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	

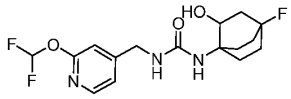
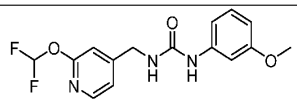
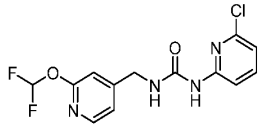
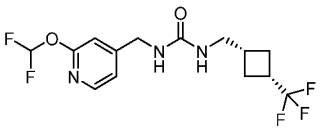
13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
14	1-[(2-methoxypyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
22	1-(3-chlorophenyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
23	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(4R)-3,4-dihydro-2H-chromen-4-yl]urea	

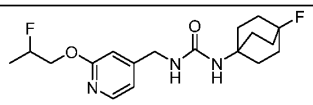
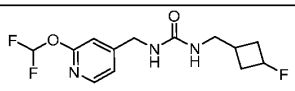
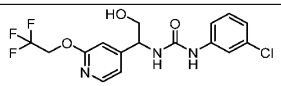
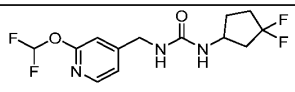
31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
32	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea	
33	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
34	1-[(2-cyanopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	

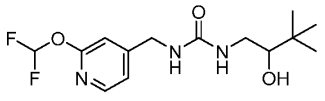
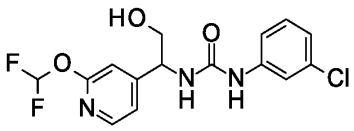
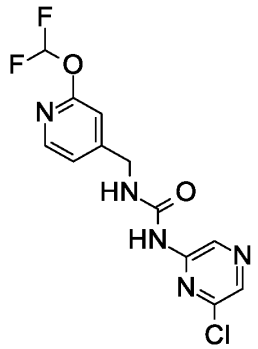
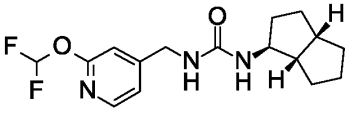
35	1-[[2-(difluoromethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
39	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-fluoro-2-methylpropyl)urea	
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	

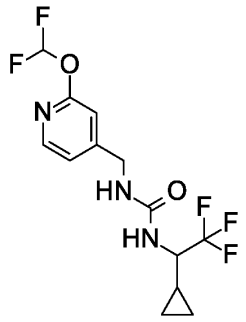
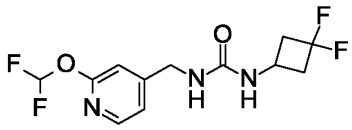
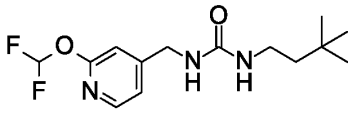
49	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxy-1-bicyclo[1.1.1]pentanyl)urea	
50	1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
58	1-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	
62	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	

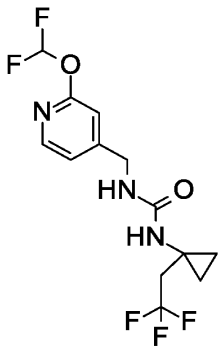
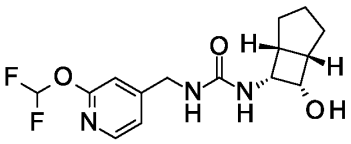
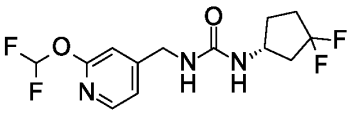
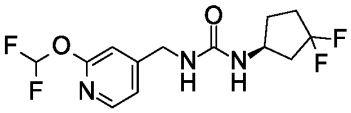
68	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[4-(trifluoromethyl)-1-bicyclo[2.2.2]octanyl]urea	
71	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
75	1-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
78	1-(1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl)-3-[[2-(difluoromethoxy)	

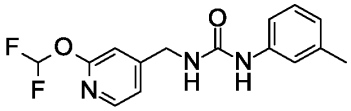
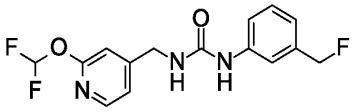
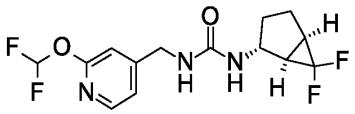
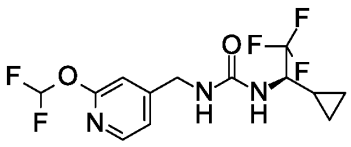
	pyridin-4-yl]methyl]urea	
82	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-2-hydroxy-1-bicyclo[2.2.2]octanyl)urea	
83	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxyphenyl)urea	
84	1-(6-chloropyridin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
87	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(1r,3r)-	

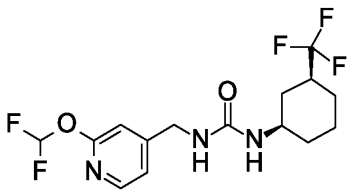
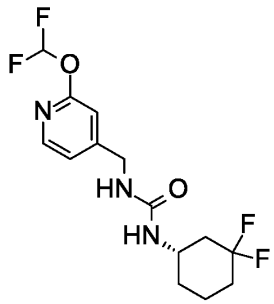
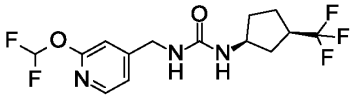
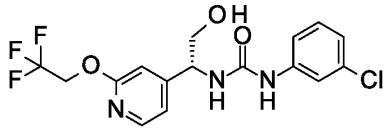
	(trifluoromethyl)cyclobutyl]methyl]urea	
88	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	
89	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea	
92	1-(3-chlorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
93	1-(3,3-difluorocyclopentyl)-3-[[2-(difluoromethoxy)	

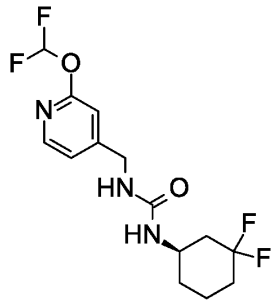
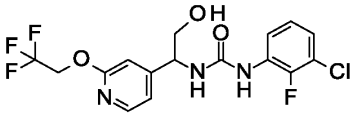
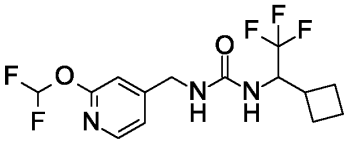
	pyridin-4-yl]methyl]urea	
95	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea	
97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
98	1-(6-chloropyrazin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
103	1-[(1S,3aS,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-	

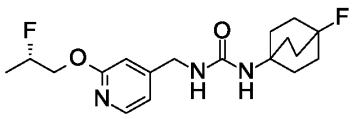
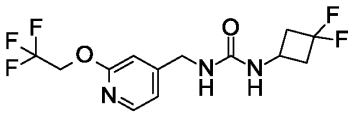
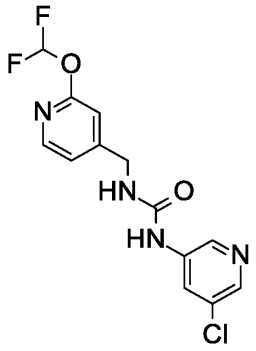
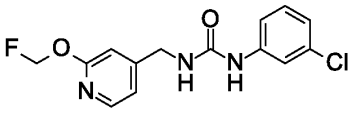
	(difluoromethoxy) pyridin-4-yl]methyl]urea	
106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
108	1-(3,3-difluorocyclobutyl)-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
109	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-(3,3-dimethylbutyl)urea	

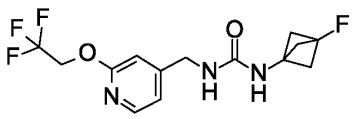
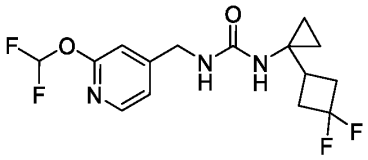
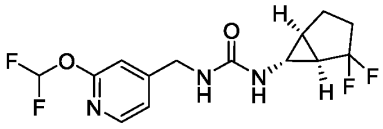
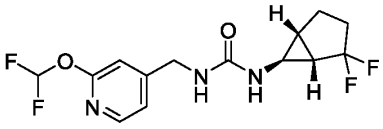
110	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2,2-trifluoroethyl)cyclopropyl]urea	
111	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6S,7R)-7-hydroxy-6-bicyclo[3.2.0]heptanyl]urea	
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)	

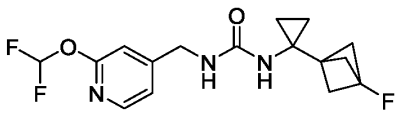
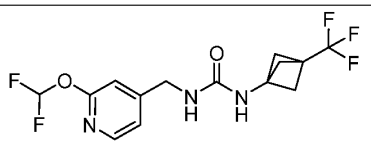
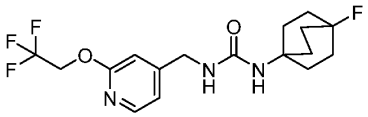
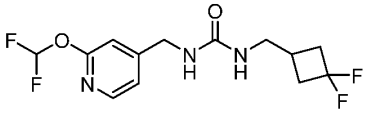
	pyridin-4-yl]methyl]urea	
126	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylphenyl)urea	
132	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(fluoromethyl)phenyl]urea	
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)	

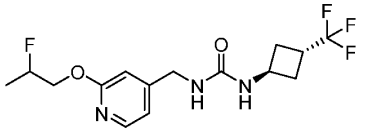
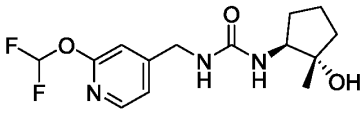
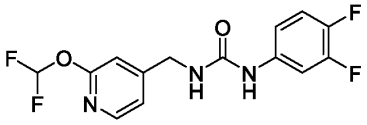
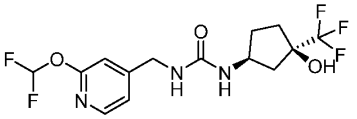
	pyridin-4-yl]methyl]urea	
138	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	
140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
144	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3R)-3-(trifluoromethyl)cyclopentyl]urea	
145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-	

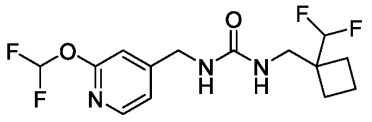
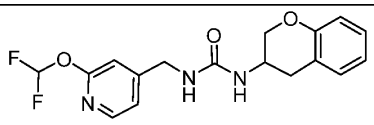
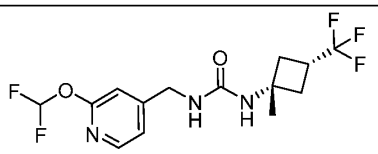
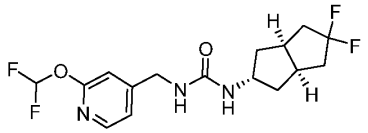
	trifluoroethoxy)pyridin-4-yl]ethyl]urea	
149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
150	1-(3-chloro-2-fluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
152	1-(1-cyclobutyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

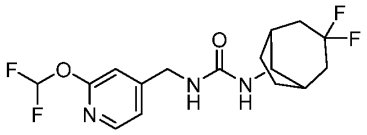
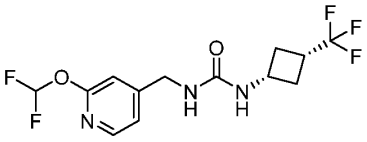
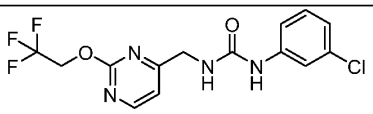
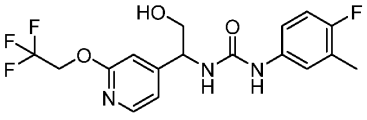
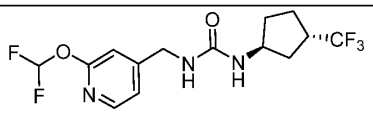
156	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]urea	
157	1-(3,3-difluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
161	1-(5-chloropyridin-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
164	1-(3-chlorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	

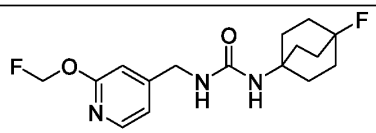
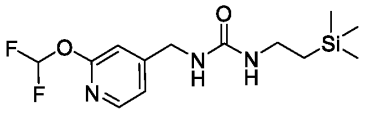
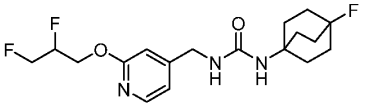
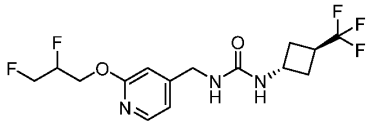
168	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
171	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
172	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
174	1-[(1S,5R,6S)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)	

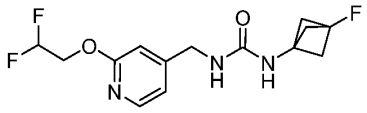
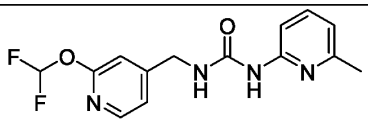
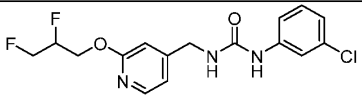
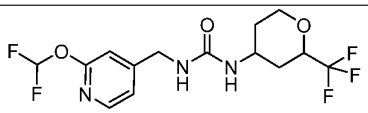
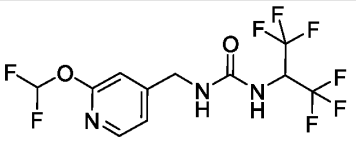
	pyridin-4-yl]methyl]urea	
177	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)cyclopropyl]urea	
178	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
180	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)	

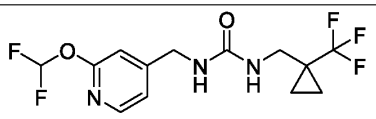
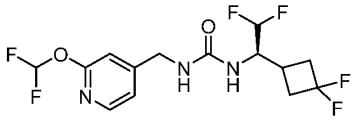
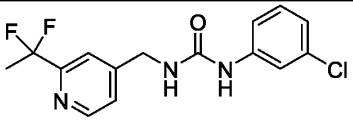
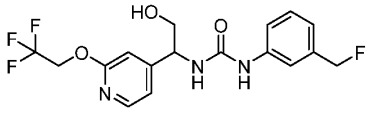
	pyridin-4-yl]methyl]urea	
183	1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
184	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,2S)-2-hydroxy-2-methylcyclopentyl]urea	
186	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-difluorophenyl)urea	
187	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-hydroxy-3-(trifluoromethyl)cyclopentyl]urea	

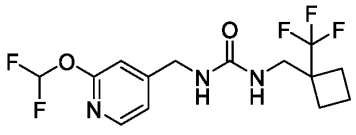
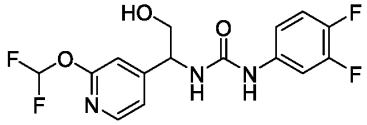
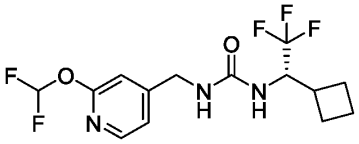
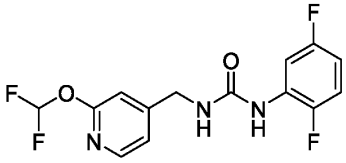
191	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluoromethyl)cyclobutyl]methyl]urea	
192	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-dihydro-2H-chromen-3-yl)urea	
194	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-1-methyl-3-(trifluoromethyl)cyclobutyl]urea	
195	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2r,3aR,6aS)-5,5-difluoro-2,3,3a,4,6,6a-hexahydro-1H-pentalen-2-yl]urea	

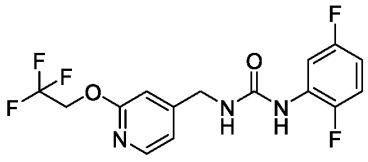
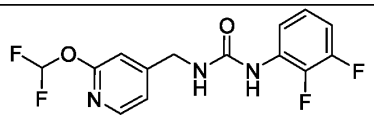
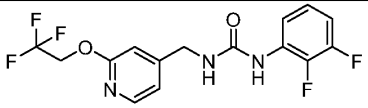
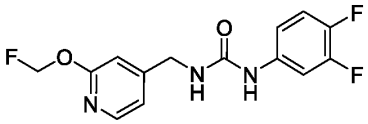
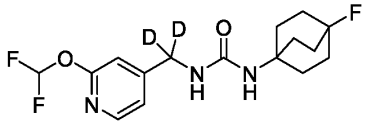
197	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3,3-difluoro-8-bicyclo[3.2.1]octanyl]urea	
198	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(trifluoromethyl)cyclobutyl]urea	
203	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]urea	
205	1-(4-fluoro-3-methylphenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
207	1-[[2-(difluoromethoxy)pyridin-4-	

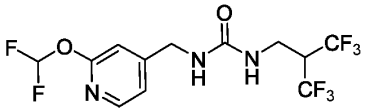
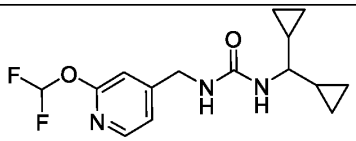
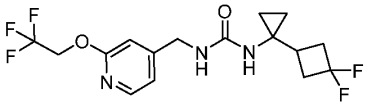
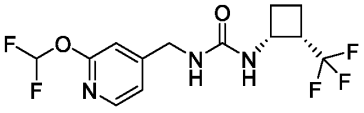
	yl]methyl]-3-[(1S,3S)-3-(trifluoromethyl)cyclopentyl]urea	
208	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
212	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-trimethylsilylethyl)urea	
213	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
214	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

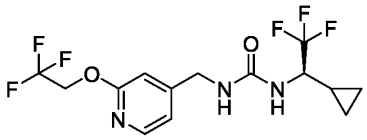
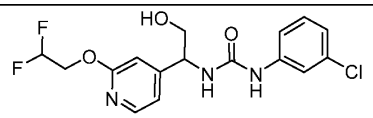
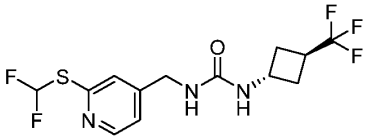
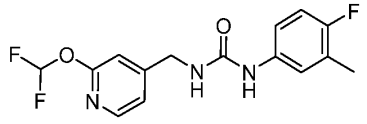
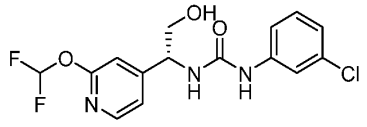
217	1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
218	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(6-methylpyridin-2-yl)urea	
220	1-(3-chlorophenyl)-3-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]urea	
226	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(trifluoromethyl)oxan-4-yl]urea	
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea	

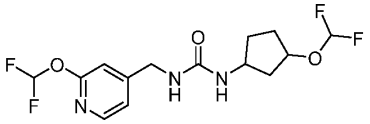
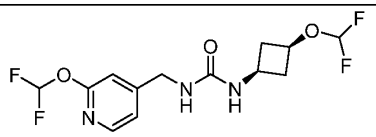
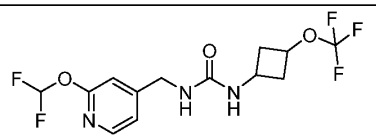
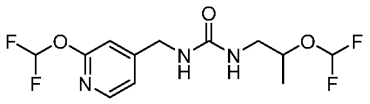
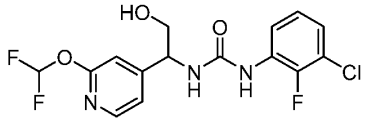
	hexafluoropropan-2-yl)urea	
229	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
230	1-[(1R)-1-(3,3-difluorocyclobutyl)-2,2-difluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
231	1-(3-chlorophenyl)-3-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]urea	
232	1-[3-(fluoromethyl)phenyl]-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

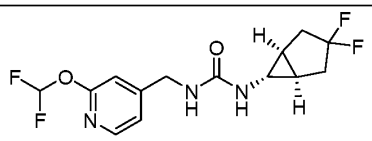
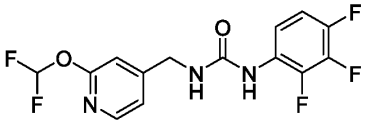
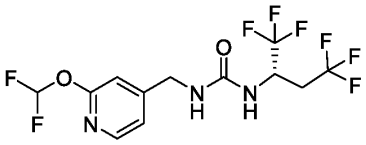
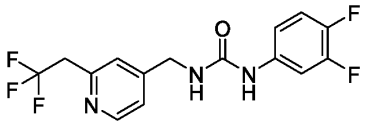
237	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclobutyl]methyl]urea	
240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
242	1-[(1S)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
244	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,5-difluorophenyl)urea	

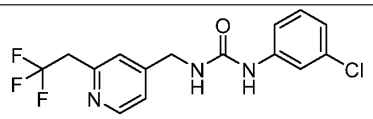
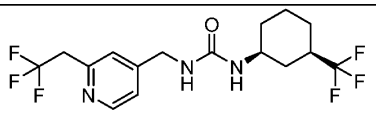
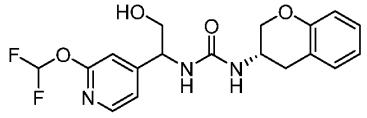
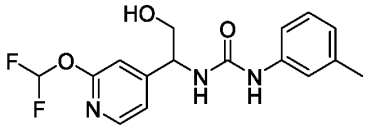
245	1-(2,5-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
247	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3-difluorophenyl)urea	
248	1-(2,3-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
249	1-(3,4-difluorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
251	1-[dideuterio-[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-	

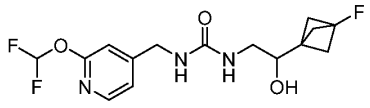
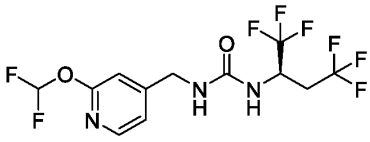
	bicyclo[2.2.2]octanyl)urea	
252	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea	
253	1-(dicyclopropylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
254	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
255	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-(trifluoromethyl)cyclobutyl]urea	

257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
259	1-(3-chlorophenyl)-3-[1-[2-(2,2-difluoroethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
260	1-[[2-(difluoromethylsulfanyl)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
261	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-3-methylphenyl)urea	
263	rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)	

	pyridin-4-yl]-2-hydroxyethyl]urea	
264	1-[3-(difluoromethoxy)cyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
265	1-[(1s,3s)-3-(difluoromethoxy)cyclobutyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
267	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethoxy)cyclobutyl]urea	
268	1-[2-(difluoromethoxy)propyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
270	1-(3-chloro-2-fluorophenyl)-3-[1-[2-	

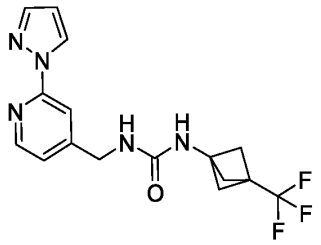
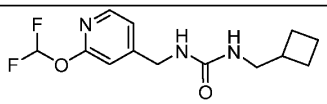
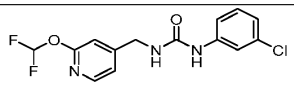
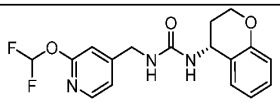
	(difluoromethoxy) pyridin-4-yl]-2-hydroxyethyl]urea	
271	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-3,3-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
272	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-(2,3,4-trifluorophenyl)urea	
273	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	
274	1-(3,4-difluorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyri	

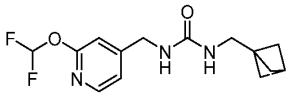
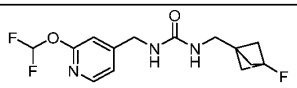
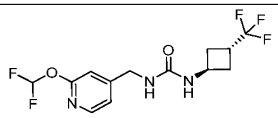
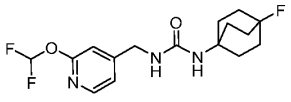
	din-4-yl]methyl]urea	
275	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
276	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
278	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(3S)-3,4-dihydro-2H-chromen-3-yl]urea	
280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea	

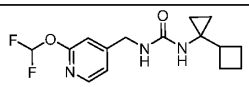
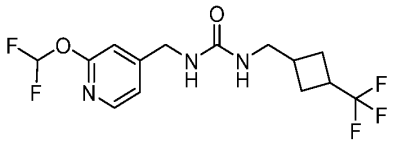
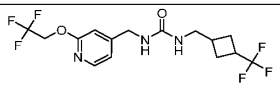
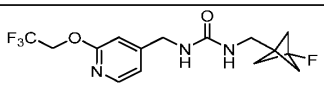
289	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]urea	
294	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	

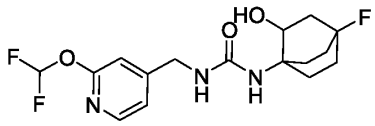
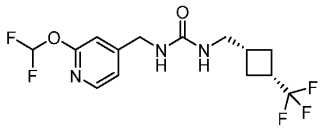
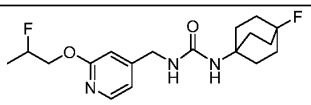
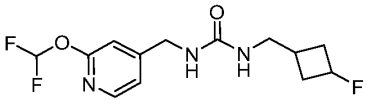
In another preferred embodiment, the compounds of formula (I) or formula (I') are selected from Table 3 (Kv7.2 EC_{50} < 1μM and selectivity >30x).

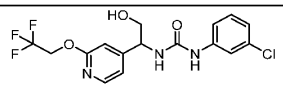
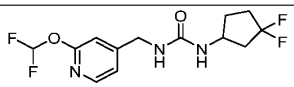
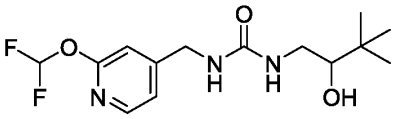
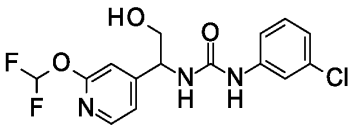
Table 3

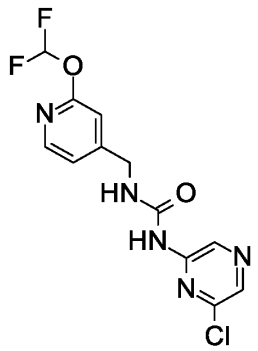
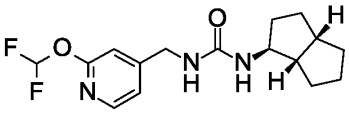
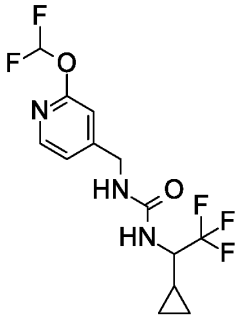
6	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
22	1-(3-chlorophenyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
23	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(4R)-3,4-dihydro-	

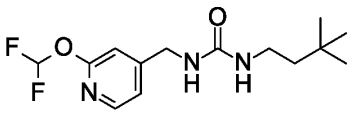
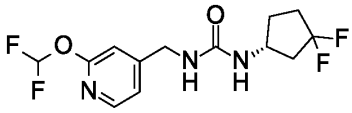
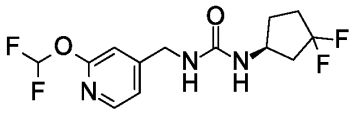
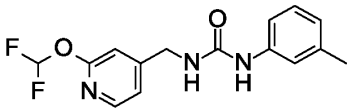
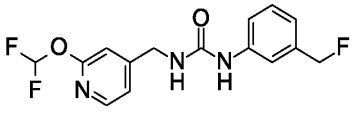
	2H-chromen-4-yl]urea	
31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
32	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea	
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-	

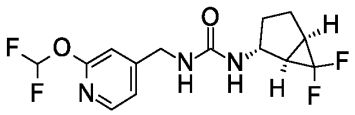
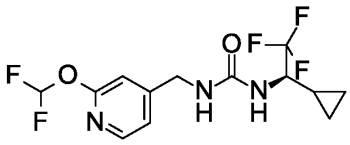
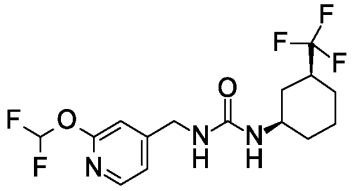
	bicyclo[2.2.2]octanyl)urea	
50	1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
62	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
71	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
75	1-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)py	

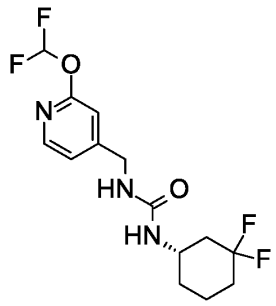
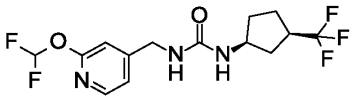
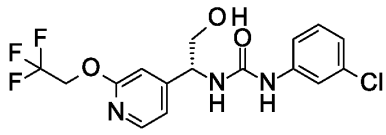
	ridin-4-yl]methyl]urea	
82	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-2-hydroxy-1-bicyclo[2.2.2]octanyl)urea	
87	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(1r,3r)-(trifluoromethyl)cyclobutyl]methyl]urea	
88	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	
89	1-[[2-(difluoromethoxy)pyridin-4-	

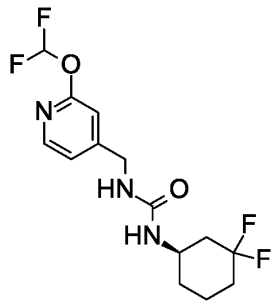
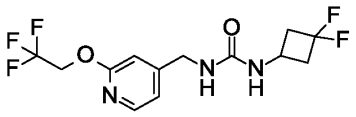
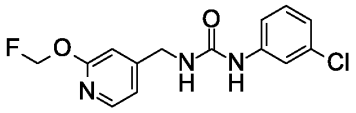
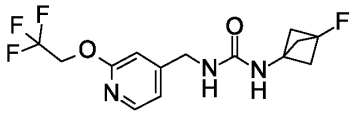
	yl]methyl]-3-[(3-fluorocyclobutyl) methyl]urea	
92	1-(3-chlorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
93	1-(3,3-difluorocyclopentyl)-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
95	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea	
97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)	

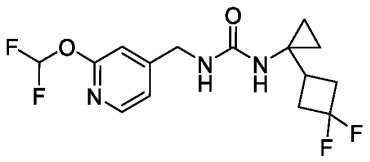
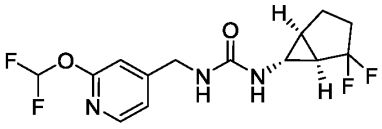
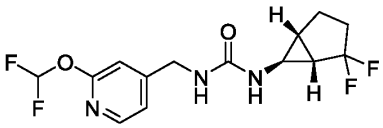
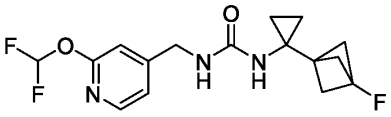
	pyridin-4-yl]-2-hydroxyethyl]urea	
98	1-(6-chloropyrazin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
103	1-[(1S,3aS,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

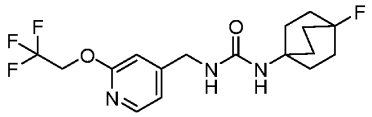
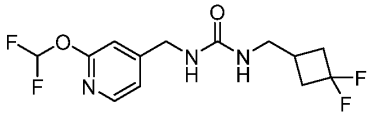
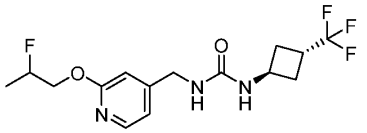
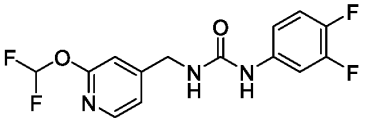
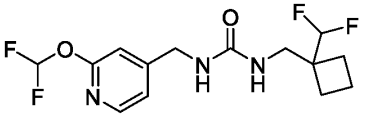
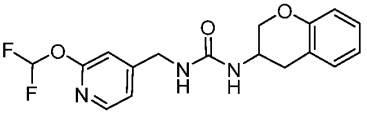
109	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-dimethylbutyl)urea	
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
126	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylphenyl)urea	
132	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-	

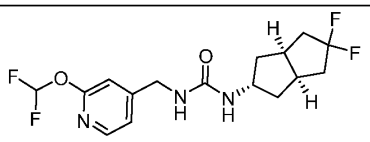
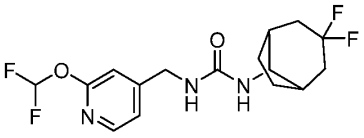
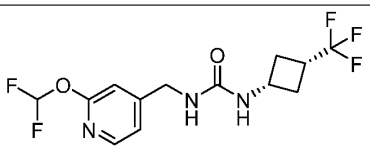
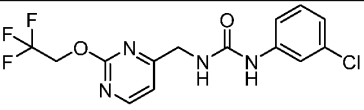
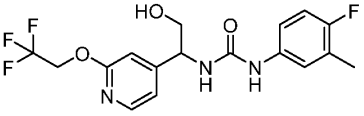
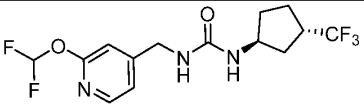
	(fluoromethyl)phenyl]urea	
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
138	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	

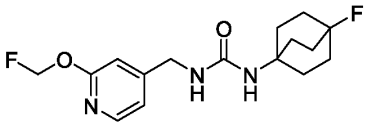
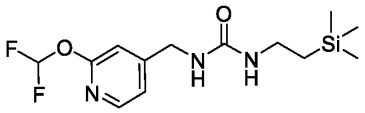
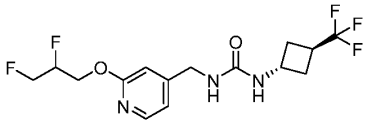
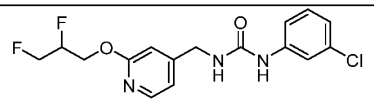
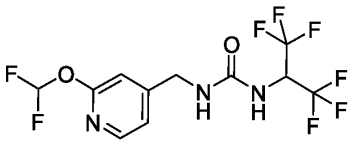
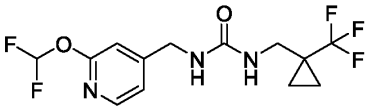
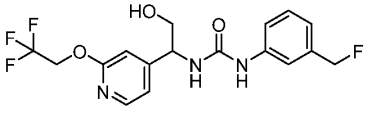
140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
144	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3R)-3-(trifluoromethyl)cyclopentyl]urea	
145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

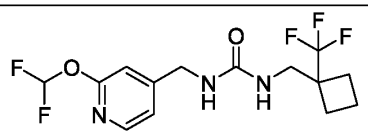
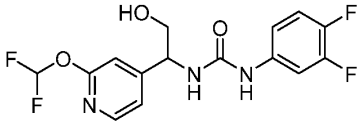
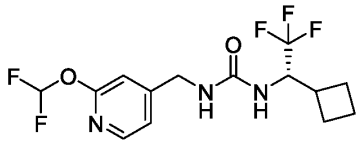
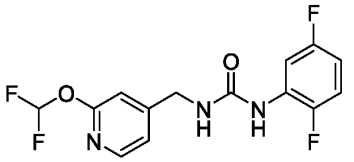
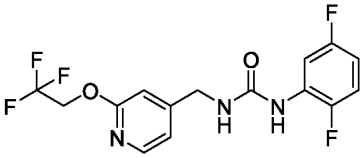
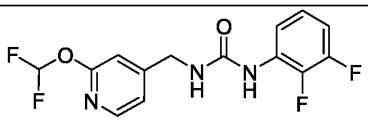
149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
157	1-(3,3-difluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
164	1-(3-chlorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
168	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

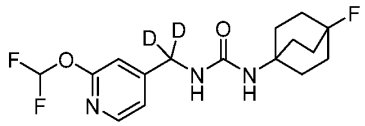
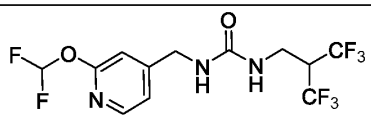
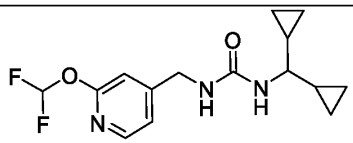
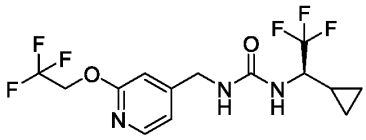
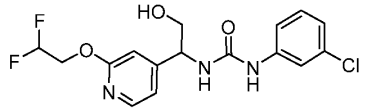
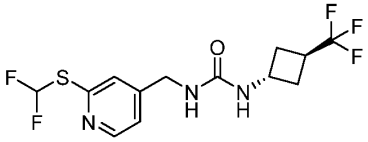
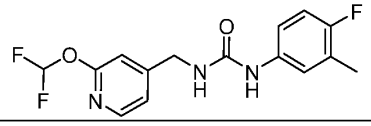
171	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
172	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
174	1-[(1S,5R,6S)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
177	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(3-fluoro-1-bicyclo[1.1.1]pent	

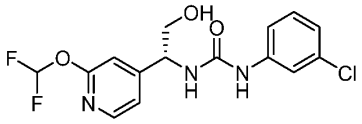
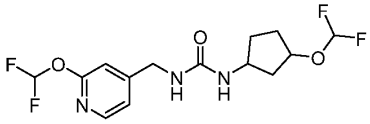
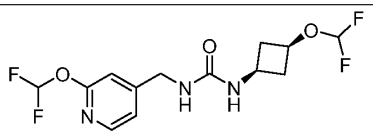
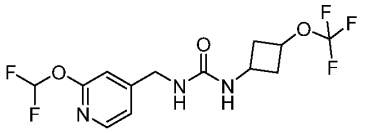
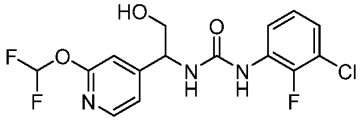
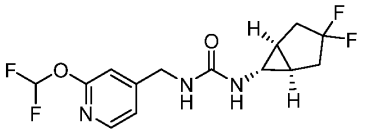
	anyl)cyclopropyl] urea	
180	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
183	1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
186	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-difluorophenyl)urea	
191	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluoromethyl)cyclobutyl]methyl]urea	
192	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-dihydro-2H-chromen-3-yl)urea	

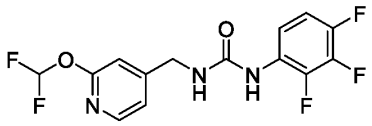
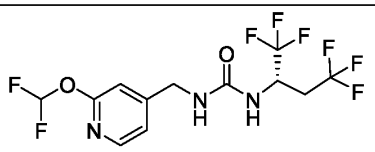
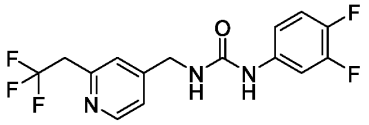
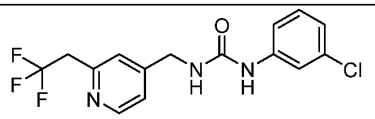
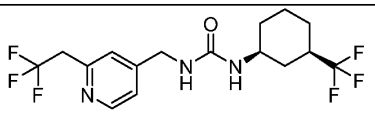
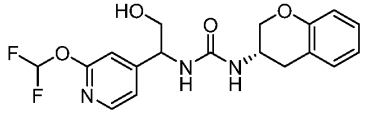
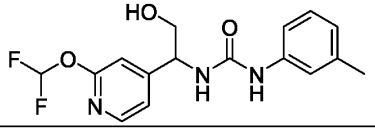
195	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2r,3aR,6aS)-5,5-difluoro-2,3,3a,4,6,6a-hexahydro-1H-pentalen-2-yl]urea	
197	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3,3-difluoro-8-bicyclo[3.2.1]octanyl]urea	
198	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(trifluoromethyl)cyclobutyl]urea	
203	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]urea	
205	1-(4-fluoro-3-methylphenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
207	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-(trifluoromethyl)cyclopentyl]urea	

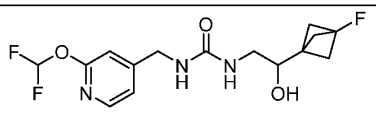
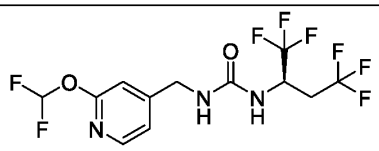
208	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
212	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-trimethylsilylethyl)urea	
214	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
220	1-(3-chlorophenyl)-3-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]urea	
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea	
229	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
232	1-[3-(fluoromethyl)phenyl]-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)py	

	ridin-4-yl]ethyl]urea	
237	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclobutyl]methyl]urea	
240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
242	1-[(1S)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
244	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,5-difluorophenyl)urea	
245	1-(2,5-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
247	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3-difluorophenyl)urea	

251	1-[dideuterio-[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
252	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea	
253	1-(dicyclopropylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
259	1-(3-chlorophenyl)-3-[1-[2-(2,2-difluoroethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
260	1-[[2-(difluoromethylsulfanyl)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
261	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-	

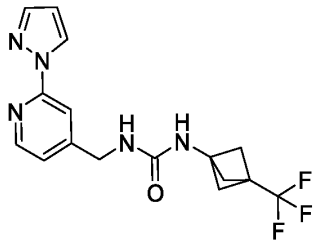
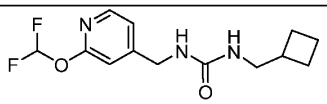
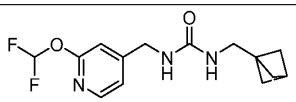
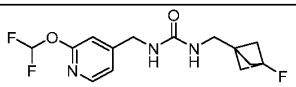
	fluoro-3-methylphenyl)urea	
263	rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
264	1-[3-(difluoromethoxy)cyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
265	1-[(1s,3s)-3-(difluoromethoxy)cyclobutyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
267	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethoxy)cyclobutyl]urea	
270	1-(3-chloro-2-fluorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
271	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-3,3-difluoro-6-bicyclo[3.1.0]hexanyl]urea	

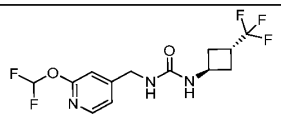
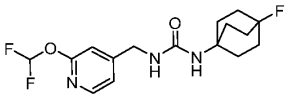
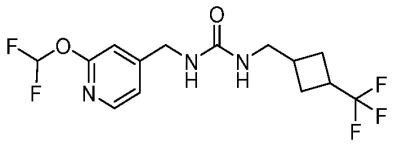
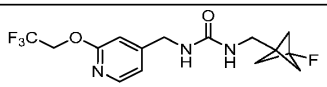
272	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3,4-trifluorophenyl)urea	
273	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	
274	1-(3,4-difluorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
275	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
276	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
278	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(3S)-3,4-dihydro-2H-chromen-3-yl]urea	
280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-	

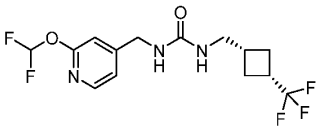
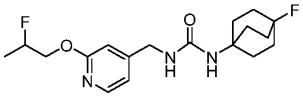
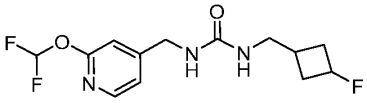
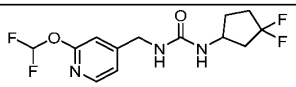
	(3-methylphenyl)urea	
289	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]urea	
294	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	

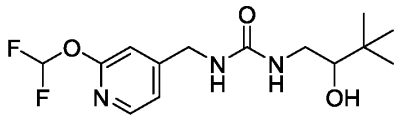
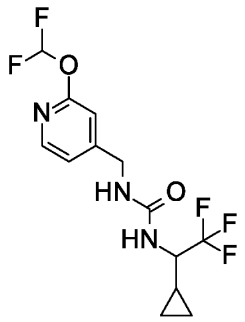
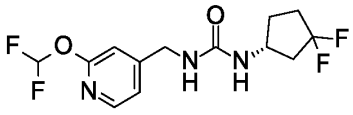
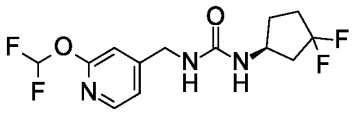
In another preferred embodiment, the compounds of formula (I) or formula (I') are selected from Table 4 (Kv7.2 EC_{50} < 1μM and selectivity >30x, and microsome clearance <20).

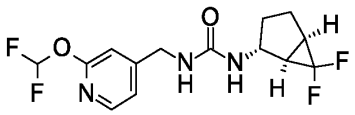
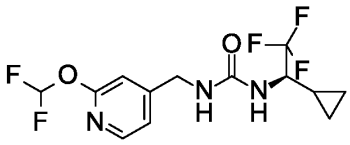
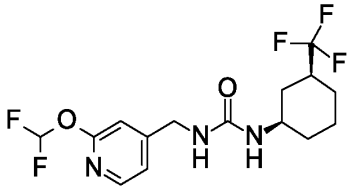
Table 4

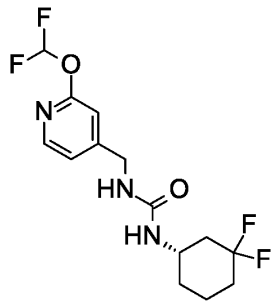
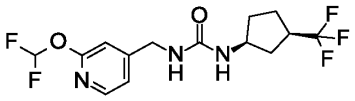
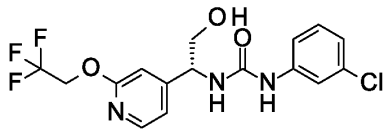
6	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
32	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-	

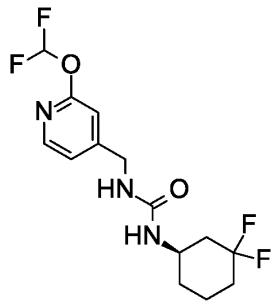
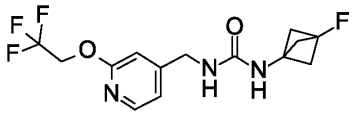
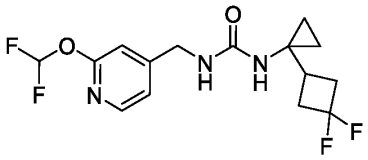
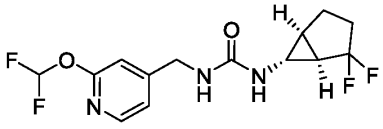
	bicyclo[1.1.1]pentanyl)methyl]urea	
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
62	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
75	1-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]-3-[[2-(2,2,2-	

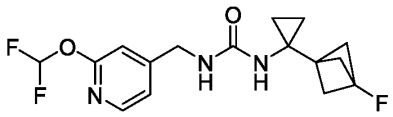
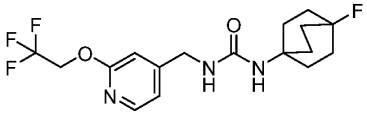
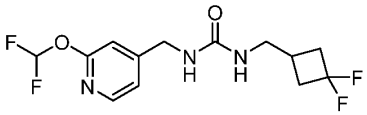
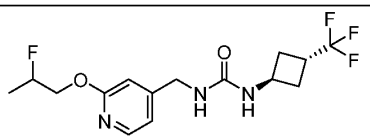
	trifluoroethoxy)pyridin-4-yl]methyl]urea	
87	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(1r,3r)-(trifluoromethyl)cyclobutyl]methyl]urea	
88	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	
89	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea	
93	1-(3,3-difluorocyclopentyl)-3-[[2-(difluoromethoxy)	

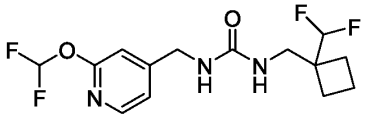
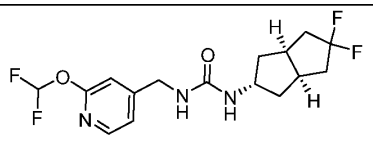
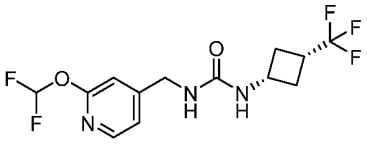
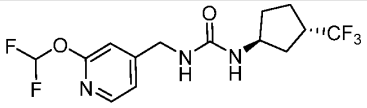
	pyridin-4-yl]methyl]urea	
95	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea	
106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)	

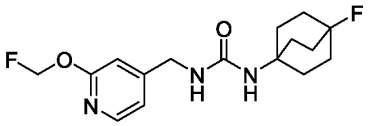
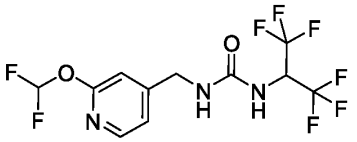
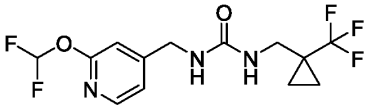
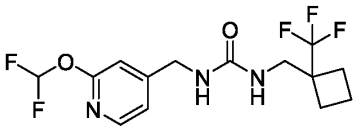
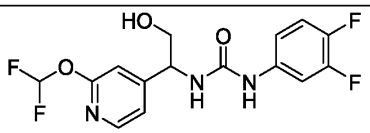
	pyridin-4-yl]methyl]urea	
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
138	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	

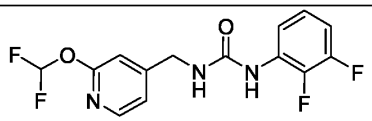
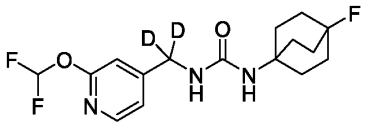
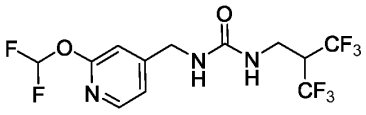
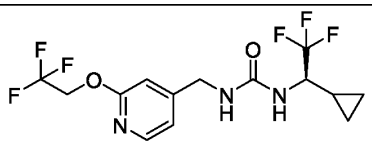
140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
144	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3R)-3-(trifluoromethyl)cyclopentyl]urea	
145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

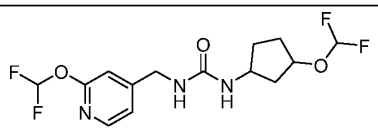
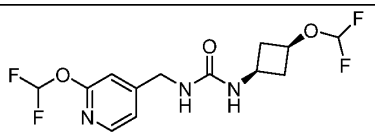
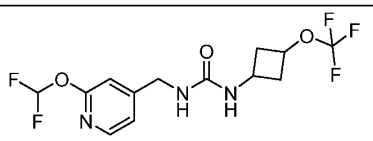
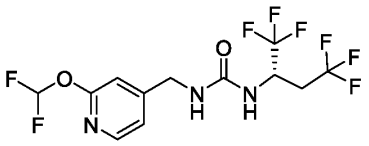
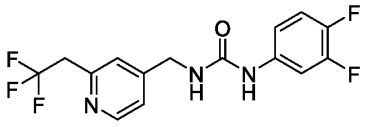
149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
168	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
171	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
172	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-2,2-difluoro-6-	

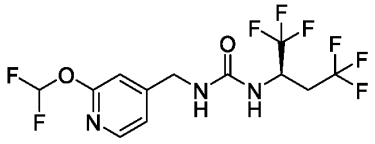
	bicyclo[3.1.0]hexanyl]urea	
177	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)cyclopropyl]urea	
180	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
183	1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

191	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluoromethyl)cyclobutyl]methyl]urea	
195	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2r,3aR,6aS)-5,5-difluoro-2,3,3a,4,6,6a-hexahydro-1H-pentalen-2-yl]urea	
198	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(trifluoromethyl)cyclobutyl]urea	
207	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-(trifluoromethyl)cyclopentyl]urea	

208	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea	
229	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
237	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclobutyl]methyl]urea	
240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-	

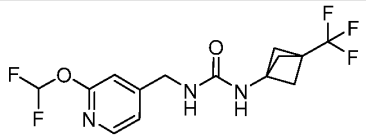
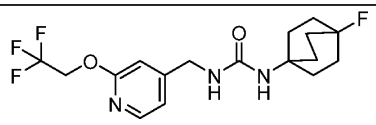
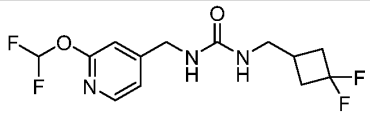
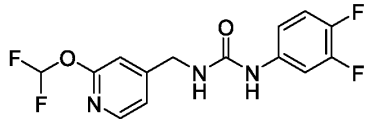
	(3,4-difluorophenyl)urea	
247	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3-difluorophenyl)urea	
251	1-[dideuterio-[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
252	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea	
257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

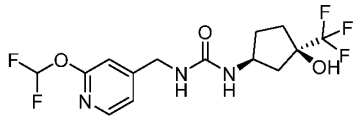
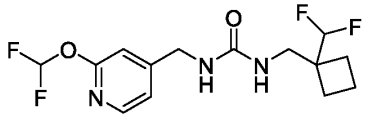
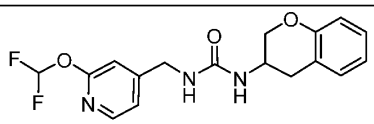
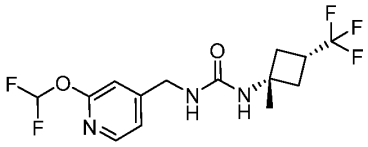
264	1-[3-(difluoromethoxy) cyclopentyl]-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
265	1-[(1s,3s)-3-(difluoromethoxy) cyclobutyl]-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
267	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[3-(trifluoromethoxy) cyclobutyl]urea	
273	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	
274	1-(3,4-difluorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyri	

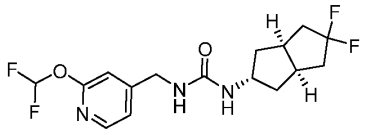
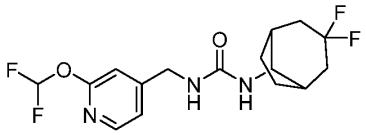
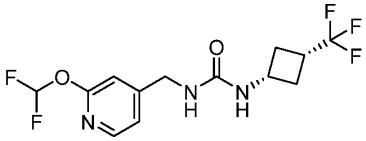
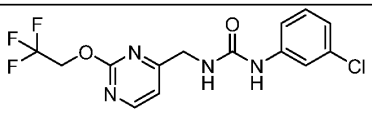
	din-4-yl]methyl]urea	
294	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	

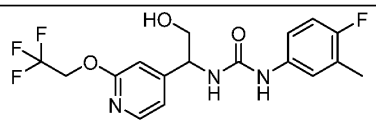
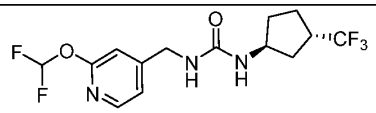
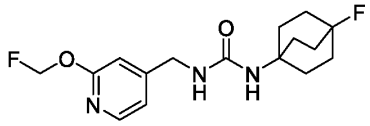
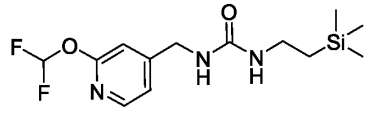
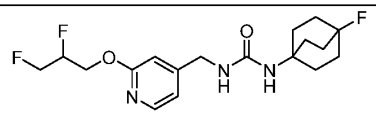
In another preferred embodiment, the compounds of formula (I) or formula (I') are selected from Table 5.

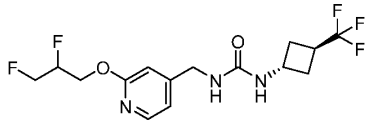
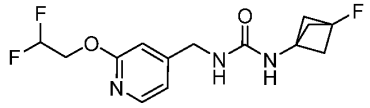
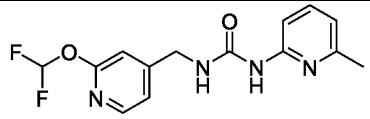
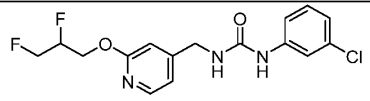
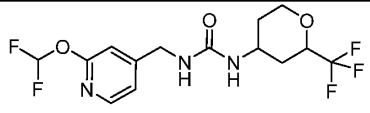
Table 5

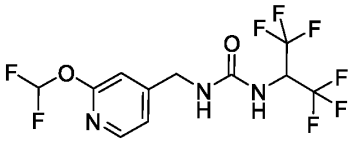
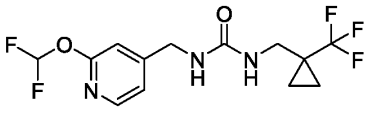
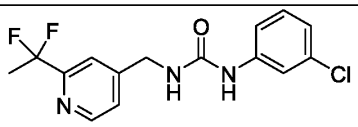
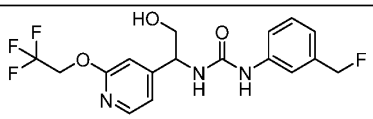
178	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
180	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
186	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-difluorophenyl)urea	

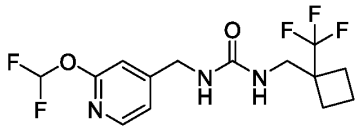
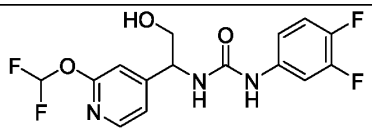
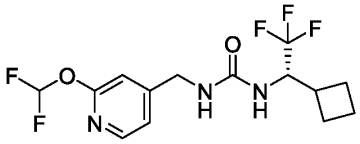
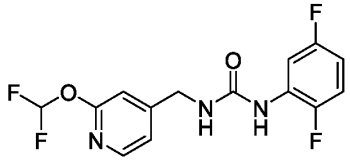
187	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-hydroxy-3-(trifluoromethyl)cyclopentyl]urea	
191	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluoromethyl)cyclobutyl]methyl]urea	
192	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-dihydro-2H-chromen-3-yl)urea	
194	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-1-methyl-3-(trifluoromethyl)cyclobutyl]urea	

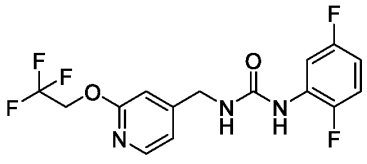
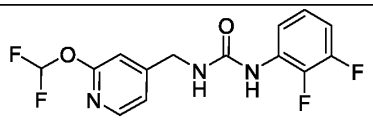
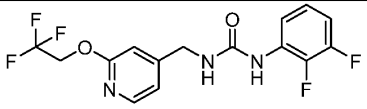
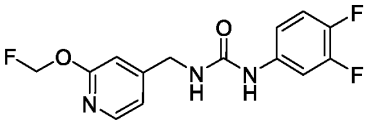
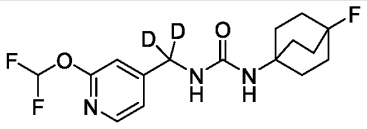
195	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2r,3aR,6aS)-5,5-difluoro-2,3,3a,4,6,6a-hexahydro-1H-pentalen-2-yl]urea	
197	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3,3-difluoro-8-bicyclo[3.2.1]octanyl]urea	
198	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(trifluoromethyl)cyclobutyl]urea	
203	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]urea	

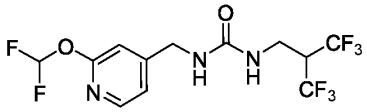
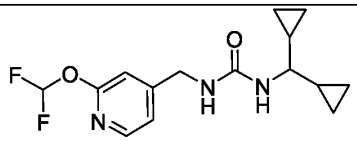
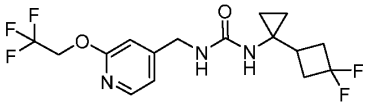
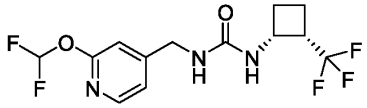
205	1-(4-fluoro-3-methylphenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
207	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-(trifluoromethyl)cyclopentyl]urea	
208	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
212	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-trimethylsilylethyl)urea	
213	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-	

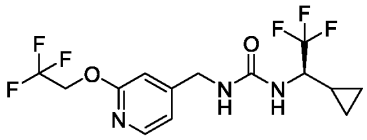
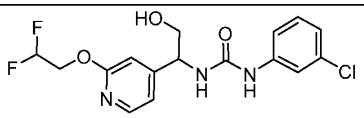
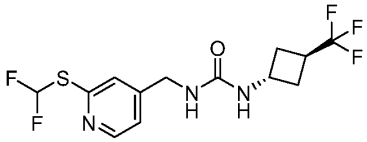
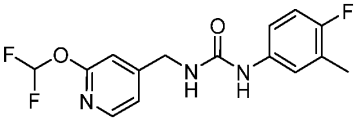
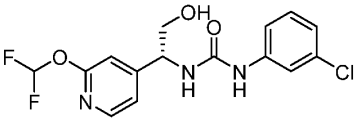
	bicyclo[2.2.2]octanyl)urea	
214	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
217	1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
218	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(6-methylpyridin-2-yl)urea	
220	1-(3-chlorophenyl)-3-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]urea	
226	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-	

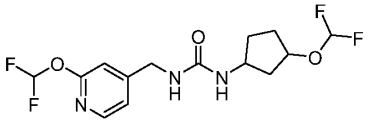
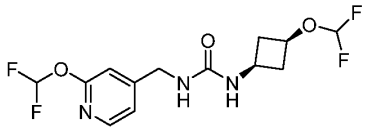
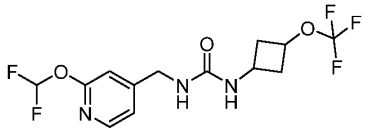
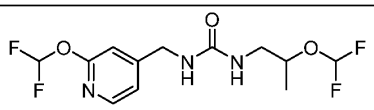
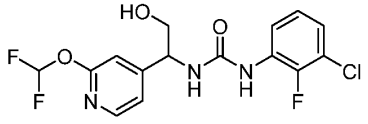
	(trifluoromethyl)oxan-4-yl]urea	
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea	
229	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
231	1-(3-chlorophenyl)-3-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]urea	
232	1-[3-(fluoromethyl)phenyl]-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

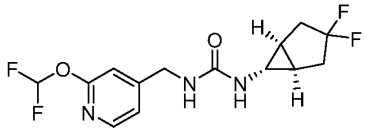
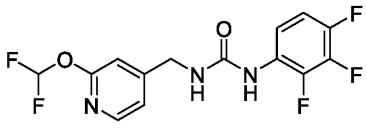
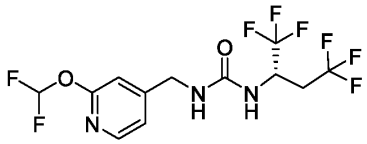
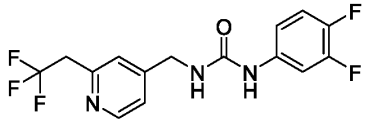
237	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclobutyl]methyl]urea	
240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
242	1-[(1S)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
244	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,5-difluorophenyl)urea	

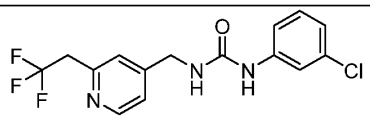
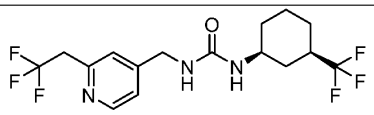
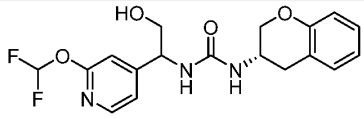
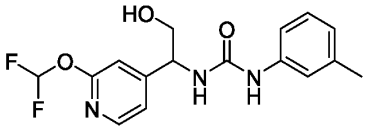
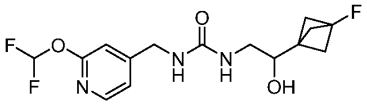
245	1-(2,5-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
247	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3-difluorophenyl)urea	
248	1-(2,3-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
249	1-(3,4-difluorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
251	1-[dideuterio-[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-	

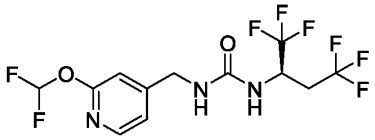
	bicyclo[2.2.2]octanyl)urea	
252	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea	
253	1-(dicyclopropylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
254	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
255	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-(trifluoromethyl)cyclobutyl]urea	

257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
259	1-(3-chlorophenyl)-3-[1-[2-(2,2-difluoroethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
260	1-[[2-(difluoromethylsulfanyl)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
261	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-3-methylphenyl)urea	
263	rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)p	

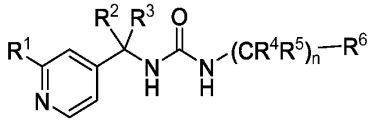
	yridin-4-yl]-2-hydroxyethyl]urea	
264	1-[3-(difluoromethoxy)cyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
265	1-[(1s,3s)-3-(difluoromethoxy)cyclobutyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
267	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethoxy)cyclobutyl]urea	
268	1-[2-(difluoromethoxy)propyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
270	1-(3-chloro-2-fluorophenyl)-3-[1-[2-(difluoromethoxy)p	

	yridin-4-yl]-2-hydroxyethyl]urea	
271	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-3,3-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
272	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3,4-trifluorophenyl)urea	
273	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	
274	1-(3,4-difluorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	

275	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
276	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
278	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(3S)-3,4-dihydro-2H-chromen-3-yl]urea	
280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea	
289	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(3-fluoro-1-bicyclo[1.1.1]penta	

	nyl)-2-hydroxyethyl]urea	
294	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	

In preferred one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from haloC_{1-6}alkoxy, haloC_{1-6}alkyl, and haloC_{1-6}alkylthio;

R^2 and $R^3$are independently selected from hydrogen, deuterium, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, hydroxy, and hydroxyC_{1-6}alkyl; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

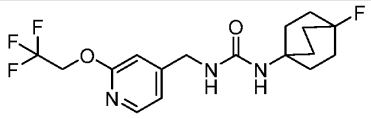
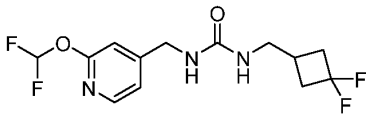
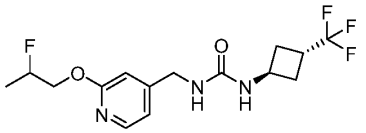
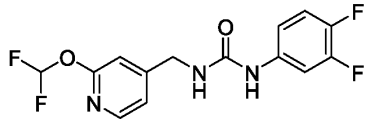
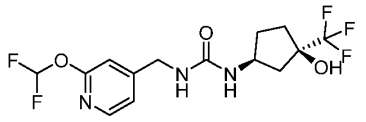
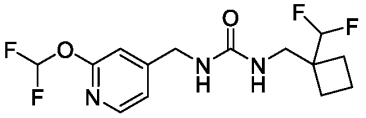
R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, $Si(C_{1-6}alkyl)_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two,

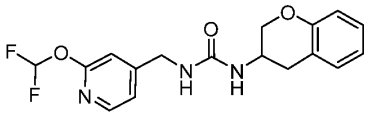
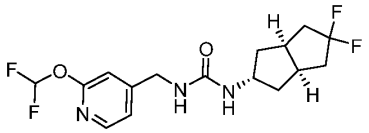
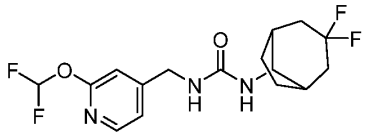
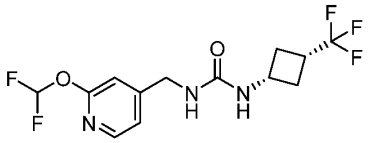
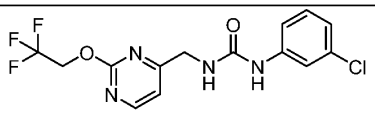
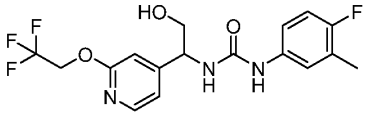
or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

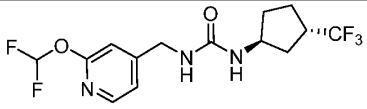
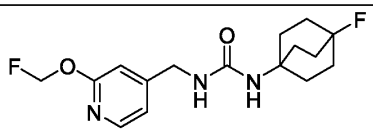
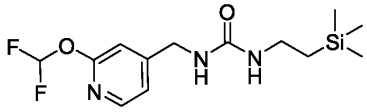
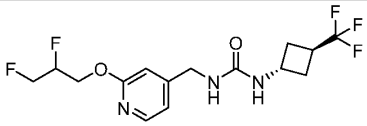
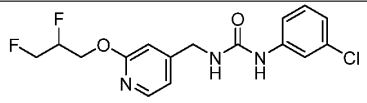
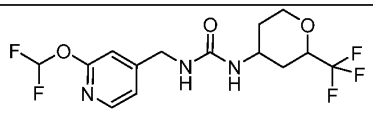
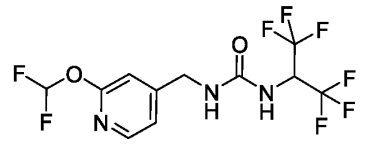
n is 0, 1, or 2.

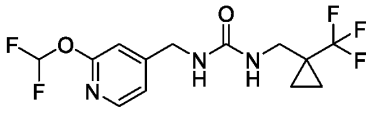
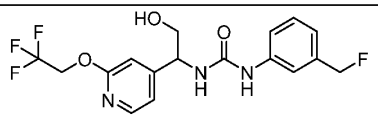
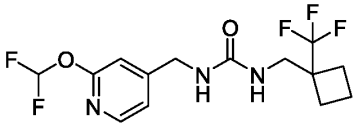
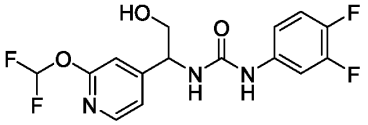
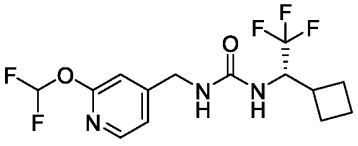
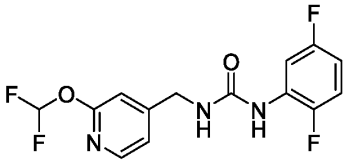
In another more preferred embodiment, the compounds of formula (I) or formula (I') are selected from Table 6.

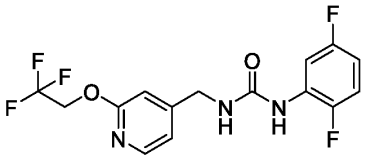
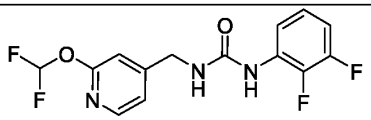
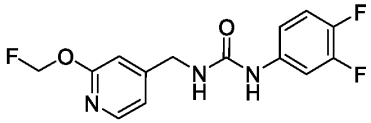
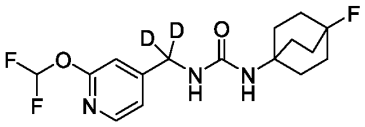
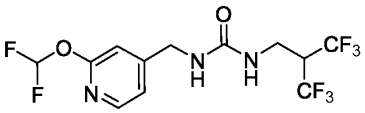
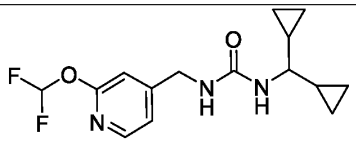
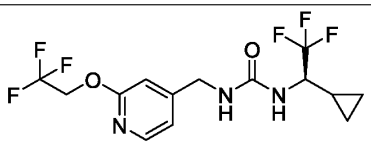
Table 6

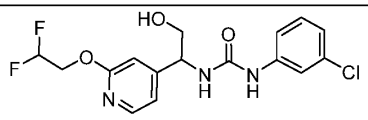
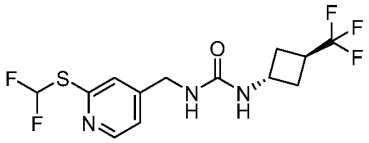
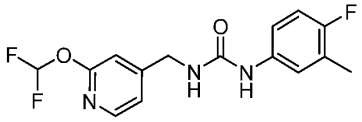
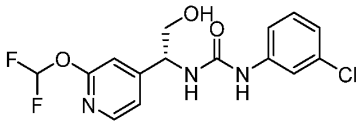
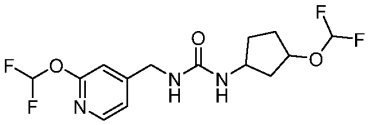
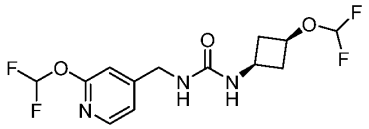
180	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
183	1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
186	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-difluorophenyl)urea	
187	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-hydroxy-3-(trifluoromethyl)cyclopentyl]urea	
191	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluoromethyl)cyclobutyl]methyl]urea	

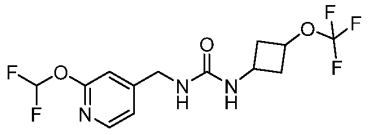
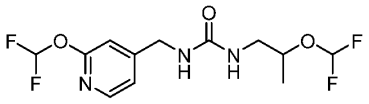
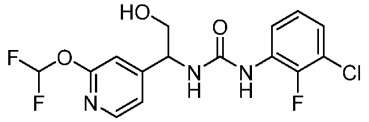
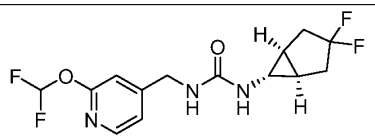
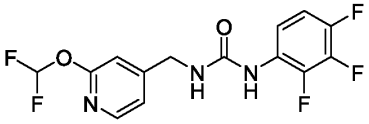
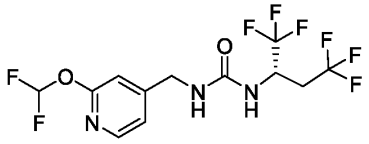
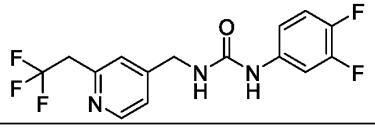
192	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-dihydro-2H-chromen-3-yl)urea	
195	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2r,3aR,6aS)-5,5-difluoro-2,3,3a,4,6,6a-hexahydro-1H-pentalen-2-yl]urea	
197	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3,3-difluoro-8-bicyclo[3.2.1]octanyl]urea	
198	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(trifluoromethyl)cyclobutyl]urea	
203	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]urea	
205	1-(4-fluoro-3-methylphenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

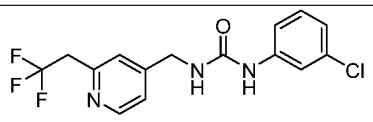
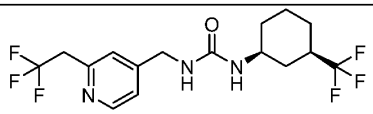
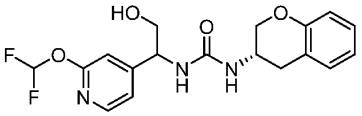
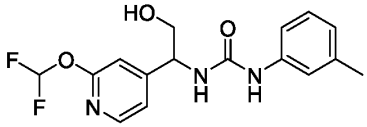
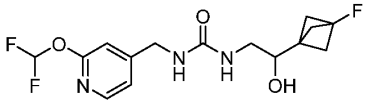
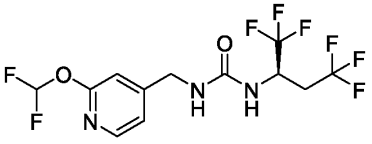
207	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-(trifluoromethyl)cyclopentyl]urea	
208	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
212	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-trimethylsilylethyl)urea	
214	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
220	1-(3-chlorophenyl)-3-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]urea	
226	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(trifluoromethyl)oxan-4-yl]urea	
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea	

229	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
232	1-[3-(fluoromethyl)phenyl]-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
237	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclobutyl]methyl]urea	
240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
242	1-[(1S)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
244	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,5-difluorophenyl)urea	

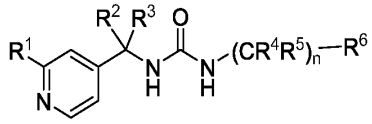
245	1-(2,5-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
247	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3-difluorophenyl)urea	
249	1-(3,4-difluorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
251	1-[dideuterio-[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
252	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea	
253	1-(dicyclopropylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyr	

	idin-4-yl]methyl]urea	
259	1-(3-chlorophenyl)-3-[1-[2-(2,2-difluoroethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
260	1-[[2-(difluoromethylsulfanyl)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
261	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-3-methylphenyl)urea	
263	rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
264	1-[3-(difluoromethoxy)cyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
265	1-[(1s,3s)-3-(difluoromethoxy)cyclobutyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

267	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethoxy)cyclobutyl]urea	
268	1-[2-(difluoromethoxy)propyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
270	1-(3-chloro-2-fluorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
271	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-3,3-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
272	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3,4-trifluorophenyl)urea	
273	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	
274	1-(3,4-difluorophenyl)-3-[[2-(2,2,2-	

	trifluoroethyl)pyridin-4-yl]methyl]urea	
275	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
276	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
278	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(3S)-3,4-dihydro-2H-chromen-3-yl]urea	
280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea	
289	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]urea	
294	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	

In a more preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from haloC_{1-6}alkoxy, haloC_{1-6}alkyl, and haloC_{1-6}alkylthio;

R^2 and $R^3$are independently selected from hydrogen, deuterium, and hydroxyC_{1-6}alkyl;

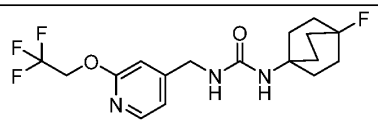
R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and hydroxy; or

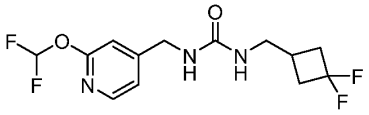
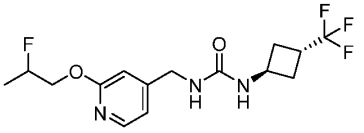
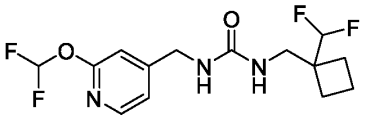
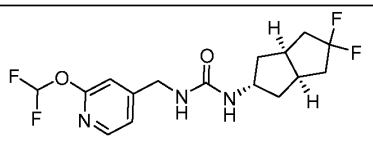
R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

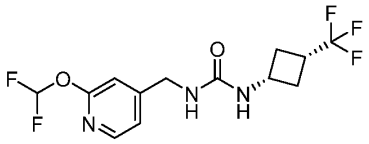
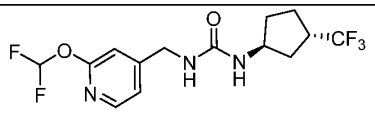
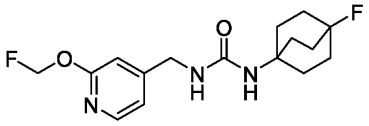
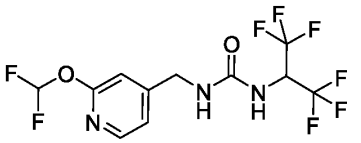
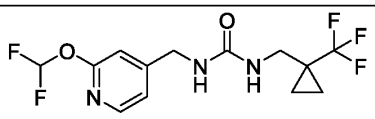
R^6 is selected from a 5-12 membered heterocycloalkyl, a 3-10 membered cycloalkyl, phenyl, $Si(C_{1-6}alkyl)_3$, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

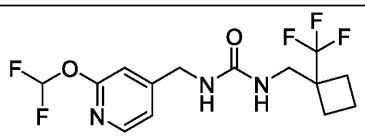
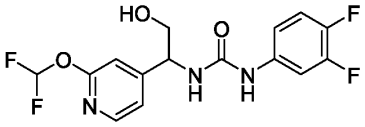
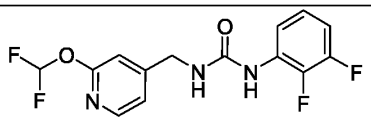
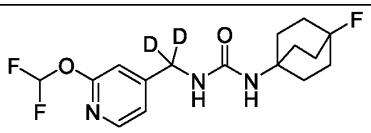
n is 0, 1, or 2.

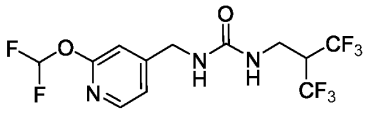
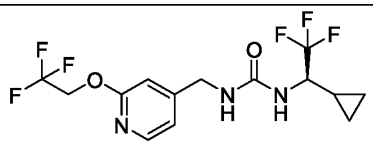
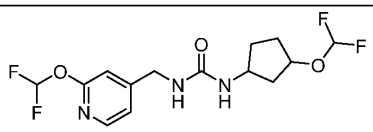
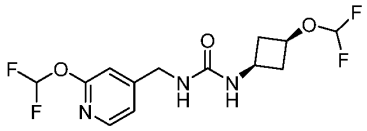
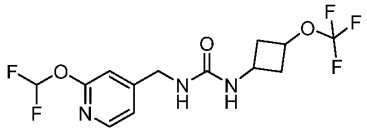
In another most preferred embodiment, the compounds of formula (I) or formula (I') are selected from Table 7.

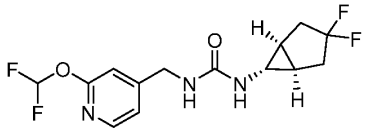
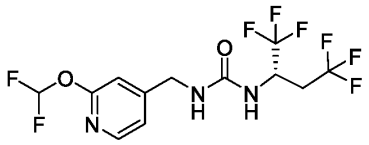
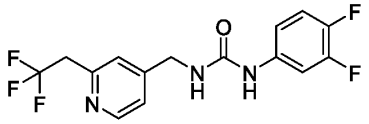
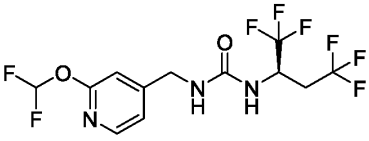
180	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyr	

	idin-4-yl]methyl]urea	
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
183	1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
191	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluoromethyl)cyclobutyl]methyl]urea	
195	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2r,3aR,6aS)-5,5-difluoro-2,3,3a,4,6,6a-hexahydro-1H-pentalen-2-yl]urea	

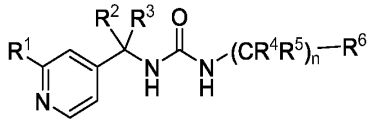
198	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(trifluoromethyl)cyclobutyl]urea	
207	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-(trifluoromethyl)cyclopentyl]urea	
208	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea	
229	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-	

	(trifluoromethyl)cyclopropyl]methyl]urea	
237	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclobutyl]methyl]urea	
240	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
247	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3-difluorophenyl)urea	
251	1-[dideuterio-[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	

252	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea	
257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
264	1-[3-(difluoromethoxy)cyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
265	1-[(1s,3s)-3-(difluoromethoxy)cyclobutyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
267	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-	

	(trifluoromethoxy)cyclobutyl]urea	
271	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-3,3-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
273	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	
274	1-(3,4-difluorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
294	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	

In a most preferred embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from haloC_{1-6}alkoxy, and haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterim, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, haloC_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and hydroxy; or

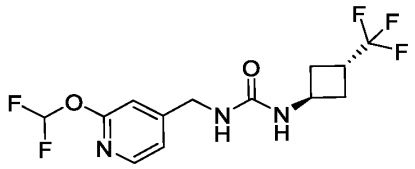
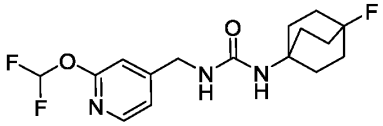
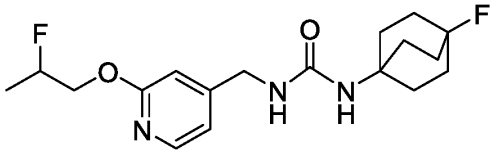
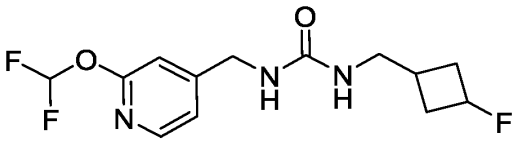
R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

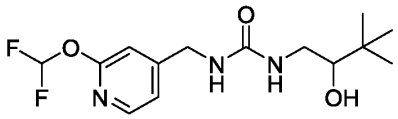
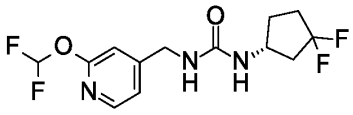
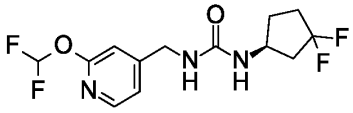
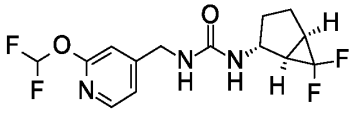
R^6 is selected from a 5-12 membered heterocycloalkyl, a 3-10 membered cycloalkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, and cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

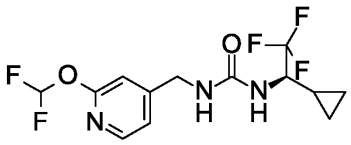
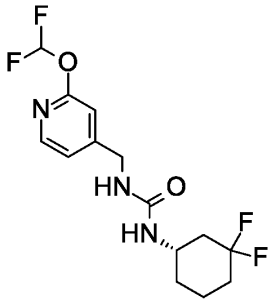
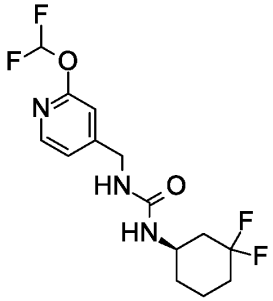
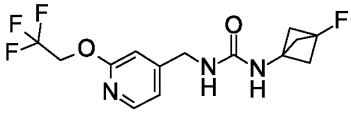
n is 0, 1, or 2.

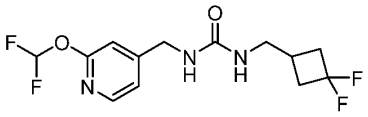
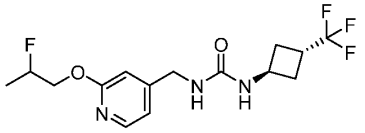
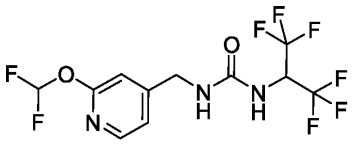
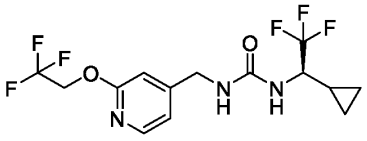
In another most preferred embodiment, the compounds of formula (I) or formula (I') are selected from Table 8.

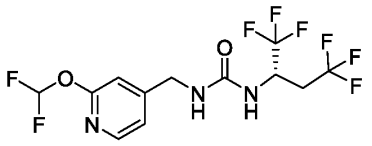
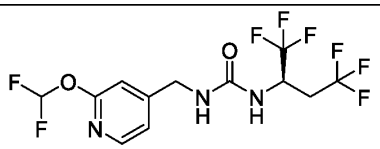
Table 8

42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
88	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	
89	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea	

95	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea	
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
168	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethoxy)py	

	ridin-4-yl]methyl]urea	
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
183	1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea	
257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

273	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	
294	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	

In any of the embodiments described in this application relating to a compound of this invention as defined herein, the corresponding embodiment is incorporated herein, e.g. for compounds selected from any of formulae (I'), (I*), (I**), (I),(II), (III), (IV) etc., or their solvates or pharmaceutically acceptable salts thereof and the respective medical use embodiments. Any embodiment described herein can be combined with any other embodiment to the extent not contracdictory.

Compounds having one or more of the following combinations of features are found to display particulary benefical Kv7.2 EC_{50} values and/or Kv7.3_7.5/Kv7.2 selectivity ratios.

Compounds having one or more of the following combinations of features are found to display particulary beneficial Kv7.2 EC_{50} values and/or Kv7.3_7.5/Kv7.2 selectivity ratios in the range of: EC_{50}<3μM, Select.>10x, EC_{50}<1μM, Select.>30x or EC_{50}<1μM, Select.>30x with favorable metabolic stability.

In one preferred embodiment, the invention provides a compound of this invention, wherein R_1 is haloC_{1-6} alkoxy and R^6 is selected from a 5-12 membered heterocycloalkyl, 6 membered heteroaryl, 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In one preferred embodiment, the invention provides a compound of this invention, wherein R_1 is haloC_{1-6} alkoxy and, wherein R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) C_{1-6}alkyl; and

e) haloC_{1-6}alkyl;

which are all optionally substituted as described herein.

In one preferred embodiment, the invention provides a compound of this invention, or a solvate or a pharmaceutically acceptable salt thereof, wherein R_1 is haloC_{1-6} alkoxy and wherein R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

which are all optionally substituted as described herein.

In one preferred embodiment, the invention provides a compound of this invention, wherein R_1 is haloC_{1-6} alkoxy, and wherein R^6 is selected from:

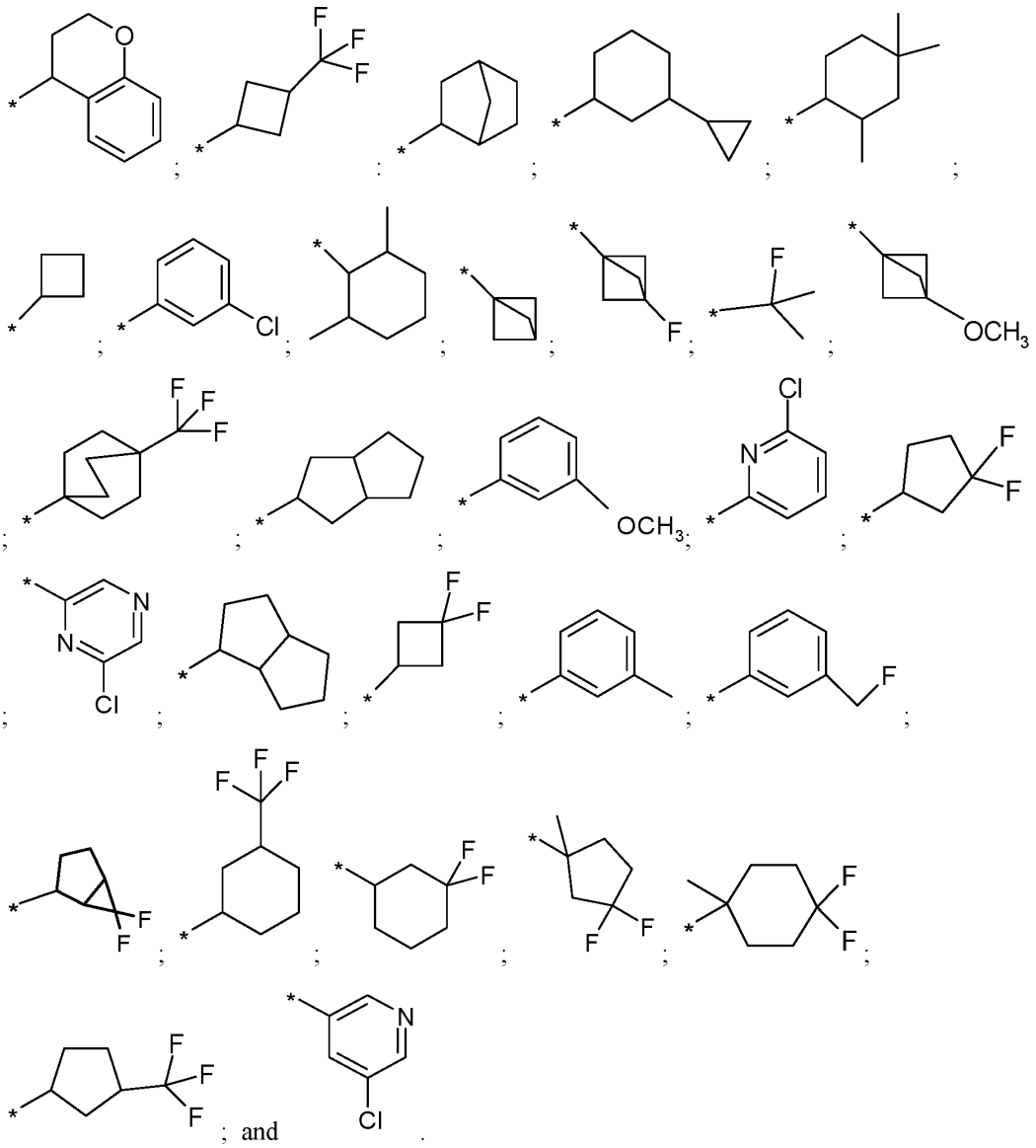
dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyrimidinyl, and pyridinyl, which are optionally substituted as described herein.

In one preferred embodiment, the invention provides a compound of this invention, wherein R_1 is haloC_{1-6} alkoxy and wherein R^6 is selected from:

dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinlyl, pyrimidinyl, and pyridinyl, which are optionally substituted as described herein.

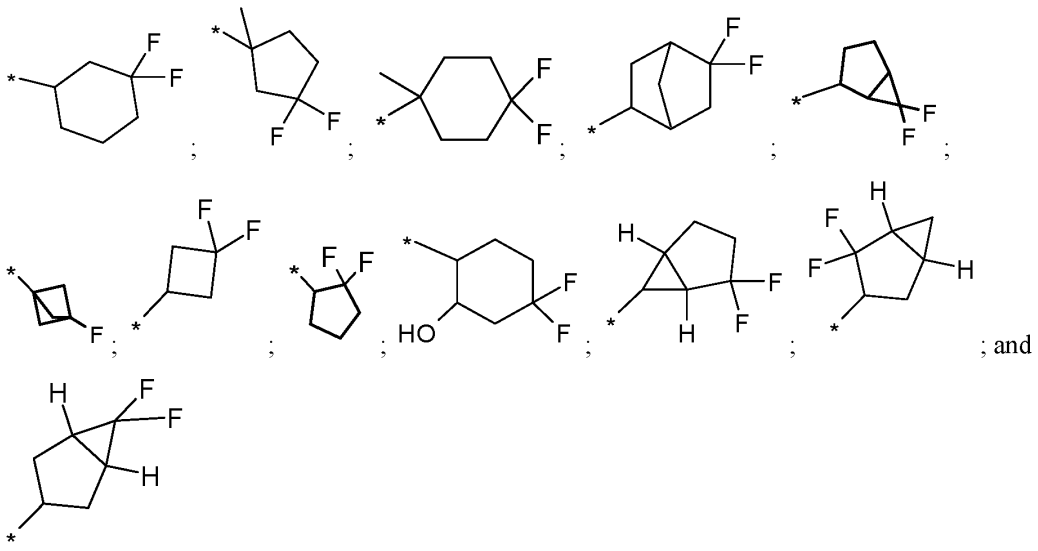
In one preferred embodiment, the invention provides a compound of this invention, R^1 is haloC_{1-6} alkoxy wherein R^6 is selected from a 5-12 membered heterocycloalkyl, 6 membered

heteroaryl, 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl having the structures:

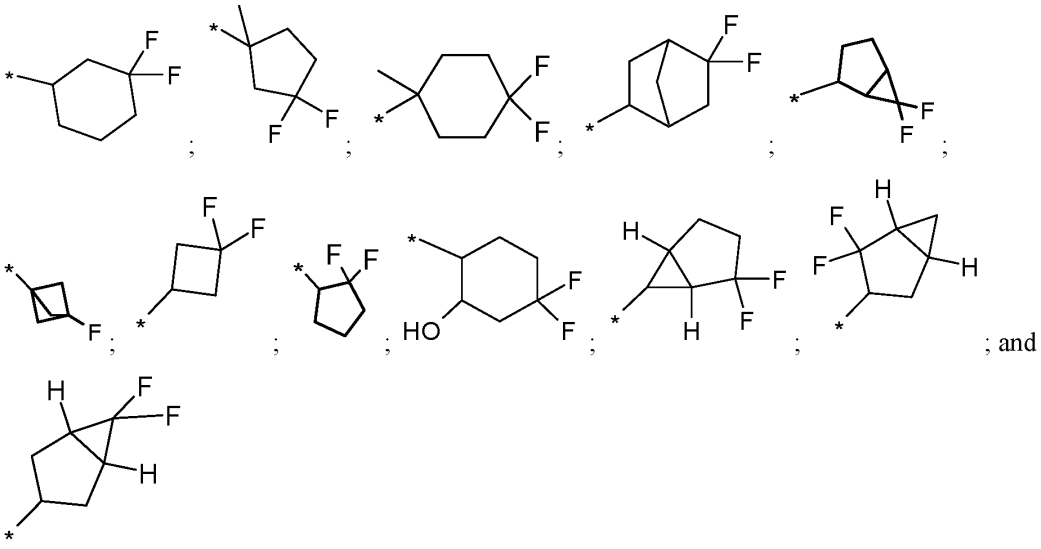


; and .

In one preferred embodiment, the invention provides a compound of this invention, R^1 is haloC_{1-6} alkoxy wherein R^6 is selected from a 5-12 membered heterocycloalkyl, 6 membered heteroaryl, 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl having the structures:



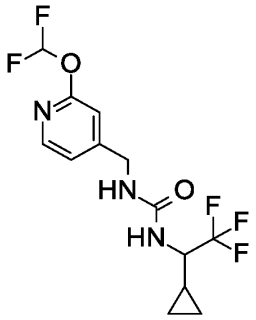
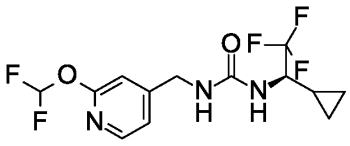
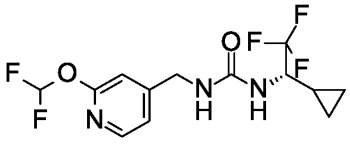
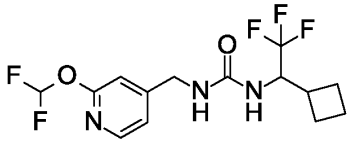
In one particularily preferred embodiment, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is selected from a 5-12 membered heterocycloalkyl, 6 membered heteroaryl, 4-10 membered cycloalkyl, and phenyl, which heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl having the structures:



In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, one of R^4 and R^5 is hydrogen and the other one is a saturated 3-5 membered cycloalkyl selected from cyclopropyl, cyclobutyl, and cyclopentyl, which are unsubstituted, and R^6 is haloC_{1-6}alkyl selected from $(CH_3)_2FC$-, CF_3CH_2-, CH_3CF_2-, CF_3- CH_2F-, and CHF_2-.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, one of R^4 and R^5 is hydrogen and the other one is a saturated 3-5 membered cycloalkyl selected from unsubstituted cyclopropyl, cyclobutyl, and cyclopentyl, and R^6 is CF_3-.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 1, one of R^4 and R^5 is hydrogen and the other one is a saturated 3-5 membered cycloalkyl selected from cyclopropyl, cyclobutyl, and cyclopentyl, which are unsubstituted, and R^6 is CF_3- wherein the non-limiting examples have the structures selected from:

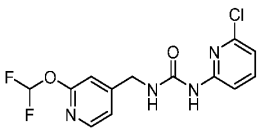
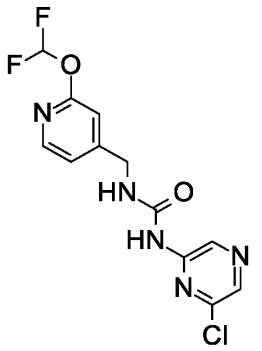
106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
135	1-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
152	1-(1-cyclobutyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

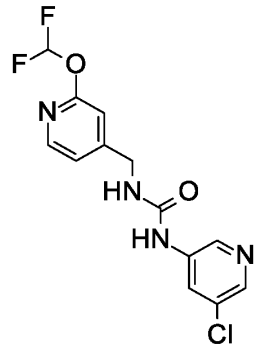
In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a 6 membered heteroaryl selected from pyrazinyl, pyrimidine and pyridine which are

substituted with one or two substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a 6 membered heteroaryl selected from pyrazinyl, pyrimidine and pyridine which are substituted with one or two substituents independently selected from Cl-, F-, and CF_3-.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a 6 membered heteroaryl selected from pyrazinyl, pyrimidine and pyridine which are substituted with one or two substituents independently selected from Cl-, F- and CF_3-, wherein the non-limiting examples have the structures selected from:

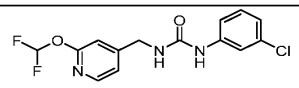
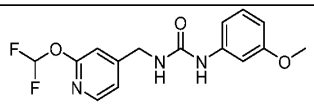
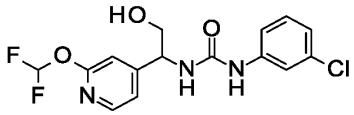
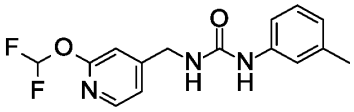
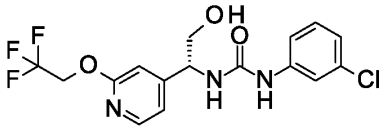
84	1-(6-chloropyridin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
98	1-(6-chloropyrazin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

161	1-(5-chloropyridin-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are both hydrogen or one of R^2 and R^3 is hydrogen and the other one is hydroxy$C_{1\text{-}6}$alkyl, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is phenyl which are substituted with one or two substituents independently selected from halogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, and halo$C_{1\text{-}6}$alkyl.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are both hydrogen or one of R^2 and R^3 is hydrogen and the other one is hydroxy$C_{1\text{-}6}$alkyl, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is phenyl which is substituted with one or two substituents independently selected from Cl-, F-, CH_3-, CH_3O-, and CF_3-.

In some preferred embodiments, , the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are both hydrogen or one of R^2 and R^3 is hydrogen and the other one is hydroxy$C_{1\text{-}6}$alkyl, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is phenyl which is substituted with one or two substituents independently selected from Cl-, F-, CH_3-, -, CH_3O-, and CF_3-, wherein the non-limiting examples have structures selected from:

22	1-(3-chlorophenyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
83	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxyphenyl)urea	
97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
126	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylphenyl)urea	
145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a the 4-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic

rings which are substituted with one or two substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

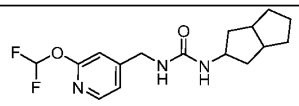
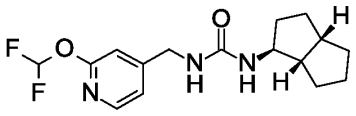
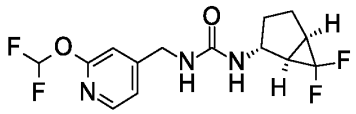
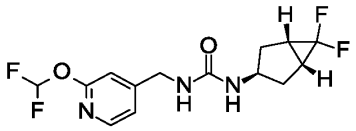
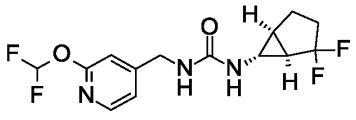
In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a the 4-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings which are substituted with one or two substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In some preferred embodiments, the invention provides a compound of this invention, wherein the 4-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings is selected from bicyclo[3.1.0]hexanyl, octahydropentalenyl, bicyclo[3.2.0]heptanyl, bicyclo[3.2.1]octanyl and hexahydropentalenyl which are optionally substituted with one or two substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In some preferred embodiments, the invention provides a compound of this invention, wherein the 4-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings is selected from bicyclo[3.1.0]hexanyl, octahydropentalenyl, bicyclo[3.2.0]heptanyl, bicyclo[3.2.1]octanyl and hexahydropentalenyl which are optionally substituted with one or two substituents independently selected from F- and CF_3-.

In some preferred embodiments, the invention provides a compound of this invention, wherein the 4-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings is selected from bicyclo[3.1.0]hexanyl, octahydropentalenyl, bicyclo[3.2.0]heptanyl, bicyclo[3.2.1]octanyl and hexahydropentalenyl which are unsubstituted.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is an unsubstituted 4-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, wherein a non-limiting example has the structure:

78	1-(1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
103	1-[(1S,3aS,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
169	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
170	1-[(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-	

	(difluoromethoxy)pyridin-4-yl]methyl]urea	

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a 4-10 membered bridged cycloakyl as described herein, which briged cycloalkyl is substituted with one or two substituents independently selected from halogen, C_{1-6}alkoxy, and haloC_{1-6}alkyl.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a 4-10 membered bridged cycloakyl as described herein, which bridged cycloalkyl is optionally substituted with one or two substituents independently selected from halogen C_{1-6}alkoxy, and haloC_{1-6}alkyl.

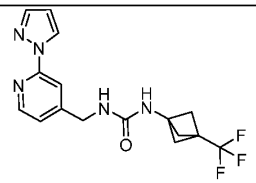
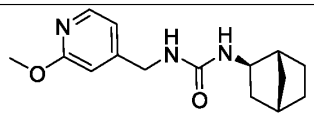
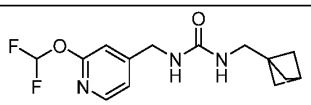
In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a 4-10 membered bridged cycloakyl as described herein, which bridged cycloalkyl is unsubstituted.

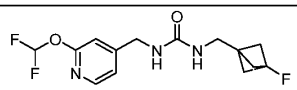
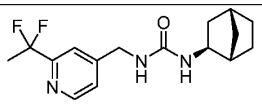
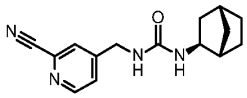
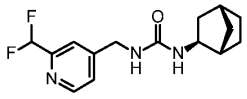
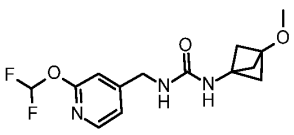
In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a 4-10 membered bridged cycloakyl as described herein, selected from bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and adamantine, which are unsubstituted.

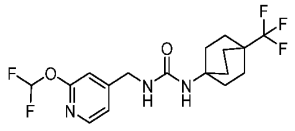
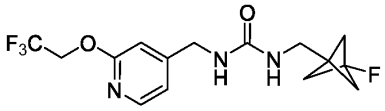
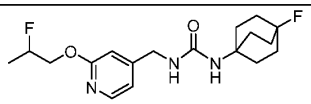
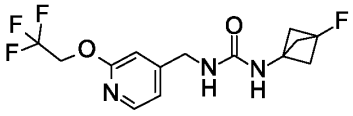
In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a 4-10

membered bridged cycloakyl as described herein, selected from bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and adamantine which are are optionally substituted with one or two substituents independently selected from F-, CH_3O-, and CF_3-.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is an unsubstituted 4-10 membered bridged cycloalkyl, wherein non-limiting examples have the structures:

6	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
14	1-[(2-methoxypyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

32	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea	
33	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
34	1-[(2-cyanopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
35	1-[[2-(difluoromethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
49	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxy-1-	

	bicyclo[1.1.1]pentanyl)urea	
68	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[4-(trifluoromethyl)-1-bicyclo[2.2.2]octanyl]urea	
75	1-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
88	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	
168	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and

CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a satuarated monocyclic cycloalkyl as described herein, which cycloalkyl is substituted with one or two substituents independently selected from halogen, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, and haloC_{1-6}alkyl.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a satuarated monocyclic cycloalkyl as described herein, which cycloalkyl is optionally substituted with one or two substituents independently selected from halogen, C_{1-6}alkyl, and haloC_{1-6}alkyl.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a satuarated monocyclic cycloalkyl as described herein, which cycloalkyl is unsubstituted.

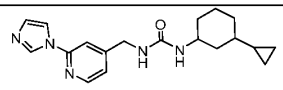
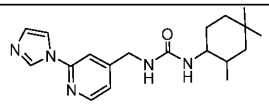
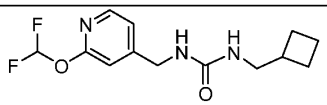
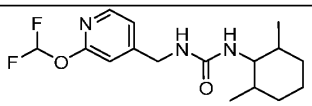
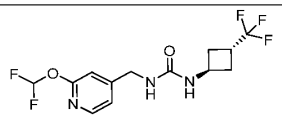
In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a saturated monocyclic cyloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl and cyclohexyl are optionally substituted with one, two, or three CF_3-.

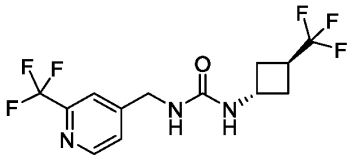
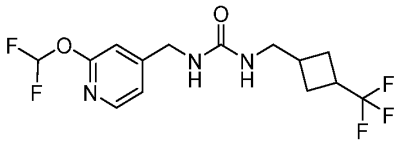
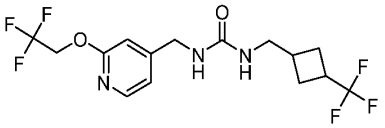
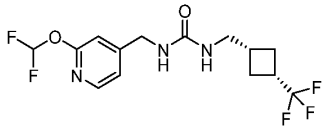
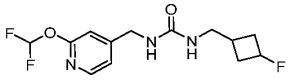
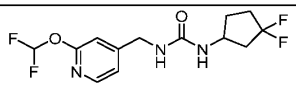
In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a saturated monocyclic cyloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl and cyclohexyl are unsubstituted.

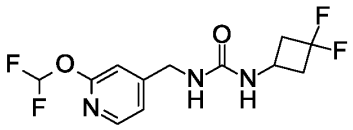
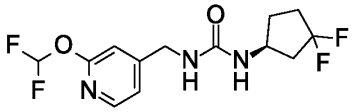
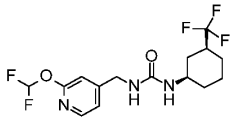
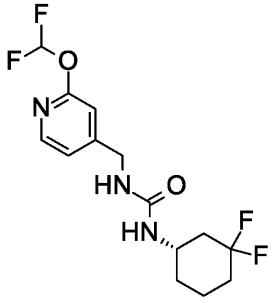
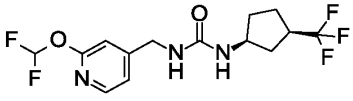
In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a saturated

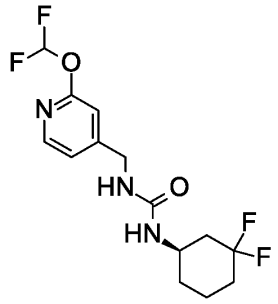
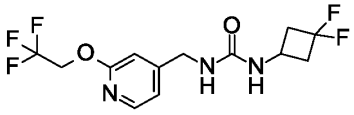
monocyclic cyloalkyl selected from cyclobutyl, cyclopentyl, and cyclohexyl, which cyclobutyl, cyclopentyl and cyclohexyl are optionally substituted with one, two, or three F-.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a saturated monocyclic 4-6 membered cycloalkyl, wherein non-limiting examples have the structures:

8	1-(3-cyclopropylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea	
9	1-[(2-imidazol-1-ylpyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	
13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
25	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,6-dimethylcyclohexyl)urea	
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

58	1-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	
62	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
71	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
87	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(1r,3r)-(trifluoromethyl)cyclobutyl]methyl]urea	
89	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea	
93	1-(3,3-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

108	1-(3,3-difluorocyclobutyl)-3-[[2-(difluoromethoxyA)pyridin-4-yl]methyl]urea	
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
138	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	
140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
144	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3R)-3-(trifluoromethyl)cyclopentyl]urea	

149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
157	1-(3,3-difluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom as described herein, which fused heterocycloalkyl is substituted with one or two substituents independently selected from halogen, $C_{1\text{-}6}$alkyl, and halo$C_{1\text{-}6}$alkyl.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom as described herein, which fused heterocycloalkyl is optionally substituted with one or two substituents independently selected from halogen, $C_{1\text{-}6}$alkyl, and halo$C_{1\text{-}6}$alkyl.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and

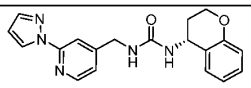
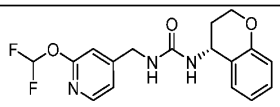
CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom as described herein, which fused heterocycloalkyl is unsubstituted.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom as described herein, which fused heterocycloalkyl is unsubstituted.

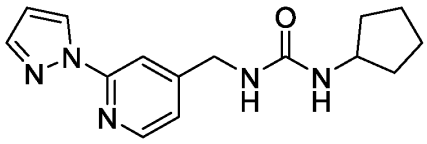
In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom as described herein, which fused heterocycloalkyl is unsubstituted dihydrochromenyl.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 R^1 is selected from pyrazolyl and imidazolyl (both as described herein), CHF_2O- and CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings which is dihydrochromenyl optionally substituted with one or two substituents independently selected from F- and CF_3-.

In some preferred embodiments, the invention provides a compound of this invention, wherein R^1 is CHF_2O- or CF_3CH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, and R^6 is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring wherein one ring comprises one O-atom as described herein, wherein non-limiting examples have the structures:

1	1-[(4R)-3,4-dihydro-2H-chromen-4-yl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
23	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(4R)-3,4-dihydro-2H-chromen-4-yl]urea	

In some embodiments, the compound of this invention is not selected from: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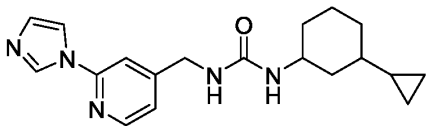
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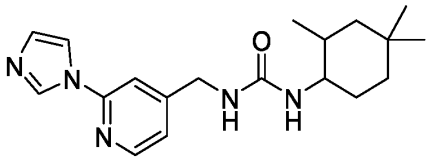
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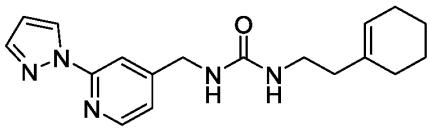
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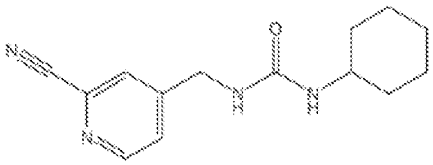

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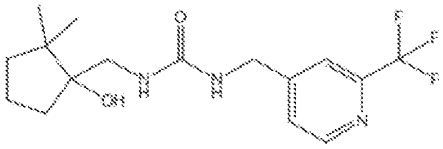

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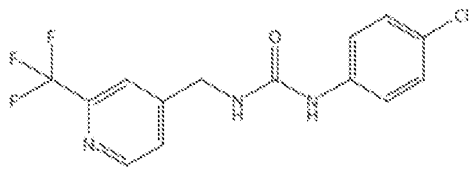

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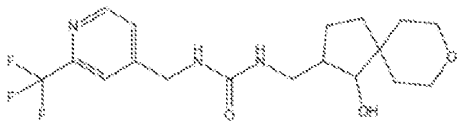

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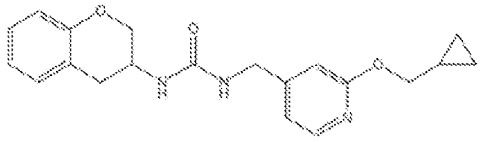
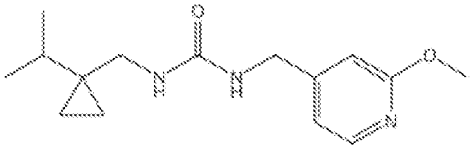
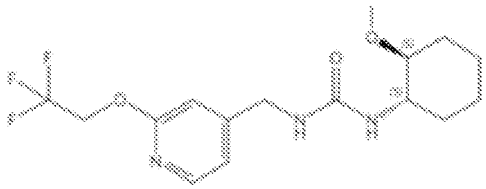


; and



.

In some embodiments the compound of this invention is not selected from:



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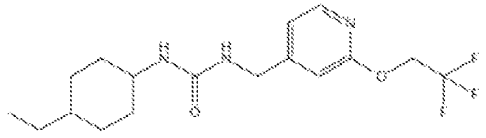

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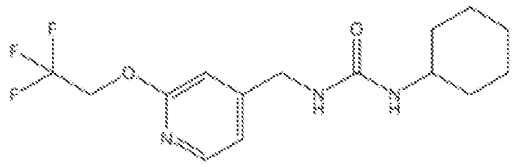

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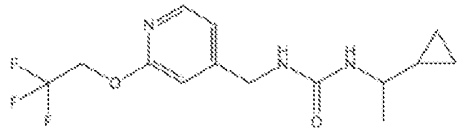

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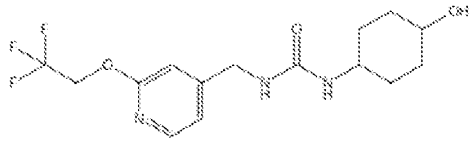

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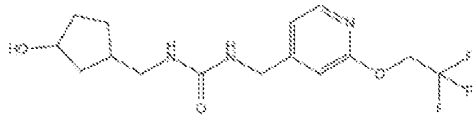

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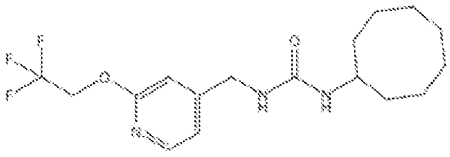
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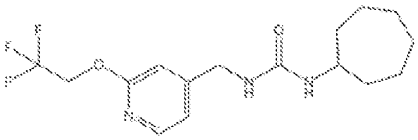
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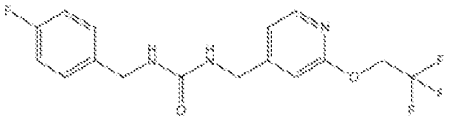
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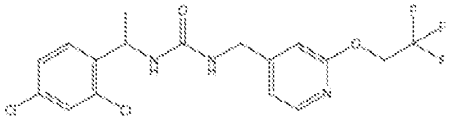
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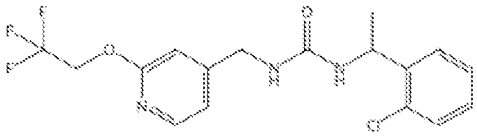
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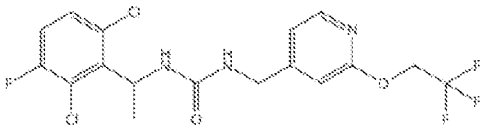
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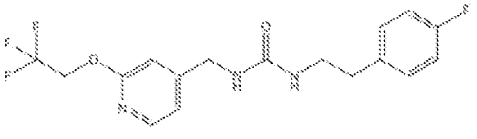
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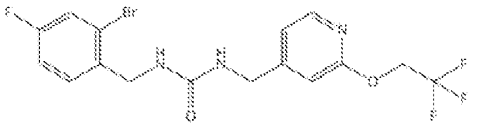
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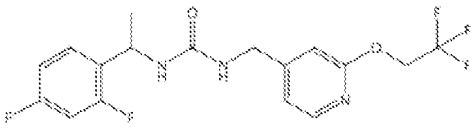
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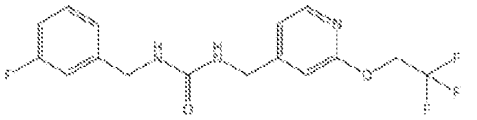
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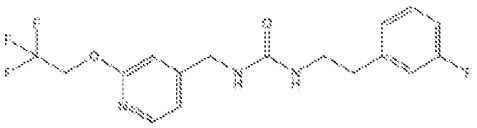
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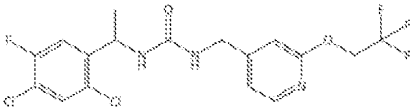
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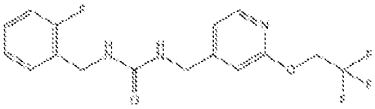
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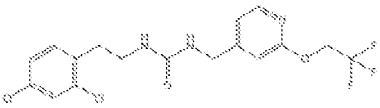
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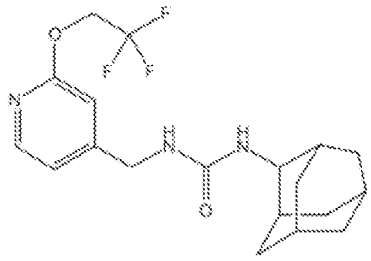

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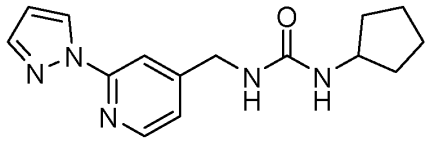
In some embodiments, the compound of this invention is not selected from:



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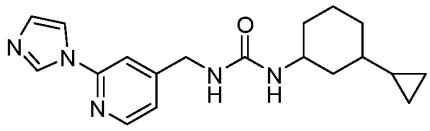

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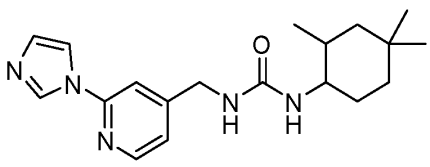
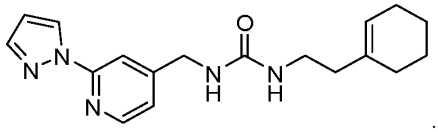


; and



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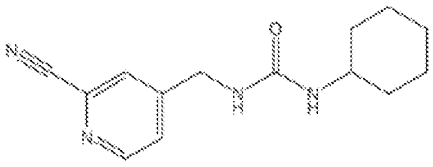
In some embodiments the compound of this invention is not selected from:



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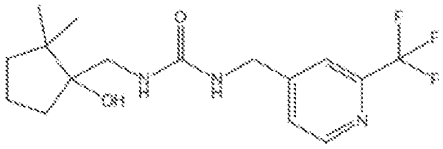

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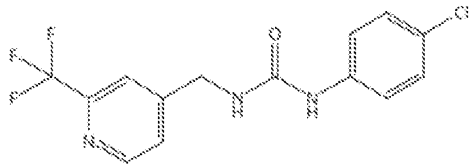

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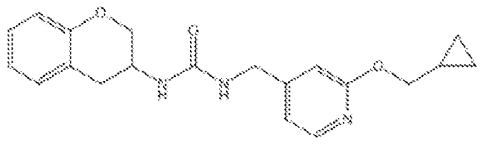
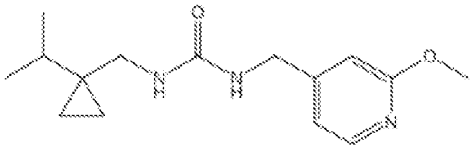


; and



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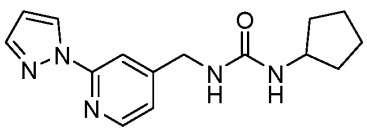
In some embodiments, the compound of this invention is not selected from:



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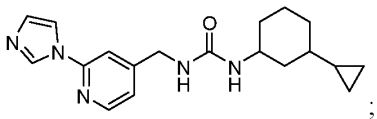
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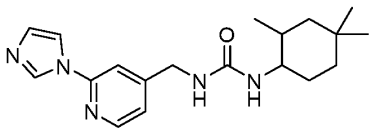
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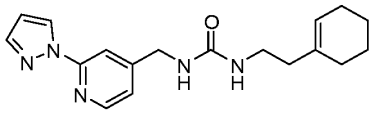
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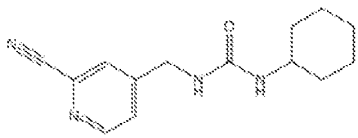
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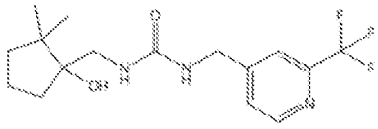
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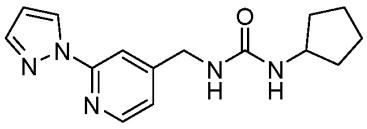
In some embodiments, the compound of this invention is not selected from: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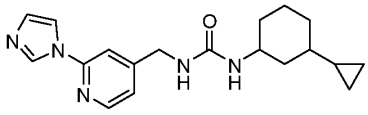
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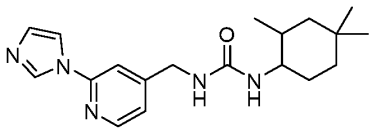
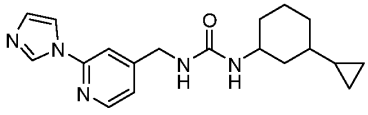


In some embodiments, the compound of this invention is not selected from: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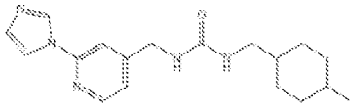
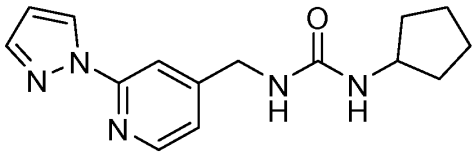


In some embodiments, the compound of this invention is not selected from: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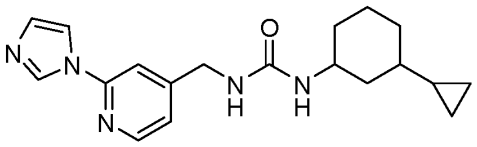
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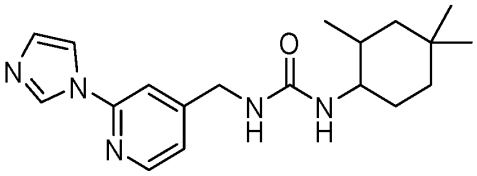
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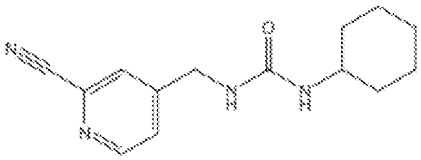

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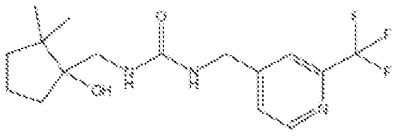

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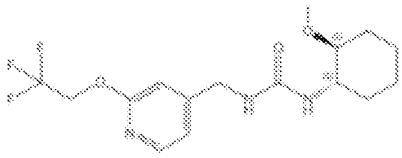
In some embodiments, the compound of this invention is not selected from:



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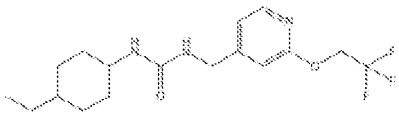

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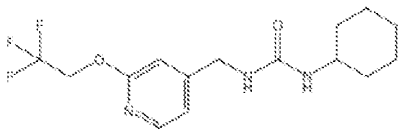

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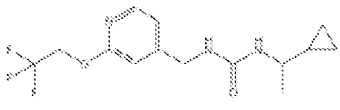

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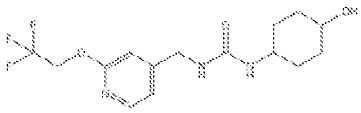
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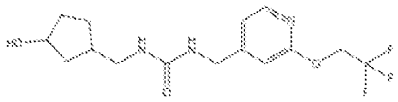
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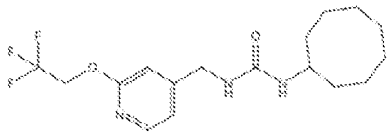
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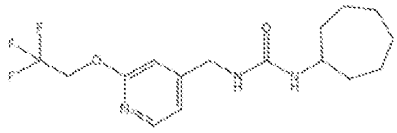
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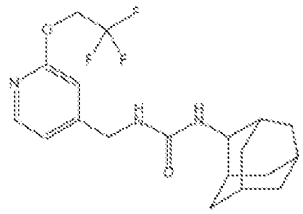
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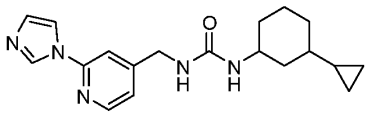
In some embodiments, the compound of this invention is not selected from: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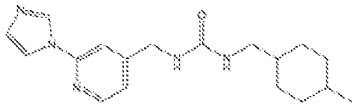
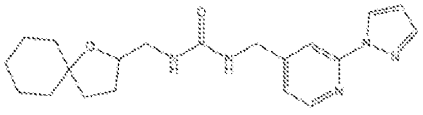
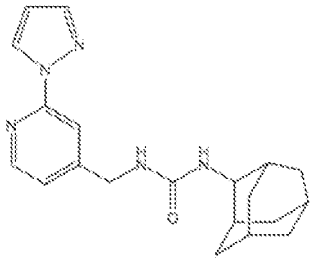

.

In some embodiments, the compound of this invention is not:

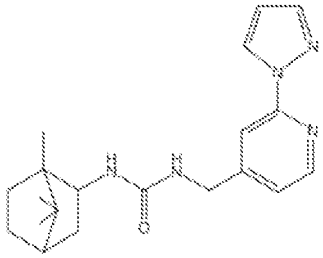


.

In some embodiments, the compound of this invention is not selected from:

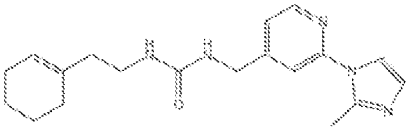


; and

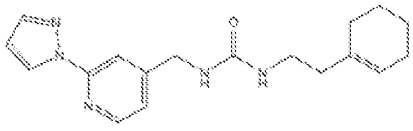


.

In some embodiments, the compound of this invention is not selected from:

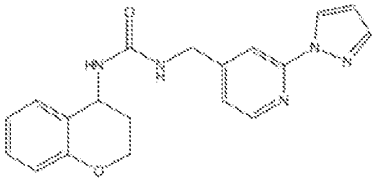


; and



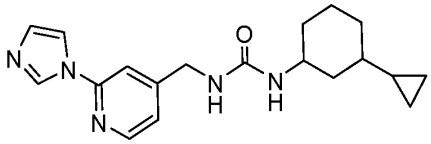
.

In some embodiments, the compound of this invention is not:



.

In some embodiments, the compound of this invention is not selected from:



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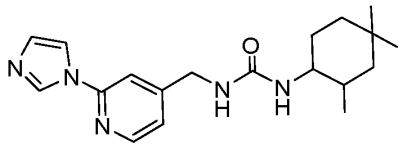
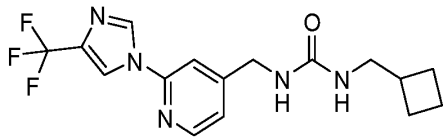
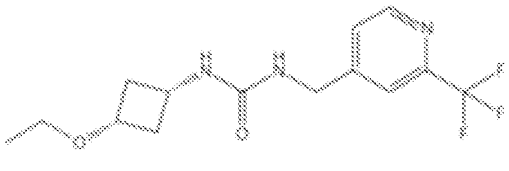


; and

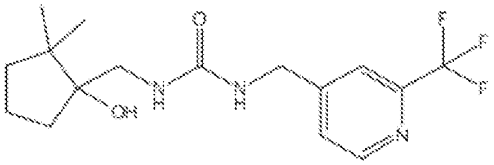


.

In some embodiments, the compound of this invention is not selected from:

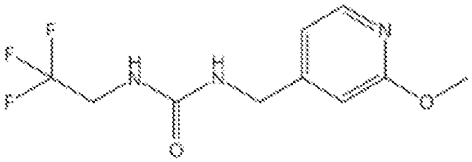


; and



.

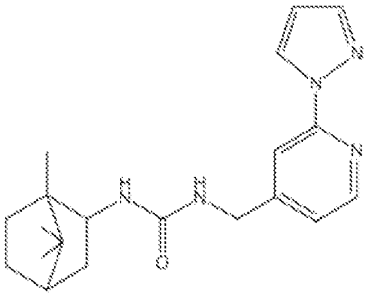
In some embodimetns, the compound of this invention is not:



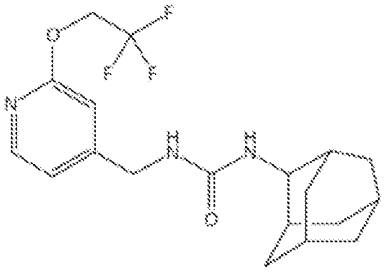
.

In some embodiments, the compound of this invention is not selected from:

5

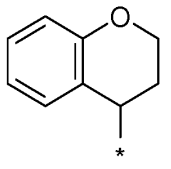
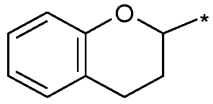
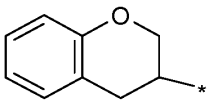


; and



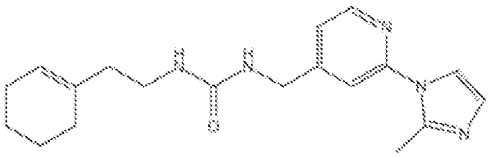
.

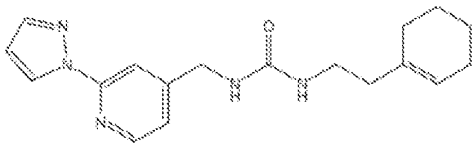
In some embodiments of the compound of this invention is not a chromen with a structure selected from:

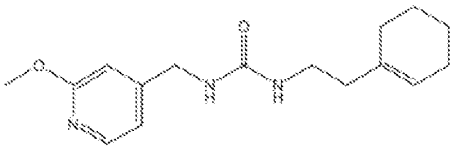

;

; and

;

which can be unsubstituted or the aromatic ring is substituted with one substitutent selected from halogen, $C_{1\text{-}6}$alkoxy, and hydroxy.

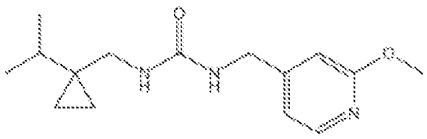
In some embodiments, the compound of this invention is not selected from:


;

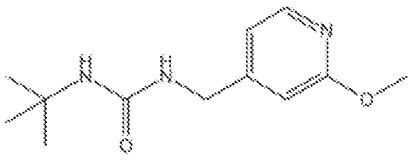

; and


.

In one embodiment, the compound of this invention is not:



In some embodiments, the compound of this invention is not:



In some embodiments of the invention, wherein R^6 is optionally substituted phenyl as described herein, R^1 is not 5 membered heteroaryl.

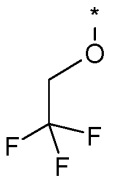
In some embodiments of the invention, wherein R^6 is optionally substituted phenyl as described herein, R^1 is not $C_{1\text{-}6}$alkoxy.

In some embodiments, when R^6 is tert-butyl, R^1 is not CF_3CH_2O-.

In some embodiments, R^1 is not CF_3CH_2O-.

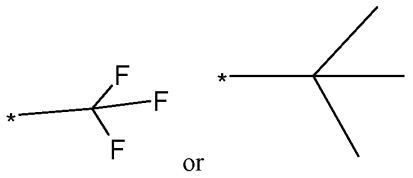
In some embodiments, the compound of formula (I) excludes compounds wherein n is 3 and the second pair of R^4 and R^5 together with the one carbon atom to which they are attached form a 3 membered cycloalkyl.

In some embodiments, the compound of formula (I) excludes compounds wherein R^1 is



, and

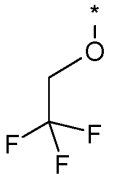
R^6 is:



or .

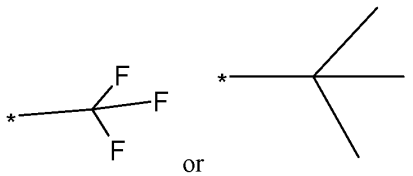
In some embodiments, the compound of formula (I) excludes compounds in which

R^1 is



, and

R^6 is:



or ,

n is 2, and R^4 and R^5 are (i) all hydrogen or (ii) within the first pair of R^4 and R^5 both are hydrogen and within the second pair of R^4 and R^5 one is hydrogen and the other one is hydroxy .

In some embodiments when n is 2, R^6 is not $C_{1\text{-}6}$alkyl.

In some embodiments when n is 2, R^6 is not halo$C_{1\text{-}6}$alkyl.

In some embodiments when n is 2, R^6 is not hydroxy.

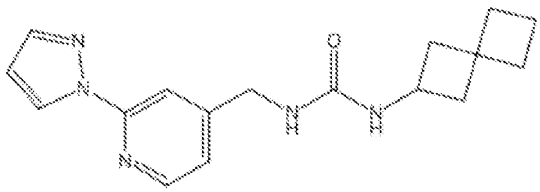
In some embodiments, R^6 does not include bicyclic or polycyclic spiro cycloalkyl ring systems.

In some cases, cycloalkyl does not include bicyclic or polycyclic spiro cycloalkyl ring systems.

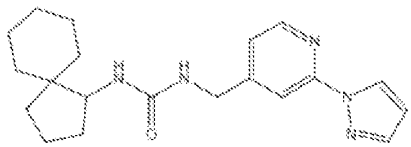
In some cases, heterocycloalkyl does not include bicyclic or polycyclic spiro heterocycloalkyl ring systems.

In some embodiments, the following compounds are excluded:

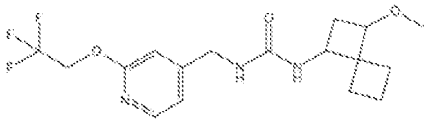
In some embodiments, the compound of this invention is not selected from:



;

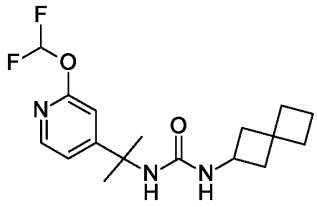


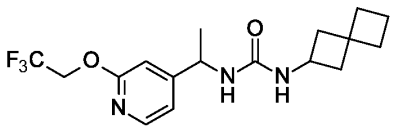
; and

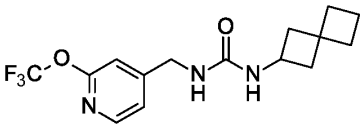


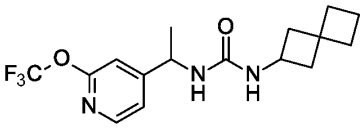
.

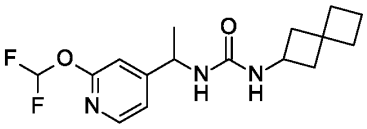
In some embodiments, if falling under the claims of this invention, the compounds of this invention do not include:

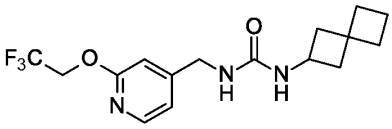


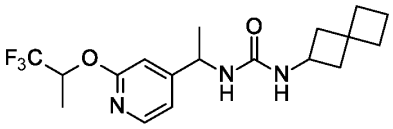


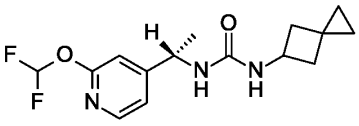


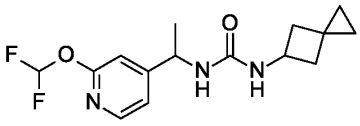




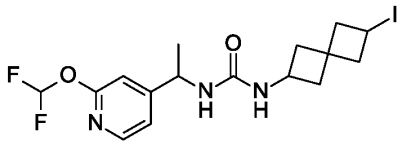


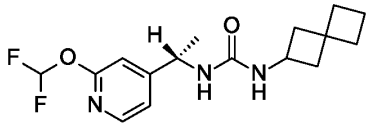






10





The aforementioned embodiments excluding compounds from some embodiments, do not apply for medical uses, pharmaceutical compositions or kits as described herein.

The compounds of the present invention have shown to be agents acting on Kv7.2 and are therefore useful for the treatment and/or prophylaxis of any of the diseases, disorders, or disabilities described herein. They are in particular useful for the therapeutic and/or prophylactic treatment of a disorder, disease, or disabilities associated with Kv7.2. More particularily, they are useful for the therapeutic and/or prophylactic treatment of a disorder, disease, or disabilities associated with Kv7.2, wherein the diseases, disorders, or disabilities are selected from behavioral disorders, mood disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus. The behavioral disorder is for example Attention Deficit Hyperactivity Disorder (ADHD). The mood disorder is for example depression. The neurodevelopment disorder is for example autism spectrum disorder (ASD) or a syndromic developmental disorder. The syndromic developmental disorder is for example Dup15q syndrome (Dup15q), Fragile X syndrome (FXS), and Angelman syndrome. The epilepsies are for example broad pediatric epilepsy, West syndrome, Ohtahara syndrome and epileptic encephalopathy. Neurodegenerative diseases are for example Alzheimer's disease, or motor neuron diseases.

The compounds of the present invention are therefore useful Kv7.2 modulators that provide for a combination of favorable pharmacological properties, such as potency, selectivity, and metabolic clearance (leading to a better therapeutic window). In particular, the compounds with R^1 being haloC_{1-6}alkoxy (such as CF_3CH_2O- and CHF_2O-) show excellent potency and selectivity. Excellent potency and selectivity are in particular observed in embodiment wherein R^1 is CF_3CH_2O- or CHF_2O- and R^6 is selected from:

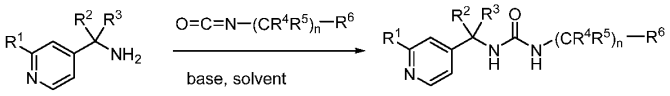
a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl; and

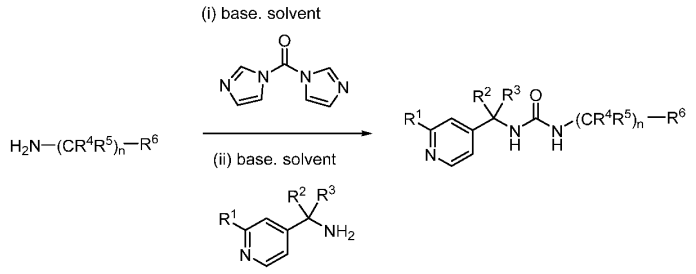
c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings,. Most favorable potency, selectivity and metabolic stability can be found in embodiments wherein R^1 is CHF_2O- or CF_3CH_2O- and is combined with R^6 as described above which R^6 is substituted with one, two, or three substituents independently selected from halogen or halo$C_{1\text{-}6}$alkyl.

It has been found that substituents at R^6 being F or CF_3- particulary provide favorable potency, selectivity and metabolic stability.

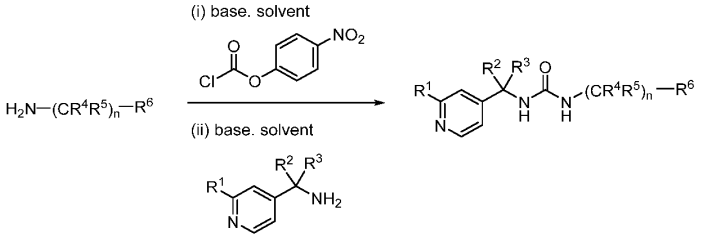
In one embodiment this invention relates to a process for the preparation of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, which comprises one of the reactions of:



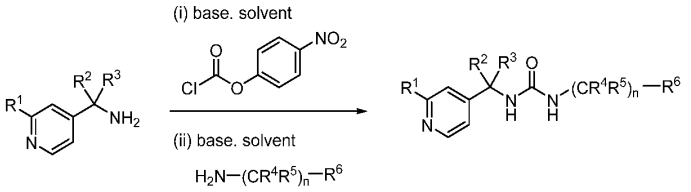
or



or



or

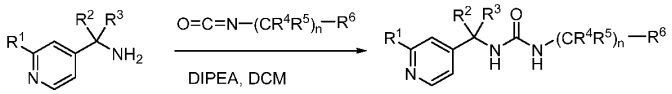


with the base selected from DIEA and TEA;

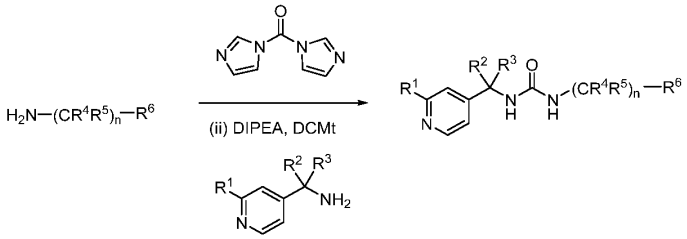
with the solvent selected from DCM and DMF;

wherein R^1, R^2, R^3, R^4, R^5, n, and R^6 are as defined herein.

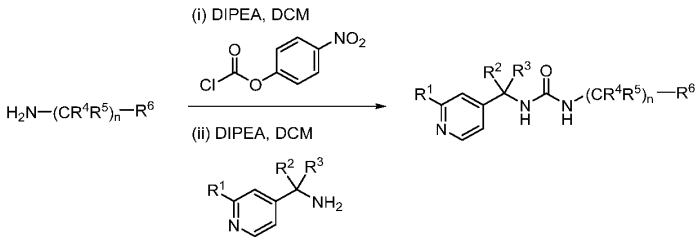
In one preferred embodiment this invention relates to a process for the preparation of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, which comprises one of the reactions of:



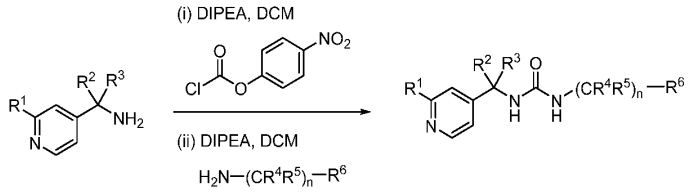
or



or



or



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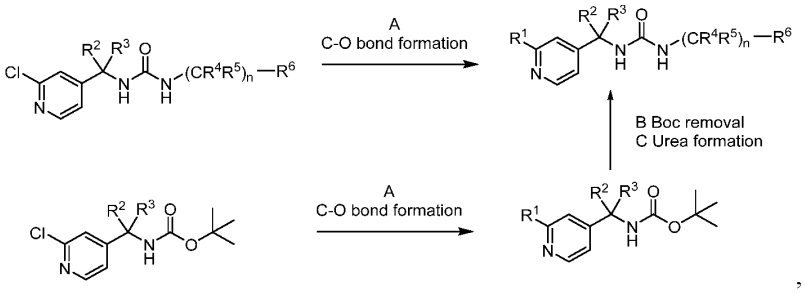
R^7 can be introduced by standard methods known to the person skilled in the art.

In one preferred embodiment, these reactions are used for R^1 being selected from 6 membered heterocycloalkyl, cyano, halogen, haloC_{1-6}alkyl, and 5 membered heteroaryl.

In one embodiment of this invention, the urea formation can be accomplished by treatment of an amine with an isocyanate (first reaction) in DCM or DMF at temperatures from RT to 40°C, or by reacting the first amine with 1,1'-carbonyldiimidazole (second reaction) in the presence of a suitable base to generate the activated urea prior to the addition of the second amine, or by reacting the first amine with para-nitrophenyl chloroformate (third reaction) or phenyl chloroformate to generate the carbamate which can be purified or used in situ with a second amine to yield the desired urea.

In one embodiment preferred conditions are using CDI with DIPEA as a base and with DCM as a solvent at 0°C for 45min and then adding the second amine and stirring at 40°C for 2-6 hours.

In one embodiment the process of making compounds of this invention comprises the following alternative reaction:



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wherein this reaction is used for the preparation of compounds, in cases wherein R^1 is any alkoxy group described herein, e.g. haloC_{1-6}alkoxy, C_{1-6}alkoxy, 4-6 membered heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or cyanoC_{1-6}alkoxy. In some embodiments, this reaction is applied in case when R^2 and R^3 are hydrogen. In some embodiments, this reaction is applied in case when R^2 and R^3 are as described herein but are not hydrogen.

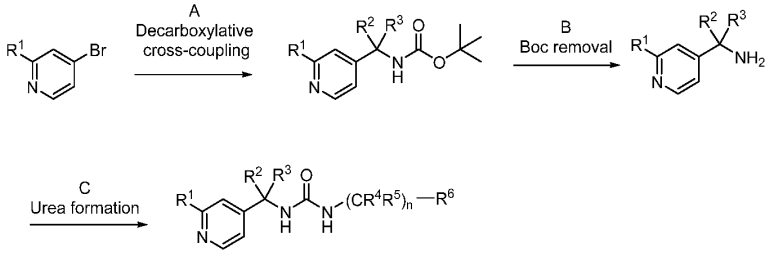
In one embodiment the process of making compounds of this invention comprises the fourth alternative reaction shown herein, wherein the C-O bond formation can be accomplished via

Buchwald-Hartwig etherification between the 2-chloro-pyridyl intermediate and a primary alcohol using a Palladium catalyst and an inorganic base in an organic solvent selected from THF, methyltetrahydrofurane, toluene, 1,4-dioxane, 1,3-dioxane, 1,2-dioxane, hexane, cyclohexane and heptanes at a temperature in the range of 70-90°C. Preferably, this reaction is performed in toluene at a temperature of about 80°C.

In one embodiment of this invention, conditions are using tBuBrettPhosPd G3 as a catalyst and cesium carbonate.

The BOC removal can be achieved by any method known to the person skilled in the art. The urea formation is, for example, as described herein.

In one embodiment this invention relates to a process of making compounds of formula (I), or solvates or pharmaceutically acceptable salts thereof, comprising the following reaction steps:



wherein R^1, R^2, R^3, R^4, R^5, n, and R^6 are as defined herein.

In one embodiment this invention relates to a process of making compounds of formula (I), or a solvate or a pharmaceutically acceptable salts thereof, using the herein reactions, wherein the reactions are used for the preparation of compounds with R^1 being any alkoxy group described herein, e.g. haloC_{1-6}alkoxy, C_{1-6}alkoxy, 4-6 membered heterocyclyloxy, halogen, C_{3-5}cycloalkylC_{1-6}alkoxy, or cyanoC_{1-6}alkoxy. In one preferred embodiment the reactions are used when R^2 is hydroxyC_{1-6}alkyl and R^3 is hydrogen.

In one embodiment this invention relates to a process of making compounds of formula (I), or a solvate or a pharmaceutically acceptable salts thereof, wherein the decarboxylative cross-

coupling reaction can be performed between a heteroaryl halide and protected □-amino acids under the combined action of visible-light photoredox-Ni catalysis and in the presence of cesium carbonate and an Iridium photocatalyst.

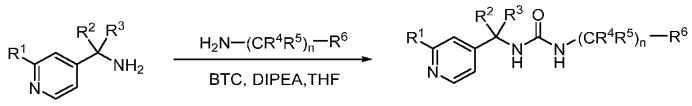
In one embodiment this invention relates to a process of making compounds of formula (I), or solvates or pharmaceutically acceptable salts thereof, wherein Boc deprotection can be carried out by treatment with HCl/Dioxane.

In one embodiment this invention relates to a process of making compounds of formula (I), or a solvate or a pharmaceutically acceptable salts thereof, wherein urea formation can be performed out via the first, second, third, and/or fourth reaction as described herein. Preferred conditions are using CDI with DIPEA as a base and with DCM as a solvent at 0°C for 1 hour and then adding the second amine and stirring at RT overnight.

In one embodiment this invention relates to a process of making compounds of formula (I), or solvates or pharmaceutically acceptable salts thereof, wherein the deprotection can be achieved by any method known to the person skilled in art, e.g. debenzylation can be performed by hydrogenation in the presence of 10% Palladium on charcoal in Ethanol/Ethyl acetate.

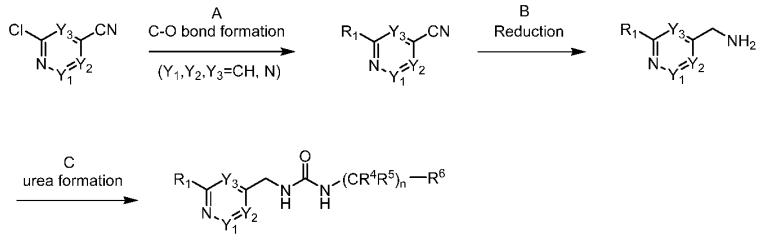
In one embodiment this invention relates to a process of making compounds of formula (I)), or solvates or pharmaceutically acceptable salts thereof, wherein isolation and purification of the compounds and intermediates described herein can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination of these procedures. However, other equivalent separation or isolation procedures could also be used. Racemic mixtures of chiral compounds of formula (I), or a solvate or a pharmaceutically acceptable salts thereof, can be separated using chiral HPLC.

In one embodiment, the invention relates to an alternative process of making compounds of formula (I), comprising the following reaction step:



The urea formation can be accomplished by treatment of an amine (or the corresponding salt, such as HCl) with bis-trichloromethyl)carbonate (triphosgene, BTC) (Scheme 4) in DCM or THF at 0°C and in the presence of a base (DIPEA), followed by addition of a second amine in solution (THF) at RT to afford the desired urea.

In one embodiment, the invention relates to the process of making a compound of formula (I`), comprising the reaction steps:



This reaction is used for the preparation of compounds with R^1 being an haloC_{1-6}alkoxy group.

Step A: The C-O bond formation in this scheme can be accomplished via Buchwald-Hartwig etherification between a chloro-heteroaryl intermediate and a primary alcohol using a Palladium catalyst and an inorganic base, or by first reacting a secondary alcohol with sodium hydride and subsequent reaction with 2-chloro-pyridyl intermediate.

Preferred conditions are using tBuBrettPhosPd G3 as a catalyst and cesium carbonate in Toluene at 80°C.

Step B: Reduction can be carried out by hydrogenation with Pd/C or by using $CoCl_2$ with sodium borohydride.

Step C: Urea formation can be performed via the other schemes described herein. Preferred conditions are using para-nitrophenyl chloroformate with DIPEA as a base and with DCM as a solvent at 0°C to RT. The carbamate intermediate can either be isolated or reacted in-situ with the second amine and stirring at RT overnight.

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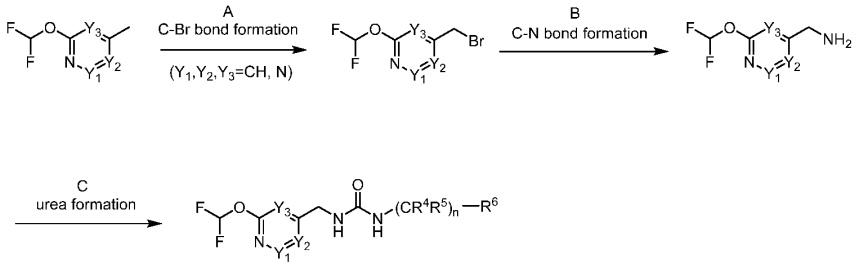
In one embodiment, the invention relates to the process of making a compound of formula (I`), comprising the reaction steps:



Step A: The C-Br bond formation in this scheme can be accomplished by reacting the corresponding methyl heteroaryl with N-bromosuccinimide in the presence of benzoyl peroxide in carbon tetrachloride.

Step B: The C-N bond formation can be accomplished by reacting the heteroaryl bromomethyl intermediate with an ammonia solution in methanol.

Step C: Urea formation can be performed via the other schemes described herein. Preferred conditions are using para-nitrophenyl chloroformate with DIPEA as a base and with DCM as a solvent at 0°C to RT. The carbamate intermediate can either be isolated or reacted in-situ with the second amine and stirring at RT overnight.

In any of the embodiments relating to a compound of formula (I`) or (I), or a solvate or a pharmaceutically acceptable salt thereof, the corresponding embodiment is incorporated herein for compounds of this invention, e.g. compounds selected from any of formulae (I*), (I**), (II), (III), (IV) etc., or their solvates or pharmaceutically acceptable salts thereof and the respective medical use embodiments. Any embodiment described herein can be combined with any other embodiment to the extent not contradicting.

Pharmaceutical Compositions and Administration

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I`) or (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I`) or (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein and one or more pharmaceutically acceptable excipients.

In one embodiment, the present invention provides a pharmaceutical composition comprising one or more pharmaceutical excipients selected form diluent, filler, extender, binder, disintegrant, glidant, humectant, coating, emulsifier or dispersing agent, compression/encapsulation aid, cream or lotion, lubricant, solution for parenteral administration, material for chewable tablets, sweetener or flavoring, suspending/gelling agent, and wet granulation agent.

In a particular embodiment, the invention provides pharmaceutical compositions which are in particular useful for the therapeutic and/or prophylactic treatment of a disorder, disease, or disabilities associated with Kv7.2.

More particularily, the pharmaceutical compositions are useful for the therapeutic and/or prophylactic treatment of a disorder, disease, or disabilities associated with Kv7.2, wherein the diseases, disorders, or disabilities are selected from behavioral disorders, mood disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus.

The compounds of formula (I`) or (I), or their solvates or pharmaceutically acceptable salts, can be used as medicaments (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatin capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of

suppositories). However, the administration can also be effected parentally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

The compounds of formula (I') or (I), or solvates or pharmaceutically acceptable salts thereof, can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées and hard gelatin capsules. Lactose, corn starch, or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées, or hard gelatin capsules.

Suitable adjuvants for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid substances, or liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, or glucose, etc.

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, or vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary in wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 0.1 mg to 20 mg per kg body weight, preferably about 0.5 mg to 4 mg per kg body weight (e.g. about 300 mg per person), divided into preferably 1-3 individual doses, which can consist, for example, of the same amounts, should be appropriate. It will, however, be clear that the upper limit given herein can be exceeded when this is shown to be indicated.

Provided herein are pharmaceutical compositions comprising a compound of formula (I`) or (I), or a solvate or a pharmaceutically acceptable salt thereof. In some embodiments the pharmaceutical compositions comprise one or more pharmaceutically acceptable excipients. Conventional procedures for the selection and preparation of suitable pharmaceutical compositions are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs," M. E. Aulton, Churchill Livingstone, 1988, which is hereby incorporated by reference in its entirety.

Further provided is a process for the preparation of a pharmaceutical composition, comprising combining one or more compounds of formula (I`) or (I), or solvates or pharmaceutically acceptable salts thereof.

Further provided is a process for the preparation of a pharmaceutical composition, comprising combining one or more compounds of formula (I`) or (I), or solvates or pharmaceutically acceptable salts thereof, with one or more pharmaceutically acceptable excipients. Pharmaceutical compositions may be prepared, for example, according to conventional dissolution, mixing, granulating, or coating methods, or combinations thereof. Such pharmaceutically acceptable excipients may include, for example, sugars (e.g., lactose, glucose, sucrose); starches (e.g., corn starch, potato starch); cellulose and its derivatives (e.g., sodium carboxymethyl cellulose, ethyl cellulose, cellulose acetate); powdered tragacanth; malt; gelatin; talc; cocoa butter and suppository waxes; oils (e.g., peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, soybean oil); glycols (e.g., propylene glycol); polyethylene glycols (PEG); esters (e.g., ethyl oleate, ethyl laurate); agar; buffering agents (e.g., magnesium hydroxide, aluminum hydroxide); alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; non-toxic compatible lubricants (e.g., sodium lauryl sulfate, magnesium stearate); coloring agents; releasing agents; coating agents; sweetening; and flavoring and perfuming agents. Preservatives and antioxidants can also be present in the pharmaceutical composition, according to the judgment of the formulator.

Depending on the intended mode of administration, the disclosed pharmaceutical compositions can be in solid, semi-solid, or liquid dosage form, such as, for example, injectables,

tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syrups, powders, liquids, suspensions, or the like, sometimes in unit dosages and consistent with conventional pharmaceutical practices. These modes may include systemic or local administration such as oral, nasal, parenteral (as by intravenous (both bolus and infusion), intramuscular, or subcutaneous injection), transdermal, vaginal, buccal, rectal, or topical (as by powders, ointments, or drops) administration modes. These modes may also include intracisternally, intraperitoneally, as an oral or nasal spray, or as a liquid aerosol or dry powder pharmaceutical composition for inhalation. In some embodiments, the pharmaceutical composition provided herein comprises one or more disclosed compounds, tautomers thereof, and/or pharmaceutically acceptable salts thereof, and is for oral administration. In other embodiments, the pharmaceutical composition is for intravenous administration.

Solid dosage forms for oral administration may include capsules (e.g., soft and hard-filled gelatin capsules), tablets, pills, powders, and granules. Solid dosage forms may be prepared, in some embodiments, with one or more coatings and/or shells such as release controlling coatings, for example enteric coatings. Solid dosage forms may be formulated to release the one or more disclosed compounds (or solvate, tautomer, or pharmaceutically acceptable salt thereof) only, or mostly, or preferentially in a certain part of the gastrointestinal tract, optionally in a delayed manner. Solid dosage forms may also include, for example, micro-encapsulated forms.

Liquid dosage forms for oral administration may include, for example, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. Such liquid compositions may include, for example, a pharmaceutically acceptable excipient such as water or other solvents, solubilizing agents, emulsifiers, oils, polyethylene glycols and fatty acid esters, adjuvants, sweetening agents, flavoring agents, or perfuming agents, or any combinations thereof. Injectible pharmaceutical compositions include, for example, sterile injectable aqueous compositions (e.g., solutions, suspensions, or emulsions), or oleaginous suspensions.

Injectable pharmaceutical compositions may comprise, in some embodiments, one or more solvents and/or diluents, such as water, Ringer's solution, U.S.P. and isotonic sodium chloride solution, sterile fixed oils, fatty acid, or any combinations thereof. In some embodiments, an

injectible pharmaceutical composition may be prepared as a lyophilized powder, for example a lyophilized powder that is to be mixed with a liquid diluent prior to injection.

In some embodiments, it may be desirable to prolong the effect of one or more compounds as disclosed herein, or pharmaceutically acceptable salt thereof, from administration through subcutaneous or intramuscular injection. Such delay may be accomplished, for example, through the use of a liquid suspension of crystalline or amorphous material with poor water solubility; or dissolving or suspending the compound, or solvate, tautomer, or pharmaceutically acceptable salt thereof, in an oil vehicle; or through an injectable depot form copmrising microencapsule matrixes comprising one or more biodegradable polymers.

Pharmaceutical compositions for rectal or vaginal administration may include suppositories that can be prepared, for example using a suitable non-irritating excipient such as cocoa butter, polyethylene glycol, or a suppository wax; or using a fatty emulsion or suspension.

Dosage forms for topical or transdermal administration may include, for example, ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants, or patches. Ophthalmic pharmaceutical compositions and ear drops may also be prepared.

The pharmaceutical compositions provided herein may be packaged in unit-dose or multidose containers, for example sealed ampoules or vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient (e.g., diluent, carrier, for example water) for injection immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, or tablets of the kind described herein. Unit dosage formulations include those containing a daily dose or unit daily sub-dose, or an appropriate fraction thereof, of the active ingredient.

The subject matter further provides veterinary compositions comprising at least one active ingredient as herein defined together with a veterinary excipient or carrier therefore. Veterinary excipients or carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary

art and are compatible with the active ingredient. These veterinary compositions may be administered parenterally, orally or by any other desired route.

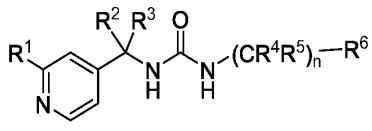
Medical use

The compounds, solvates, pharmaceutically acceptable salts, or pharmaceutical compositions comprising the same as described herein may be useful as pharmaceuticals for the therapeutic and/or prophylactic treatment of a disorder, disease or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides a method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising administering an effective amount of compounds, solvates, pharmaceutically acceptable salts, or pharmaceutical compositions thereof as described herein.

In one embodiment, the present invention provides a method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising administering an effective amount of compounds, solvates, pharmaceutically acceptable salts, or pharmaceutical compositions thereof as described herein, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

In one embodiment, the present invention provides a method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocylcloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

In one embodiment, the present invention provides a method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising a compound selected from any of formulae (I*), (I**), (I), (II), (III), etc., or a solvate or a pharmaceutically acceptable salt thereof, any exemplified compound, any embodiment, or combinations of embodiments, as described herein.

In one embodiment, the present invention provides a method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in

need thereof, comprising a compound selected from any list of compounds as described herein, or solvates or pharmaceutically acceptable salts thereof.

In one embodiment, the present invention provides a method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising a compound selected from any of Tables 1-9, or a solvate or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein the disorder, disease, or disability associated with Kv7.2 is selected from behavioral disorders, mood disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus.

In one embodiment, the present invention provides the above method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the behavioral disorder is Attention Deficit Hyperactivity Disorder (ADHD).

In one embodiment, the present invention provides the above method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the mood disorder is depression.

In one embodiment, the present invention provides the above method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the neurodevelopment disorder is selected from autism spectrum disorder (ASD) and syndromic developmental disorders.

In one embodiment, the present invention provides the above method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject

in need thereof, wherein the syndromic developmental disorder is selected from Dup15q syndrome (Dup15q), Fragile X syndrome (FXS) and Angelman syndrome.

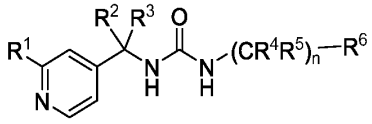
In one embodiment, the present invention provides the above method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the epilepsies are selected from broad pediatric epilepsy, West syndrome, Ohtahara syndrome, and epileptic encephalopathy.

In one embodiment, the present invention provides the above method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the neurodegenerative diseases are selected from Alzheimer's disease and motor neuron diseases.

In one embodiment, the present invention provides a method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising administering an effective amount of pharmaceutical compositions as described herein.

Further provided herein is a compound, a solvate, a pharmaceutically acceptable salt or a pharmaceutical composition thereof, as described herein, for use as therapeutically active substance.

In one embodiment, the present invention provides the use of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-}

$_{6}$alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

as therapeutically active substance.

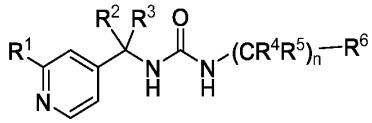
In one embodiment, the present invention provides the use of a compound selected from any of formulae (I*), (I**), (I), (II), (III), etc., or a solvate or a pharmaceutically acceptable salt thereof, any exemplified compound, any embodiment, or combinations of embodiments, as described herein, as therapeutically active substance.

In one embodiment, the present invention provides the use of a compound selected from any of Tables 1-9, or a solvate or a pharmaceutically acceptable salt thereof, as therapeutically active substance.

In one embodiment, the present invention provides the use of a compound selected from any list of compounds described herein, or a solvate or a pharmaceutically acceptable salt thereof, as therapeutically active substance.

Further provided herein is a compound, a solvate, a pharmaceutically acceptable salt, or a pharmaceutical composition thereof, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides a compound selected from any of formulae (I*), (I**), (I), (II), (III), etc., or a solvate or a pharmaceutically acceptable salt thereof, any exemplified compound, any embodiment, or combinations of embodiments, as described herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides a compound selected from any of Tables 1-9, or a solvate or a pharmaceutically acceptable salt thereof, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides a compound selected from any list of compounds, or a solvate or a pharmaceutically acceptable salt thereof as described herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides a compound, or a solvate or a pharmaceutically acceptable salt thereof as described herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein such disorder, disease, or disability is selected from behavioral disorders, mood

disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus.

In one embodiment, the present invention provides a compound, or a solvate or a pharmaceutically acceptable salt thereof, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the behavioral disorder is Attention Deficit Hyperactivity Disorder (ADHD).

In one embodiment, the present invention provides a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the mood disorder is depression.

In one embodiment, the present invention provides a compound, or a solvate, or a pharmaceutically acceptable salt thereof, as descriebed herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the neurodevelopment disorder is selected from autism spectrum disorder (ASD) and syndromic developmental disorders.

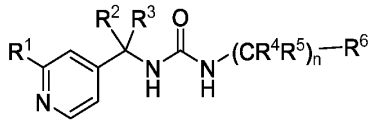
In one embodiment, the present invention provides a compound, or a solvate or a pharmaceutically acceptable salt thereof as described herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the syndromic developmental disorder is selected from Dup15q syndrome (Dup15q), Fragile X syndrome (FXS) and Angelman syndrome.

In one embodiment, the present invention provides a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the epilepsies are selected from broad pediatric epilepsy, West syndrome, Ohtahara syndrome, and epileptic encephalopathy.

In one embodiment, the present invention provides a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the neurodegenerative diseases are selected from Alzheimer's disease and motor neuron diseases.

Further provided herein is the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides the use of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides the use of a compound selected from any of formulae (I*), (I**), (I), (II), (III), etc., or solvate or a pharmaceutically acceptable salt thereof, any exemplified compound, any embodiment, or combinations of embodiments, as described herein , as described herein, for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof .

In one embodiment, the present invention provides the use of a compound selected from any of Tables 1-9, or solvate or a pharmaceutically acceptable salt thereof, for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the invention provides the use a compound selected from any list of compounds described herein, or a solvate or a pharmaceutically acceptable salt thereof, for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the invention provides for the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof,

wherein the disorder, disease, or disability associated with Kv7.2 is selected from behavioral disorders, mood disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus.

In one embodiment, the invention provides for the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the behavioral disorder is Attention Deficit Hyperactivity Disorder (ADHD).

In one embodiment, the invention provides for the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the mood disorder is depression.

In one embodiment, the invention provides for the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the neurodevelopment disorder is selected from autism spectrum disorder (ASD) and syndromic developmental disorders.

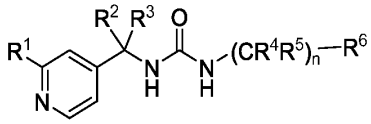
In one embodiment, the invention provides for the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the syndromic developmental disorder is selected from Dup15q syndrome (Dup15q), Fragile X syndrome (FXS) and Angelman syndrome.

In one embodiment, the invention provides for the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the epilepsies are selected from broad pediatric epilepsy, West syndrome, Ohtahara syndrome, and epileptic encephalopathy.

In one embodiment, the invention provides for the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, the neurodegenerative diseases are selected from Alzheimer's disease and motor neuron diseases.

Further provided herein is the use of a compound, a solvate, a pharmaceutical composition thereof, for the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides the use of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3,

for the manufacture of a medicament for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides the use of a compound selected from any of formulae (I*), (I**), (I), (II), (III), etc., or a solvate or a pharmaceutically acceptable salt thereof, any exemplified compound, any embodiment, or combinations of embodiments, as described herein, for the manufacture of a medicament for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides the use a compound selected from any of Tables 1-9, or a solvate or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides the use of a compound selected from any list of compounds described herein, or a solvate or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the manufacture of a medicament

for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the disorder, disease, or disability associated with Kv7.2 is selected from behavioral disorders, mood disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus.

In one embodiment, the present invention provides the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the manufacture of a medicament for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the behavioral disorder is Attention Deficit Hyperactivity Disorder (ADHD).

In one embodiment, the present invention provides the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the manufacture of a medicament for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the mood disorder is depression.

In one embodiment, the present invention provides the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the manufacture of a medicament for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the neurodevelopment disorder is selected from autism spectrum disorder (ASD) and syndromic developmental disorders.

In one embodiment, the present invention provides the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the manufacture of a medicament for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the syndromic developmental disorder is selected from Dup15q syndrome (Dup15q), Fragile X syndrome (FXS) and Angelman syndrome.

In one embodiment, the present invention provides the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the manufacture of a medicament for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability

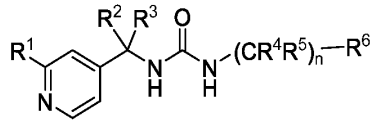
associated with Kv7.2 in a subject in need thereof, wherein the epilepsies are selected from broad pediatric epilepsy, West syndrome, Ohtahara syndrome, and epileptic encephalopathy.

In one embodiment, the present invention provides the use of a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the manufacture of a medicament for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, the neurodegenerative diseases are selected from Alzheimer's disease and motor neuron diseases.

Further provided a pharmaceutical composition comprising a compound as described herein, or solvate or a pharmaceutically acceptable salt thereof.

Further provided a pharmaceutical composition comprising a compound as described herein, or solvate or a pharmaceutically acceptable salt thereof, wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

In one particularily preferred embodiment, the invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

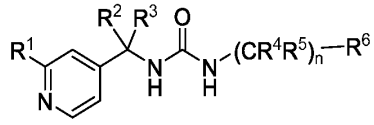
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

In one particularily preferred embodiment, the invention providess a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, and hydroxy; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, and hydroxy; or

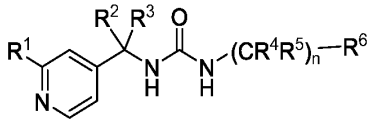
R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl;

n is 0, 1, 2, or 3;

and wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

In one particularily preferred embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl and hydroxy;

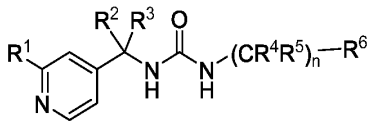
R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

In one particularily preferred embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl and hydroxy;

R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl; or

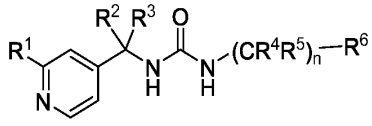
R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

and wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

In one particularily preferred embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

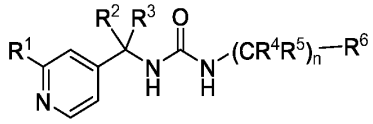
R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl and hydroxy;

R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

In one particularily preferred embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl,

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, oxo, cyano, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

and wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

In one particularily preferred embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one particularily prefered embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the disorder, disease, or disability is selected from behavioral disorders, mood disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus.

In one particularily preferred embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the behavioral disorder is Attention Deficit Hyperactivity Disorder (ADHD).

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the mood disorder is depression.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described

herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the neurodevelopment disorder is selected from autism spectrum disorder (ASD) and syndromic developmental disorders.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the syndromic developmental disorder is selected from Dup15q syndrome (Dup15q), Fragile X syndrome (FXS) and Angelman syndrome.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the epilepsies are selected from broad pediatric epilepsy, West syndrome, Ohtahara syndrome, and epileptic encephalopathy.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the neurodegenerative diseases are selected from Alzheimer's disease and motor neuron diseases.

In one embodiment, the present invention provides a pharmaceutical composition as described above comprising a compound selected from any of formulae (I*), (I**), (I), (II), (III), etc., or a solvate or a pharmaceutically acceptable salt thereof, any exemplified compound, any embodiment, or combinations of embodiments, as described herein.

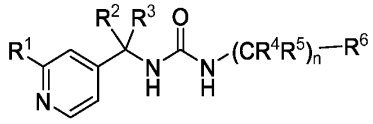
In one embodiment, the present invention provides a pharmaceutical composition as described above cmprising a compound is selected from any of Tables 1-9, or a solvate or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a pharmaceutical composition as described above comprising a compound selected from any list of compounds described herein, or a solvate or a pharmaceutically acceptable salt thereof.

Further provided a pharmaceutical composition comprising a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in a method of the therapeutic and/or prophylactic treatment of disorder, disease or disability associated with Kv7.2 in a subject in need thereof.

Further provided a pharmaceutical composition comprising a compound as described herein, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, and one or more pharmaceutically acceptable excipients, for use in a method of the therapeutic and/or prophylactic treatment of disorder, disease or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the invention provides a pharmaceutical composition for use in a method of treatment comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

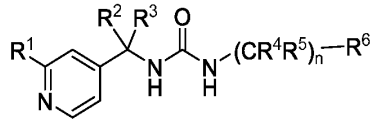
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

In one embodiment, the invention provides a pharmaceutical composition for use in a method of treatment comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

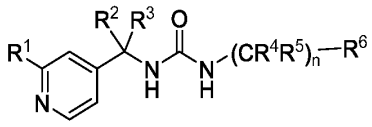
R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

and wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

In one embodiment, the present invention provides a pharmaceutical composition for use in a method of treatment comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl and hydroxy;

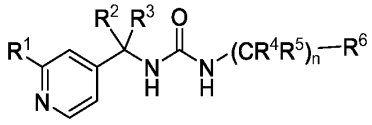
R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, hydroxy, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

In one embodiment, the present invention provides a pharmaceutical composition for use in a method of treatment comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl and hydroxy;

R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl; or

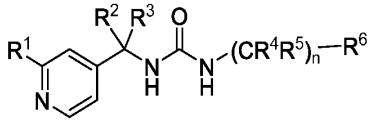
R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, haloC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

and wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

In one embodiment, the present invention provides a pharmaceutical composition for use in a method of treatment comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

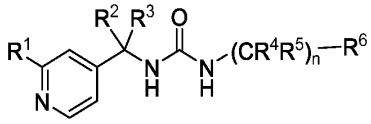
R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl and hydroxy;

R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

In one embodiment, the present invention provides a pharmaceutical composition for use in a method of treatment comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl,

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected

from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

and wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

In one embodiment, the present invention provides a pharmaceutical composition for use in a method of treatment comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof as described herein, for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides a pharmaceutical composition for use in a method of treatment comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the disorder, disease, or disability is selected from behavioral disorders, mood disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus.

In one embodiment, the present invention provides a pharmaceutical composition for use in a method of treatment comprises a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the behavioral disorder is Attention Deficit Hyperactivity Disorder (ADHD).

In one embodiment, the present invention provides a pharmaceutical composition for use in a method of treatment comprises a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the therapeutic and/or prophylactic treatment of a

disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the mood disorder is depression.

In one embodiment, the present invention provides a pharmaceutical composition for use in a method of treatment comprises a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the neurodevelopment disorder is selected from autism spectrum disorder (ASD) and syndromic developmental disorders.

In one embodiment, the present invention provides a pharmaceutical composition for use in a method of treatment comprises a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the syndromic developmental disorder is selected from Dup15q syndrome (Dup15q), Fragile X syndrome (FXS) and Angelman syndrome.

In one embodiment, the present invention provides a pharmaceutical composition for use in a method of treatment comprises a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the epilepsies are selected from broad pediatric epilepsy, West syndrome, Ohtahara syndrome, and epileptic encephalopathy.

In one embodiment, the present invention provides a pharmaceutical composition for use in a method of treatment comprises a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the neurodegenerative diseases are selected from Alzheimer's disease and motor neuron diseases.

In one embodiment, the present invention provides a pharmaceutical composition as described above comprising a compound selected from any of formulae (I*), (I**), (I), (II), (III),

etc., or a solvate or a pharmaceutically acceptable salt thereof, any exemplified compound, any embodiment, or combinations of embodiments, as described herein..

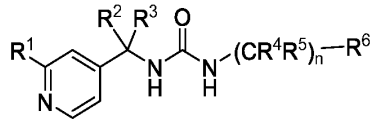
In one embodiment, the present invention provides a pharmaceutical composition as described above comprising a compound selected from any of Tables 1-9, or a solvate or a pharmaceutically acceptable salt thereof.

In one embodiment, the present invention provides a pharmaceutical composition as described above comprising a compound selected from any list of compounds described herein, or a solvate or a pharmaceutically acceptable salt thereof.

Further provided a pharmaceutical composition comprising a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

Further provided a pharmaceutical composition comprising a compound, or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease or disability associated with Kv7.2 in a subject in need thereof, wherein the pharamaceutical further comprises one or more pharmaceutically acceptable excipients.

In one embodiment, the invention provides a pharmaceutical composition for use in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

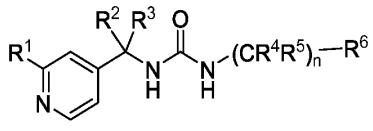
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

In one embodiment, the invention provides a pharmaceutical composition for use in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

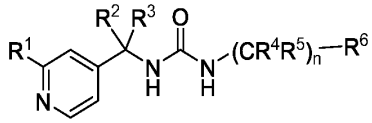
R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

and wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

In one embodiment, the present invention provides a pharmaceutical composition for use in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl and hydroxy;

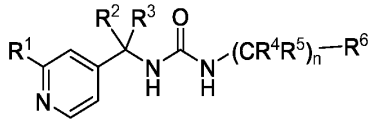
R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

In one embodiment, the present invention provides a pharmaceutical composition for use in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl and hydroxy;

R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl; or

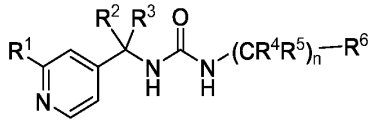
R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

and wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

In one embodiment, the present invention provides a pharmaceutical composition for use in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl, wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

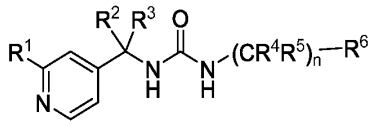
R^2 and R^3 are independently selected from hydrogen, C_{1-6}alkyl, hydroxyC_{1-6}alkyl and hydroxy;

R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

In one embodiment, the present invention provides a pharmaceutical composition for use in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, and C_{1-6}alkyl,

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2;

and wherein the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

In one embodiment, the present invention provides a pharmaceutical composition for use in the manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the disorder, disease, or disability is selected from behavioral disorders,

mood disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the behavioral disorder is Attention Deficit Hyperactivity Disorder (ADHD).

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the mood disorder is depression.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the neurodevelopment disorder is selected from autism spectrum disorder (ASD) and syndromic developmental disorders.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the syndromic developmental disorder is selected from Dup15q syndrome (Dup15q), Fragile X syndrome (FXS) and Angelman syndrome.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described

herein, for use in manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the epilepsies are selected from broad pediatric epilepsy, West syndrome, Ohtahara syndrome, and epileptic encephalopathy.

In one embodiment, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, as described herein, for use in manufacture of a medicament for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the neurodegenerative diseases are selected from Alzheimer's disease and motor neuron diseases.

In one embodiment, the present invention provides a pharmaceutical composition as described above comprising a compound selected from any of formulae (I*), (I**), (I), (II), (III), etc., or a solvate or a pharmaceutically acceptable salt thereof, any exemplified compound, any embodiment, or combinations of embodiments, as described herein..

In one embodiment, the present invention provides a pharmaceutical composition as described above comprising a compound is selected from any of Tables 1-9, or a solvate or a pharmaceutically acceptable salt thereof.

In one embodiment, the pharmaceutical composition as described above comprises a compound selected from any list of compounds described herein, or a solvate or a pharmaceutically acceptable salt thereof.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy; wherein the heterocyclyloxy is optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from a 4-6 membered

heterocyclyloxy, halogen, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy; wherein the heterocyclyloxy is optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from cyano, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from haloC_{1-6}alkoxy, and haloC_{1-6}alkyl.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from cyano, CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, CF_3CH_2O-, CH_3CF_2-, CHF_2-, and CF_3-.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, and CF_3CH_2O-.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is CHF_2O-.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is pyrazinyl or imidazolyl which are optionally substituted with halogen or haloC_{1-6}alkyl.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is unsubstituted pyrazinyl or unsubstituted imidazolyl.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or pharmaceutially acceptable salt thereof, wherein (i) both R^2 and R^3 are hydrogen, or (ii) one of R^2 and R^3 is hydrogen and the other one is hydroxyC_{1-6}alkyl.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 is hydrogen and the other one is hydroxyC_{1-6}alkyl selected from $HOCH_2$-, $HOCH_2CH_2$-, $HOCH_2CH_2CH_2$-, and $HOCH_2CH_2CH_2CH_2$-.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein the hydroxyC_{1-6}alkyl is $HOCH_2$-.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein both R^2 and R^3 are hydrogen.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0 or 1.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1 and (i) both R^4 and R^5 are hydrogen, (ii) one of R^4 and R^5 is hydrogen and the other one is hydroxy or C_{1-6}alkyl.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein one of R^4 and R^5 is hydrogen and the other one is hydroxyC_{1-6}alkyl selected from $HOCH_2$-, $HOCH_2CH_2$-, $HOCH_2CH_2CH_2$-, and $HOCH_2CH_2CH_2CH_2$-.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein the hydroxyC_{1-6}alkyl is $HOCH_2$-.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 1 and both R^4 and R^5 are hydrogen.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl.

Some of the aforementioned embodiments, wherein R^1, R^2, R^3, R^4, R^5, and n are as described herein and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is optionally substituted with one, two, or three substituents independently selected from from Cl-, F-, CH_3-, CH_3CH_2-, CF_3-, cyclopropyl, CH_3O-, cyano, and hydroxy.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CF_3-, cyclopropyl, and CH_3O-.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is optionally substituted with one, two, or three substituents independently selected from F- and CF_3-.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; or a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, or a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl; and

e) haloC_{1-6}alkyl;

which are optionally substituted as described herein.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from:

a) a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, or a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings,

d) phenyl; and

e) haloC_{1-6}alkyl;

which are optionally substituted as described herein.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from:

a) a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom;

b) a 6 membered heteroaryl; and

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, or a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings; which are optionally substituted as described herein.

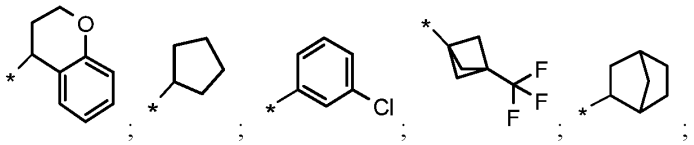
Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from:

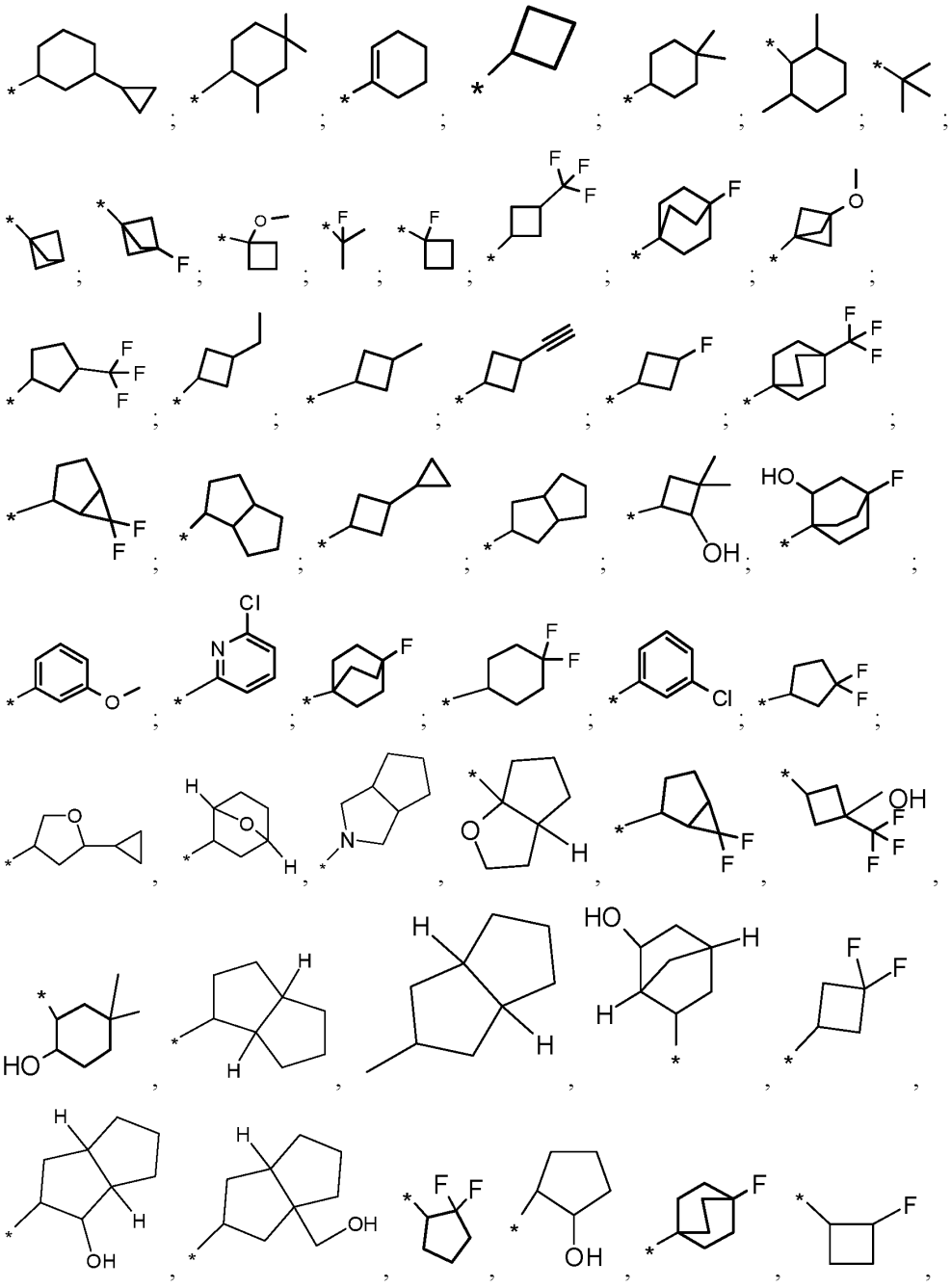
dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, cyclohexenyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, cyclobutyl, tert-butyl, $(CH_3)_2CF$-, bicyclo[3.1.0]hexanyl, octahydropentalenyl, pyrazinyl, pyridinyl, and pyrimidinyl; which are substituted as described herein.

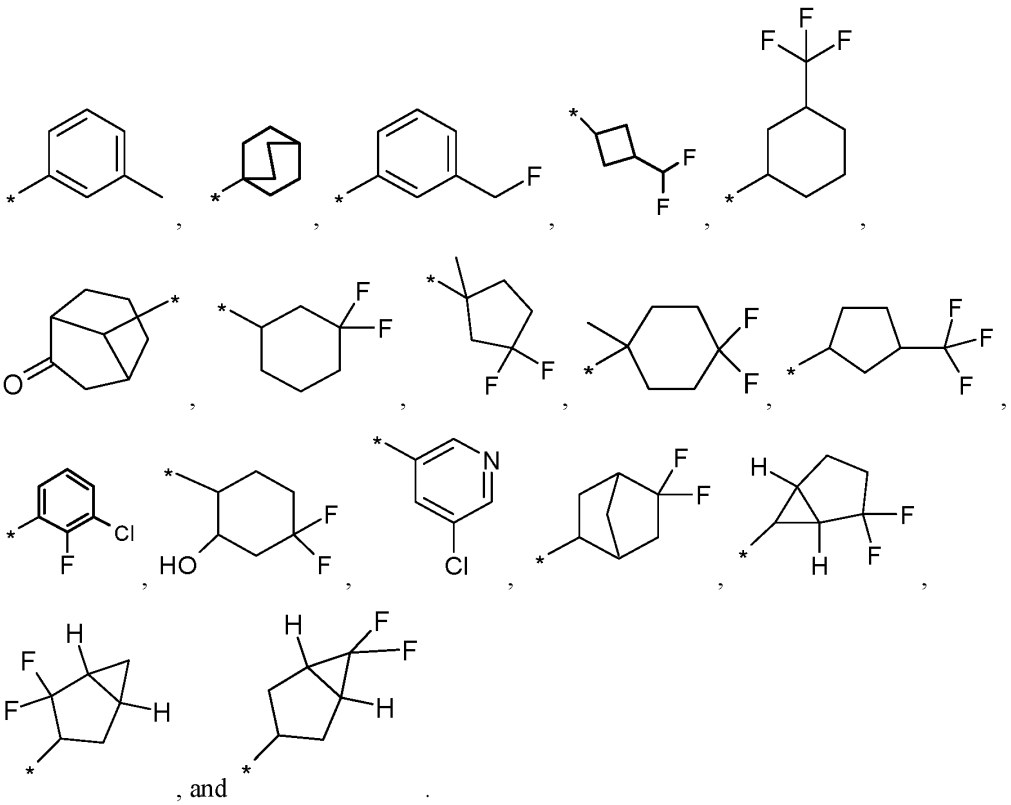
Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from:

dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, cyclobutyl, bicyclo[1.1.1]pentanyl, pyrazinyl, pyrimidinyl, and pyridinyl; which are optionally substituted as described herein.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from:







, and .

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CHF_2O-, unsubstituted pyrazinyl, unsubstituted imidazolyl, CH_3O-, $(CH_3)CF_2$-, CN-, CHF_2-, CF_3-, CF_3CH_2O-, CH_3CFHCH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, or R^4 and R^5 together with the carbon atom to which they are attached, form cyclopropyl, and R^6 is selected from a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, a 6 membered heteroaryl; and a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings; which are optionally substituted as described herein.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CHF_2O- or unsubstituted imidazolyl, R^2 and R^3 are hydrogen, n is 0 or 1, R^4 and R^5 are hydrogen, or R^4 and R^5 together with the carbon atom to which they are attached, form cyclopropyl, and R^6 is selected from a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, or a 6 membered heteroaryl; and a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings,; which are optionally substituted as described herein.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from CHF_2O- or unsubstituted imidazolyl, R^2 and R^3 are hydrogen, n is 0; and R^6 is selected from a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, or a 6 membered heteroaryl; and a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, which are optionally substituted as described herein.

Some of the aforementioned embodiments comprise a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is substituted with one or two F- or CF_3-.

Some of the aforementioned embodiments in this section medical use may instead of a compound of formula (I) or other formulae comprise a compound of formula (I`) as described herein.

In addition to the options defined in this section medical use, the compound of formula (I) may also comprise compounds as provided under the paragraphs Additional Options for

Variables, Additional Options for R^1, Additional Options for R^4 and R^5, and Additional Options for R^6, Preferences and Embodiments Involving Additional Options, and Additional Exclusions.

Combination Therapy

Compounds of the invention may be combined with one or more other compounds of the invention or one or more other therapeutic agent as any combination thereof, in the treatment of the diseases, disorders, or disabilities provided herein. For example, a compound of the invention may be administered simultaneously, sequentially or separately in combination with other therapeutic agents known to be useful for the treatment of a disease or disorder selected from those recited herein.

In some embodiments, a compound provided herein may be combined with another therapeutically active agent having a synergistic effect in the treatment of any diseases, disorders, or disabilities described herein.

As used herein "combination" refers to any mixture or permutation of one or more compounds of the invention and one or more other compounds of the invention or one or more additional therapeutic agent. Unless the context makes clear otherwise, "combination" may include simultaneous or sequentially delivery of a compound of the invention with one or more therapeutic agents. Unless the context makes clear otherwise, "combination" may include dosage forms of a compound of the invention with another therapeutic agent. Unless the context makes clear otherwise, "combination" may include routes of administration of a compound of the invention with another therapeutic agent. Unless the context makes clear otherwise, "combination" may include formulations of a compound of the invention with another therapeutic agent. Dosage forms, routes of administration and pharmaceutical compositions include, but are not limited to, those described herein.

Articles of manufacture

In one embodiment, the present invention provides an article of manufacture, or "kit", containing materials useful for the treatment of the disorder, disease, or disability described herein is provided.

In one embodiment of the invention, the kit comprises a container comprising a compound of formula (I`) or (I), a solvate, a pharmaceutically acceptable salt, or a pharmaceutical compositionthereof, as described in any embodiment of this invention.

In one embodiment, the present invention provides a kit comprising a container comprising a compound of formula (I`) or (I), a solvate, a pharmaceutically acceptable salt, or a pharmaceutical composition thereof, as described herein.

In one embodiment, the present invention provides a a kit comprising a compound selected from any of formulae (I*), (I**), (I`), (I), (II), (III), etc., or a solvate or a pharmaceutically acceptable salt thereof, any exemplified compound, any embodiment, or combinations of embodiments, or pharmaceutical composition thereof, as described herein.

In one embodiment, the present invention provides a kit, wherein the compound is selected from any of Tables 1-9, a solvate, a pharmaceutically acceptable salt, or a pharmaceutical composition thereof, as described herein.

In one embodiment, the present invention provides a kit for use in the treatment of a disorder, disease, or disability associated with Kv7.2, comprising:

a) a first pharmaceutical composition comprising a compound, or a solvate or a pharmaceutically acceptable salt of this invention; and
b) instructions for use.

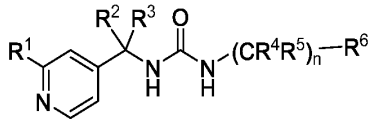
In one embodiment, the present invention provides a kit for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 comprising:

a) a compound, or a pharmaceutical composition, or a pharmaceutical composition for use thereof; as described herein; and

b) instructions for use.

In one embodiment, the present invention provides a kit for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 selected from behavioral disorders, mood disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus, comprising:

a) a first pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt, a pharmaceutical composition, or a pharmaceutical composition for use; as described herein:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5, together with the one carbon atom to which they are attached, form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3;

and

b) instructions for use.

In one embodiment, the present invention provides a kit for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2. These disorders, diseases or disabilities can be selected from behavioral disorders, mood disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus, comprising a compound, a pharmaceutical composition, or a pharmaceutical composition for use thereof, as described herein.

In one embodiment, the present invention provides a kit for use as described herein, wherein the behavioral disorder Attention Deficit Hyperactivity Disorder (ADHD).

In one embodiment, the present invention provides a kit for use as described herein, wherein the mood disorder is depression.

In one embodiment, the present invention provides a kit for use as described herein, wherein the neurodevelopment disorder is selected from autism spectrum disorder (ASD) and syndromic developmental disorders.

In one embodiment, the present invention provides a kit for use as described herein, wherein the syndromic developmental disorder is selected from Dup15q syndrome (Dup15q), Fragile X syndrome (FXS), and Angelman syndrome.

In one embodiment, the present invention provides a kit for use as described herein, wherein the epilepsies are selected from broad pediatric epilepsy, West syndrome, Ohtahara syndrome, and epileptic encephalopathy.

In one embodiment, the present invention provides a kit for use as described herein, wherein the neurodegenerative diseases are selected from Alzheimer's disease, and motor neuron diseases.

In one embodiment, the present invention provides a kit for use as described herein, wherein the kit further comprises a label or package insert, on or associated with the container. The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

Suitable containers include, e.g., bottles, vials, syringes, blister pack, etc. The container may be formed from a variety of materials such as glass or plastic.

The container may hold a compound of this invention or a formulation thereof which is effective for treating the condition and may have a sterile access port (e.g., the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is a compound of this invention. The label or package insert indicates that the composition is used for treating the condition of choice, such as cancer. In addition, the label or package insert may indicate that the patient to be treated is one having a disorder such as a hyperproliferative disorder, neurodegeneration, cardiac hypertrophy, pain, migraine or a neurotraumatic disease or event. In one embodiment, the label or package inserts indicates that the composition comprising a compound of this invention can be used to treat a disorder resulting from abnormal cell growth. The label or package insert may also indicate that the composition can be used to treat other disorders. Alternatively, or additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials

desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

In one embodiment, the present invention provides a kit for use as described herein, wherein the kit further comprises directions for the administration of the compounds of this invention and, if present, the second pharmaceutical formulation. For example, if the kit comprises a first composition comprising a compound of this invention, and a second pharmaceutical formulation, the kit may further comprise directions for the simultaneous, sequential or separate administration of the first and second pharmaceutical compositions to a patient in need thereof.

In one embodiment, the present invention provides a kit for use as described herein, wherein the kits are suitable for the delivery of solid oral forms of a compound of this invention, such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If desired, a memory aid can be provided, e.g. in the form of numbers, letters, or other markings or with a calendar insert, designating the days in the treatment schedule in which the dosages can be administered.

In one embodiment, the present invention provides a kit for use as described herein, wherein the kit comprises (a) a first container with a compound of this invention contained therein; and optionally (b) a second container with a second pharmaceutical formulation contained therein, wherein the second pharmaceutical formulation comprises a second compound with anti-hyperproliferative activity. Alternatively, or additionally, the kit may further comprise a third container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

In one embodiment, the present invention provides a kit for use as described herein, wherein the kit comprises a composition of this invention and a second therapeutic agent, the kit may comprise a container for containing the separate compositions such as a divided bottle or a divided foil packet, however, the separate compositions may also be contained within a single, undivided container. Typically, the kit comprises directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., oral and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

Some of the aforementioned embodiments in this section articles of manufacture may instead of a compound of formula (I) or other formulae comprise a compound of formula (I`) as described herein.

In addition to the options defined in this section articles of manufacture, the compound of formula (I) may also comprise compounds as provided under the paragraphs Additional Options for Variables, Additional Options for R^1, Additional Options for R^4 and R^5, and Additional Options for R^6, Preferences and Embodiments Involving Additional Options, and Additional Exclusions.

Methods of manufacturing

The preparation of compounds of formula (I'), (I), or solvates or pharmaceutically acceptable salts thereof, may be carried out in sequential or convergent synthetic routes.

Syntheses of the invention are shown in the following general schemes. The skills required for carrying out the reaction and purification of the resulting products are known to those persons skilled in the art. The substituents and indices used in the following description of the processes have the significance given herein, unless indicated to the contrary.

In any of the embodiments relating to schemes or examples described in this application relating to a compound of this invention, any embodiment can be combined with any other embodiment unless contradictory.

If one of the starting materials, intermediates or compounds of formula (I') or (I) contain one or more functional groups which are not stable or are reactive under the reaction conditions of one or more reaction steps, appropriate protective groups (as described e.g., in "Protective Groups in Organic Chemistry" by T. W. Greene and P. G. M. Wutts, 5th Ed., 2014, John Wiley & Sons, N.Y.) can be introduced before the critical step applying methods well known in the art. Such protective groups can be removed at a later stage of the synthesis using standard methods described in the literature.

If starting materials or intermediates contain stereogenic centers, compounds of formula (I') or (I) can be obtained as mixtures of diastereomers or enantiomers, which can be separated by methods well known in the art e.g., chiral HPLC, chiral SFC, or chiral crystallization. Racemic compounds can e.g., be separated into their antipodes via diastereomeric salts by crystallization with optically pure acids or by separation of the antipodes by specific chromatographic methods using either a chiral adsorbent or a chiral eluent. It is equally possible to separate starting materials and intermediates containing stereogenic centers to afford diastereomerically/enantiomerically enriched starting materials and intermediates. Using such diastereomerically/enantiomerically enriched starting materials and intermediates in the synthesis of compounds of formula (I') or (I) will typically lead to the respective diastereomerically/enantiomerically enriched compounds of formula (I') or (I).

A person skilled in the art will acknowledge that in the synthesis of compounds of formula (I') or (I) - insofar not desired otherwise - an "orthogonal protection group strategy" will be applied, allowing the cleavage of several protective groups one at a time each without affecting other protective groups in the molecule. The principle of orthogonal protection is well known in the art and has also been described in literature (e.g. Barany and R. B. Merrifield, *J. Am. Chem. Soc.* **1977**, *99*, 7363; H. Waldmann et al., *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2056).

A person skilled in the art will acknowledge that the sequence of reactions may be varied depending on reactivity and nature of the intermediates.

In more detail, the compounds of this invention, i.e. compounds selected from formulae (I'), (I), (I*), (I**), (II), (III), (IV) etc. or their solvates or pharmaceutically acceptable salts, can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. Also, for reaction conditions described in literature affecting the described reactions see for example: *Comprehensive Organic Transformations: A Guide to Functional Group Preparations, 2nd Edition, Richard C. Larock. John Wiley & Sons, New York, NY. 1999).* It was found convenient to carry out the reactions in the presence or absence of a solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve the reagents, at least to some extent. The described reactions can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. It is convenient to carry out the described reactions in a temperature range between -78°C to reflux. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents. However, a period of from 0.5 hours to several days will usually suffice to yield the described intermediates and compounds. The reaction sequence is not limited to the one displayed in the schemes, however, depending on the starting materials and their respective reactivity, the sequence of reaction steps can be freely altered.

If starting materials or intermediates are not commercially available or their synthesis is not described in literature, they can be prepared in analogy to existing procedures for close analogues or as outlined in the experimental section.

Abbreviations

EtOAc is ethyl acetate

CDI is 1,1'-carbonyldiimidazole

DCM is dichloromethane

DIPEA is N,N-diisopropylethylamine

DMF is N,N-dimethylformamide

FA is formic acid

HCl is hydrogen chloride

HPLC is high pressure liquid chromatography

LCMS is liquid chromatography mass spectrometry

$NaHCO_3$ is sodium hydrogen carbonate

NaOH is sodium hydroxide

MeOH is methanol

$MgSO_4$ is magnesium sulfate

PYBROP is bromotripyrrolidinophosphonium hexafluorophosphate

o/n is overnight

RT is room temperature

TLC is thin-layer chromatography

CHO is chinese hamster ovary

CMV is cytomegalovirus

FBS is fetal bovine serum

NEAA is non-essential amino acids

NaCl is sodium chloride

KCl is potassium chloride

$CaCl_2$ is calcium chloride

$MgCl_2$ is magnesium chloride

HEPES is 4-(*2*-hydroxyethyl)-1-piperazine ethanesulfonic acid

NMDG is N-methyl-D-glucamine diatrizoate

EGTA is ethylene glycol-bis(□-aminoethyl ether)-N,N,N',N'-tetraacetic acid

EDTA is ethylenediaminetetraacetic acid

DPBS is Dulbecco's phosphate-buffered saline

mV is millivolt

TEA is tetraethylammonium

NADPH is nicotinamide adenine dinucleotide phosphate

CL_{int} is intrinsic clearance

ACN is acetonitrile

AIBN is azobisisobutyronitrile

BTC is bis(trichloromethyl) carbonate

CO2 is carbon dioxide

DAST is diethylaminosulfur trifluoride

DMSO is dimethylsulfoxide

Gly is glycine

HgO is mercury(II) oxide

IPA is isopropyl alcohol

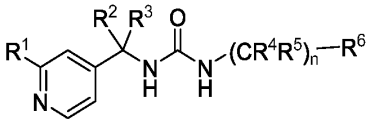
LiCl is lithium chloride

$Ti(OEt)_4$ is titanium(IV) isopropoxide

TMAF is tetramethylammonium fluoride

$TMSCF_3$ is (trifluoromethyl)trimethylsilane

The present invention provides compounds of formula (I), or a solvate or a pharmaceutically acceptable salts thereof:



(I).

The preparation of compounds of formula (I), or solvates or pharmaceutically acceptable salts thereof may be carried out by reacting an amine with an isocyanate (Scheme 1), or by reacting one amine with carbonyl di-imidazole followed by addition of the second amine in-situ, or by first reacting an amine with para-nitro-phenyl chloroformate or phenyl chloroformate to yield the corresponding carbamate intermediate, which can be purified or used in situ by addition of a second amine. Syntheses of the compounds of the invention are shown in the following Schemes and in the description of 294 specific examples. The skills required for carrying out the reaction and purification of the resulting products are known to those skilled in the art. Similar reactiones can be used to prepare compounds of formula (I').

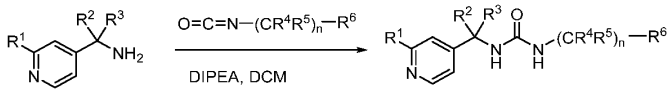
In more detail, the compounds this invention, i.e. compounds selected from formulae (I'), (I), (I*), (I**), (II), (III), (IV) etc. or solvates or pharmaceutically acceptable salts thereof can be manufactured by the methods given in the examples or by analogous methods. Starting materials

are either commercially available or can be prepared by methods analogous to the methods given below or by methods known in the art.

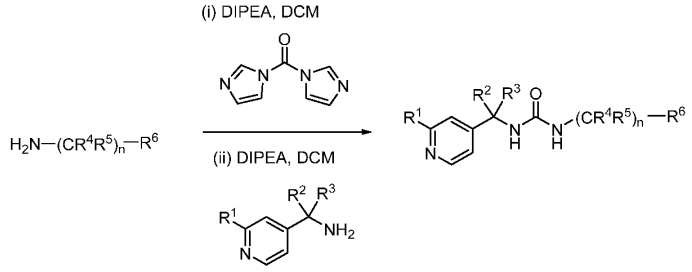
General Procedures

For more information on the general procedures, please refer to the embodiments relating to the process of making compounds of formula (I'), (I), or solvates or pharmaceutically acceptable salts thereof as described herein.

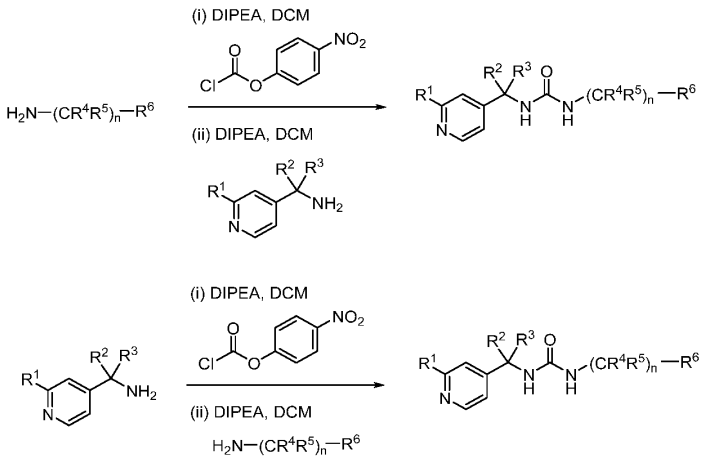
Scheme 1: Synthesis of compounds of formula I using isocyanates



Scheme 2: Synthesis of compounds of formula I using CDI



Scheme 3: Synthesis of compounds of formula I using 4-nitrophenyl chloroformate



wherein R^1, R^2, R^3, R^4, R^5, n, and R^6 are as defined herein.

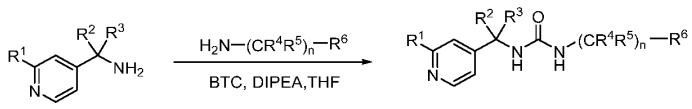
These reactions are preferably used for R^1 being selected from 7-12 membered heterocycloalkyl, cyano, halogen, haloC_{1-6}alkyl, and 5 membered heteroaryl.

The urea formation can be accomplished by treatment of an amine (or the corresponding salt, such as HCl) with an isocyanate (Scheme 1) in DCM or DMF at temperatures from RT to 40°C, or by reacting the first amine with 1,1'-carbonyldiimidazole (Scheme 2) in a solvent (DCM, AcN, THF) and in the presence of a suitable base (DIPEA, NEt3) to generate the activated urea prior to the addition of the second amine (or the corresponding salt), or by reacting the first amine with

para-nitrophenyl chloroformate (Scheme 3) or phenyl chloroformate in a solvent (AcN, THF) and in the presence of a base (DIPEA, NEt3), to generate the carbamate which can be purified or used in situ with a second amine to yield the desired urea.

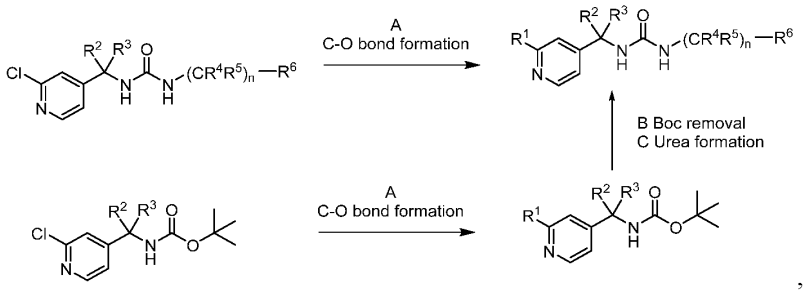
Preferred conditions are using CDI with DIPEA as a base and with DCM as a solvent at 0°C for 45 min and then adding the second amine and stirring at 40°C for 2-6 hours.

Scheme 4: Alternative synthesis of compounds of formula(I)



The urea formation can be accomplished by treatment of an amine (or the corresponding salt, such as HCl) with bis-trichloromethyl)carbonate (triphosgene, BTC) (Scheme 4) in DCM or THF at 0°C and in the presence of a base (DIPEA), followed by addition of a second amine in solution (THF) at RT to afford the desired urea.

Scheme 5: Synthesis of compounds of Formula I



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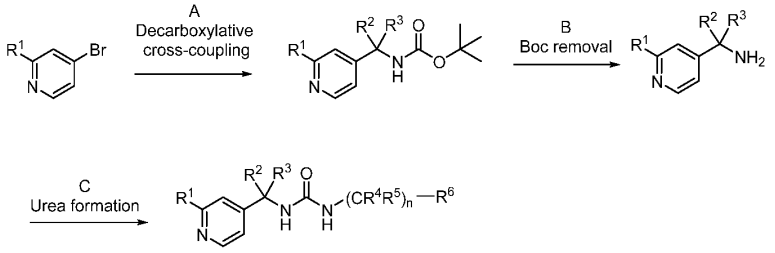
wherein this reaction is used for the preparation of compounds with R^1 being any alkoxy group described herein, e.g. haloC_{1-6}alkoxy, C_{1-6}alkoxy, 4-6 membered heterocyclyloxy, halogen, or C_{3-5}cycloalkylC_{1-6}alkoxy. This reaction can be applied in cases when R^2 and R^3 are hydrogen and in other cases.

Step A: The C-O bond formation can be accomplished via Buchwald-Hartwig etherification between the 2-chloro-pyridyl intermediate and a primary alcohol using a Palladium catalyst and an inorganic base in toluene at 80°C.

Preferred conditions are using tBuBrettPhosPd G3 as a catalyst and cesium carbonate.

Scheme 6: Synthesis of compounds of formula I



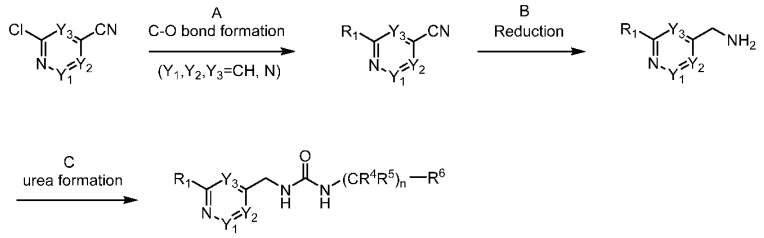
wherein R^1, R^2, R^3, R^4, R^5, n, and R^6 are as defined herein which this reaction is used for the preparation of compounds with R^1 being any alkoxy group described herein, e.g. haloC_{1-6}alkoxy, C_{1-6}alkoxy, 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkoxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or cyanoC_{1-6}alkoxy. In one preferred embodiment is used when R^2 is hydroxyC_{1-6}alkyl and R^3 is hydrogen.

Step A: The decarboxylative cross-coupling reaction can be performed between an heteroaryl halide and protected α-amino acids under the combined action of visible-light photoredox-Ni catalysis and in the presence of cesium carbonate and an Iridium photocatalyst.

Step B: Boc deprotection can be carried out by treatment with HCl/Dioxane.

Step C: Urea formation can be performed out via schemes 1-3. Preferred conditions are using CDI with DIPEA as a base and with DCM as a solvent at 0°C for 1 hour and then adding the second amine and stirring at RT overnight. In cases where R^2 or R^3 is protected as a benzyl ether, deprotection to the alcohol can be performed by hydrogenation in the presence of 10% Palladium on charcoal in Ethanol/Ethyl acetate, or with BBr_3 in DCM.

Scheme 7: Synthesis of compounds of Formula I`



This reaction is used for the preparation of compounds with R^1 being an haloC_{1-6}alkoxy group.

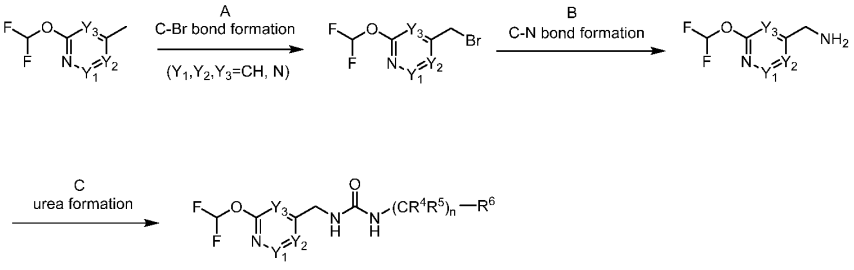
Step A: The C-O bond formation in Scheme 7 can be accomplished via Buchwald-Hartwig etherification between a chloro-heteroaryl intermediate and a primary alcohol using a Palladium catalyst and an inorganic base, or by first reacting a secondary alcohol with sodium hydride and subsequent reaction with 2-chloro-pyridyl intermediate.

Preferred conditions are using tBuBrettPhosPd G3 as a catalyst and cesium carbonate in Toluene at 80°C.

Step B: Reduction can be carried out by hydrogenation with Pd/C or by using $CoCl_2$ with sodium borohydride.

Step C: Urea formation can be performed out via Schemes 1-4. Preferred conditions are using para-nitrophenyl chloroformate with DIPEA as a base and with DCM as a solvent at 0°C to RT. The carbamate intermediate can either be isolated or reacted in-situ with the second amine and stirring at RT overnight.

Scheme 8: Synthesis of compounds of Formula I`



Step A: The C-Br bond formation in Scheme 8 can be accomplished by reacting the corresponding methyl heteroaryl with N-bromosuccinimide in the presence of benzoyl peroxide in carbon tetrachloride.

Step B: The C-N bond formation can be accomplished by reacting the heteroaryl bromomethyl intermediate with an ammonia solution in methanol.

Step C: Urea formation can be performed out via schemes 1-4. Preferred conditions are using para-nitrophenyl chloroformate with DIPEA as a base and with DCM as a solvent at 0°C to RT. The carbamate intermediate can either be isolated or reacted in-situ with the second amine and stirring at RT overnight.

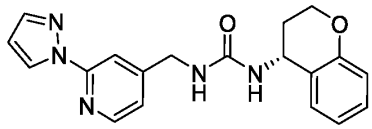
Isolation and purification of the compounds

Isolation and purification of the compounds and intermediates described herein can be carried out, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography or a combination of these procedures. However, other equivalent separation or isolation procedures could, of course, also be used. Mixture of chiral compounds of formula (I`) or (I) can be separated using preparative chiral HPLC purifications.

Chiral HPLC purifications were performed on an AccQPrep HP125 (Teledyne ISCO) system, with a 5 μm 250 mm x 21.2mm i.d. chiral column (Amylose-1, Cellulose-1, or Cellulose-4) from Phenomenex, running at a flow rate of 20.8 mL min-1 with UV (214 and 254 nm) and ELS detection. Eluents: water; acetonitrile.

Examples

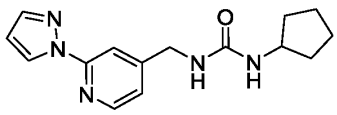
Example 1: 1-[(4R)-3,4-dihydro-2H-chromen-4-yl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea



To (2-(1H-pyrazol-1-yl)pyridin-4-yl)methanamine (52mg, 0.3mmol) in DCM (0.2ml) in an ice bath was added phenyl chloroformate (47mg, 0.3mmol) followed by DIPEA (0.1ml, 0.6mmol). The reaction was stirred at ~0°C for 45min. (R)-chroman-4-amine hydrochloride (57mg, 0.3mmol) was then added and the reaction was stirred at 40°C for 3 hours. The solvent was removed in vacuo. DMF (2ml) was added and purification by preparative HPLC afforded the title compound as a white solid (42% yield).

MS (m/z): 350.6 [M+H]+.

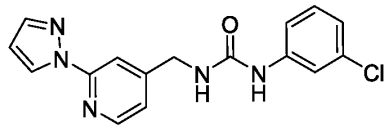
Example 2: 1-cyclopentyl-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea



The compound can be prepared by methods similar to those described herein.

MS (m/z): 285.9 [M+H]+.

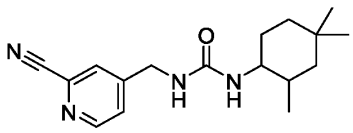
Example 4: 1-(3-chlorophenyl)-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea



(2-(1H-pyrazol-1-yl)pyridin-4-yl)methanamine (35mg, 0.2mmol) and 3-chlorophenyl isocyanate (30.7mg, 0.2mmol) were dissolved in DCM (2 ml) with DIPEA (0.2mmol). The reaction was stirred at RT for 2 hours. An extraction with EtOAc (10ml) and water (10ml) was performed. The organic phase was dried ($MgSO_4$) and concentrated. Purification by preparative HPLC afforded the desired product as a white solid (62% yield).

MS (m/z): 328.5 [M+H]+.

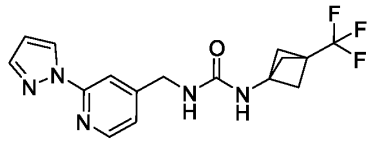
Example 5: 1-[(2-cyanopyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea



To a solution of 2,4,4-trimethylcyclohexan-1-amine (18.5mg, 0.13mmol) in DCM (0.5ml) in an ice bath was added 1,1'-carbonyldiimidazole (23mg, 0.14mmol) and DIPEA (0.4mmol). The reaction was stirred at ~0°C for 45min, then 4-(aminomethyl)picolinonitrile di-hydrochloride (27mg, 0.13mmol) was added and the reaction was stirred at 35°C for 6 hours. The solvent was removed in vacuo. DMF (2ml) was added and purification by preparative HPLC afforded the title compound as a white solid (31% yield).

MS (m/z): 301.4 [M+H]+.

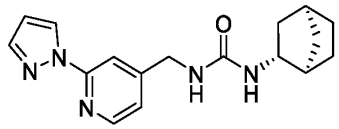
Example 6: 1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (94% yield) using (2-(1H-pyrazol-1-yl)pyridin-4-yl)methanamine, 3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 352.1 [M+H]+.

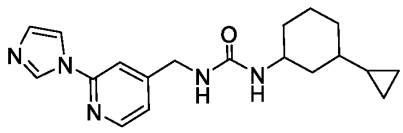
Example 7: 1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[rac-(1R,2R, 4S)-2-bicyclo[2.2.1]heptanyl]urea



rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl-2-amine (22mg, 0.2mmol) was dissolved in acetonitrile (3ml) and DIPEA (0.3ml), then cooled to 0°C. 4-nitrophenyl chloroformate (40mg, 0.2mmol) was added and stirred for 1 hour while temperature was left to reach RT. Then (2-(1H-pyrazol-1-yl)pyridin-4-yl)methanamine (70mg, 0.4mmol) was added and the reaction was stirred for 4 hours. Purification by preparative HPLC afforded the title compound as a white solid (41% yield).

MS (m/z): 312.2 [M+H]+.

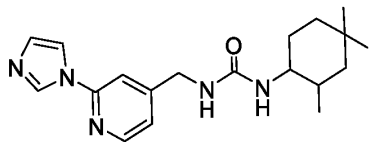
Example 8: 1-(3-cyclopropylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea



The compound can be prepared by methods similar to those described herein.

MS (m/z): 340.1[M+H]+.

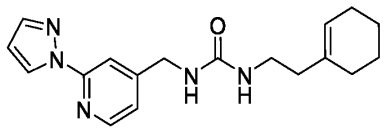
Example 9: 1-[(2-imidazol-1-ylpyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea



The compound can be prepared by methods similar to those described herein.

MS (m/z): 342.1[M+H]+.

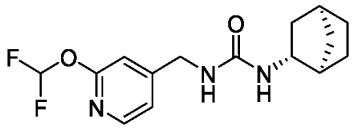
Example 10: 1-[2-(cyclohexen-1-yl)ethyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea



The compound can be prepared by methods similar to those described herein.

MS (m/z): 326.6 [M+H]+.

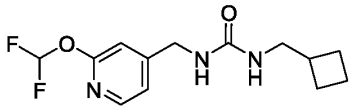
Example 12: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (78% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptan-2-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 312.5 [M+H]+.

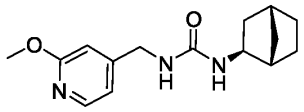
Example 13: 1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (89% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, cyclobutylmethanamine and 1,1'-carbonyldiimidazole.

MS (m/z): 286.4 [M+H]+.

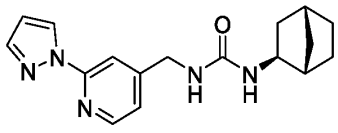
Example 14: 1-[(2-methoxypyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (51% yield) using (2-methoxypyridin-4-yl)methanamine, rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptan-2-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 276.1 [M+H]+.

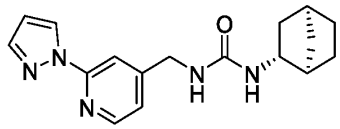
Example 15: 1-[(1S,2S,4R)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea



The title compound was obtained via chiral separation of Example **7** (97.5%ee, 31.6% yield) as a white solid (Cellulose-4 column, in water:MeCN 55:45).

MS (m/z): 312.5 [M+H]+.

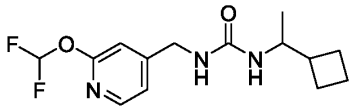
Example 16: 1-[(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea



The title compound was obtained via chiral separation of Example **7** (97.5%ee, 32.2% yield) as a white solid (Cellulose-4 column, in water:MeCN 55:45).

MS (m/z): 312.8 [M+H]+.

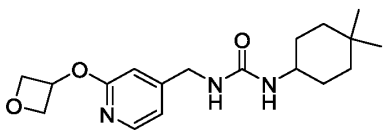
Example 17: 1-(1-cyclobutylethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (56% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1-cyclobutylethan-1-amine and 1,1`-carbonyldiimidazole.

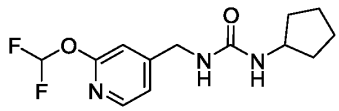
MS (m/z): 299.9 [M+H]+.

Example 18: 1-(4,4-dimethylcyclohexyl)-3-[[2-(oxetan-3-yloxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (10% yield) using (2-(oxetan-3-yloxy)pyridin-4-yl)methanamine, 4,4-dimethylcyclohexan-1-amine and 1,1'-carbonyldiimidazole.

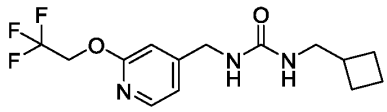
Example 20: 1-cyclopentyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (83% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, cyclopentanamine and 1,1'-carbonyldiimidazole.

MS (m/z): 285.9 [M+H]+.

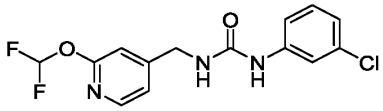
Example 21: 1-(cyclobutylmethyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (62% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, cyclobutylmethanamine and 1,1'-carbonyldiimidazole.

MS (m/z): 317.9 [M+H]+.

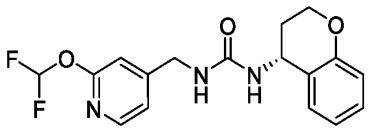
Example 22: 1-(3-chlorophenyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (18% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine and 3-chlorophenyl isocyanate.

MS (m/z): 327.9 [M+H]+.

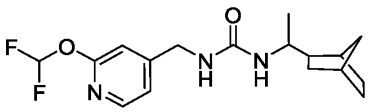
Example 23: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(4R)-3,4-dihydro-2H-chromen-4-yl]urea



The title compound was obtained in analogy to Example **5** as a white solid (57% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (R)-chroman-4-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 349.9 [M+H]+.

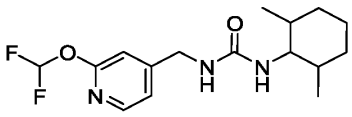
Example 24: 1-[1-(2-bicyclo[2.2.1]heptanyl)ethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (64% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1-(2-bicyclo[2.2.1]heptan-2-yl)ethan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 340.1 [M+H]+.

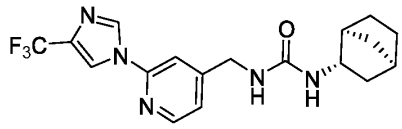
Example 25: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,6-dimethylcyclohexyl)urea



The title compound was obtained in analogy to Example **5** as a white solid (57% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 2,6-dimethylcyclohexan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 328.0 [M+H]+.

Example 26: 1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea



a) 4-((bis(tert-butoxycarbonyl)amino)methyl)pyridine 1-oxide

Tert-butyl (tert-butoxycarbonyl)(pyridin-4-ylmethyl)carbamate (1g, 3.24mmol) and 3-chloroperoxybenzoic acid (2.14 mL (77%), 0.56 g/mL, 5.35mmol) were mixed in a flask and DCM (35mL) was added. The reaction was complete after minutes by TLC and 1 N NaOH solution (40ml) and DCM (40ml) were added. The aqueous phase was extracted with DCM (2x40ml). The combined organic phase was dried ($MgSO_4$) and evaporated in vacuo to afford 4-((bis(tert-butoxycarbonyl)amino)methyl)pyridine 1-oxide as a yellow oil (1.1 g, 3.79 mmol, 100% yield).

MS (m/z): 325 [M+H]+.

b) tert-butyl N-(tert-butoxycarbonyl)-N-({2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl}methyl)carbamate

To an N_2 flushed flask containing 4-((bis(tert-butoxycarbonyl)amino)methyl)pyridine 1-oxide (400mg, 1.23mmol), was added DCM (6mL) followed by DIPEA (0.81mL, 4.62mmol) and 4-(trifluoromethyl)-1H-imidazole (218.14mg, 1.6mmol). The reaction mixture was sonicated to get the imidazole into solution. PYBROP (747.3mg, 1.6mmol) was added and left to stir at RT o/n. DCM (30ml) and saturated $NaHCO_3$ solution (25ml) were added and partitioned. The organic layer was dried ($MgSO_4$) and evaporated in vacuo to afford a crude pale yellow oil (1.35g). Purification

by flash chromatography on silica eluting with Heptane-32%EtOAc/Heptane (gradient) afforded the desired tert-butyl N-(tert-butoxycarbonyl)-N-({2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl}methyl)carbamate (463mg, 1.05mmol, 85% yield)

MS (m/z): 443 [M+H]+.

c) (2-(4-(trifluoromethyl)-1H-imidazol-1-yl)pyridin-4-yl)methanamine

To a solution of tert-butyl N-(tert-butoxycarbonyl)-N-({2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl}methyl)carbamate (460mg, 1.04mmol) in Ethyl Acetate (4mL) under N_2, HCl (4M in Dioxane) (4.16 mL, 16.64 mmol) was added slowly. The reaction was stirred at RT under N_2 o/n. The reaction mixture was cooled in an ice bath and filtered off and washed with cold ether. The white precipitate was collected and dried under vacuum to afford (2-(4-(trifluoromethyl)-1H-imidazol-1-yl)pyridin-4-yl)methanamine as an off-white solid (264mg, 0.84mmol, 80.7% yield).

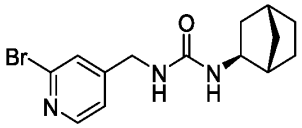
MS (m/z): 243 [M+H]+.

d) 1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea

The title compound was obtained in analogy to Example **5** as a white solid (62% yield) using (2-(4-(trifluoromethyl)-1H-imidazol-1-yl)pyridin-4-yl)methanamine, rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl-2-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 380 [M+H]+.

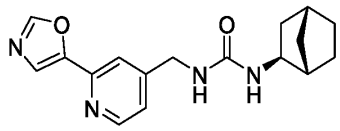
Example 27: 1-[(2-bromopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (13% yield) using (2-bromopyridin-4-yl)methanamine, rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl-2-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 324 [M+H]+.

Example 28: 1-[[2-(1,3-oxazol-5-yl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea



a) tert-butyl N-{[2-(1,3-oxazol-5-yl)pyridin-4-yl]methyl}carbamate

In a round bottom flask was combined 4-(N-Boc-aminomethyl)-2-bromopyridine (120mg, 0.42mmol), 5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-oxazole (89.7mg, 0.46mmol) and potassium carbonate (115.5mg, 0.84mmol) in Acetonitrile (2mL) and Water (2mL). The solution was sparged with N_2 for 5 minutes before 1,1'-bis(di-tert-butylphosphino)Ferrocene Palladium dichloride (13.6mg, 0.02mmol) was added and sparging continued for a further 5 minutes. The reaction mixture was then heated to 80°C under N_2 for 2 hours. The reaction mixture was cooled to rt and partitioned between EtOAc and water, the layers were separated and the aqueous extracted with EtOAc once more. Combined organics were dried over $MgSO_4$ and concentrated under reduced pressure to yield a brown oil. This was purified by flash chromatography on silica eluting with 0 to 100% Ethyl Acetate in Heptane to yield tert-butyl N-{[2-(1,3-oxazol-5-yl)pyridin-4-yl]methyl}carbamate (100 mg, 0.36 mmol, 87% yield) as a yellow oil.

MS (m/z): 276.1 [M+H]+.

b) (2-(oxazol-5-yl)pyridin-4-yl)methanamine

To tert-butyl N-{[2-(1,3-oxazol-5-yl)pyridin-4-yl]methyl}carbamate (160mg, 0.58mmol) dissolved in Ethyl Acetate (3.5mL) was added HCl (3.63mL (4M in Dioxane), 14.53mmol) slowly.

The reaction mixture was then let to stir at RT under N_2 for 90 minutes (precipitate formed within the first few minutes). The reaction mixture was cooled to 0°C using an ice bath for 10 minutes, precipitate was then filtered off, washing with cold diethyl ether. The product was then washed off the sinter with methanol and concentrated. This yielded (2-(oxazol-5-yl)pyridin-4-yl)methanamine dihydrochloride (98mg, 0.39mmol, 68% yield) as a beige solid.

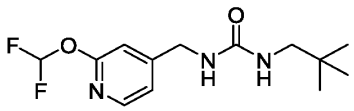
MS (m/z): 176.1 [M+H]+.

c) 1-[[2-(1,3-oxazol-5-yl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl] urea

The title compound was obtained in analogy to Example **5** as a white solid (26% yield) using (2-(oxazol-5-yl)pyridin-4-yl)methanamine dihydrochloride, rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl-2-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 313.2 [M+H]+.

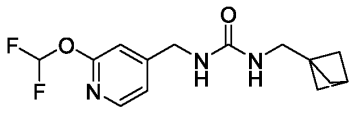
Example 29: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,2-dimethylpropyl)urea



The title compound was obtained in analogy to Example **4** as a white solid (65% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine and 1-isocyanato-2,2-dimethylpropane.

MS (m/z): 288.2 [M+H]+.

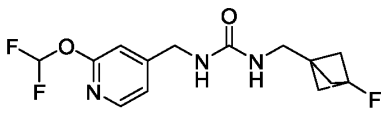
Example 31: 1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (51% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, bicyclo[1.1.1]pentan-1-ylmethanamine and 1,1'-carbonyldiimidazole.

MS (m/z): 298.2 [M+H]+.

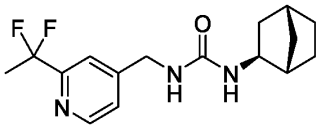
Example 32: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (57% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (3-fluorobicyclo[1.1.1]pentan-1-yl)methanamine and 1,1'-carbonyldiimidazole.

MS (m/z): 316.1 [M+H]+.

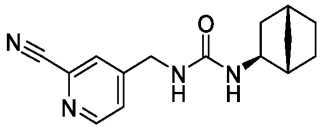
Example 33: 1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (54% yield) using (2-(1,1-difluoroethyl)pyridin-4-yl)methanamine, rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl-2-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 310.2 [M+H]+.

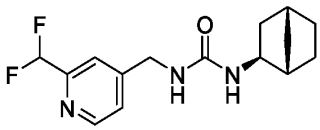
Example 34: 1-[(2-cyanopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (48% yield) using 4-(aminomethyl)picolinonitrile, rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl-2-amine and para-nitrophenyl chloroformate.

MS (m/z): 271.2 [M+H]+.

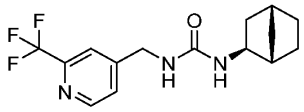
Example 35: 1-[[2-(difluoromethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (71% yield) using (2-(difluoromethyl)pyridin-4-yl)methanamine, rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl-2-amine and para-nitrophenyl chloroformate.

MS (m/z): 296 [M+H]+.

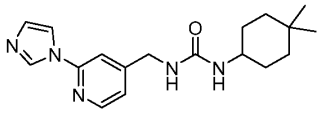
Example 36: 1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (53% yield) using (2-(trifluoromethyl)pyridin-4-yl)methanamine, rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl-2-amine and para-nitrophenyl chloroformate.

MS (m/z): 314 [M+H]+.

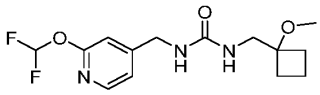
Example 37: 1-(4,4-dimethylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (37% yield) using (2-(1H-imidazol-1-yl)pyridin-4-yl)methanamine, 4,4-dimethylcyclohexan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 328 [M+H]+.

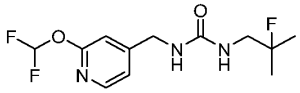
Example 38: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-methoxycyclobutyl)methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (27% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1-methoxycyclobutyl)methanamine and para-nitrophenyl chloroformate.

MS (m/z): 316 [M+H]+.

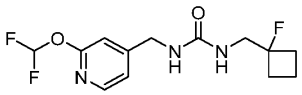
Example 39: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-fluoro-2-methylpropyl)urea



The title compound was obtained in analogy to Example **7** as a white solid (58% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 2-fluoro-2-methylpropan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 292 [M+H]+.

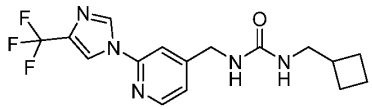
Example 40: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclobutyl)methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (14% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1-fluorocyclobutyl)methanamine and para-nitrophenyl chloroformate.

MS (m/z): 304 [M+H]+.

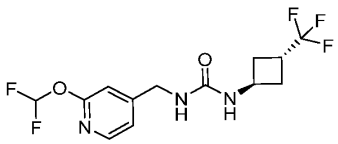
Example 41: 1-(cyclobutylmethyl)-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (70% yield) using (2-(4-(trifluoromethyl)-1H-imidazol-1-yl)pyridin-4-yl)methanamine and (isocyanatomethyl)cyclobutane.

MS (m/z): 354 [M+H]+.

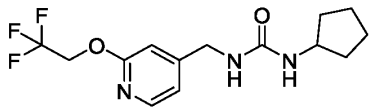
Example 42: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (37% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 340 [M+H]+.

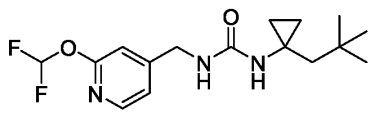
Example 43: 1-cyclopentyl-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (61% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine and isocyanatocyclopentane.

MS (m/z): 318 [M+H]+.

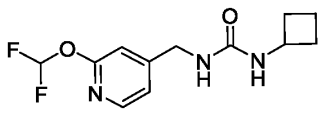
Example 44: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2-dimethylpropyl)cyclopropyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (42% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1-neopentylcyclopropan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 328 [M+H]+.

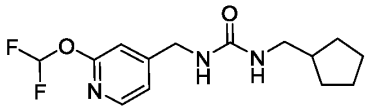
Example 45: 1-cyclobutyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (25% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, cyclobutanamine and para-nitrophenyl chloroformate.

MS (m/z): 272 [M+H]+.

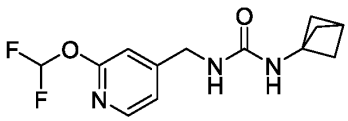
Example 46: 1-(cyclopentylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (40% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, cyclopentylmethanamine and para-nitrophenyl chloroformate.

MS (m/z): 300 [M+H]+.

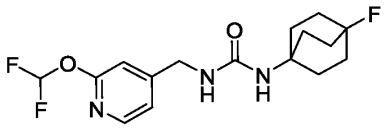
Example 47: 1-(1-bicyclo[1.1.1]pentanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (44% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, bicyclo[1.1.1]pentan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 284 [M+H]+.

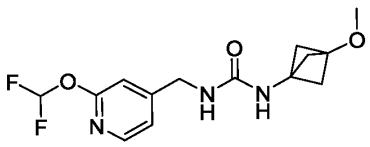
Example 48: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea



The title compound was obtained in analogy to Example **7** as a white solid (23% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 4-fluorobicyclo[2.2.2]octan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 344 [M+H]+.

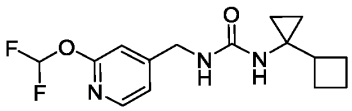
Example 49: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxy-1-bicyclo[1.1.1]pentanyl)urea



The title compound was obtained in analogy to Example **7** as a white solid (25% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3-methoxybicyclo[1.1.1]pentan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 314 [M+H]+.

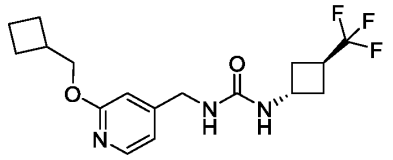
Example 50: 1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (37% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1-cyclobutylcyclopropan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 280 [M+H]+.

Example 54: 1-[[2-(cyclobutylmethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea



a) 1-[(2-chloropyridin-4-yl)methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea

The title compound was obtained in analogy to Example **5** as a white solid (61% yield) using (2-chloropyridin-4-yl)methanamine hydrochloride, (1r,3r)-3-(trifluoromethyl)cyclobutan1-amine hydrochloride and 1,1'-carbonyldiimidazole.

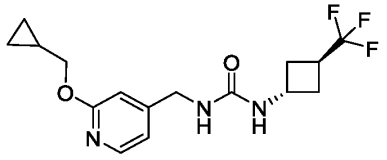
MS (m/z): 308 [M+H]+.

b) 1-[[2-(cyclobutylmethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl) cyclobutyl]urea

1-[(2-chloropyridin-4-yl)methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea (60mg, 0.19mmol, 1eq), tBuBrettPhosPd G3 (5.0mg, 0.01mmol, 0.03eq) and cesium carbonate (95.3mg, 0.29mmol, 1.5eq) were combined in a dry 10ml flask. This was flushed with nitrogen before adding Toluene (1.5mL) and cyclobutanemethanol (27.8µL, 0.91 g/mL, 0.29mmol, 1.5eq). The resultant brown mixture was heated at 80°C under N_2 for 2 hours. The reaction mixture was allowed to cool then diluted with CH_2Cl_2 and filtered through Celite. The solvent was removed in vacuo to afford a crude solid, which was dissolved in DMSO (2ml) and purified by preparative HPLC to afford the desired product as a white solid (13mg, 18.7% yield)

MS (m/z): 358 [M+H]+.

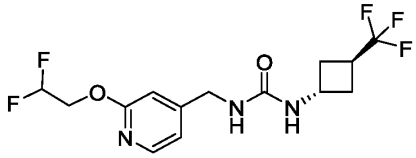
Example 55: 1-[[2-(cyclopropylmethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **54** as a white solid (21% yield) using 1-[[2-chloropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea and cyclopropylmethanol.

MS (m/z): 344 [M+H]+.

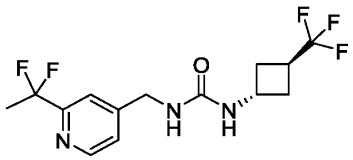
Example 56: 1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (30% yield) using (2-(2,2-difluoroethoxy)pyridin-4-yl)methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 354 [M+H]+.

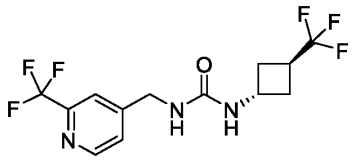
Example 57: 1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (57% yield) using (2-(1,1-difluoroethyl)pyridin-4-yl)methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 338 [M+H]+.

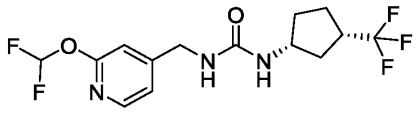
Example 58: 1-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (60% yield) using (2-(trifluoromethyl)pyridin-4-yl)methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 342 [M+H]+.

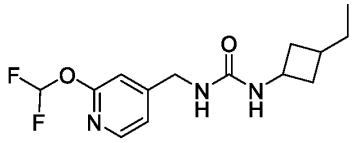
Example 59: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (42% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,3S)-3-(trifluoromethyl)cyclopentan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 354.2 [M+H]+.

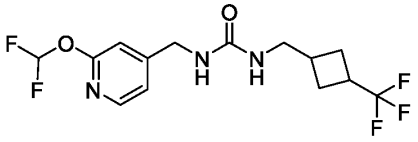
Example 60: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethylcyclobutyl)urea



The title compound was obtained in analogy to Example **7** as a white solid (47% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3-ethylcyclobutan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 300.2 [M+H]+.

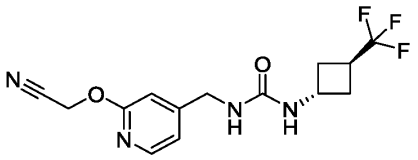
Example 62: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (43% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (3-(trifluoromethyl)cyclobutyl)methanamine and para-nitrophenyl chloroformate.

MS (m/z): 354.2 [M+H]+.

Example 63: 1-[[2-(cyanomethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea



a) tert-butyl ((2-(cyanomethoxy)pyridin-4-yl)methyl)carbamate and tert-butyl ((1-(cyanomethyl)-2-oxo-1,2-dihydropyridin-4-yl)methyl)carbamate mixture:

To a flask containing tert-butyl ((2-hydroxypyridin-4-yl)methyl)carbamate (200mg, 0.89mmol) and potassium carbonate (246.51mg, 1.78mmol), Acetonitrile (6 mL) was added with stirring followed by Bromoacetonitrile (93.18µL, 1.72g/mL, 1.34mmol). The mixture was stirred at RT under N_2 for 2 days. The reaction mixture was partitioned between EtOAc (2x30ml) and water/brine (25ml). The combined organic phase was dried ($MgSO_4$) and evaporated in vacuo to afford a crude brown oil (230mg). Purification by flash chromatography on silica eluting with DCM - 5% MeOH/DCM afforded a mixture of tert-butyl ((2-(cyanomethoxy)pyridin-4-yl)methyl)carbamate and tert-butyl ((1-(cyanomethyl)-2-oxo-1,2-dihydropyridin-4-yl)methyl)carbamate with the undesired N-alkylated product as the main component as a sticky yellow foam (205mg, 87.3%).

MS (m/z): 264 [M+H]+.

b) 2-[4-(aminomethyl)-2-oxopyridin-1-yl]acetonitrile and 2-((4-(aminomethyl)pyridin-2-yl)oxy)acetonitrile mixture:

To a mixture of the N-alkylated and O-alkylated intermediate (600mg, 2.28mmol) in Ethyl Acetate (10mL), HCl (11.39mL (4M in Dioxane), 45.58 mmol) was added. After 2 hours the reaction was complete by LCMS. The reaction was cooled to 0°C and the precipitate was filtered off and washed through with cold ether, then dried to afford the impure mixture of 2-[4-(aminomethyl)-2-oxopyridin-1-yl]acetonitrile hydrochloride and 2-((4-(aminomethyl)pyridin-2-yl)oxy)acetonitrile (480mg, 106%), which was taken on without further purification.

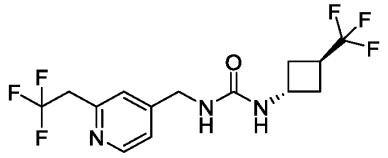
MS (m/z): 164 [M+H]+.

c) 1-[[2-(cyanomethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea

The title compound was obtained in analogy to Example **5** as a white solid (1% yield) using a mixture of 2-((4-(aminomethyl)pyridin-2-yl)oxy)acetonitrile and 2-[4-(aminomethyl)-2-oxopyridin-1-yl]acetonitrile, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 329 [M+H]+.

Example 64: 1-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea



a) tert-butyl-((2-(hydrazineylidenemethyl)pyridin-4-yl)methyl)carbamate

To a solution of tert-butyl N-[(2-formylpyridin-4-yl)methyl]carbamate (300 mg, 1.27 mmol) in methanol (8mL), hydrazine monohydrate (79%) (74.71µL, 1.02g/mL, 1.52mmol) was added and the resultant solution stirred at RT. After 1hr LCMS indicated that the reaction was complete. The reaction was concentrated in vacuo to afford tert-butyl-((2-(hydrazineylidenemethyl)pyridin-4-yl)methyl)carbamate as a yellow oil which was used without further purification.

MS (m/z): 251 [M+H]+.

b) tert-butyl ((2-(2,2,2-trifluoroethyl)pyridin-4-yl)methyl)carbamate

A flask containing tert-butyl-((2-(hydrazineylidenemethyl)pyridin-4-yl)methyl)carbamate (317.88mg, 1.27mmol) and 1-trifluoromethyl-1,2-benziodoxol-3-(1H)-one (441.47mg, 1.4mmol) was flushed with N_2. DMSO (6.5mL) and trifluoroacetic acid (0.1 mL, 1.27 mmol) were then added sequentially. The resultant mixture was heated at 50°C o/n, then allowed to cool and partitioned between EtOAc (40ml) and water (20ml). The organic layer was washed sequentially with further water (2x20ml) and brine (20ml), then concentrated and dried ($MgSO_4$) to afford a crude oil. Purification by flash chromatography on silica eluting with DCM and 3% MeOH/DCM (gradient) afforded tert-butyl ((2-(2,2,2-trifluoroethyl)pyridin-4-yl)methyl)carbamate as an oil (133mg, 36.1%).

MS (m/z): 291 [M+H]+.

c) (2-(2,2,2-trifluoroethyl)pyridin-4-yl)methanamine

To a solution of tert-butyl ((2-(2,2,2-trifluoroethyl)pyridin-4-yl)methyl)carbamate (130mg, 0.45mmol) in Ethyl Acetate (2mL), HCl (2.24 mL (4M in Dioxane), 8.96 mmol) was added and the mixture stirred o/n at RT. A white precipitate formed and LCMS indicated that the deprotection was complete. The reaction was cooled in an ice bath, ether was added and the precipitate was filtered off and washed through with further cold ether. The white solid was dried in vacuo at 40°C o/n to afford (2-(2,2,2-trifluoroethyl)pyridin-4-yl)methanamine as its di-HCl salt (91 mg, 77.2%) which was taken on without further purification.

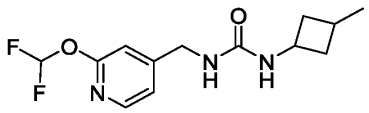
MS (m/z): 191 [M+H]+.

d) 1-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea

The title compound was obtained in analogy to Example **5** as a white solid (58% yield) using (2-(2,2,2-trifluoroethyl)pyridin-4-yl)methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 356 [M+H]+.

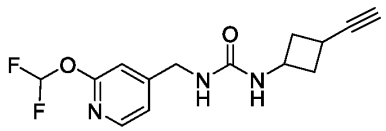
Example 65: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylcyclobutyl)urea



The title compound was obtained in analogy to Example **7** as a white solid (51% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3-methylcyclobutan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 286.2 [M+H]+.

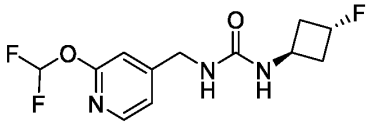
Example 66: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethynylcyclobutyl)urea



The title compound was obtained in analogy to Example 7 as a white solid (48% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3-ethynylcyclobutan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 296.2 [M+H]+.

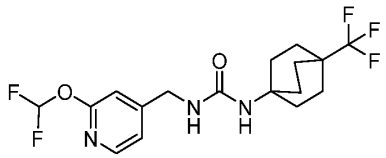
Example 67: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1*r*,3*r*)-3-fluorocyclobutyl)urea



The title compound was obtained in analogy to Example 7 as a white solid (31% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3-fluorocyclobutan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 290.2 [M+H]+.

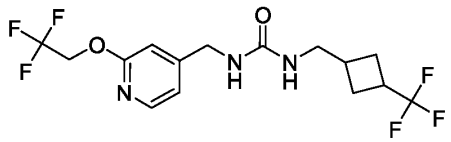
Example 68: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[4-(trifluoromethyl)-1-bicyclo[2.2.2]octanyl]urea



The title compound was obtained in analogy to Example 7 as a white solid (48% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 4-(trifluoromethyl)bicyclo[2.2.2]octan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 394.2 [M+H]+.

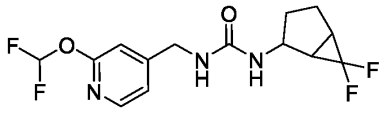
Example 71: 1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (21% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, (3-(trifluoromethyl)cyclobutyl)methanamine and 1,1'-carbonyldiimidazole.

MS (m/z): 386 [M+H]+.

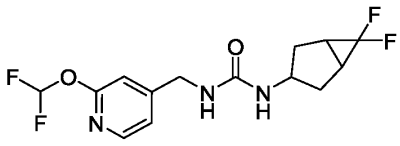
Example 73: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (68% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 6,6-difluorobicyclo[3.1.0]hexan-2-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 334 [M+H]+.

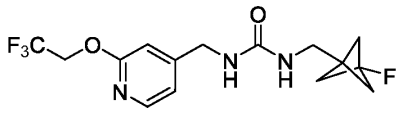
Example 74: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (33% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 6,6-difluorobicyclo[3.1.0]hexan-3-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 334 [M+H]+.

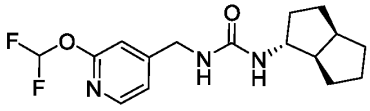
Example 75: 1-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (71% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (3-fluorobicyclo[1.1.1]pentan-1-yl)methanamine and 1,1'-carbonyldiimidazole.

MS (m/z): 348 [M+H]+.

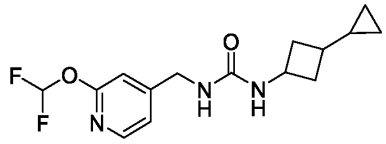
Example 76: 1-[(1R,3aR,6aR)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (63% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1R,3aR,6aR)-octahydropentalen-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 326 [M+H]+.

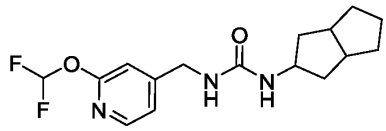
Example 77: 1-(3-cyclopropylcyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (20% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3-cyclopropylcyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 312 [M+H]+.

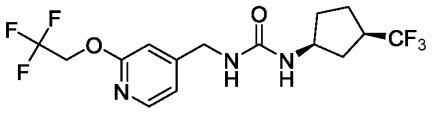
Example 78: 1-(1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (7% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, octahydropentalen-2-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 326 [M+H]+.

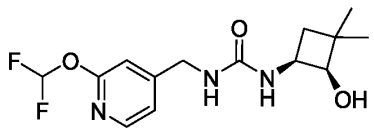
Example 79: 1-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (48% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, rac-(1R,3S)-3-(trifluoromethyl)cyclopentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 386 [M+H]+.

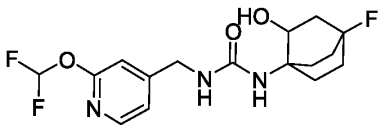
Example 81: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (50% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (rac-1R,4S)-4-amino-2,2-dimethylcyclobutan-1-ol and 1,1'-carbonyldiimidazole.

MS (m/z): 316 [M+H]+.

Example 82: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-2-hydroxy-1-bicyclo[2.2.2]octanyl)urea



a) ethyl 8-acetyl-1,4-dioxaspiro[4.5]decane-8-carboxylate

To a stirred solution of ethyl 1,4-dioxaspiro [4.5]decane-8-carboxylate (50 g, 233.3 mmol, 1 equiv.) in THF (300 mL) was added LDA (350 mL, 350.0 mmol, 1.50 equiv) at -78 °C under N_2 atmosphere. The mixture was stirred at -78°C for 1 hour. Then acetyl chloride (10.99 g, 140.0 mmol, 1.5 equiv) was added. The mixture was stirred for 1 hour. Upon completion of the reaction, it was quenched with NH_4Cl aqueous solution. Water was added and the resulting solution was extracted with EtOAc for 3 times. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography eluying with Petroleum ether: EtOAc (3:10) to afford ethyl 8-acetyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (27 g, 45.1% yield) as light yellow oil.

b) ethyl 1-acetyl-4-oxocyclohexane-1-carboxylate

To a stirred solution of ethyl 8-acetyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (27 g, 105.3 mmol, 1 equiv) in H_2O (45 mL) and Acetone (60 mL) was added conc. HCl (15 mL). The mixture was stirred at 65°C under N_2 atmosphere. The mixture was stirred for 2 hours. Upon completion of the reaction, the resulting mixture was concentrated under vacuum. Then water was added, and the resulting solution was extracted with EtOAc for 3 times. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with Petroleum ether: EtOAc (3:1) to afford ethyl 1-acetyl-4-oxocyclohexane-1-carboxylate (15 g, 67% yield) as light-yellow oil.

c) ethyl 4-hydroxy-2-oxobicyclo[2.2.2]octane-1-carboxylate

To a stirred solution of sodium ethoxide (9.62 g, 141.3 mmol, 2 equiv.) in EtOH (200 mL) was added ethyl 1-acetyl-4-oxocyclohexane-1-carboxylate (15 g, 70.6 mmol, 1.00 equiv.) at 0°C under N_2 atmosphere. The mixture was stirred at room temperature for 15~25 minutes. Upon completion of the reaction, the resulting mixture was diluted with EtOAc (5 L), filtering through silica gel and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with Petroleum ether: EtOAc (2:1) to afford ethyl 4-hydroxy-2-oxobicyclo[2.2.2]octane-1-carboxylate (7 g, 46.7% yield) as a light yellow solid.

d) ethyl 4-fluoro-2-oxobicyclo[2.2.2]octane-1-carboxylate

To a stirred solution of ethyl 4-hydroxy-2-oxobicyclo[2.2.2]octane-1-carboxylate (7 g, 32.9 mmol, 1equiv) in DCM (50 mL) was added DAST (26.5 g, 164.5 mmol, 5 equiv) at -78°C under N_2 atmosphere. The mixture was stirred for 1 hour at -78°C. Then the cold bath was removed, and it was allowed to warm to room temperature gradually. After stirred at room temperature for another 1 h, the mixture was poured into ice water and extracted with DCM for 3 times. The organic layers were combined, washed with $NaHCO_3$ aqueous solution, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel column chromatography, eluted with Petroleum ether: EtOAc (3:1) to afford ethyl 4-fluoro-2-oxobicyclo[2.2.2]octane-1-carboxylate (3.1 g, 43.9% yield) as a light yellow solid.

e) 4-fluoro-2-oxobicyclo[2.2.2]octane-1-carboxylic acid

To a stirred solution of ethyl 4-fluoro-2-oxobicyclo[2.2.2]octane-1-carboxylate (2.0 g, 9.3 mmol) in EtOH (30 mL) at 0°C was added a solution of KOH (1.05 g, 18.6 mmol, 2 equiv.) in water (6 mL) and the mixture was stirred at 0C for 2-4 hours. Upon completion of the reaction, diluted HCl (1 M) was added into the mixture to adjust the pH = 6 at 0C and then toluene was added. The solvent was removed under vacuum and the residue was purified by preparative TLC (EtOAc/THF, v/v=1/1) to give 4-fluoro-2-oxobicyclo[2.2.2]octane-1-carboxylic acid (700 mg, 40.3% yield) as a light yellow solid.

f) 1-((2-(difluoromethoxy)pyridin-4-yl)methyl)-3-(4-fluoro-2-oxobicyclo[2.2.2]octan-1-yl)urea

To a stirred solution of 4-fluoro-2-oxobicyclo[2.2.2]octane-1-carboxylic acid (300 mg, 1.6 mmol) in toluene (10 mL) was added Et3N (489 mg, 4.8 mmol, 3.0 equiv.) and followed by diphenyl phosphoryl azide (887 mg, 3.2 mmol, 2 equiv.). The mixture was stirred at room temperature for 1 hour and 95C for another half an hour. Then (2-(difluoromethoxy)pyridin-4-yl)methanamine (280 mg, 1.6 mmol, 1.0 equiv.) in the mixture of toluene and DMF (1 mL, v/v=4/1) was added and the resulting mixture was stirred at 95°C for 1 hour. Upon completion of the reaction, the resulting mixture was cooled to room temperature and then directly purified by preparative TLC (Petroleum ether/EtOAc, v/v=1/1) to give 1-((2-(difluoromethoxy)pyridin-4-yl)methyl)-3-(4-fluoro-2-oxobicyclo[2.2.2]octan-1-yl)urea (100 mg, 17.4% yield) as a white solid.

MS (m/z): 358 [M+H]+

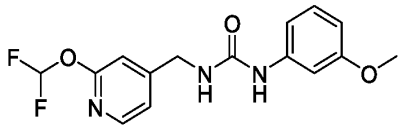
g) 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-2-hydroxy-1-bicyclo[2.2.2]octanyl)urea

To a stirred solution of 1-((2-(difluoromethoxy)pyridin-4-yl)methyl)-3-(4-fluoro-2-oxobicyclo[2.2.2]octan-1-yl)urea (60 mg, 168 umol) in MeOH (2 mL) was added $NaBH_4$ (13 mg, 336 mmol, 2 equiv.) in portions. The mixture was stirred at room temperature for half an hour. Upon completion of the reaction, three drops of water was added and the solvents was removed

under vacuum. The residue was diluted with THF and purified by preparative TLC (Petroleum ether/EtOAc, v/v=2/3) to give the title product (32.6 mg, 54% yield) as a white solid.

MS (m/z): 360 [M+H]+.

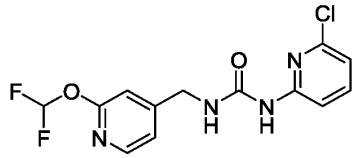
Example 83: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxyphenyl)urea



The title compound was obtained in analogy to Example **5** as a white solid (26% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3-methoxyaniline, and 1,1'-carbonyldiimidazole.

MS (m/z): 324.2 [M+H]+.

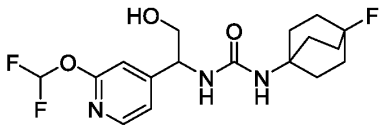
Example 84: 1-(6-chloropyridin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (89% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 6-chloropyridin-2-amine and para-nitrophenyl chloroformate.

MS (m/z): 329.2 [M+H]+.

Example 85: 1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea



a) tert-butyl N-[2-(benzyloxy)-1-[2-(difluoromethoxy)pyridin-4-yl]ethyl]carbamate

To a stirred solution of 4-bromo-2-(difluoromethoxy)pyridine (448mg, 2mmol) in DMF (20 mL) was added N-Boc-O-benzyl-L-serine 97% (886mg, 3mmol), Nickel (II) Chloride dimethoxyethane adduct (22mg, 0.1mmol), cesium carbonate (977.5mg, 3mmol), (4,4'-Di-t-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-κ*N*)phenyl-κ*C*]iridium(III) hexafluorophosphate (22.4mg, 0.02mmol), and 4,4'-di-tert-butyl-2,2'-dipyridyl (26.8mg, 0.1mmol). The mixture was sparged with nitrogen for 15 mins, then the septum cap was sealed with parafilm and the reaction was subjected to blue light (30W, 450 nm) irradiation with liquid cooling at 25°C. After 20 hours irradiation was stopped, and the mixture was poured onto saturated aqueous $NaHCO_3$ (200mL) and extracted with ether (3 x 75mL). The combined organics were successively washed with water and brine, dried ($MgSO_4$) and evaporated to afford a yellow oil that was redissolved in DCM, evaporated onto silica and purified by flash chromatography eluting with 0 to 74% Ethyl Acetate in Heptane to yield tert-butyl N-[2-(benzyloxy)-1-[2-(difluoromethoxy)pyridin-4-yl]ethyl]carbamate (451mg, 57.2%) as a yellow oil.

MS (m/z): 395 [M+H]+.

b) 2-(benzyloxy)-1-(2-(difluoromethoxy)pyridin-4-yl)ethan-1-amine

To a stirred solution of tert-butyl N-[2-(benzyloxy)-1-[2-(difluoromethoxy)pyridin-4-yl]ethyl]carbamate (445mg, 1.13mmol) in Ethyl Acetate (10mL) was added HCl (4M in Dioxane) (2.82mL (4M), 11.28mmol) and the reaction was allowed to stir overnight. Another 5 equivalent 4N HCl (1.4 mL) was added and the reaction was stirred for 6 hours. The reaction mixture was diluted with ether (10mL), filtered, washed with ether (x 3) and sucked dry. The resultant solid was dried at 40°C under high vacuum for 2.5 hours to afford the titled product (336 mg, 89%) as a white solid.

MS (m/z): 295 [M+H]+.

c) 3-[2-(benzyloxy)-1-[2-(difluoromethoxy)pyridin-4-yl]ethyl]-1-{4-fluorobicyclo[2.2.2]octan-1-yl}urea

A solution of 4-fluorobicyclo[2.2.2]octan-1-amine hydrochloride (61.09mg, 0.34mmol) and DIPEA (0.24mL, 1.36mmol) in dry DCM (1.0mL) was placed under N_2 and cooled to 0°C. A solution of 1,1'-carbonyldiimidazole (0.04mL, 1.3g/mL, 0.34mmol) in dry DCM (1.0 mL) was added and left to stir at 0°C for 1 hour, after which time a solution of 2-(benzyloxy)-1-(2-(difluoromethoxy)pyridin-4-yl)ethan-1-amine (100mg, 0.34mmol) in dry DCM (1.0mL) was added and left to warm to rt o/n. The reaction was then concentrated, and the crude was purified by flash chromatography on silica eluting with 0 to 100% ethyl acetate in heptane to give the title product (20mg, 12.7%) as a white solid.

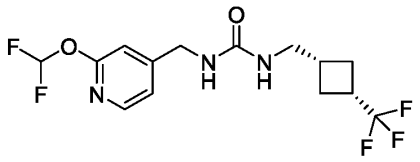
MS (m/z): 464.4 [M+H]+.

d)1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea

1-(2-(benzyloxy)-1-(2-(difluoromethoxy)pyridin-4-yl)ethyl)-3-(4-fluorobicyclo[2.2.2]octan-1-yl)urea (25mg, 0.05mmol) was dissolved in ethanol (1mL) and Ethyl Acetate (1mL). Palladium (5.74mg (10%), 0.01mmol) was added. Hydrogen was then added and the reaction was left to stir at RT o/n. The reaction was then filtered and concentrated and the crude was purified by preparative HPLC to yield the title product as a white solid (74%).

MS (m/z): 374.4 [M+H]+.

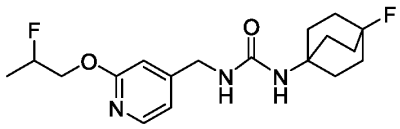
Example 87: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(1r,3r)-(trifluoromethyl)cyclobutyl]methyl]urea



The title compound was obtained by chiral HPLC separation of Example **62** (100%ee, 15% yield) as a white solid (Amylose 1 column in 40:60 water:MeCN).

MS (m/z): 354.2 [M+H]+.

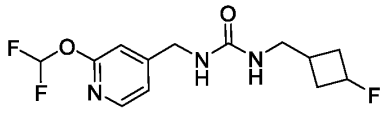
Example 88: 1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (50% yield) using (2-(2-fluoropropoxy)pyridin-4-yl)methanamine, 4-fluorobicyclo[2.2.2]octan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 345.4 [M+H]+.

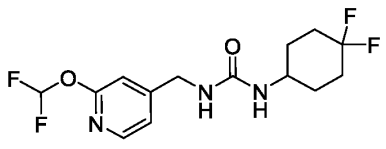
Example 89: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (52% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (3-fluorocyclobutyl)methanamine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 304 [M+H]+.

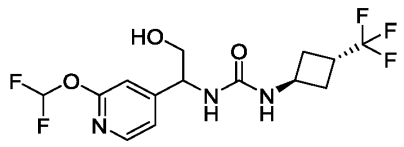
Example 90: 1-(4,4-difluorocyclohexyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (39% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 4,4-difluorocyclohexan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 336 [M+H]+.

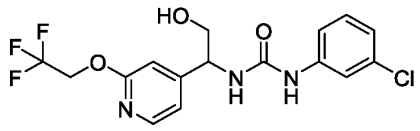
Example 91: 1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **85** as a colorless gum using 4-bromo-2-(difluoromethoxy)pyridine, N-Boc-O-benzyl-L-serine and (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine.

MS (m/z): 370.2 [M+H]+.

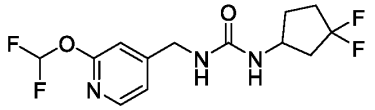
Example 92: 1-(3-chlorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea



The title compound was obtained in analogy to Example **85** as a white solid using 4-bromo-2-(2,2,2-trifluoroethoxy)pyridine, N-Boc-O-benzyl-L-serine and 3-chlorophenyl isocyanate.

MS (m/z): 390.2 [M+H]+.

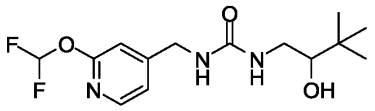
Example 93: 1-(3,3-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (69% yield) solid using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3,3-difluorocyclopentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 322 [M+H]+.

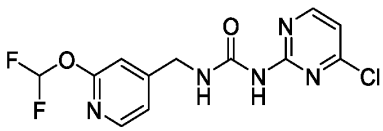
Example 95: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea



The title compound was obtained in analogy to Example **7** as a white solid (50% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1-amino-3,3-dimethylbutan-2-ol and para-nitrophenyl chloroformate.

MS (m/z): 318 [M+H]+.

Example 96: 1-(4-chloropyrimidin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



a) 4-nitrophenyl ((2-(difluoromethoxy)pyridin-4-yl)methyl)carbamate

A solution of (2-(difluoromethoxy)pyridin-4-yl)methanamine (150 mg, 0.86 mmol) and DIPEA (0.15 mL, 0.86 mmol) in dry DCM (3.0 mL) was added to a solution of 4-Nitrophenyl

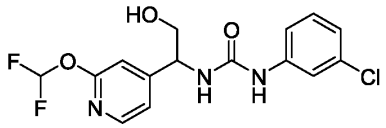
chloroformate (173.6 mg, 0.86 mmol) in dry DCM (3.0 mL) under N_2 at 0°C. The reaction was stirred at 0C for 15 mins then concentrated to give the crude carbamate, which was partitioned between water and EtOAc (x3), the organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and concentrated. The crude was purified by flash chromatography on silica eluting in EtOAc in heptane 0 to 100 % to yield the carbamate as a white solid (159mg, 53% yield).

b) 1-(4-chloropyrimidin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea

Sodium hydride (51.68 mg (60%), 1.29 mmol) was added to a stirred solution of 2-amino-4-chloropyrimidine (223.17 mg, 1.72 mmol) in THF (3.0 mL) under N_2 at 0°C. A solution of 4-nitrophenyl ((2-(difluoromethoxy)pyridin-4-yl)methyl)carbamate (100 mg, 0.29mmol) in THF (3.0 mL) was then added dropwise at 0°C and left to stir for 30 mins, the reaction was then quenched with a couple of drops of acetic acid. Reaction was partition between sat. NH_4Cl (aq) and EtOAc (x3), combined organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and concentrated. The crude was purified by reverse phase automated flash chromatography eluting with 10 to 100% pH 4 Acetonitrile in pH 4 water. The product containing fractions were collected and concentrated and the crude was purified by preparative HPLC automated flash chromatography eluting with 5 to 95% ACN/0.1%FA in Water/0.1% FA to yield the title product (20mg, 21% yield) as a white solid.

MS (m/z): 330.2 [M+H]+.

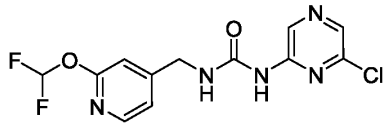
Example 97: 1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea



The title compound was obtained in analogy to Example **85** as an orange solid using 4-bromo-2-(difluoromethoxy)pyridine, N-Boc-O-benzyl-L-serine and 3-chloroaniline.

MS (m/z): 358.2 [M+H]+.

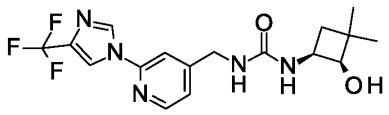
Example 98: 1-(6-chloropyrazin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **96** as a cream solid (42% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 2-Amino-6-chloropyrazine and para-nitrophenyl chloroformate.

MS (m/z): 330 [M+H]+.

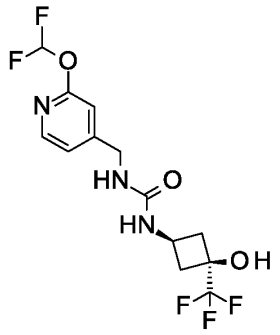
Example 99: 1-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (63% yield) using (2-(4-(trifluoromethyl)-1H-imidazol-1-yl)pyridin-4-yl)methanamine bis-hydrochloride, rac-(1R,4S)-4-amino-2,2-dimethylcyclobutan-1-ol hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 384 [M+H]+.

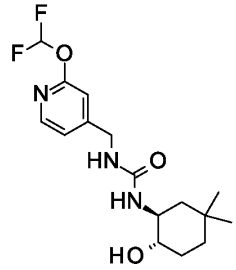
Example 100: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1*s*,3*s*)-3-hydroxy-3-(trifluoromethyl)cyclobutyl]urea:



The title compound was obtained in analogy to Example **5** as a white solid (22% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1s,3s)-3-amino-1-(trifluoromethyl)cyclobutan-1-ol and 1,1'-carbonyldiimidazole.

MS (m/z): 356 [M+H]+.

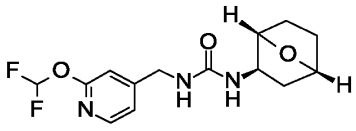
Example 101: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-5,5-dimethylcyclohexyl]urea



The title compound was obtained in analogy to Example **5** as an off-white solid (9% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,2R)-2-amino-4,4-dimethylcyclohexan-1-ol hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 344 [M+H]+.

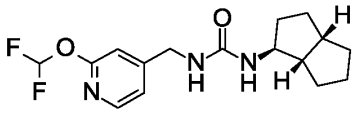
Example 102: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S)-7-oxabicyclo[2.2.1]heptan-2-yl]urea



The title compound was obtained in analogy to Example **5** as a white solid (55% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,2S,4S)-7-oxabicyclo[2.2.1]heptan-2-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 314 [M+H]+.

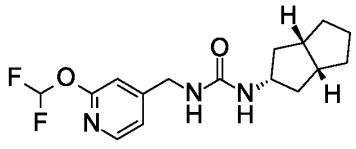
Example 103: 1-[(1S,3aS,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (36% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1S,3aS,6aS)-octahydropentalen-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 326 [M+H]+.

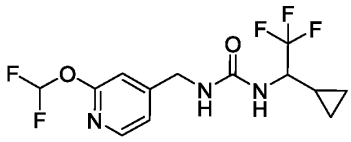
Example 105: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3aR,6aS)-1,2,3,3a,4,5,6,6a



The title compound was obtained as a white solid (14% yield) via chiral separation of Example **78** (Amylose-1 column in 55:45 water:MeCN).

MS (m/z): 326 [M+H]+.

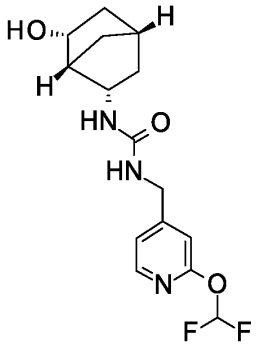
Example 106: 1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (20% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1-cyclopropyl-2,2,2-trifluoroethan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 340 [M+H]+.

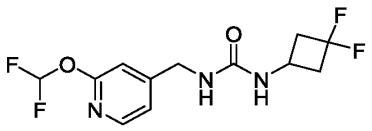
Example 107: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S,6R)-6-hydroxy-2-bicyclo[2.2.1]heptanyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (31% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine hydrochloride, rac-(1R,2R,4S,6S)-6-aminobicyclo[2.2.1]heptan-2-ol hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 328.2 [M+H]+.

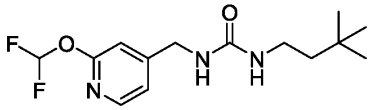
Example 108: 1-(3,3-difluorocyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (38% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3,3-difluorocyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 308.2 [M+H]+.

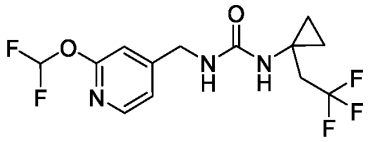
Example 109: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-dimethylbutyl)urea



The title compound was obtained in analogy to Example **5** as a white solid (30% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine hydrochloride, 3,3-dimethylbutan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 302 [M+H]+.

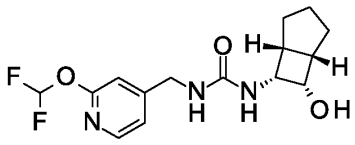
Example 110: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2,2-trifluoroethyl)cyclopropyl]urea



The title compound was obtained in analogy to Example **5** as an off-white solid (49% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1-(2,2,2-trifluoroethyl)cyclopropan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 340 [M+H]+.

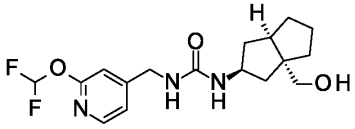
Example 111: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6S,7R)-7-hydroxy-6-bicyclo[3.2.0]heptanyl]urea



The title compound was obtained in analogy to Example **5** as a colorless gum (1% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,5S,6S,7R)-7-aminobicyclo[3.2.0]heptan-6-ol hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 328 [M+H]+.

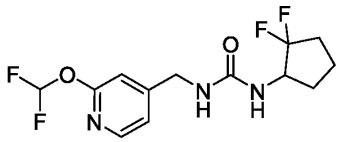
Example 112: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(2R,3aS,6aS)-6a-(hydroxymethyl)-2,3,3a,4,5,6-hexahydro-1H-pentalen-2-yl]urea



The title compound was obtained in analogy to Example **5** as an off-white solid (25% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-[(2R,3aS,6aS)-2-aminooctahydropentalen-3a-yl]methanol hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 356 [M+H]+.

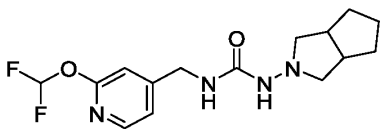
Example 113: 1-(2,2-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as an off-white solid (55% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 2,2-difluorocyclopentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 322 [M+H]+.

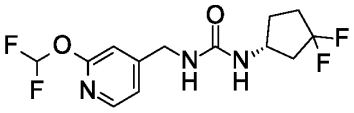
Example 114: 1-(3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white wax (23% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine hydrochloride, hexahydrocyclopenta[c]pyrrol-2(1H)-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 327 [M+H]+.

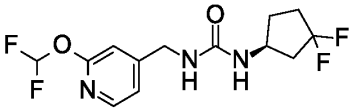
Example 115: 1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (17% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine hydrochloride, (1R)-3,3-difluorocyclopentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 322 [M+H]+.

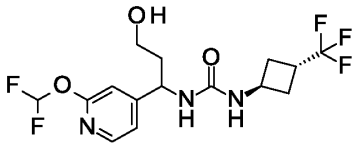
Example 116: 1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (12% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine hydrochloride, (1S)-3,3-difluorocyclopentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 322 [M+H]+.

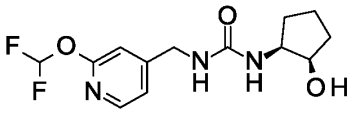
Example 117: 1-[1-[2-(difluoromethoxy)pyridin-4-yl]-3-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **85** as a colorless gum using 4-bromo-2-(difluoromethoxy)pyridine, 4-(benzyloxy)-2-[(tertbutoxycarbonyl)amino] butanoic acid and (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine.

MS (m/z): 384.2 [M+H]+.

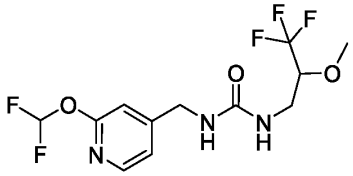
Example 118: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxycyclopentyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (44% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1S,2R)-2-aminocyclopentan-1-ol hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 302.2 [M+H]+.

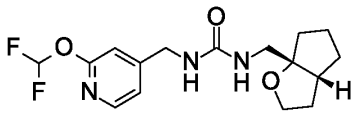
Example 119: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3,3-trifluoro-2-methoxypropyl)urea



The title compound was obtained in analogy to Example **5** as a white solid (30% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3,3,3-trifluoro-2-methoxypropan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 344 [M+H]+.

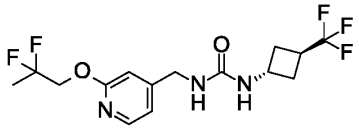
Example 120: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[rac-(3aR,6aR)-2,3,3a,4,5,6-hexahydrocyclopenta[b]furan-6a-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (47% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(3aR,6aR)-hexahydrocyclopenta[b]furan-6aylmethanamine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 342 [M+H]+.

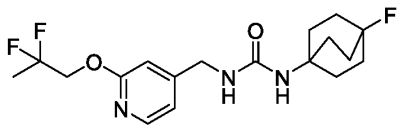
Example 121: 1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (19% yield) using [2-(2,2-difluoropropoxy)pyridin-4-yl]methanamine hydrochloride, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 368 [M+H]+.

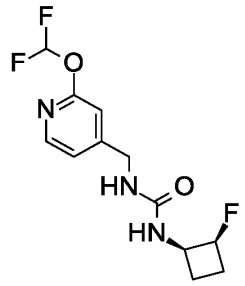
Example 122: 1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea



The title compound was obtained in analogy to Example **5** as a white solid (12% yield) using [2-(2,2-difluoropropoxy)pyridin-4-yl]methanamine hydrochloride, 4-fluorobicyclo[2.2.2]octan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 372 [M+H]+.

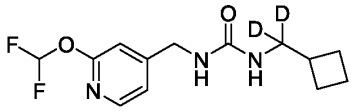
Example 123: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-fluorocyclobutyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (53% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,2S)-2-fluorocyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 290 [M+H]+.

Example 125: 1-[cyclobutyl(dideuterio)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



a) cyclobutylmethan-d2-amine hydrochloride

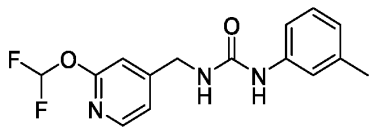
Lithium aluminum deuteride (155.3 mg, 3.7 mmol) was added portionwise to a solution of cyclobutanecarbonitrile (0.23 mL, 0.87 g/mL, 2.47 mmol) in THF-d8 (4 mL) at 0C under N_2. The

reaction was warmed to rt and stirred for 2 h. 0.15 mL of D_2O was added and then 0.15 mL (15%) NaOD (aq) and finally 0.3 mL of D_2O. The reaction mixture was then filtered and washed with THF. HCl (4M in Dioxane) (2 mL) was then added and the reaction was stirred for 30 min and then concentrated. Cool ether was added and the solution was then filtered and washed with more ether. The titled product was obtained as a white solid (150 mg, 49.2%).

b) 1-[cyclobutyl(dideuterio)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea
The title compound was obtained in analogy to Example **7** as a white solid (87% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, cyclobutylmethan-d2-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 288.2 [M+H]+.

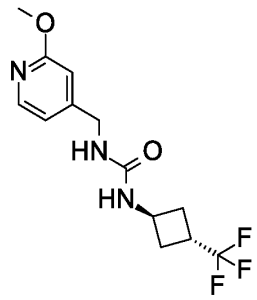
Example 126: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylphenyl)urea



The title compound was obtained in analogy to Example **96** as a white solid (48% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, m-toluidine and para-nitrophenyl chloroformate.

MS (m/z): 308.2 [M+H]+.

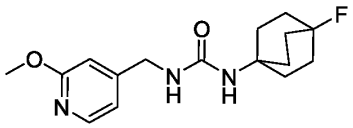
Example 128: 1-[(2-methoxypyridin-4-yl)methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **5** as an off-white solid (33% yield) using (2-methoxypyridin-4-yl)methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 304 [M+H]+.

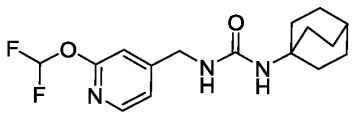
Example 129: 1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[(2-methoxypyridin-4-yl)methyl]urea



The title compound was obtained in analogy to Example **5** as an off-white solid (31% yield) using (2-methoxypyridin-4-yl)methanamine, 4-fluorobicyclo[2.2.2]octan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 308 [M+H]+.

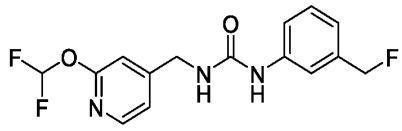
Example 131: 1-(1-bicyclo[2.2.2]octanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a cream colored gum (2% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, bicyclo[2.2.2]octan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 326 [M+H]+.

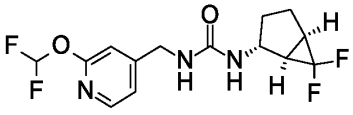
Example 132: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(fluoromethyl)phenyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (23% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3-(fluoromethyl)aniline and para-nitrophenyl chloroformate.

MS (m/z): 326 [M+H]+.

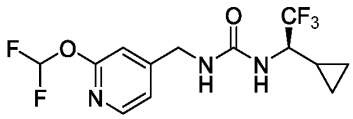
Example 133: 1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained as a white solid single trans-diastereomer (100%de, 16% yield) via chiral separation of Example **73** (Cellulose-4 column in 55:45 water:MeCN).

MS (m/z): 334 [M+H]+.

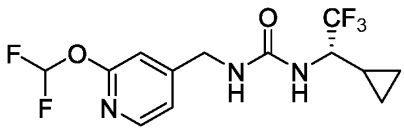
Example 134: 1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (74% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1R)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 340 [M+H]+.

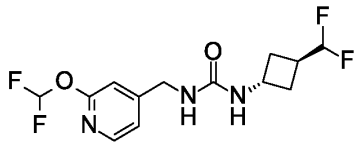
Example 135: 1-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (68% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1S)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 340 [M+H]+.

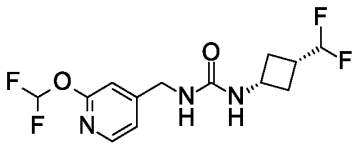
Example 136: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(difluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (72% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1r,3r)-3-(difluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 322 [M+H]+.

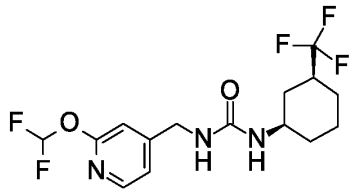
Example 137: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(difluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (61% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1s,3s)-3-(difluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 322 [M+H]+.

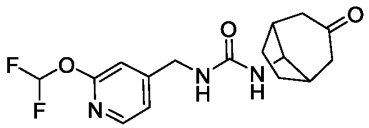
Example 138: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (82% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,3S)-3-(trifluoromethyl)cyclohexan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 368 [M+H]+.

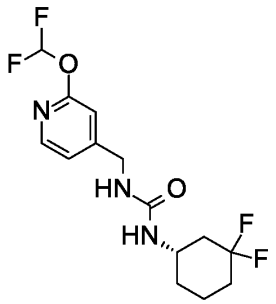
Example 139: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3-oxo-8-bicyclo[3.2.1]octanyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (58% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 8-aminobicyclo[3.2.1]octan-3-one and para-nitrophenyl chloroformate.

MS (m/z): 340 [M+H]+.

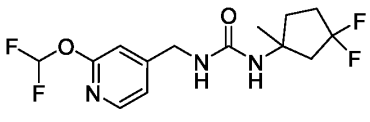
Example 140: 1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a cream colored solid (38% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1S)-3,3-difluorocyclohexan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 336 [M+H]+.

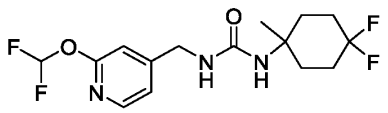
Example 142: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-difluoro-1-methylcyclopentyl)urea



The title compound was obtained in analogy to Example **7** as a cream colored solid (54% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3,3-difluoro-1-methylcyclopentan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 336 [M+H]+.

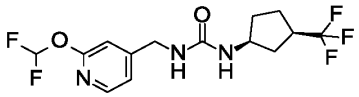
Example 143: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4,4-difluoro-1-methylcyclohexyl)urea



The title compound was obtained in analogy to Example **7** as a cream colored solid (64% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 4,4-difluoro-1-methylcyclohexan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 350 [M+H]+.

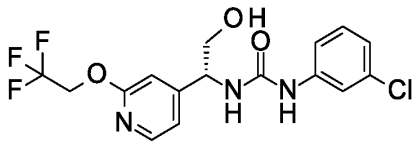
Example 144: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3R)-3-(trifluoromethyl)cyclopentyl]urea



The racemate title compound was obtained in analogy to Example **7** as a white solid (72% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,3S)-3-(trifluoromethyl)cyclopentan-1-amine hydrochloride and para-nitrophenyl chloroformate. Chiral separation (Amylose-1 column in 55:45 water:MeCN) afforded the title compound (96.6%ee, 68% yield) as a white solid (as well as the other enantiomer as example 146).

MS (m/z): 354 [M+H]+.

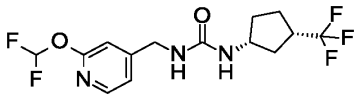
Example 145: 1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea



The title compound was obtained as a white solid (98%ee, 44% yield) via chiral separation of Example **92** (Cellulose-4 column in 60:40 water:MeCN).

MS (m/z): 390.2 [M+H]+.

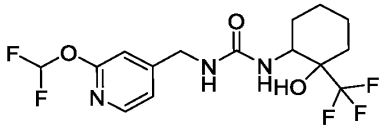
Example 146: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea



The title compound is the other enantiomer obtained through chiral separation described in Example 144. It was obtained as a white solid (100% ee, 72% yield).

MS (m/z): 354 [M+H]+.

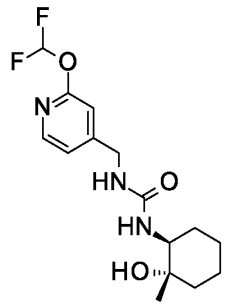
Example 147: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-hydroxy-2-(trifluoromethyl)cyclohexyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (52% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 2-amino-1-(trifluoromethyl)cyclohexan-1-ol and para-nitrophenyl chloroformate.

MS (m/z): 384 [M+H]+.

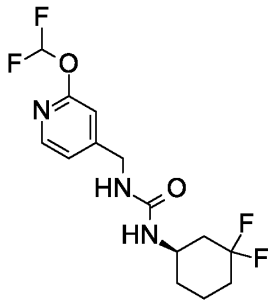
Example 148: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-2-methylcyclohexyl]urea



The title compound was obtained in analogy to Example **7** as a cream colored solid (59% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1S,2S)-2-amino-1-methylcyclohexan-1-ol and para-nitrophenyl chloroformate.

MS (m/z): 330 [M+H]+.

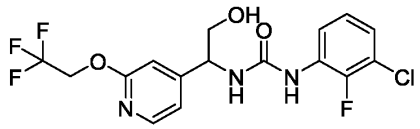
Example 149: 1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **85** as a white solid using 4-bromo-2-(2,2,2-trifluoroethoxy)pyridine, N-Boc-O-benzyl-L-serine and 3-chloro-2-fluoroaniline. The final benzylether deprotection was achieved using BBr3 in DCM instead of hydrogenation.

MS (m/z): 336 [M+H]+.

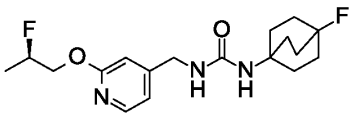
Example 150: 1-(3-chloro-2-fluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea



The title compound was obtained in analogy to Example **85** as a white solid using 4-bromo-2-(2,2,2-trifluoroethoxy)pyridine, N-Boc-O-benzyl-L-serine and 3-chloro-2-fluoroaniline. The final benzylether deprotection was achieved using BBr3 in DCM instead of hydrogenation.

MS (m/z): 408.2 [M+H]+.

Example 151: 1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]urea



a) tert-butyl (R)-((2-(2-fluoropropoxy)pyridin-4-yl)methyl)carbamate

Tert-Butyl (2-chloropyridin-4-yl)methylcarbamate (1 g, 4.12 mmol), tBuBrettPhos Pd G3 (105.6 mg, 0.12mmol) and cesium carbonate (2.01g, 6.18 mmol) were combined in a dry 50ml flask. This was flushed with nitrogen before adding degassed Toluene (15 mL) with (2R)-2-fluoropropan-1-ol (482.6 mg, 6.18 mmol) as a solution. The resultant brown mixture was heated at 80°C under N_2 for 2hrs and then allowed to cool and left o/n. The reaction mixture was diluted with CH_2Cl_2, and filtered through Celite. The filtrate was evaporated in vacuo to afford a crude solid (1.4 g), which was purified by flash chromatography on silica eluting with heptane-30%EtOAc/heptane to afford the desired product as a white solid (960 mg, 82%).

MS (m/z): 285 [M+H]+.

b) (R)-(2-(2-fluoropropoxy)pyridin-4-yl)methanamine

To a solution of tert-butyl (R)-((2-(2-fluoropropoxy)pyridin-4-yl)methyl)carbamate (955 mg, 3.36 mmol) in Ethyl Acetate (15 mL), HCl (4M in Dioxane) (16.8 mL, 67.2 mmol) was added and the mixture stirred o/n. A white precipitate had formed. The reaction was cooled in an ice bath and some cold ether was added. The precipitate was filtered off and washed with further cold ether. Further drying on a hi-vac line at 40C afforded the desired product as a white solid (820 mg, 95%).

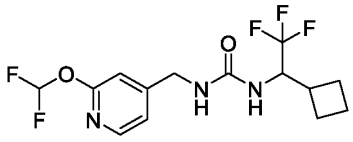
MS (m/z): 185 [M+H]+.

c) 1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]urea

The title compound was obtained in analogy to Example **5** as a white solid (24% yield) using (R)-(2-(2-fluoropropoxy)pyridin-4-yl)methanamine hydrochloride, 4-fluorobicyclo[2.2.2]octan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 354 [M+H]+.

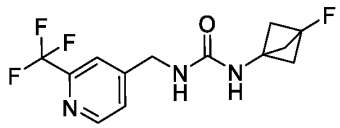
Example 152: 1-(1-cyclobutyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (10% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1-cyclobutyl-2,2,2-trifluoroethanamine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 354 [M+H]+.

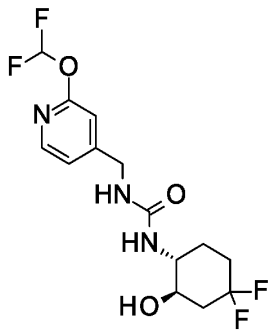
Example 153: 1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as an off-white wax (34% yield) using [2-(trifluoromethyl)pyridin-4-yl]methanamine, 3-fluorobicyclo[1.1.1]pentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 304 [M+H]+.

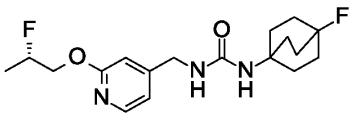
Example 154: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-4,4-difluoro-2-hydroxycyclohexyl]urea



The title compound was obtained in analogy to Example **7** as a cream colored solid (59% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,2R)-2-amino-5,5-difluorocyclohexan-1-ol hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 352 [M+H]+.

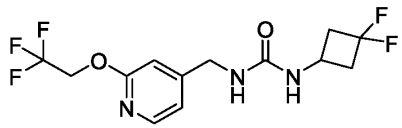
Example 156: 1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **151** as a white solid using tert-Butyl (2-chloropyridin-4-yl)methylcarbamate, (2S)-2-fluoropropan-1-ol, 4-fluorobicyclo[2.2.2]octan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 354 [M+H]+.

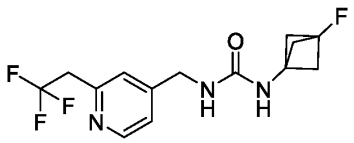
Example 157: 1-(3,3-difluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (19% yield) using [2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methanamine, 3,3-difluorocyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 340 [M+H]+.

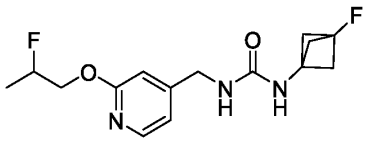
Example 159: 1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (30% yield) using [2-(2,2,2-trifluoroethyl)pyridin-4-yl]methanamine, 3-fluorobicyclo[1.1.1]pentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 318 [M+H]+.

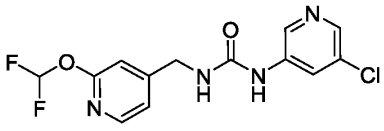
Example 160: 1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **151** as a white solid using tert-Butyl (2-chloropyridin-4-yl)methylcarbamate, 2-fluoropropan-1-ol, 3-fluorobicyclo[1.1.1]pentan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 312 [M+H]+.

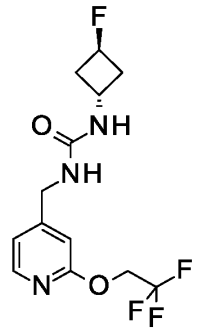
Example 161: 1-(5-chloropyridin-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as an off-white solid (5% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 5-chloropyridin-3-amine and para-nitrophenyl Chloroformate.

MS (m/z): 329 [M+H]+.

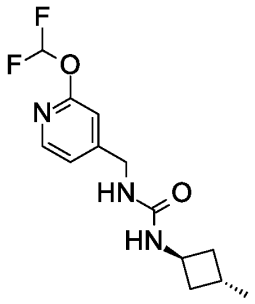
Example 162: 1-((1r,3r)-3-fluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as An off-white solid (30% yield) using [2-(2,2,2-trifluoroethyl)pyridin-4-yl]methanamine, (1r,3r)-3-fluorocyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 322 [M+H]+.

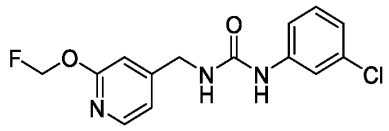
Example 163: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1r,3r)-3-methylcyclobutyl)urea



The title compound was obtained in analogy to Example **7** as an off-white solid (63% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1s,3r)-3-methylcyclobutan-1-amine hydrochloride and para-nitrophenyl Chloroformate.

MS (m/z): 286 [M+H]+.

Example 164: 1-(3-chlorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea



a) 4-bromo-2-(fluoromethoxy)pyridine

2-[(4-bromopyridin-2-yl)oxy]acetic acid (500 mg, 2.15 mmol), Selectfluor (2.29 g, 6.46 mmol), (4,4'-Di-t-butyl-2,2'-bipyridine)bis[3,5-difluoro-2-[5-trifluoromethyl-2-pyridinyl-κ*N*)phenyl-κ*C*]iridium(III) hexafluorophosphate (24.2 mg, 21.55 μmol) and cesium carbonate (702.12 mg, 2.15 mmol) were added to a 30 mL vial and purged under N_2. A degassed mixture of Water (10 mL) and Acetonitrile (10 mL) was then added and the reaction was irradiated under a blue LED at 25°C for 24 h. Reaction was confirmed via LCMS, the reaction was then diluted in water and product was extracted with EtOAc (x3), and organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and concentrated. The crude was purified by automated flash chromatography eluting with 0 to 36% ethyl acetate in heptane to yield 4-bromo-2-(fluoromethoxy)pyridine (200 mg, 45% yield) as a colorless oil.

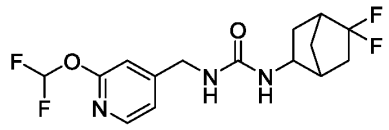
MS (m/z): 206 [M+H]+.

b) 1-(3-chlorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea

The title compound was obtained in analogy to Example **85** as a white solid using 4-bromo-2-(fluoromethoxy)pyridine, Boc-Gly-OH and 3-chlorophenyl isocyanate.

MS (m/z): 390.2 [M+H]+.

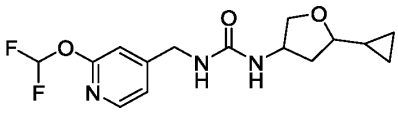
Example 165: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,4R)-5,5-difluoro-2-bicyclo[2.2.1]heptanyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (65% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 5,5-difluorobicyclo[2.2.1]heptan-2-amine hydrochloride and para-nitrophenyl Chloroformate.

MS (m/z): 348 [M+H]+.

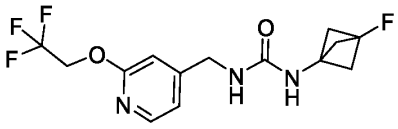
Example 166: 1-(5-cyclopropyloxolan-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (80% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 5-cyclopropyloxolan-3-amine and para-nitrophenyl Chloroformate.

MS (m/z): 328 [M+H]+.

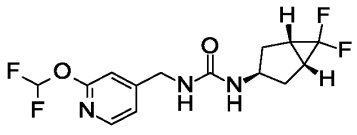
Example 168: 1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (39% yield) using [2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methanamine hydrochloride, 3-fluorobicyclo[1.1.1]pentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 334 [M+H]+.

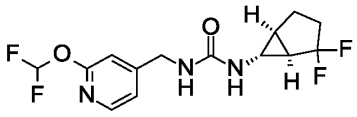
Example 169: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3s,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea



The title compound was obtained as a white solid (44% yield) via chiral separation of Example **74** (Amylose-1 in in 60:40 water:MeCN).

MS (m/z): 334 [M+H]+.

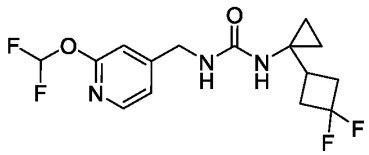
Example 170: 1-[(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



Purification by chiral separation of Example **172** (cellulose 4 column in 55:45 water:MeCN) afforded the title product (100%ee, 18.6% yield) as a white solid.

MS (m/z): 334 [M+H]+.

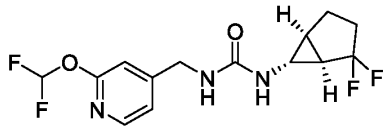
Example 171: 1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to example 7 as a white solid (79% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1-(3,3-difluorocyclobutyl)cyclopropan-1-amine hydrochloride and 4-nitrophenyl chloroformate.

MS (m/z): 348 [M+H]+.

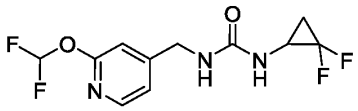
Example 172: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (68% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,5S,6R)-2,2-difluorobicyclo[3.1.0]hexan-6-amine hydrochloride and N,N'-carbonyldiimidazole.

MS (m/z): 334 [M+H]+.

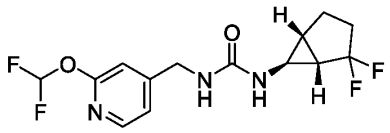
Example 173: 1-(2,2-difluorocyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as an off-white solid (22% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine hydrochloride, 2,2-difluorocyclopropan-1-amine hydrochloride and N,N'-carbonyldiimidazole.

MS (m/z): 294 [M+H]+.

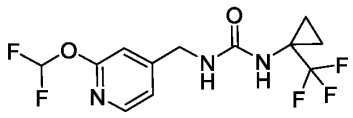
Example 174: 1-[(1S,5R,6S)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound is the other enantiomer isolated by chiral separation of Example **172** (cellulose 4 column in 55:45 water:MeCN) (97.4%ee, 19.4% yield) as a white solid.

MS (m/z): 334 [M+H]+.

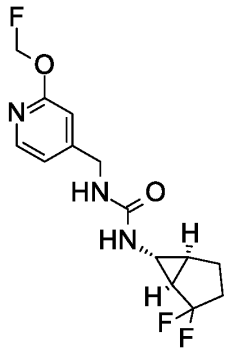
Example 175: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(trifluoromethyl)cyclopropyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (88.2% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine hydrochloride and 1-isocyanato-1-(trifluoromethyl)cyclopropane.

MS (m/z): 326 [M+H]+.

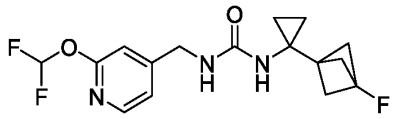
Example 176: 1-[[2-(fluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]urea



The title compound was obtained in analogy to Example **164** as a white solid using 2-[(4-bromopyridin-2-yl)oxy]acetic acid, Selectfluor, Boc-Gly-OH and (1R,5S,6R)-2,2-difluorobicyclo[3.1.0]hexan-6-amine hydrochloride.

MS (m/z): 316 [M+H]+.

Example 177: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)cyclopropyl]urea



a) 3-(dibenzylcarbamoyl)bicyclo[1.1.1]pentane-1-carboxylate

To a stirred mixture of 3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (5 g, 29.4 mmol, 1 equiv) and dibenzyl amine (6.09 g, 30.8 mmol, 1.05 equiv) in ACN (100 mL) at 0°C were added N,N,N′,N′-tetramethylchloroformamidinium hexafluorophosphate (TCFH) (12.37 g, 44.075 mmol, 1.5 equiv) and NMI (7.24 g, 88.179 mmol, 3.00 equiv). The mixture was stirred overnight at room temperature. Upon completion of reaction, water was added, and the resulting solution was extracted with DCM for 3 times. The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by silica gel chromatography (Petroleum ether: EtOAc=3:1) to give methyl 3-(dibenzylcarbamoyl)bicyclo[1.1.1]pentane-1-carboxylate (10 g, 97.4%) as a light yellow solid.

MS (m/z): 350.2 [M+H]+.

b) 3-(dibenzylcarbamoyl)bicyclo[1.1.1]pentane-1-carboxylic acid

To a stirred solution of methyl 3-(dibenzylcarbamoyl)bicyclo[1.1.1]pentane-1-carboxylate (10 g, 28.6 mmol, 1 equiv) in THF (80 mL) and MeOH (20 mL) was added a solution of LiOH (3.43 g, 143.1 mmol, 5 equiv) in H_2O (20 mL). The mixture was stirred at 0°C for 2 hours. Upon completion of reaction, the organic solvent was removed under vacuum. The mixture was acidified to pH 4~5 with diluted hydrochloric acid. The resulting mixture was extracted with DCM (50 mL for 5 times). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by reverse phase separation eluting with Water (0.1% FA), acetonitrile to give 3-(dibenzylcarbamoyl)bicyclo[1.1.1]pentane-1-carboxylic acid (8 g, 83.4%) as a colorless oil.

MS (m/z): 334.2 [M+H]+.

c) *N,N*-dibenzyl-3-fluorobicyclo[1.1.1]pentane-1-carboxamide

To a mixture of $AgNO_3$ (0.06 g, 0.33 mmol, 0.1 equiv) and SelectFluor (3.49 g, 9.84 mmol, 3 equiv) was added a solution of 3-(dibenzylcarbamoyl)bicyclo[1.1.1]pentane-1-carboxylic acid (1.1 g, 3.28 mmol, 1 equiv) in ACN (20 mL). H_2O (3 mL) was then added and the mixture was stirred at 80°C for 10 hours. Upon completion of reaction, the mixture was extracted with EtOAc for 3 times. The organic layers were combined, washed with brine dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by reverse phase separation eluting with Water (0.1% NH_4HCO_3), acetonitrile to give *N,N*-dibenzyl-3-fluorobicyclo[1.1.1]pentane-1-carboxamide (360 mg, 35.5%) as light yellow oil.

MS (m/z): 310.2 [M+H]+.

d) *N,N*-dibenzyl-1-{3-fluorobicyclo[1.1.1]pentan-1-yl}cyclopropan-1-amine

To a stirred solution of ethylmagnesium bromide (3.78 mL, 6.8 mmol, 1.8 M in Et_2O, 3.5 equiv) in THF (15 mL) at -78°C under nitrogen atmosphere was added a solution of $Ti(i\text{-}PrO)_4$ (0.82 mL) in THF (1 mL) dropwise. The resulting solution was stirred at -78°C for 0.5 hour. A solution of *N,N*-dibenzyl-3-fluorobicyclo[1.1.1]pentane-1-carboxamide (600 mg, 1.94 mmol, 1 equiv) in THF (1 mL) was then added. The mixture was warmed to room temperature and stirred for 2 hours. Upon completion of reaction, the mixture was diluted with EtOAc (50 mL) and filtrated through a silica gel column (washed with 200 mL of EtOAc). The filtrate was concentrated under vacuum. The residue was purified by reverse phase separation eluting with Water (0.1% NH_4HCO_3), acetonitrile to give *N,N*-dibenzyl-1-{3-fluorobicyclo[1.1.1]pentan-1-yl}cyclopropan-1-amine (188 mg, 25.1%) as light yellow oil.

MS (m/z): 322.2 [M+H]+.

e) 1-{3-fluorobicyclo[1.1.1]pentan-1-yl}cyclopropan-1-amine

To a solution of *N,N*-dibenzyl-1-{3-fluorobicyclo[1.1.1]pentan-1-yl}cyclopropan-1-amine (850 mg, 2.64 mmol, 1 equiv) in THF (8 mL) and MeOH (8 mL) at 0°C was added Pd/C (600 mg, 0.56

mmol, 0.21 equiv, 10%) and the mixture was stirred at 10°C for 2 hours. Upon completion of reaction, the catalyst was filtrated out and washed with THF (10 mL for 3 times). The filtrate was concentrated under vacuum at 0~10C to give the crude of 1-{3-fluorobicyclo[1.1.1]pentan-1-yl}cyclopropan-1-amine (500 mg), which was used without further purification.

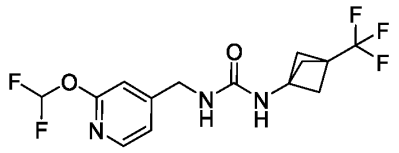
MS (m/z): 175.1 [M+H]+.

f) 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(3-fluoro-1-bicyclo[1.1.1]pentanyl) cyclopropyl]urea

The title compound was obtained in analogy to Example **7** as a white solid (2% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1-(3-fluorobicyclo[1.1.1]pentan-1-yl)cyclopropan-1-amine and 4-nitrophenyl chloroformate.

MS (m/z): 342.2 [M+H]+.

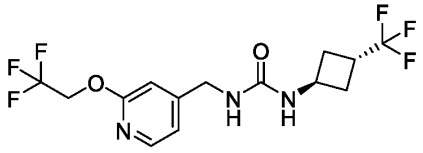
Example 178: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (34% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 352.1 [M+H]+.

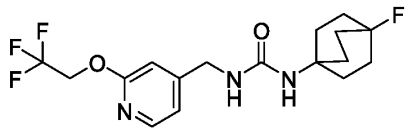
Example 179: 1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (83% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine and 1,1'-carbonyldiimidazole.

MS (m/z): 372.1 [M+H]+.

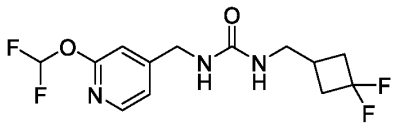
Example 180: 1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (42.6% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, 4-fluorobicyclo[2.2.2]octan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 376.2 [M+H]+.

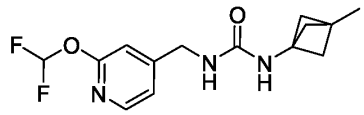
Example 181: 1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (57.2% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (3,3-difluorocyclobutyl)methanamine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 322.1 [M+H]+.

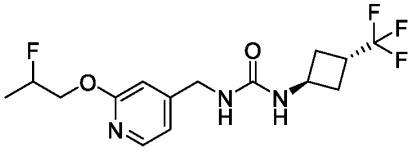
Example 182: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methyl-1-bicyclo[1.1.1]pentanyl)urea



The title compound was obtained in analogy to Example **5** as a cream solid (49.7% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3-methylbicyclo[1.1.1]pentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 298.1 [M+H]+.

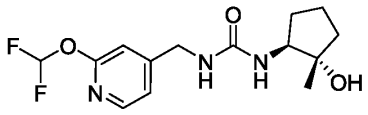
Example 183: 1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (30% yield) using [2-(2-fluoropropoxy)pyridin-4-yl]methanamine hydrochloride, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 350.2 [M+H]+.

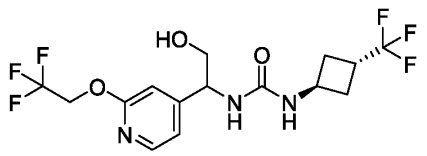
Example 184: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,2S)-2-hydroxy-2-methylcyclopentyl]urea



The title compound was obtained in analogy to Example **5** as a colorless gum (91.8% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1S,2S)-2-amino-1-methylcyclopentan-1-ol and 1,1'-carbonyldiimidazole.

MS (m/z): 316.1 [M+H]+.

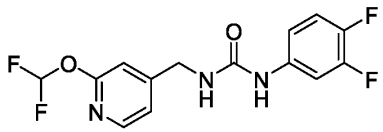
Example 185: 1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **7** as a white solid using 2-amino-2-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethanol hydrochloride, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 402.1 [M+H]+.

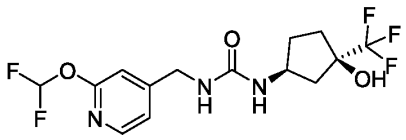
Example 186: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-difluorophenyl)urea



The title compound was obtained in analogy to Example **4** as a cream solid (66.4% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine and 1,2-difluoro-4-isocyanatobenzene.

MS (m/z): 330.1 [M+H]+.

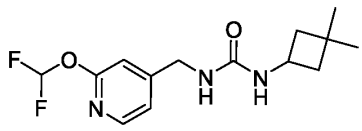
Example 187: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-hydroxy-3-(trifluoromethyl)cyclopentyl]urea



The title compound was obtained in analogy to Example **5** as a colorless gum (6.5% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine hydrochloride, (3-amino-1-(trifluoromethyl)cyclopentan-1-ol hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 370.1 [M+H]+.

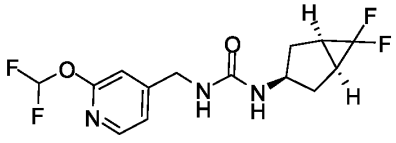
Example 188: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-dimethylcyclobutyl)urea



The title compound was obtained in analogy to Example **5** as a white solid (34.4% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3,3-dimethylcyclobutan1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 300.2 [M+H]+.

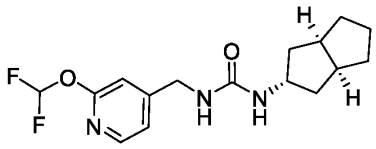
Example 189: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3r,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea



The title compound was obtained as a white solid (13.6% yield, 89%ee) via chiral separation of Example **74** (Amylose-1 column in 55:45 water:MeCN).

MS (m/z): 334.1 [M+H]+.

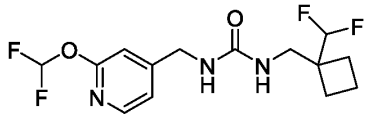
Example 190: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2s,3aR,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]urea



The title compound was obtained as a white solid (14.5% yield) via chiral separation of Example **78** (Cellulose-4 column in 60:40 water:MeCN).

MS (m/z): 326.2 [M+H]+.

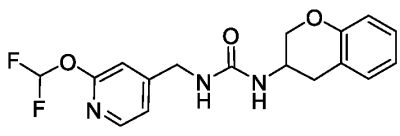
Example 191: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluoromethyl)cyclobutyl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (1.1% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine hydrochloride, [1-(difluoromethyl) cyclobutyl]methanamine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 336.1 [M+H]+.

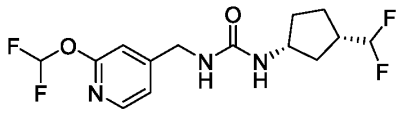
Example 192: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-dihydro-2H-chromen-3-yl)urea



The title compound was obtained in analogy to Example **7** as a white solid (56.4% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3,4-dihydro-2H-1-benzopyran-3-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 350.1 [M+H]+.

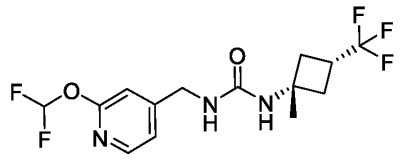
Example 193: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(difluoromethyl)cyclopentyl]urea



The title compound was obtained in analogy to Example **7** as an off-white solid (60.0% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1R,3S)-3-(difluoromethyl)cyclopentan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 336.1 [M+H]+.

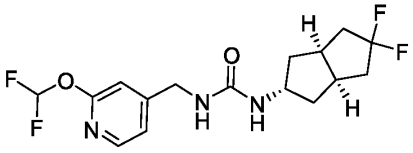
Example 194: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-1-methyl-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **7** as an off-white solid (50.0% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1-methyl-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 354.1 [M+H]+.

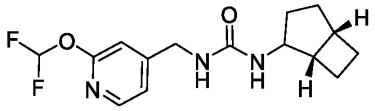
Example 195: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2r,3aR,6aS)-5,5-difluoro-2,3,3a,4,6,6a-hexahydro-1H-pentalen-2-yl]urea



The title compound was obtained in analogy to Example **7** as a white solid (48.0% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (2S,3aR,6aS)-5,5-difluorohexahydro-1H-pentalen-2 amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 362.2 [M+H]+.

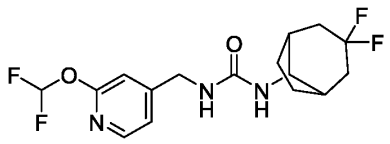
Example 196: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5R)-2-bicyclo[3.2.0]heptanyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (68.5% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,5R)-bicyclo[3.2.0]heptan-2-amine and para-nitrophenyl chloroformate.

MS (m/z): 312.1 [M+H]+.

Example 197: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3,3-difluoro-8-bicyclo[3.2.1]octanyl]urea

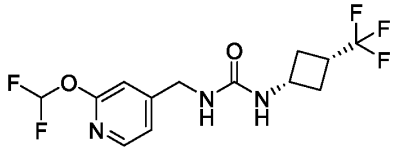


To a 8 mL vial was added 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3-oxo-8-bicyclo[3.2.1]octanyl]urea (Example **139**) (50 mg, 0.15 mmol), cooled to 0°C under N_2. DAST (38.62 µL, 1.23 g/mL, 0.29 mmol) was added dropwise. After the addition, the cooling bath was removed, and the mixture stirred at room temperature under N_2 for 2h. The reaction mixture was

poured slowly on to ice (150g) and diluted with DCM (50mL), washed with brine (50mL). The organic layer was separated, dried ($MgSO_4$), filtered and concentrated under vacuum to give a gum. Purification by preparative HPLC (eluting with 5 to 95% ACN/0.1%FA in Water/0.1% FA) afforded the title product (1.95 mg, 0.01 mmol, 3.7% yield) as a white solid.

MS (m/z): 362.1 [M+H]+.

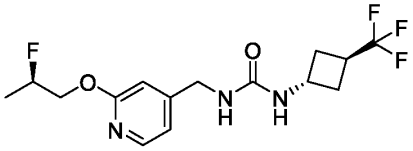
Example 198: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (81.6% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1s,3s)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 340.1 [M+H]+.

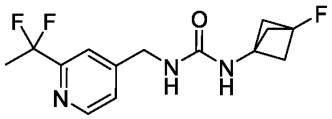
Example 199: 1-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (40.1% yield) using (R)-(2-(2-fluoropropoxy)pyridin-4-yl)methanamine dihydrochloride, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 350.2 [M+H]+.

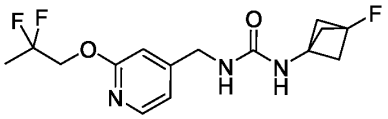
Example 200: 1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea



The title compound was obtained in analogy to Example **5** as a white solid (29.7% yield) using [2-(1,1-difluoroethyl)pyridin-4-yl]methanamine, 3-fluorobicyclo[1.1.1]pentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 300.1 [M+H]+.

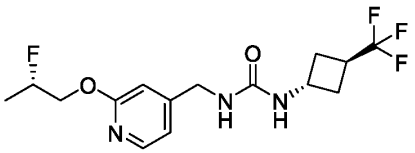
Example 201: 1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea



The title compound was obtained in analogy to Example **5** as a white solid (71.4% yield) using [2-(2,2-difluoropropoxy)pyridin4-yl]methanamine hydrochloride, 3-fluorobicyclo[1.1.1]pentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 330.1 [M+H]+.

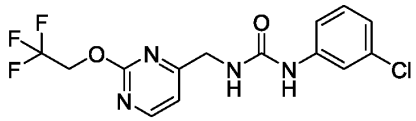
Example 202: 1-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **151** as a white solid using tert-butyl ((2-chloropyridin-4-yl)methyl)carbamate, (2S)-2-fluoropropan-1-ol, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 350.2 [M+H]+.

Example 203: 1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]urea



a) 2-(2,2,2- trifluoroethoxy)pyrimidine4-carbonitrile

2-Chloropyrimidine-4-carbonitrile (800 mg, 5.73 mmol), 2,2,2-trifluoroethanol (627.95 µL, 1.37 g/mL, 8.6 mmol) and cesium carbonate (2801.97 mg, 8.6 mmol) were combined in dry Toluene (28 mL) then bubbled with N_2. tBuBrettPhos Pd G3 (97.97 mg, 0.11 mmol) was then added, and the reaction was bubbled with N_2, sealed and heated at 80C for 16h. The reaction was then filtered through a sinter and the pad washed with 30ml EtOAc. The combined organics were concentrated in vacuo, dry-loaded onto silica and purified by silica gel chromatography (eluting with DCM and Heptane) to yield the product (344 mg, 1.69 mmol, 29.5% yield) as a yellowish oil.

MS (m/z): 204 [M+H]+.

b) [2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methanamine

2-(2,2,2-trifluoroethoxy)pyrimidine-4-carbonitrile (229 mg, 1.13 mmol) was dissolved in Ethyl Acetate (14 mL) and acetic acid (2.3 mL) then evacuated and backfilled with N_2. 10% Palladium on carbon (119.98 mg, 0.11 mmol) was then added and the reaction was then evacuated and backfilled with H_2 and shaken for 16h. The reaction was filtered through a celite pad. The pad was washed with EtOAc (30 mL) and the combined organics were concentrated in vacuo. The crude was dissolved in DCM and loaded onto a SCX2 cartridge. The cartridge was washed with DCM then MeOH then DCM. Product was then eluted with 3:1 DCM:7M NH_3 in MeOH and

isolated as a red oil (199.8 mg, 0.96 mmol, 85.5% yield), which was carried forward without further purification.

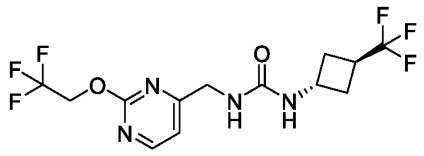
MS (m/z): 208 [M+H]+.

c) 1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]urea

The title compound was obtained in analogy to Example **4** as an off-white solid (15.0% yield) using [2-(2,2,2- trifluoroethoxy)pyrimidin4-yl]methanamine and 3-chlorophenyl isocyanate.

MS (m/z): 361.1 [M+H]+.

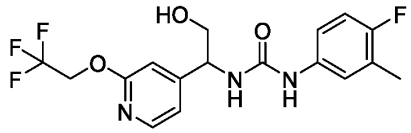
Example 204: 1-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **5** as an off-white solid (0.4% yield) using [2-(2,2,2- trifluoroethoxy)pyrimidin4-yl]methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 373.1 [M+H]+.

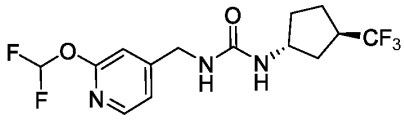
Example 205: 1-(4-fluoro-3-methylphenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea



The title compound was obtained in analogy to Example **85** as a white solid using 4-bromo-2-(2,2,2-trifluoroethoxy)pyridine, N-Boc-O-benzyl-L-serine and 1-fluoro-4-isocyanato-2-methylbenzene.

MS (m/z): 388.1 [M+H]+.

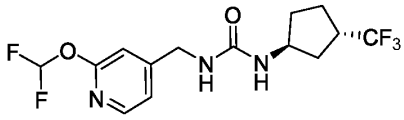
Example 206: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3R)-3-(trifluoromethyl)cyclopentyl]urea



A solution of bis(trichloromethyl) carbonate (155.0 mg, 0.522 mmol) in DCM (13 mL) was treated with 1-[2-(difluoromethoxy)pyridin-4-yl]methanamine (272.9 mg, 1.567 mmol) and DIPEA (843.9 mg, 6.530 mmol) in THF (30 mL) at 0°C under nitrogen atmosphere followed by the addition of 3-(trifluoromethyl)cyclopentan-1-amine (200 mg, 1.31 mmol) in THF (30 mL) dropwise at 0°C. The resulting mixture was stirred for 1 h at 25°C, then concentrated under vacuum. The residue was purified by reverse phase flash chromatography (eluting with 10-50% MeCN in water) to afford the racemate product 1-((2-(difluoromethoxy)pyridin-4-yl)methyl)-3-(3-(trifluoromethyl)cyclopentyl)urea (100 mg, 21.7% yield) as white solid. The racemate was separated on a CHIRAL ART Amylose-C NEO column (25 cm, 5 μm) in 10% IPA: 10mM NH_3-MeOH. 2 peaks were isolated (RT1: 7.295min; RT2: 10.448min). The first peak was then separated on a CHIRALPAK IH column (25 cm, 5 μm) in 20% IPA: CO_2 to give the title product as the first eluting peak (15.1 mg, 3.27% yield) as a white solid.

MS (m/z): 354.1 [M+H]+.

Example 207: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-(trifluoromethyl)cyclopentyl]urea

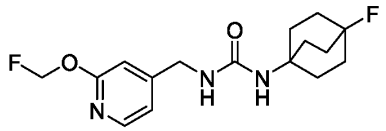


The title product is the second eluting peak from chiral separation of 1-((2-(difluoromethoxy)pyridin-4-yl)methyl)-3-(3-(trifluoromethyl)cyclopentyl)urea (Example **206**),

separated on a CHIRALPAK IH column (25 cm, 5 μm) in 20% IPA: CO_2 to give the product (16.9 mg, 24.4% yield) as a white solid.

MS (m/z): 354.1 [M+H]+.

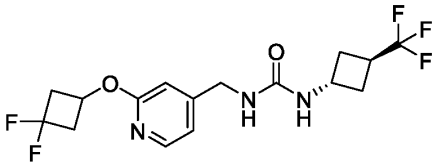
Example 208: 1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **85** as a white solid using 4-bromo-2-(fluoromethoxy)pyridine, Boc-Gly-OH, 4-fluorobicyclo[2.2.2]octan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 326.2 [M+H]+.

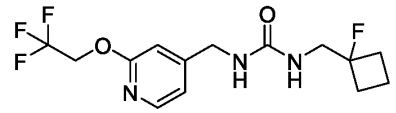
Example 209: 1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **151** as a white solid using tert-butyl ((2-chloropyridin-4-yl)methyl)carbamate, 3,3-difluorocyclobutan-1-ol, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 380.1 [M+H]+.

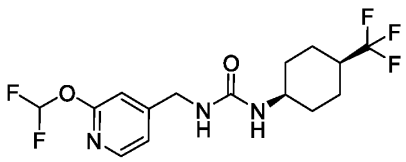
Example 210: 1-[(1-fluorocyclobutyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (25.0% yield) using [2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methanamine, (1-fluorocyclobutyl)methanamine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 336.1 [M+H]+.

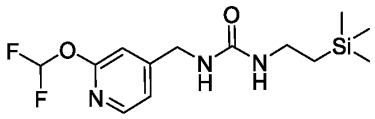
Example 211: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,4s)-4-(trifluoromethyl)cyclohexyl]urea



The title compound was obtained in analogy to Example **7** as a cream solid (40.1% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1s,4s)-4-(trifluoromethyl)cyclohexan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 328.1 [M+H]+.

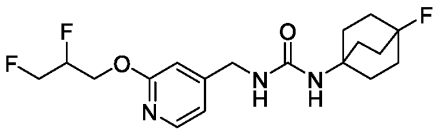
Example 212: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-trimethylsilylethyl)urea



The title compound was obtained in analogy to Example **7** as a yellowish solid (63.0% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (2-aminoethyl)trimethylsilane hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 318.2 [M+H]+.

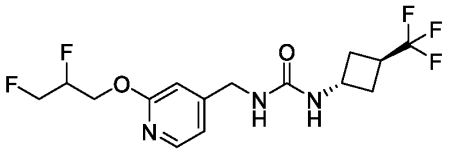
Example 213: 1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea



The title compound was obtained in analogy to Example **151** as a white solid using tert-butyl ((2-chloropyridin-4-yl)methyl)carbamate, 2,3-difluoropropan-1-ol, 4-fluorobicyclo[2.2.2]octan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 372.2 [M+H]+.

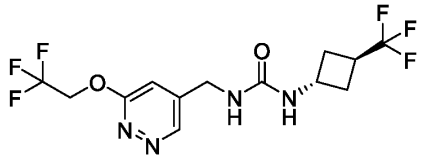
Example 214: 1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (98.0% yield) using (2-(2,3-difluoropropoxy)pyridin-4-yl)methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 368.1 [M+H]+.

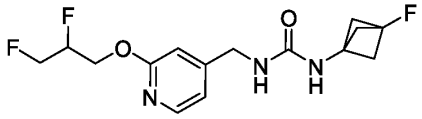
Example 215: 1-[[6-(2,2,2-trifluoroethoxy)pyridazin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **203** as an orange glass using 6-chloropyridazine-4-carbonitrile, 2,2,2-trifluoroethanol, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 373.1 [M+H]+.

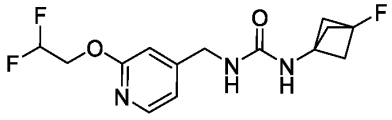
Example 216: 1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea



The title compound was obtained in analogy to Example **7** as a white solid (76.5% yield) using (2-(2,3-difluoropropoxy)pyridin-4-yl)methanamine, 3-fluorobicyclo[1.1.1]pentan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 330.2 [M+H]+.

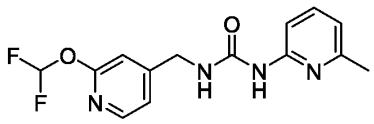
Example 217: 1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea



The title compound was obtained in analogy to Example **5** as an off-white solid (41.8% yield) using [2-(2,2-difluoroethoxy)pyridin-4-yl]methanamine, 3-fluorobicyclo[1.1.1]pentan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 316.1 [M+H]+.

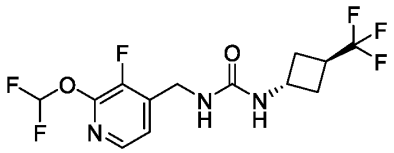
Example 218: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(6-methylpyridin-2-yl)urea



The title compound was obtained in analogy to Example **7** as a white solid (18.5% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 6-methyl-2-pyridinamine and para-nitrophenyl chloroformate.

MS (m/z): 309.1 [M+H]+.

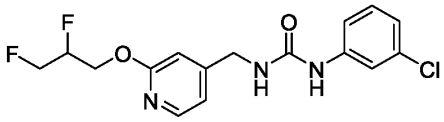
Example 219: 1-[[2-(difluoromethoxy)-3-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (63.6% yield) using [2-(difluoromethoxy)-3-fluoropyridin-4-yl]methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 358.1 [M+H]+.

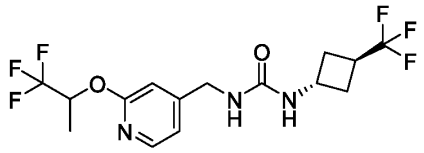
Example 220: 1-(3-chlorophenyl)-3-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (20.2% yield) using (2-(2,3-difluoropropoxy)pyridin-4-yl)methanamine, 3-chloroaniline and para-nitrophenyl chloroformate.

MS (m/z): 356.1 [M+H]+.

Example 221: 1-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(1,1,1-trifluoropropan-2-yloxy)pyridin-4-yl]methyl]urea



a) 2-[(1,1,1-trifluoropropan-2- yl)oxy]pyridine-4-carbonitrile

1,1,1-Trifluoro-2-propanol (1.42 g, 12.45 mmol) was dissolved in dry DMF (30 mL) then treated with sodium hydride (398.37 mg (60%), 9.96 mmol) and stirred under N_2 for 5 mins. A solution of 2-chloroisonicotinonitrile (690 mg, 4.98 mmol) in dry DMF (20 mL) was then added and the reaction was stirred at rt for 1h. The reaction was then quenched with 200 µL of AcOH and then concentrated in vacuo. The crude was then poured onto 400ml sat $NaHCO_3$ and extracted with 2x200ml EtOAc, the organics were then washed with 100ml H O, 100ml 5% LiCl, 100ml sat brine, dried over $MgSO_4$ and concentrated onto silica and purified by silica gel chromatography (eluting in 9:1 Heptane:EtOAc) to yield the product (507.2 mg, 2.35 mmol, 47.1% yield) as a colourless oil.

b) (2-((1,1,1-trifluoropropan-2-yl)oxy)pyridin-4-yl)methanamine

Cobalt (II) chloride (360.4 mg, 2.78 mmol) was added to a solution of 2-[(1,1,1-trifluoropropan-2-yl)oxy]pyridine-4-carbonitrile (300 mg, 1.39 mmol) in Methanol (10 mL) and THF (10 mL) under N_2 at 0°C. The mixture was stirred for 1 min, then sodium borohydride (525.06 mg, 13.88 mmol) was added portionwise over 10min, then allowed to slowly warm to RT and left to stir o/n. EtOAc was added, and the mixture was filtered through a plug of celite. The filtrate was washed with water (basified with a few mls NH_3(aq)), then the aqueous layer was extracted with further EtOAc (50ml). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to afford the product as a crude light brown liquid (303 mg, 1.38 mmol, 99.2% yield), which was used without further purification.

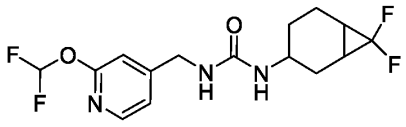
MS (m/z): 221 [M+H]+.

c) 1-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(1,1,1-trifluoropropan-2-yloxy)pyridin-4-yl]methyl]urea

The title compound was obtained in analogy to Example **5** as a white solid (34% yield) using (2-((1,1,1-trifluoropropan-2-yl)oxy)pyridin-4-yl)methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 386.1 [M+H]+.

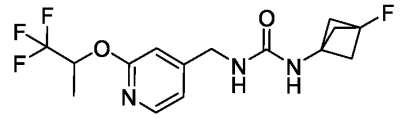
Example 222: 1-(7,7-difluoro-3-bicyclo[4.1.0]heptanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a cream solid (53.2% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 7,7-difluorobicyclo[4.1.0]heptan-3-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 348.1 [M+H]+.

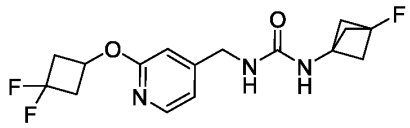
Example 223: 1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(1,1,1-trifluoropropan-2-yloxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (28.8% yield) using (2-((1,1,1-trifluoropropan-2-yl)oxy)pyridin-4-yl)methanamine, 3-fluorobicyclo[1.1.1]pentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 348.1 [M+H]+.

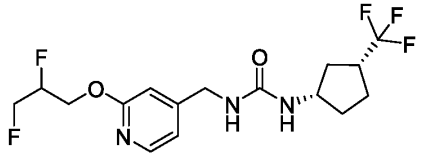
Example 224: 1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea



The title compound was obtained in analogy to Example **5** as a white solid (28.8% yield) using [2-(3,3-difluorocyclobutoxy)pyridin-4-yl]methanamine dihydrochloride, 3-fluorobicyclo[1.1.1]pentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 342.1 [M+H]+.

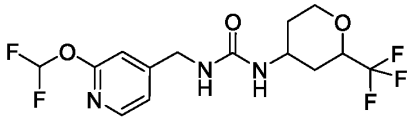
Example 225: 1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (68.2% yield) using (2-(2,3-difluoropropoxy)pyridin-4-yl)methanamine, (1S,3R)-3-(trifluoromethyl)cyclopentan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 382.2 [M+H]+.

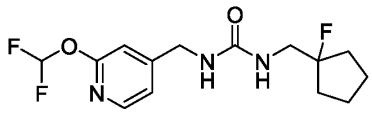
Example 226: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(trifluoromethyl)oxan-4-yl]urea



The title compound was obtained in analogy to Example **7** as a cream gum (54.5% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 2-(trifluoromethyl)oxan-4-amine and para-nitrophenyl chloroformate.

MS (m/z): 370.1 [M+H]+.

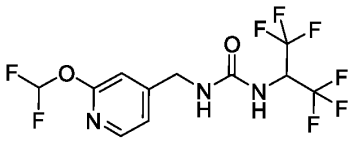
Example 227: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclopentyl)methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (65.0% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1-fluorocyclopentyl)methanamine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 318.1 [M+H]+.

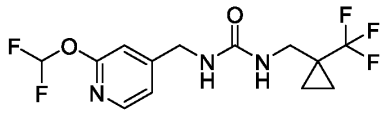
Example 228: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea



The title compound was obtained in analogy to Example **7** as a white solid (1.2% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1,1,1,3,3,3-hexafluoropropan-2-amine and para-nitrophenyl chloroformate.

MS (m/z): 368.1 [M+H]+.

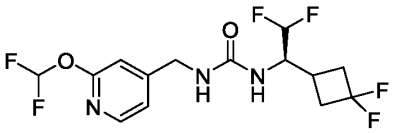
Example 229: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (69.0% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, [1-(trifluoromethyl)cyclopropyl]methanamine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 340.1 [M+H]+.

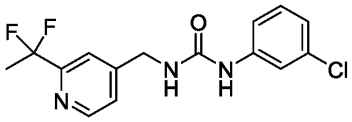
Example 230: 1-[(1R)-1-(3,3-difluorocyclobutyl)-2,2-difluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (54.1% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1R)-1-(3,3-difluorocyclobutyl)-2,2-difluoroethanamine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 372.1 [M+H]+.

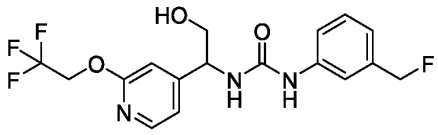
Example 231: 1-(3-chlorophenyl)-3-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (58.9% yield) using [2-(1,1-difluoroethyl)pyridin-4-yl]methanamine and 3-chlorophenyl isocyanate.

MS (m/z): 326.1 [M+H]+.

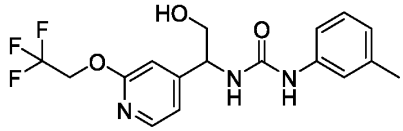
Example 232: 1-[3-(fluoromethyl)phenyl]-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea



The title compound was obtained in analogy to Example 7 as a white solid (74.9% yield) using 2-amino-2-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethanol, 3-(fluoromethyl)aniline and para-nitrophenyl chloroformate.

MS (m/z): 388.1 [M+H]+.

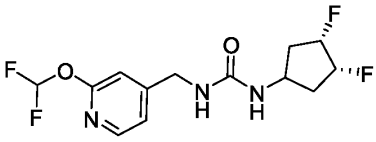
Example 233: 1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-(3-methylphenyl)urea



The title compound was obtained in analogy to Example 7 as a white solid (43.1% yield) using 2-amino-2-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethanol, m-toluidine and para-nitrophenyl chloroformate.

MS (m/z): 370.1 [M+H]+.

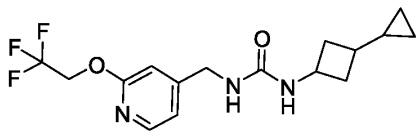
Example 234: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(3R,4S)-3,4-difluorocyclopentyl]urea



The title compound was obtained in analogy to Example 7 as a white solid (61.4% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(3R,4S)-3,4-difluorocyclopentan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 322.1 [M+H]+.

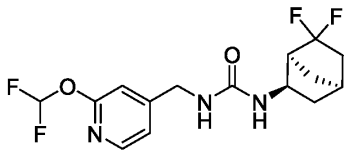
Example 235: 1-(3-cyclopropylcyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (84.5% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, 3-cyclopropylcyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 344.2 [M+H]+.

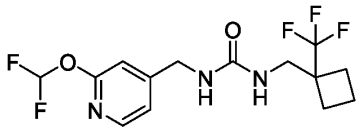
Example 236: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S)-6,6-difluoro-2-bicyclo[2.2.1]heptanyl]urea



To a solution of rac-(1R,2S,4R)-6,6-difluorobicyclo[2.2.1]heptane-2-carboxylic acid (105 mg, 0.6 mmol) in Toluene (2 mL), was added triethylamine (0.09 mL, 0.63 mmol) followed by diphenyl phosphoryl azide (0.14 mL, 1.28 g/mL, 0.63 mmol). The reaction vessel was flushed with N_2 and heated at relfux for 2h, then allowed to cool. A solution of 1-[2-(difluoromethoxy)pyridin-4-yl]methanamine (114.18 mg, 0.66 mmol) in DCM (0.5 mL) was then added followed by further triethylamine (0.09 mL, 0.63 mmol). The reaction was stirred at RT o/n., then concentrated in vacuo to afford a crude oil (450mg), which was dissolved in DMSO (4ml) and purified by preparative HPLC chromatography to afford the desired product as a white solid (136 mg, 0.39 mmol, 65.7% yield).

MS (m/z): 348.1 [M+H]+.

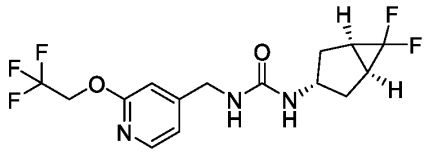
Example 237: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclobutyl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (48.2% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, [1-(trifluoromethyl)cyclobutyl]methanamine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 354.1 [M+H]+.

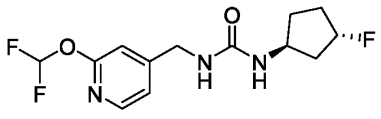
Example 238: 1-[(1R,3s,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (86.0% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, (1R,3s,5S)-6,6-difluorobicyclo[3.1 0]hexan-3-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 366.1 [M+H]+.

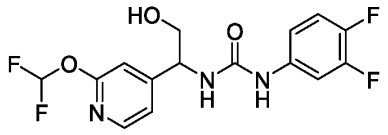
Example 239: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-fluorocyclopentyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (41.4% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1S,3S)-3-fluorocyclopentan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 304.1 [M+H]+.

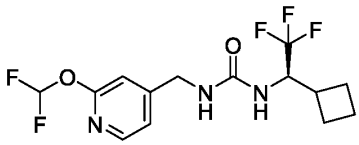
Example 240: 1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea



The title compound was obtained in analogy to Example **4** as a white solid (47.7% yield) using 2-amino-2-[2-(difluoromethoxy)pyridin4-yl]ethanol and 1,2-difluoro-4-isocyanatobenzene.

MS (m/z): 360.1 [M+H]+.

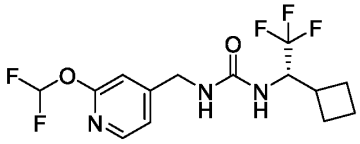
Example 241: 1-[(1R)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained by chiral HPLC separation of Example **152** (29% yield, 100%ee) as a white solid (Amylose 1 column in 55:45 water:MeCN).

MS (m/z): 354.1 [M+H]+.

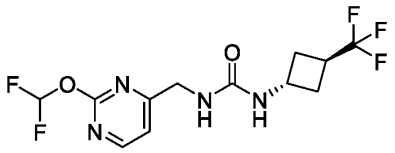
Example 242: 1-[(1S)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound is the other enantiomer obtained by chiral HPLC separation of Example **152** (30% yield, 100%ee) as a white solid (Amylose 1 column in 55:45 water:MeCN).

MS (m/z): 354.1 [M+H]+.

Example 243: 1-[[2-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



a) 4-(bromomethyl)-2-difluoromethoxy)pyrimidine

2-(difluoromethoxy)-4-methylpyrimidine (1.05 g (95%), 6.23 mmol) was dissolved in carbon tetrachloride (24 mL) then treated with N-bromosuccinimide (1.22 g, 6.85 mmol) then benzoyl peroxide (100.6 mg (75%), 311.48 µmol) and heated at 80°C for 16h under N_2. The reaction was heated for a further 24h. The reaction was then cooled to rt, diluted with 40ml sat $NaHCO_3$ and extracted with 40ml DCM. The aqueous layer was then extracted with 40ml EtOAc and the combined organics were then dried over $MgSO_4$ and concentrated in vacuo. The crude was dry-loaded onto silica and purified by silica gel chromatography (eluting with 1:1 Heptane:DCM) to afford the desired product (453.9 mg, 1.9 mmol, 30.5% yield).

MS (m/z): 241 [M+H]+.

b) [2-(difluoromethoxy)pyrimidin-4-yl]methanamine

4-(bromomethyl)-2-(difluoromethoxy)pyrimidine (453.9 mg, 1.9 mmol) was dissolved in 7M Ammonia in MeOH (40.7 mL, 7M , 284.85 mmol), sealed and stirred at rt for 16h. The reaction

was concentrated in vacuo. The crude was diluted with 20ml of 10% NH_4OH and extracted with 2x30ml EtOAc. The organics were washed with a further 10ml 10% NH_4OH, dried over $MgSO_4$ and concentrated in vacuo. The crude was dry-loaded onto silica and purified by silica gel chromatography (eluting with 15:1 DCM:1.75M NH3 in MeOH) to afford the product (173.5 mg, 0.99 mmol, 52.2% yield) as a red liquid.

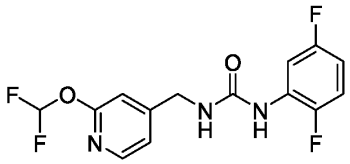
MS (m/z): 176 [M+H]+.

c) 1-[[2-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea

The title compound was obtained in analogy to Example **7** as a white solid (58.3% yield) using [2-(difluoromethoxy)pyrimidin-4-yl]methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 341.1 [M+H]+.

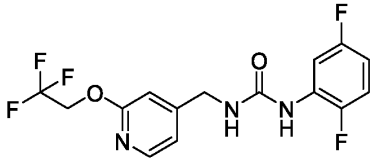
Example 244: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,5-difluorophenyl)urea



The title compound was obtained in analogy to Example **4** as a white solid (77.1% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine and 1,4-difluoro-2-isocyanatobenzene.

MS (m/z): 330.1 [M+H]+.

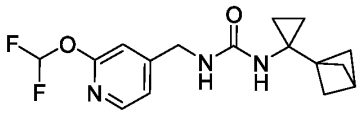
Example 245: 1-(2,5-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (81.4% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine and 1,4-difluoro-2-isocyanatobenzene.

MS (m/z): 362.1 [M+H]+.

Example 246: 1-[1-(1-bicyclo[1.1.1]pentanyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



a) N,N-dibenzyl-3-bromobicyclo[1.1.1]pentane-1-carboxamide

A solution of bromine (5.72 g, 35.78 mmol) in dibromomethane (40 mL) was added dropwise to a vigorously stirred solution of 3-(dibenzylcarbamoyl)bicyclo[1.1.1]pentane-1-carboxylic acid (8 g, 23.85 mmol) in boiling dibromomethane (100 ml) in the presence of HgO (5.68 g, 26.24 mmol). The mixture was boiled for 3 h, cooled to room temperature, the separated precipitate was filtered off and washed with dibromomethane (2 × 10 ml). Dibromomethane was distilled off in a vacuum, the residue was treated with boiling hexane (4 × 75 ml), hexane was evaporated in a vacuum and the residue was purified by silica gel chromatography (eluting with 10% ethyl acetate: petroleum ether) to give the product (4 g, 45.3% yield) as a light yellowish solid.

MS (m/z): 370.1 [M+H]+.

b) N,N-dibenzylbicyclo[1.1.1]pentane-1-carboxamide

To a stirred solution of N,N-dibenzyl-3-bromobicyclo[1.1.1]pentane-1-carboxamide (4.0 g, 10.80 mmol) and Tri-n-butyltin hydride (3.77 g, 12.96 mmol) in Toluene (80 mL) was added AIBN (0.89 g, 5.40 mmol). The mixture was stirred overnight at 110°C. Upon completion of reaction, the organic solvent was removed under vacuum. Water was added and the mixture was extracted with DCM (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by reverse phase

chromatography (eluting with 50-100% acetonitrile in water (0.1% FA) to give the product (2.2 g, 69.9% yield) as a colorless oil.

MS (m/z): m/z = 292.2 [M+H]+.

c) N,N-dibenzyl-1-(bicyclo[1.1.1]pentan-1-yl)cyclopropan-1-amine

To a solution of tetraethoxytitanium (2.58 g, 11.33 mmol) in THF (30 mL) at -78°C under nitrogen atmosphere was added ethylmagnesium bromide (8.39 mL, 15.1 mmol). A solution of N,N-dibenzylbicyclo[1.1.1]pentane-1-carboxamide (2.2 g, 7.55 mmol) in THF (30 mL) was then added. The mixture was warmed to room temperature and stirred for 2 hours. Upon completion of reaction, the mixture was diluted with EtOAc (200 mL) and filtrated through a silica gel column (washed with 500 mL of EtOAc). The filtrate was concentrated under vacuum. The residue was purified by reverse phase HPLC (eluting with 50-100% acetonitrile in water (0.1% NH_4HCO_3) to give the product (600 mg, 26.2% yield) as colorless oil.

MS (m/z): m/z = 304.2 [M+H]+.

d) 1-(bicyclo[1.1.1]pentan-1-yl)cyclopropan-1-amine

To a solution of N,N-dibenzyl-1-(bicyclo[1.1.1]pentan-1-yl)cyclopropan-1-amine (800 mg, 2.64 mmol) in THF (10 mL) and MeOH (10 mL) at 0°C was added 10% Pd/C (600 mg, 0.56 mmol) and the mixture was stirred at 10°C for 2 hours. Upon completion of reaction, the catalyst was filtrated out and washed with THF (3 x 10 mL). The filtrate was concentrated under vacuum at 0~10°C to give the crude product (250 mg, 30.8% yield), which was used without further purification.

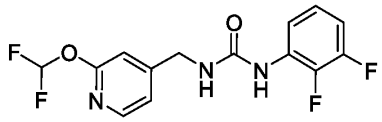
MS (m/z): m/z = 124.1 $[M+H]^+$.

e) 1-[1-(1-bicyclo[1.1.1]pentanyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea

The title compound was obtained in analogy to Example **7** as a white solid (9% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 1-(bicyclo[1.1.1]pentan-1-yl)cyclopropan-1-amine, and para-nitrophenyl chloroformate.

MS (m/z): 324.2 [M+H]+.

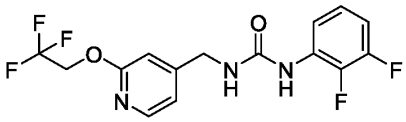
Example 247: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3-difluorophenyl)urea



The title compound was obtained in analogy to Example **4** as a white solid (88.1% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine and 1,2-difluoro-3-isocyanatobenzene.

MS (m/z): 330.1 [M+H]+.

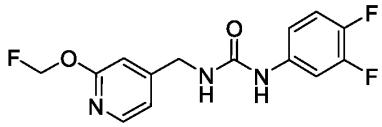
Example 248: 1-(2,3-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (76.3% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine and 1,2-difluoro-3-isocyanatobenzene.

MS (m/z): 362.1 [M+H]+.

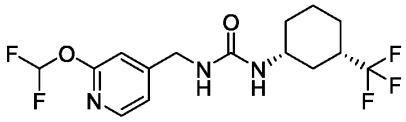
Example 249: 1-(3,4-difluorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (64.3% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine and 1,2-difluoro-4-isocyanatobenzene.

MS (m/z): 312.1 [M+H]+.

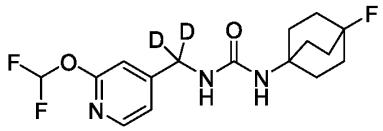
Example 250: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea



The title compound was obtained by chiral HPLC separation of Example **138** (22.3% yield, 100%de) as a white solid (Amylose 1 column in 55:45 water:MeCN).

MS (m/z): 368.1 [M+H]+.

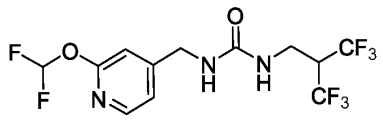
Example 251: 1-[dideuterio-[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea



The title compound was obtained in analogy to Example **85** as a white solid using 4-bromo-2-(difluoromethoxy)pyridine, ((tertbutoxycarbonyl)amino)($^2H_2$)acetic acid, 4-fluorobicyclo[2.2.2]octan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 346.2 [M+H]+.

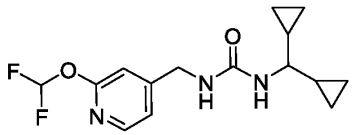
Example 252: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (38.1% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 2-(aminomethyl)-1,1,1,3, 3,3-hexafluoropropane and para-nitrophenyl chloroformate.

MS (m/z): 382.1 [M+H]+.

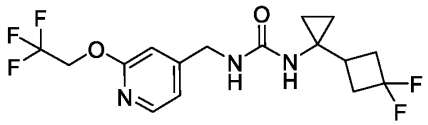
Example 253: 1-(dicyclopropylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (77.6% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, dicyclopropylmethanamine and para-nitrophenyl chloroformate.

MS (m/z): 312.2 [M+H]+.

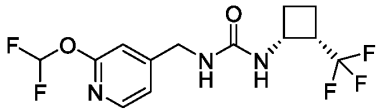
Example 254: 1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (81.7% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, 1-(3,3-difluorocyclobutyl)cyclopropan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 380.1 [M+H]+.

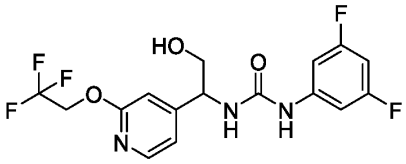
Example 255: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (44.2% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,2S)-2-(trifluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 340.1 [M+H]+.

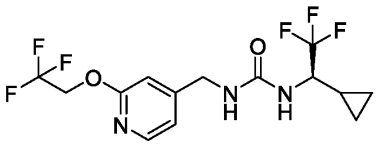
Example 256: 1-(3,5-difluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (19.4% yield) using 2-amino-2-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethanol hydrochloride and 1,3-difluoro-5-isocyanatobenzene.

MS (m/z): 392 [M+H]+.

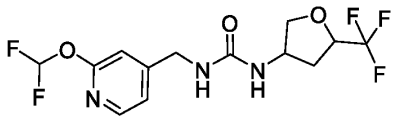
Example 257: 1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (56.6% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, (1R)-1-cyclopropyl-2,2,2-trifluoroethanamine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 372.2 [M+H]+.

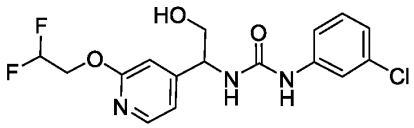
Example 258: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[5-(trifluoromethyl)oxolan-3-yl]urea



The title compound was obtained in analogy to Example **7** as a white solid (72.9% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 5-(trifluoromethyl)oxolan-3-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 356.1 [M+H]+.

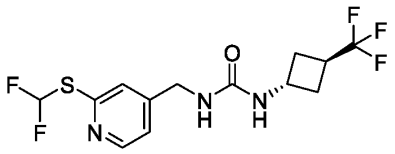
Example 259: 1-(3-chlorophenyl)-3-[1-[2-(2,2-difluoroethoxy)pyridin-4-yl]-2-hydroxyethyl]urea



The title compound was obtained in analogy to Example **85** as a white solid using 4-bromo-2-(2,2-difluoroethoxy)pyridine, N-Boc-O-benzyl-L-serine, and 3-chlorophenyl isocyanate.

MS (m/z): 372.1 [M+H]+.

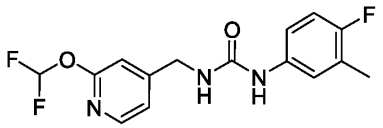
Example 260: 1-[[2-(difluoromethylsulfanyl)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (34% yield) using (2-((difluoromethyl)thio)pyridin-4-yl)methanamine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 356.1 [M+H]+.

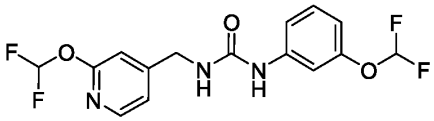
Example 261: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-3-methylphenyl)urea



The title compound was obtained in analogy to Example **4** as a white solid (66.8% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine and 1-fluoro-4-isocyanato-2-methylbenzene.

MS (m/z): 326.1 [M+H]+.

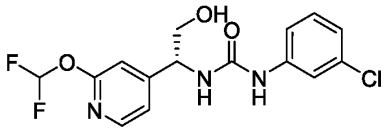
Example 262: 1-[3-(difluoromethoxy)phenyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (74.9% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine and 1-(difluoromethoxy)-3-isocyanatobenzene.

MS (m/z): 360.1 [M+H]+.

Example 263: rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea



a) rel-(2R)-2-[(tertbutoxycarbonyl)amino]-2-[2-(difluoromethoxy)pyridin-4-yl]ethyl (2R)-3,3,3-trifluoro-2-methoxy-2- phenylpropanoate

(2S)-(+)-2-Methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride (0.54 mL, 1.35 g/mL, 2.89 mmol) was added to a solution of tert-butyl N-(1-(2-(difluoromethoxy)pyridin-4-yl)-2-hydroxyethyl)carbamate (800 mg, 2.63 mmol), DIPEA (0.92 mL, 5.26 mmol) and DMAP (64.24 mg, 0.53 mmol) in dry DCM (25 mL) under N_2 and stirred for 2 h. The reaction was then diluted

in water and product was extracted with DCM (x3), and organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and concentrated. The crude was purified by silica gel chromatography (eluting with 0 to 40% Ethyl Acetate in Heptane) to give 2-[(tert-butoxycarbonyl)amino]-2-[2-(difluoromethoxy)pyridin-4-yl]ethyl (2R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (1.1 g, 2.11 mmol, 80.4% yield) as a colourless oil. Further purification by chiral HPLC separation (Amylose 1 column in 55:45 water:MeCN) gave the title compound as a colorless oil (31.8% yield, 95%ee).

MS (m/z): 521.4 [M+H]+.

b) tert-butyl N-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]carbamate

Potassium hydroxide (75.45 mg, 1.34 mmol) was added to a solution of rel-(2R)-2-[(tertbutoxycarbonyl)amino]-2-[2-(difluoromethoxy)pyridin4-yl]ethyl (2R)-3,3,3-trifluoro-2-methoxy-2- phenylpropanoate (350 mg, 0.67 mmol) in Methanol (6 mL) and stirred at rt for 2 h. The reaction was then quenched with 10% NH_3 (aq) 40 mL and product was extracted with EtOAc (60 mL x 3), and organic layers were combined, washed with brine, dried with $MgSO_4$, filtered and concentrated. The crude was purified by silica gel chromatography (eluting with 0 to 100% Ethyl Acetate in Heptane) to give the title product as a colorless oil.

MS (m/z): 305.2 [M+H]+.

c) rel-(2R)-2-amino-2-[2-(difluoromethoxy)pyridin-4-yl]ethanol

Trifluoroacetic acid (0.15 mL, 1.97 mmol) was added to a solution of tert-butyl N-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]carbamate (120 mg, 0.39 mmol) in DCM (2 mL) and stirred at rt overnight. The reaction was then loaded onto an SCX cartridge and washed with DCM/MeOH. The product was washed off with DCM/ 7 N NH3 in MeOH. The basic fraction was concentrated to obtain the title product (60 mg, 0.29 mmol, 74.5% yield) as a colorless oil.

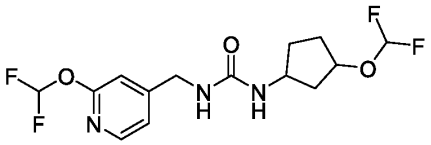
MS (m/z): 205.2 [M+H]+.

d) rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea

The title compound was obtained in analogy to Example **4** as a white solid (38.0% yield) using rel-(2R)-2-amino-2-[2-(difluoromethoxy)pyridin-4-yl]ethanol and 3-chlorophenyl isocyanate.

MS (m/z): 358.1 [M+H]+.

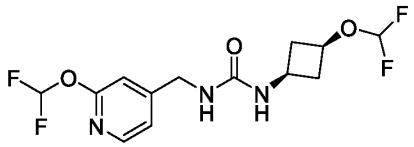
Example 264: 1-[3-(difluoromethoxy)cyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (77.8% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3-(difluoromethoxy)cyclopentan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 352.1 [M+H]+.

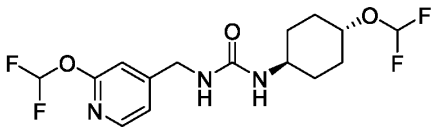
Example 265: 1-[(1s,3s)-3-(difluoromethoxy)cyclobutyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (63.3% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1s,3s)-3-(difluoromethoxy)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 338.1 [M+H]+.

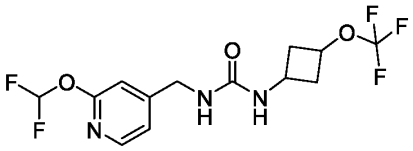
Example 266: 1-[(1r,4r)-4-(difluoromethoxy)cyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (77.6% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1r,4r)-4-(difluoromethoxy)cyclohexan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 366.1 [M+H]+.

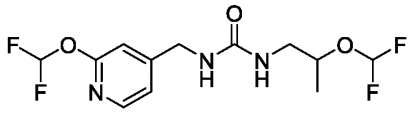
Example 267: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethoxy)cyclobutyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (76.9% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 3-(trifluoromethoxy)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 356.1 [M+H]+.

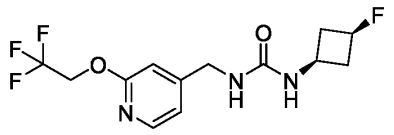
Example 268: 1-[2-(difluoromethoxy)propyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (74.8% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 2-(difluoromethoxy)propan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 326.1 [M+H]+.

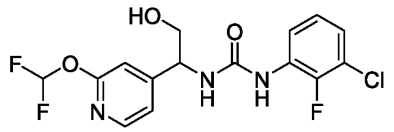
Example 269: 1-((1s,3s)-3-fluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (77.7% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, (1s,3s)-3-fluorocyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 322.1 [M+H]+.

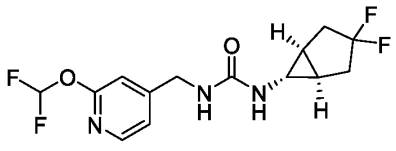
Example 270: 1-(3-chloro-2-fluorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (53.2% yield) using 2-amino-2-[2-(difluoromethoxy)pyridin-4-yl]ethanol hydrochloride and 1-chloro-2-fluoro-3-isocyanatobenzene.

MS (m/z): 376.1 [M+H]+.

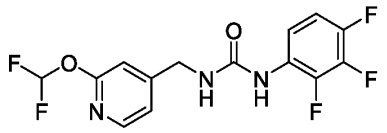
Example 271: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-3,3-difluoro-6-bicyclo[3.1.0]hexanyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (70.0% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, rac-(1R,5S,6R)-3,3-difluorobicyclo[3.1.0]hexan-6-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 334 [M+H]+.

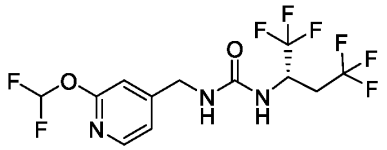
Example 272: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3,4-trifluorophenyl)urea



The title compound was obtained in analogy to Example **4** as a white solid (91.1% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine and 1,2,3-trifluoro-4-isocyanatobenzene.

MS (m/z): 348.1 [M+H]+.

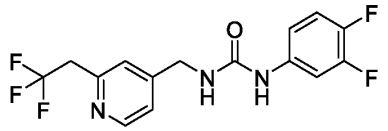
Example 273: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea



The title compound was obtained in analogy to Example **4** as a white solid (6.0% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine and (2S)-1,1,1,4,4,4- hexafluoro-2-isocyanatobutane.

MS (m/z): 382.1 [M+H]+.

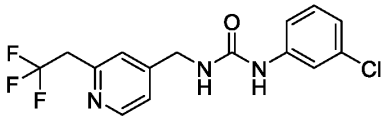
Example 274: 1-(3,4-difluorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (84% yield) using (2-(2,2,2-trifluoroethyl)pyridin-4-yl)methanamine and 1,2-difluoro-4-isocyanatobenzene.

MS (m/z): 346.1 [M+H]+.

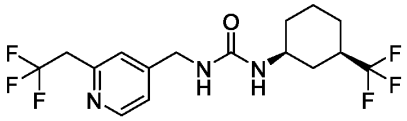
Example 275: 1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (74.2% yield) using (2-(2,2,2-trifluoroethyl)pyridin-4-yl)methanamine and 3-chlorophenyl isocyanate.

MS (m/z): 344.1 [M+H]+.

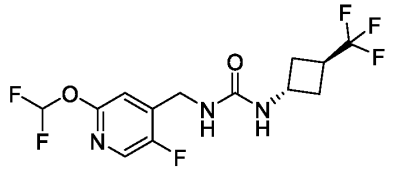
Example 276: 1-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (77.8% yield) using (2-(2,2,2-trifluoroethyl)pyridin-4-yl)methanamine, rac-(1R,3S)-3-(trifluoromethyl)cyclohexan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 384.2 [M+H]+.

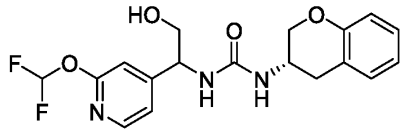
Example 277: 1-[[2-(difluoromethoxy)-5-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **85** using 4-bromo-2- (difluoromethoxy)-5-fluoropyridine, Boc-Gly-OH, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine and para-nitrophenyl chloroformate.

MS (m/z): 358.1 [M+H]+.

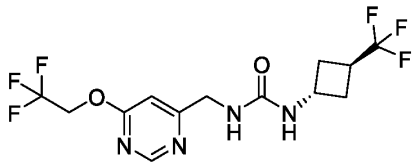
Example 278: rel-1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(3S)-3,4-dihydro-2H-chromen-3-yl]urea



1-(chroman-3-yl)-3-(1-(2-(difluoromethoxy)pyridin-4-yl)-2-hydroxyethyl)urea was obtained in analogy to Example **7** as a white solid (17.0% yield) using 2-amino-2-[2-(difluoromethoxy)pyridin-4-yl]ethanol hydrochloride, 3,4-dihydro-2H-1-benzopyran-3-amine and para-nitrophenyl chloroformate. Chiral HPLC separation (Cellulose-4 column in 55:45 water:MeCN) gave the title compound as a white solid (41.7% yield).

MS (m/z): 380.1 [M+H]+.

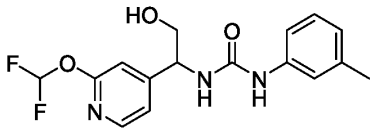
Example 279: 1-[[6-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (71.6% yield) using [6-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methanamine hydrochloride, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 373.1 [M+H]+.

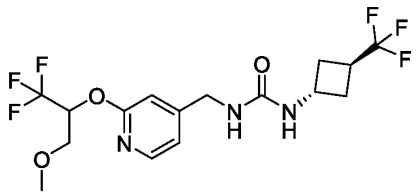
Example 280: 1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea



The title compound was obtained in analogy to Example **4** as a white solid (56.9% yield) using 2-amino-2-[2-(difluoromethoxy)pyridin-4-yl]ethanol hydrochloride and 1-isocyanato-3-methylbenzene.

MS (m/z): 338.2 [M+H]+.

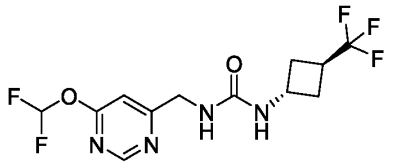
Example 281: 1-[[2-(1,1,1-trifluoro-3-methoxypropan-2-yl)oxypyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **221** as a white solid using 1,1,1-trifluoro-3-methoxypropan-2-ol, 2-chloroisonicotinonitrile, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 416 [M+H]+.

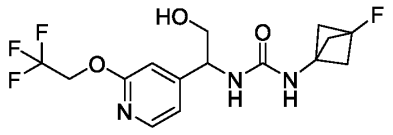
Example 282: 1-[[6-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **243** using 4-(difluoromethoxy)-6-methylpyrimidine, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 341 [M+H]+.

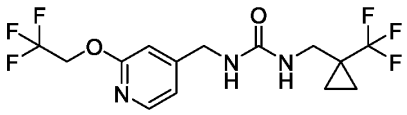
Example 283: 1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea



The title compound was obtained in analogy to Example **5** as a white solid (48.5% yield) using 2-amino-2-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethanol hydrochloride, 3-fluorobicyclo[1.1.1]pentan-1-amine hydrochloride and 1,1'-carbonyldiimidazole.

MS (m/z): 364.1 [M+H]+.

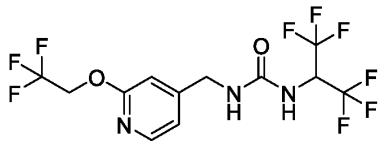
Example 284: 1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (85.3% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, [1-(trifluoromethyl)cyclopropyl] methanamine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 372.1 [M+H]+.

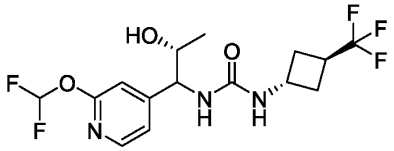
Example 285: 1-(1,1,1,3,3,3-hexafluoropropan-2-yl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **4** as a white solid (95.8% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine and 1,1,1,3,3,3-hexafluoro-2-isocyanatopropane.

MS (m/z): 400.1 [M+H]+.

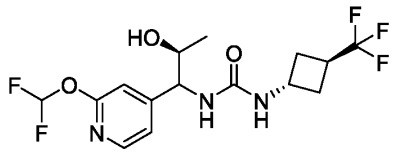
Example 286: 1-[(2R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **85** as a white solid using 4-bromo-2-(difluoromethoxy)pyridine, (2S,3R)-3-(benzyloxy)-2-[(tertbutoxycarbonyl)amino]butanoic acid, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 384.2 [M+H]+.

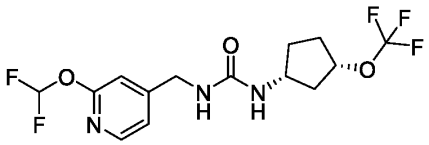
Example 287: 1-[(2S)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea



The title compound was obtained in analogy to Example **85** as a white solid using 4-bromo-2-(difluoromethoxy)pyridine, (2R,3S)-3-(benzyloxy)-2-[(tertbutoxycarbonyl)amino]butanoic acid, (1r,3r)-3-(trifluoromethyl)cyclobutan-1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 384.2 [M+H]+.

Example 288: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethoxy)cyclopentyl]urea



a) tert-butyl N-[(1S,3R)-3-(trifluoromethoxy)cyclopentyl]carbamate

Tert-butyl ((1S,3R)-3-hydroxycyclopentyl)carbamate (50 mg, 0.25 mmol), silver trifluoromethanesulfonate (191.5 mg, 0.75 mmol), 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (264.03 mg, 0.75 mmol) and potassium fluoride (57.73 mg, 0.99 mmol) were added to two 8 mL vial and then purged under N_2. Dry Ethyl Acetate (3 mL) was then added followed by trifluoromethyltrimethylsilane (0.11 mL, 0.96 g/mL, 0.75 mmol) and 2-fluoropyridine (0.06 mL, 1.12 g/mL, 0.75 mmol). The two vials were stirred under N_2 (one 24 h and the other for 48 h). The two vials were quenched in air, then combined and diluted in EtOAC. The reaction mixture was filtered through celite, and washed with EtOAc. The crude was purified by silica gel flash chromatography (eluting with 0 to 100% Ethyl Acetate in Heptane) to give the title product (200 mg, 0.74 mmol) as an orange solid.

b) (1R,3S)-3-(trifluoromethoxy)cyclopentan-1-amine hydrochloride

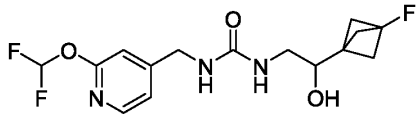
HCl (4M in Dioxane) (1.86 mL, 7.43 mmol) was added to a solution of tert-butyl N-[(1R,3S)-3-(trifluoromethoxy)cyclopentyl]carbamate (200 mg, 0.74 mmol) in Ethyl Acetate (8 mL) and stirred at rt overnight. A couple of drops of cold diethyl ether was then added to the suspension, which was then filtered under vacuum. The solid was then washed with more cold diethyl ether to obtain the title product (55 mg, 0.27 mmol, 36.0% yield) as an off-white solid.

c) 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethoxy)cyclopentyl] urea

The title compound was obtained in analogy to Example **7** as a white solid (54.9% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (1R,3S)-3-(trifluoromethoxy)cyclopentan1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 384.2 [M+H]+.

Example 289: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]urea



a) 3-fluoro-N-methoxy-N-methylbicyclo[1.1.1]pentane-1-carboxamide

A solution of 3-fluorobicyclo[1.1.1]pentane-1-carboxylic acid (2 g, 15.37 mmol) in DCM (32 mL) under N_2 was cooled to 0C. DMF (0.16 mL) was added followed by oxalyl chloride in DCM (11.53 mL (2M), 23.06 mmol) slowly dropwise. After addition was complete, the reaction mixture was allowed to warm to RT and stirred for 1h. It was then cooled to 0°C. and a solution of N,O-Dimethylhydroxylamine hydrochloride (2.25 g, 23.06 mmol) and DIPEA (4.02 mL, 23.06 mmol) in DCM (16 mL) was then added and the mixture allowed to warm to RT o/n. $NaHCO_3$ sol. (60ml) was added and extracted with DCM (60ml). Dried ($MgSO_4$) organic layer and concentrated in vacuo to afford a crude liquid, which was purified by silica gel chromatography

eluting with 30% EtOAc/pentane in pentane to afford the desired product as a pale yellowish liquid (2.06 g, 11.89 mmol, 77.4% yield).

MS (m/z): 174 [M+H]+.

b) 1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-2-nitroethanol

A solution of 3-fluoro-N-methoxy-N-methylbicyclo[1.1.1]pentane-1-carboxamide (440 mg, 2.54 mmol) in diethyl ether (6.5 mL) was cooled to 0°C under N_2. Lithium aluminum hydride (2.54 mL, 1M in THF, 2.54 mmol) was added dropwise. Stirred for 1 h at 0°C. To quench, 0.1ml water was added followed by 0.1ml 2N NaOH and 0.3 ml water. Stirred for 10min. Added 700mg $MgSO_4$ and filtered to afford a solution of aldehyde intermediate. In another flask Nitromethane (6.92 mL, 1.12 g/mL, 127.03 mmol) was cooled to 0C and treated with potassium tert-butoxide (42.76 mg, 0.38 mmol). The aldehyde solution was then added to this slowly. The reaction was stirred at 0°C for 1h then warmed to room temperature and stirred for 16 h. The solution was concentrated in vacuo. After careful evaporation at 40 mbar (30°C bath), the crude material was dissolved in a minimum of DCM and purified by silica gel chromatography (eluting with DCM) to afford the desired product as a colorless liquid (330 mg, 1.88 mmol, 74.2% yield).

MS (m/z): 174 [M-H]-.

c) 2-amino-1-(3-fluorobicyclo[1.1.1]pentan-1-yl)ethan-1-ol

To a solution of 1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-2-nitroethanol (330 mg, 1.88 mmol) in diethyl ether (5 mL) under N_2 at 0°C , lithium aluminum hydride (4.71 mL, 1M in THF, 4.71 mmol) was added dropwise. Allowed to warm to RT and left to stir o/n. The reaction mixture was cooled to 0°C and 1eq of $LiAlH_4$ was added, and the reaction was allowed to warm to RT. After 4 h it was cooled to 0°C and was added sequentially water (0.25ml), 15% NaOH (0.25ml) and water 0.75ml and stirred at 0°C for 5 mins. The reaction was treated with 700mg of $MgSO_4$ and stirred vigorously for 10 mins at RT then filtered through a pad of celite. The pad was washed with Et_2O and the combined filtrates were treated with HCl (4M in Dioxane) (2.68 mL (4M), 10.74 mmol) and stirred

for 10mins. This was concentrated in vacuo and azeotroped with toluene to afford the desired product as its HCl salt (200 mg, 1.1 mmol, 58.4% yield).

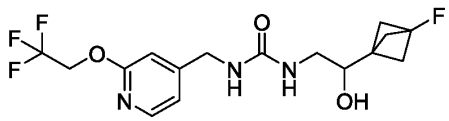
MS (m/z): 146 [M+H]+.

d) 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]urea

The title compound was obtained in analogy to Example **7** as a colorless gum (41.6% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 2-amino-1-(3-fluorobicyclo[1.1.1]pentan-1-yl)ethanol hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 346.1 [M+H]+.

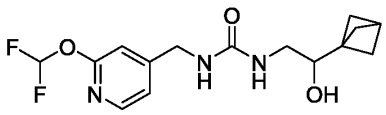
Example 290: 1-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a colorless solid (38.5% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, 2-amino-1-(3-fluorobicyclo[1.1.1]pentan-1-yl)ethanol hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 378.1 [M+H]+.

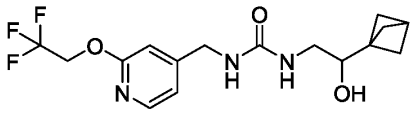
Example 291: 1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **289** as a colorless gum (42.1% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, 2-amino-1-(bicyclo[1.1.1]pentan-1-yl)ethanol hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 328.1 [M+H]+.

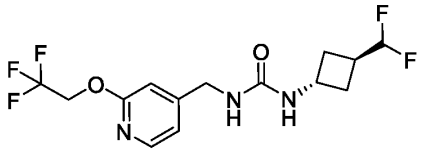
Example 292: 1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a colorless gum (42.9% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, 2-amino-1-(bicyclo[1.1.1]pentan-1-yl)ethanol hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 360.2 [M+H]+.

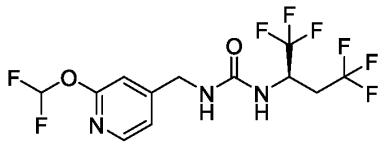
Example 293: 1-[(1r,3r)-3-(difluoromethyl)cyclobutyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea



The title compound was obtained in analogy to Example **7** as a white solid (83.0% yield) using (2-(2,2,2-trifluoroethoxy)pyridin-4-yl)methanamine, (1r,3r)-3-(difluoromethyl)cyclobutan1-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 354.1 [M+H]+.

Example 294: 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea



a) (*S*)-2-methyl-*N*-(3,3,3-trifluoropropylidene)propane-2-sulfinamide

A solution of 3,3,3-trifluoropropanal (1.8 g, 16.5 mmol) in THF (10 mL) was treated with (*S*)-2-methylpropane-2-sulfinamide (2 g, 16.5 mmol) and $Ti(OEt)_4$ (7.5 g, 33 mmol) under nitrogen atmosphere. The mixture was stirred for 1 h at 80°C. The resulting mixture was filtered, and the filter cake was washed with EtOAc (200 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluting with petroleum ether / EtOAc (1:2) to afford the desired product (1 g, 28% yield) as a yellow solid.

MS (m/z): 216 [M+H]+.

b) (*S*)-*N*-[(2*R*)-1,1,1,4,4,4-hexafluorobutan-2-yl]-2-methylpropane-2-sulfinamide

A solution of (*S*)-2-methyl-*N*-(3,3,3-trifluoropropylidene)propane-2-sulfinamide (1 g, 4.65 mmol) in THF (10 mL) was treated with TMAF (0.65 g, 6.969 mmol) at 25C under nitrogen atmosphere followed by the addition of $TMSCF_3$ (0.99 g, 6.97 mmol) at -55°C. The mixture was allowed to warm to RT and stirred overnight. The resulting mixture was extracted with EtOAc (10 ml). The combined organic layers were washed with water (10 ml), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluting with petroleum ether/EtOAc 1:1) to afford the desired product (100 mg, 7.6% yield) as a yellow solid.

MS (m/z): 286 [M+H]+.

c) (2*R*)-1,1,1,4,4,4-hexafluorobutan-2-amine

A solution of (*S*)-*N*-[(2*R*)-1,1,1,4,4,4-hexafluorobutan-2-yl]-2-methylpropane-2-sulfinamide (100 mg, 0.35 mmol) in HCl (gas) in Et_2O (5 mL) was stirred for 3 h at 25°C under nitrogen

atmosphere. The resulting mixture was concentrated under vacuum. The crude product was used in the next step directly without further purification.

MS (m/z): 182 [M+H]+.

d) 1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea

The title compound was obtained in analogy to Example **7** as a white solid (15.5% yield) using (2-(difluoromethoxy)pyridin-4-yl)methanamine, (2*R*)-1,1,1,4,4,4-hexafluorobutan-2-amine hydrochloride and para-nitrophenyl chloroformate.

MS (m/z): 382.1 [M+H]+.

BIOLOGICAL EXPERIMENTS

The potency of Kv7 potentiators was determined using the SyncroPatch 384 (Nanion) high throughput electrophysiology platform.

Example 295 Cell Culture

CHO cells stably expressing either human Kv7.2, Kv7.4 or Kv7.5/7.3 under a constitutive CMV promoter were used for these studies. Cells were maintained in F12 Hams+1mM L-glutamine (Hyclone) supplemented with 10% FBS (Sigma), 0.3x NEAA (Non-essential Gamino-acids) and 400ug/ml G418 at 37°C in 5% CO_2. Cells were cultured in T-225 flasks (Nunc) for 2-3 days to reach 85-95% confluence prior to electrophysiological recording.

Example 296 Solutions

Solutions were of the following composition:

Earle's balanced salt solution (in mM): 135 NaCl, 5.4 KCl, 5 Glucose, 2 $CaCl_2$, 1 $MgCl_2$, 5 HEPES, pH 7.4. Seal enhancer solution (in mM): 90 NaCl, 3 KCl, 35 $CaCl_2$, 10 $MgCl_2$, 10 HEPES, pH 7.4. Extracellular recording solution (in mM): 71 NaCl, 70 NMDG, 13 KCl, 5

Glucose, 2 $CaCl_2$, 1 $MgCl_2$, 10 HEPES, pH 7.4. Intracellular recording solution (in mM): 130 KF, 20 KCl, 4 EGTA, 10 HEPES, 2 EDTA, 0.01 Escin, pH 7.2.

Example 297 Cell Preparation

Cells were harvested for electrophysiological recording upon reaching appropriate confluence. Cells were first washed in DPBS (Hyclone, Cat #SH30028.03) and then 2 ml of Accutase (MP Biomedicals #1000449) was added at 28°C until ~90% of cells were suspended. F12 HAM's media + 1 mM L-glutamine (Hyclone, SH30026.02) was then added to the flask to dilute the accutase. Cells were then triturated until a single cell suspension was achieved, a cell count was performed, and cells were centrifuged for 2 min. at 1,000 rpm. Media was then aspirated, and cells were resuspended in Earle's balanced salt solution to a concentration of 0.75 X 10^6 cells/ml and allowed to recover for 25 min at 10°C.

Example 298 SyncroPatch Recording

At the beginning of each assay, 20 µl of cell suspension was dispensed into each well of a multi-hole 384-well SyncroPatch chip by the onboard pipettor. Cell sealing was initiated, and seal enhancer solution was added to facilitate seal formation. Upon completion of sealing, cells were washed 3 times with extracellular recording solution and the assay voltage protocol was started. Human Kv7.2, Kv7.4 or Kv7.5/7.3 channels were evaluated using a voltage protocol in which cells were voltage-clamped at a holding potential of -60 mV. Potassium currents were continuously activated with a series of three voltage steps to -30 mV for 3 seconds, 40 mV for 1 second and -90 mV for 4 seconds with 12 seconds between successive voltage sweeps. Potassium currents were measured from the –90 mV repolarizing step. Baseline current was assessed for 3.5 minutes prior to the addition of 5.6 µM zinc pyrithione (1µM for Kv7.4). Kv7.2, Kv7.4 or Kv7.5/7.3 current in the presence of zinc pyrithione was acquired over five minutes to allow channels to reach steady state activity prior to addition of test agents. Channel activity was monitored for three minutes preceding the addition of 30 µM ML-213 (3 minutes) to achieve maximum activation. 150 mM

TEA with 10 μM XE-991 was applied for 2 minutes to measure the leak current during maximum inhibition of Kv7.2, Kv7.4 or Kv7.5/7.3 channels.

Example 299 Data Analysis

Data were collected on the SyncroPatch platform using PatchControl software (Nanion) and processed and analyzed using DataControl Software (Nanion). Percent activation was calculated from potassium current as follows: The average current for the 5 sweeps in the presence of zinc pyrithione immediately preceding test agent addition was taken as the 'control' data. Likewise, the average potassium current in the presence of test agents 5 sweeps immediately preceding addition of 30 μM ML-213 was determined for 'drug' data. The average potassium current 5 sweeps immediately prior to addition of 150 mM TEA + 10 μM XE-991 was determined for 'max activation' data while average currents from 5 sweeps immediately following addition of TEA was determined for 'max inhibition' data. Percent activation for each of the 384-wells of a sealchip was calculated as (('drug' – 'max inhibition')/('max activation' – 'max inhibition'))*100 with Pipeline Pilot (Accelrys). Percent activation was plotted as a function of concentration and concentration-response curves were fitted with a logistic equation {Y is Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))} for determination of the EC_{50} (IDBS ABASE). EC_{50} values for human Kv7.2 are provided in Table 1.

Example 300 Microsomal clearance

Pooled mixed gender human liver microsomes were purchased from BioIVT at a concentration of 20 mg protein/mL and stored at -80°C. Incubations were conducted in V-bottomed 350 μL polypropylene 96-well plates. Compounds were diluted in phosphate buffer (final concentrations 0.5 μM compound, 0.5 % DMSO) and mixed with diluted liver microsomes (fc 0.25 mg/mL). This mixture was aliquoted onto the assay plate (six wells per compound) and pre-warmed at 37°C for ten minutes. Addition of NADPH (fc 0.5mM, final incubation volume 100 μL) to each well started the time course. Reactions were stopped at 0.5, 3, 5, 10, 20 & 30 minutes by addition of 150 μL acetonitrile containing internal standard (IS; 0.125 μg/mL daidzein) and stopped samples were removed to a clean polypropylene plate. At the end of the assay the plate

was refrigerated for an hour and then centrifuged at 3000 rpm for 10 minutes at 4°C. A sample of the supernatant was removed to a fresh plate and diluted 10-fold with 50:50 acetonitrile: water, then heat sealed. Analysis was by liquid chromatography coupled with tandem rmass spectrometry (LC-MS/MS) for analyte and IS levels. Ratios of the analyte and IS peak areas were generated for results calculation (IS ratio). Dextromethorphan and verapamil were included in each experiment as controls for high clearance compounds. IS ratio data were converted into natural log values which were plotted against time and a linear regression fit applied. The slope of the line was returned and converted into the elimination constant (k_{el}) by multiplying by -1. The elimination constant was used to calculate the *in vitro* CL_{int}: *in vitro* CL_{int} (µL/min/mg protein) is k_{el} * (1000/protein conc in mg/mL).

Example 301 Assessment of glutathione (GSH) adduct formation *in vitro* using human liver microsomes

Reagents

All chemicals and reagents used were of the highest quality available. Pooled mixed gender human liver microsomes (HLM) from 150 individuals (UltraPoolTM HLM 150) were purchased from BD Biosciences (Cat. no. 452117, Woburn, MA. USA). Leucine-enkephalin acetate salt hydrate (CAS 81678-16-2), β-nicotinamide adenine dinucleotide phosphate reduced tetrasodium salt (NADPH) (CAS 2646-71-1), diclofenac (CAS 239-346-4), nefazodone (CAS 82752-99-6), and troglitazone (CAS 134308-13-7) were purchased from Sigma-Aldrich.

Incubation of human liver microsomes

All compounds including solvent control were incubated using a 96-deep-well plate (Eppendorf) at 20 µM (addition of 1 µL of 10 mM dimethyl sulfoxide (DMSO) stock solution) in 450 µL of 0.1 M sodium phosphate buffer at pH 7.4 containing human liver microsomes (HLM). Microsomal protein concentration was 1 mg/mL. Pipetting was performed using a pipetting robot. The buffer was prepared at room temperature by combining 2.62 g $NaH_2PO_4.1H_2O$ and 14.43 g $Na_2HPO_4.2H_2O$ dissolved in H_2O (Millipore, >18 MΩ) to a weight of 1000 g (pH 7.4). After 5 min of preincubation at 37 °C the reaction was started by adding 50 µL of buffer containing GSH

(100 mM) and NADPH (20 mM). Fresh stock solutions of GSH and NADPH were prepared straight before each experiment. The final concentrations were 5 mM for GSH and 1 mM for NADPH. After 60 min of incubation at 37 °C (shaking at 800 rpm) the reaction was quenched with 500 µL of ice-cold acetonitrile and centrifuged at 5000 g at 25 °C for 11 min. Before analysis by liquid chromatography/tandem mass spectrometry (LC/MS/MS) the supernatant was split into two fractions, 450 and 400 µL each, followed by evaporation using a nitrogen gas stream at 35 °C to a volume of approximately 150 µL.

Liquid chromatography and mass spectrometry

Chromatographic separation of metabolites was performed on an ACQUITY UPLC system (Waters, Milford, MA, USA) using an ACQUITY UPLC HSS T3 C18 column (2.1 × 50 mm, 1.8 µm). The mobile phases consisted of A: water containing 0.1% formic acid and B: acetonitrile containing 0.1% formic acid. The flow rate was 0.5 mL/min, starting condition was 100% A. The LC gradient started at 1 min and was increased for 3.5 min to 70% B and to 100% B after 4.6 min. After 1.4 min at 100% B the starting conditions were applied and equilibrated for 2.4 min prior to the next injection. Data were acquired in positive ionization mode over the mass range of m/z 98 to 980 using a XEVO G1 QTof mass spectrometer (Waters, Milford, MA, USA) operated with an electrospray ionization (ESI) source. The capillary voltage was 3 kV, the cone voltage 25 V. Two scan functions (MSE mode) were monitored with a scan time of 0.1 s. The collision energy (CE) in function 1 was 6 eV and in function 2 ramped from 10 to 45 eV. Leucine-enkephalin was used as a lock mass (m/z 556.2771) for internal calibration at a concentration of 500 pmol/mL and a flow rate of 50 µL/min.

Data processing

The resulting MSE data files were processed in batch mode using Mass-MetaSite (Application version MetaSite CLI 5.1.0 Mass 3.2.0 Build date April 14 2015; Molecular Discovery, Ltd, Middlesex, UK. The maximum metabolite count limit was set to 30 within the retention time range of 0.5 to 6 min. Mass-MetaSite was run in the GSH mode. The annotation of GSH-specific metabolite peaks was based on the following GSH-specific neutral losses (in Da): 307.0838,

305.0682, 273.0961, 146.0692, 129.0426, 75.0320, 232.0696, and 249.0961, and the following fragment ions at m/z 308.0911, 162.0219, 130.0499, 177.0328, and 179.0485.

Results

The compounds shown in Table 9 were tested by this method and shown not to form covalent adducts with glutathione (GSH) when incubated in human liver microsomes.

Table 9

Example	Name
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea
88	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea
89	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea
95	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea
134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea

140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea
149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea
168	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea
183	1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(1,1,1,3,3,3-hexafluoropropan-2-yl)urea
257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea
273	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea
294	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea

Example 302

A compound of this invention can be used in a manner known per se as the active ingredient for the production of tablets of the following composition:

Per tablet

Active ingredient	200 mg
Microcrystalline cellulose	155 mg
Corn starch	25 mg
Talc	25 mg
Hydroxypropylmethylcellulose	20 mg
	425 mg

Example 303

A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, can be used in a manner known per se as the active ingredient for the production of capsules of the following composition:

	Per capsule
Active ingredient	100.0 mg
Corn starch	20.0 mg
Lactose	95.0 mg
Talc	4.5 mg
Magnesium stearate	0.5 mg
	220.0 mg

The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not

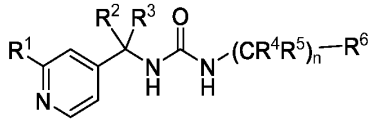
restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

All patents, patent applications and publications cited in this application are hereby incorporated by reference in their entirety for all purposes to the same extent as if each individual patent, patent application or publication were so individually denoted.

Specific Embodiments and Combinations

The following numbered clauses represent specific embodiments and combinations of features forming part of the present invention.

1. A pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

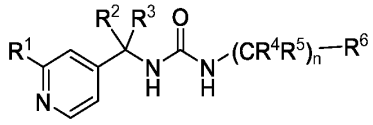
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

2. A pharmaceutical composition according to clause 1 comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, and hydroxyC_{1-6}alkyl;

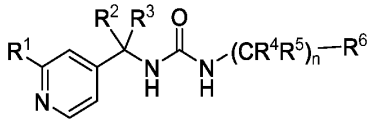
R^4 and R^5 are independently selected from hydrogen, a saturated monocyclic 3-5 membered cycloalkyl, and C_{1-6}alkyl, or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

3. A pharmaceutical composition according to clause 1 or 2 comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, or 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, a saturated monocyclic 3-5 membered cycloalkyl and hydroxyC_{1-6}alkyl,

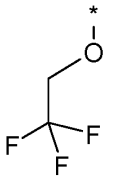
R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or

phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, hydroxy, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

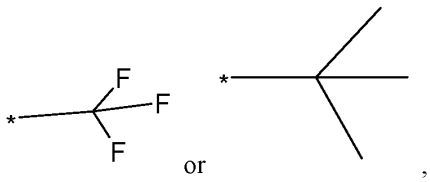
4. A pharmaceutical composition according to any one of clauses 1-3, wherein the compound of formula (I) excludes compounds in which all of the following applies:

R^1 is



,

R^6 is:



,

n is 2, and R^4 and R^5 are (i) all hydrogen or (ii) within the first pair of R^4 and R^5 both are hydrogen and within the second pair of R^4 and R^5 one is hydrogen and the other one is hydroxy.

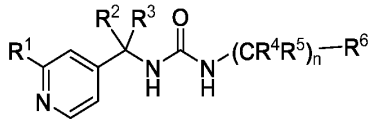
5. A pharmaceutical composition according to any one of clauses 1-4, wherein the compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0 or 1.

6. A pharmaceutical composition according to any one of clauses 1-5, wherein the compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 7-10 membered bicycylic fused cycloalkyl, a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl group, a 7-10 membered bicycylic fused cycloalkyl, phenyl, and a haloC_{1-6}alkyl.

7. A pharmaceutical composition according to any one of clauses 1-6, wherein the compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 7-10 membered bicycylic fused cycloalkyl, a 4-10 membered bridged cycloalkyl, a saturated monocyclic 4-6 membered cycloalkyl group, and a 7-10 membered bicycylic fused cycloalkyl.

8. A pharmaceutical composition according to any one of clauses 1-7, wherein the pharmaceutical composition further comprises one or more pharmaceutical excipients.

9. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

10. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 9, wherein R^1 is selected from cyano, haloC_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy; wherein the heterocyclyloxy and cycloakylalkoxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl.

11. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 9 or 10, wherein R^1 is selected from cyano, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl.

12. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 9-10, wherein R^1 is selected from cyano, CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, CF_3CH_2O-, CH_3CF_2-, CHF_2-, and CF_3-.

13. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 12, wherein R^1 is selected from CHF_2O-, CH_3CF_2O-, CH_3CFHCH_2O-, and CF_3CH_2O-.

14. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 12 or 13, wherein R^1 is CHF_2O- or CH_3CF_2O-.

15. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 9, wherein R^1 is 5 membered heteroaryl selected from pyrazolyl and imidazolyl which are optionally substituted with one, two, or three substituents indendently selected from halogen or haloC_{1-6}alkyl.

16. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 15, wherein R^1 is unsubstituted pyrazolyl or unsubstituted imidazolyl.

17. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof according to any one of clauses 9-16, wherein (i) both R^2 and R^3 are hydrogen, or (ii) one of R^2 and R^3 is hydrogen and the other one is hydroxyC_{1-6}alkyl.

18. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 17, wherein one of R^2 and R^3 is hydrogen and the other one is hydroxyC_{1-6}alkyl selected from $HOCH_2$-, $HOCH_2CH_2$-, $HOCH_2CH_2CH_2$-, and $HOCH_2CH_2CH_2CH_2$-.

19. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 18, wherein the hydroxyC_{1-6}alkyl is $HOCH_2$- or $HOCH_2CH_2$-.

20. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 17, wherein both R^2 and R^3 are hydrogen.

21. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 9-20, wherein n is 0 or 1.

22. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 21, wherein n is 0.

23. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 21, wherein n is 1.

24. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 23, wherein n is 1 and (i) both R^4 and R^5 are hydrogen, (ii) one of R^4 and R^5 is hydrogen and the other one is C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, or C_{1-6}alkoxy.

25. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 24, wherein one of R^4 and R^5 is hydrogen and the other one is a methyl (CH_3-) or methoxy (CH_3O-).

26. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 24, wherein the saturated monocyclic 3-5 membered cycloalkyl is unsubsituted cyclopropyl.

27. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 24, wherein n is 1 and both R^4 and R^5 are hydrogen.

28. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 9-24, wherein R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl.

29. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof according to any one of clauses 9-28, wherein R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, C_{1-6}alkyl, haloC_{1-6}alkyl, and phenyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

30. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof according to any one of clauses 9-29, wherein R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

31. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 30, wherein R^6 is optionally substituted with one, two, or three substituents independently selected from from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, cyano, and hydroxy.

32. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 31, wherein R^6 is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CF_3-, cyclopropyl, and CH_3O-.

33. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 31 or 32, wherein R^6 is optionally substituted with one, two, or three substituents independently selected from F- and CF_3-.

34. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 29-33, wherein R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) $C_{1\text{-}6}$alkyl; and

e) halo$C_{1\text{-}6}$alkyl,

optionally substituted according to any one of clauses 29-33 and 38-39.

35. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 34, wherein R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl; and

c) a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings.

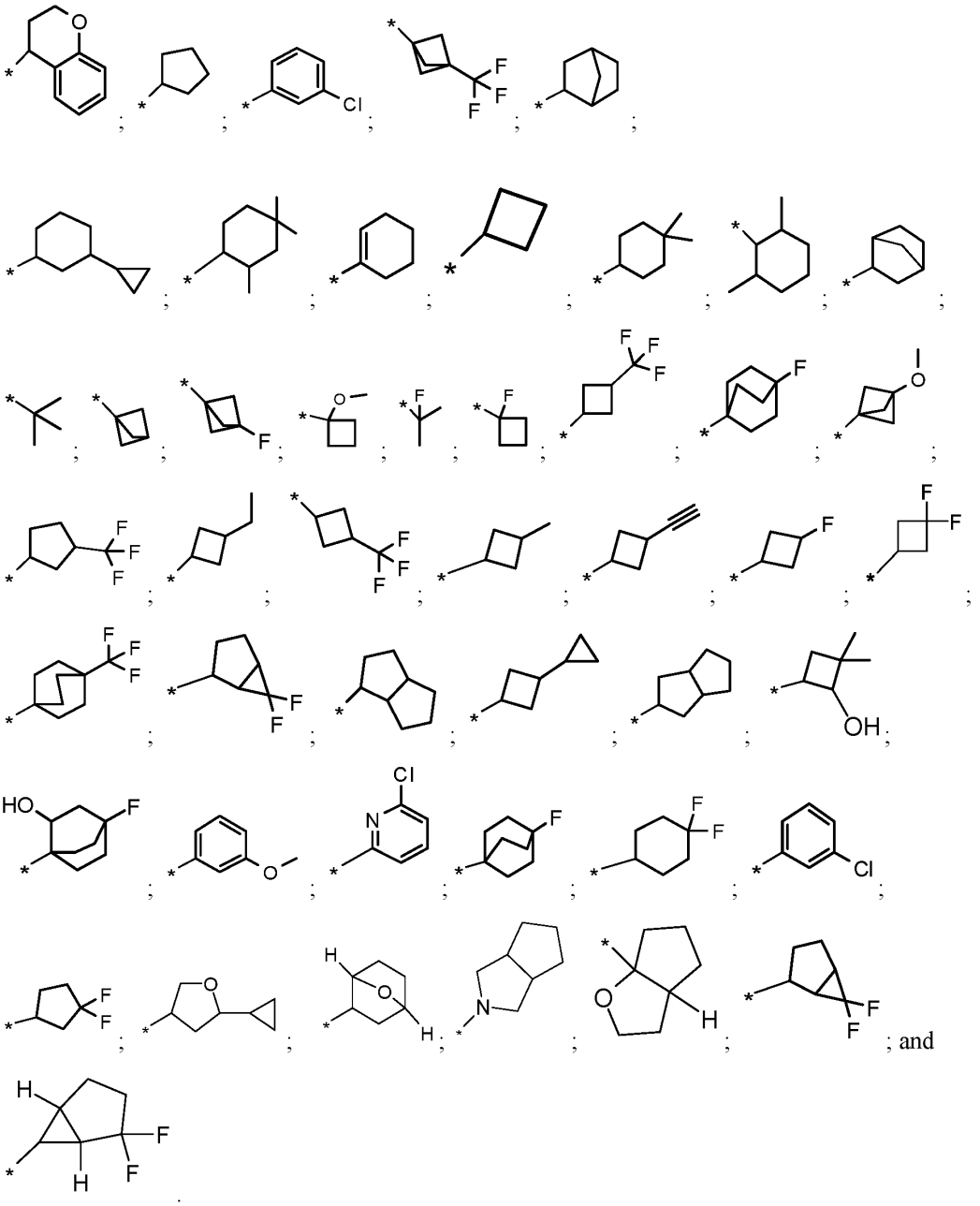
36. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 29-35, wherein R^6 is selected from:

dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, CHF_2-, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyridinyl, and pyrimidinyl.

37. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 29-36, wherein R^6 is selected from:

dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyridinyl, and pyrimidinyl.

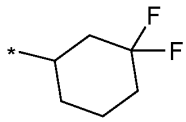
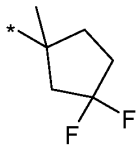
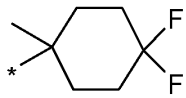
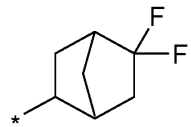
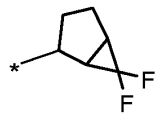
38. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 29-37, wherein R^6 is selected from:

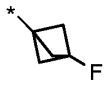
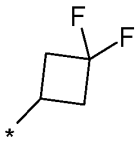
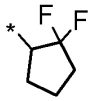
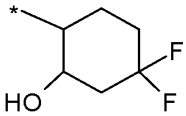
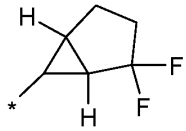
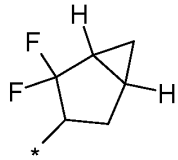


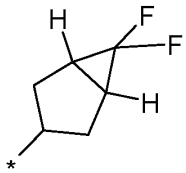
; and

.

39. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 38, wherein R^6 is selected from:

 ;  ;  ; X;  .  ;

 ;  ;  ;  ;  ;  , and

 .

40. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 29-39, wherein R^1 is selected from CHF_2O-, unsubstituted pyrazolyl, unsubstituted imidazolyl, CH_3O-, $(CH_3)CF_2$-, CN-, CHF_2-, CF_3-, CF_3CH_2O-, CH_3CFHCH_2O-, R^2 and R^3 are hydrogen, n is 0 or 1, (i) R^4 and R^5 are hydrogen, or (ii) one of R^4 and R^5 are hydrogen and the other is cyclopropyl, or (iii) R^4 and R^5 together with the one carbon atom to which they are attached, form cyclopropyl, and R^6 is selected from a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, a 7-10 membered bridged heterosystem, wherein the bridge comprises an O-atom, a 6 membered heteroaryl; and a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, all optionally substituted according to any one of clauses 29-33 and 38-39.

41. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 40, wherein R^1 is selected from CHF_2O- or unsubstituted imidazolyl, R^2 and R^3 are hydrogen, n is 0 or 1, (i) R^4 and R^5 are hydrogen, or (ii) one of R^4 and R^5 are hydrogen and the other is cyclopropyl, or (iii) R^4 and R^5 together with the one carbon atom to which they are attached, form cyclopropyl, and R^6 is selected from a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, a 7-10 membered bridged heterosystem, wherein the bridge comprises an O-atom; a 6 membered heteroaryl; and a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, all optionally substituted according to any one of clauses 29-33 and 38-39.

42. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 40 or 41, wherein R^1 is selected from CHF_2O- and unsubstituted imidazolyl, R^2 and R^3 are hydrogen, n is 0; and R^6 is selected from a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, a 7-10 membered bridged heterosystem, wherein the bridge comprises an O-atom; a 6 membered heteroaryl; and a 4-10 membered cycloalkyl selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings; all optionally substituted according to any one of clauses 29-33 and 38-39.

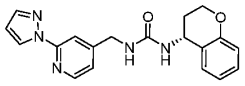
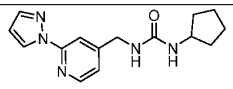
43. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 40-42, wherein R^1 is CHF_2O- and R^6 is substituted with one or two F- or CF_3-.

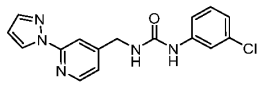
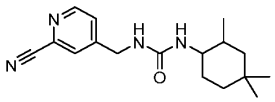
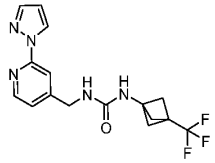
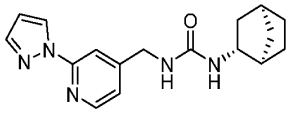
44. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 43, wherein R^1 is CHF_2O- and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings; all substituted with one or two F- or CF_3-.

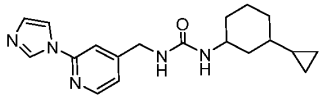
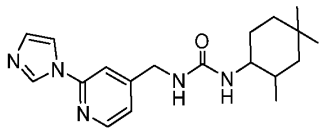
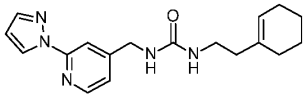
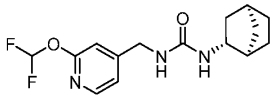
45. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 40-44 wherein R^1 is CHF_2O-, n is 0 or 1, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; all substituted with substituted with one or two F- or CF_3-.

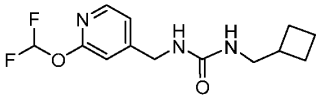
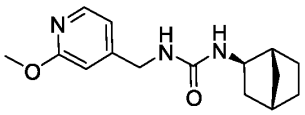
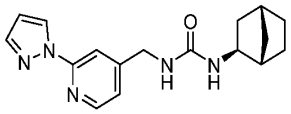
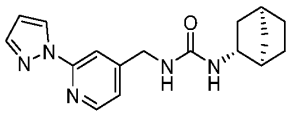
46. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to 45, wherein R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings; all substituted with one or two F- or CF_3-.

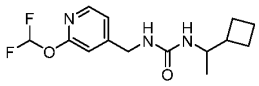
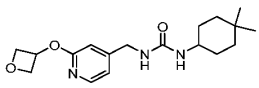
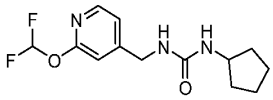
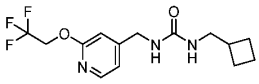
47. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 9-46, or a pharmaceutical composition according to any one of clauses 1-6, wherein the compound is selected from:

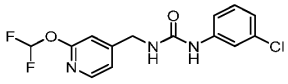
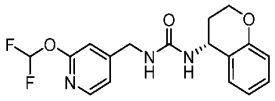
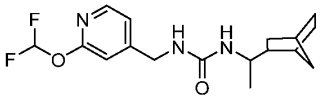
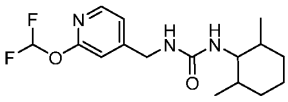
Example	Name	Structure
1	1-[(4R)-3,4-dihydro-2H-chromen-4-yl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
2	1-cyclopentyl-3-[(2-pyrazol-1-	

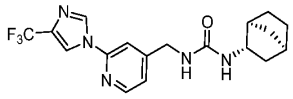
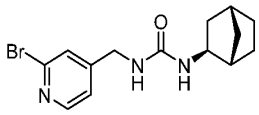
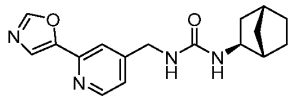
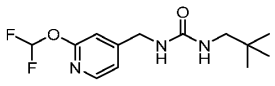
Example	Name	Structure
	ylpyridin-4-yl)methyl]urea	
4	1-(3-chlorophenyl)-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
5	1-[(2-cyanopyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	
6	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
7	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-	

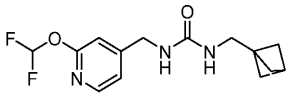
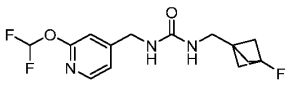
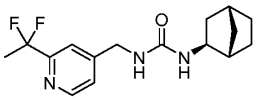
Example	Name	Structure
	bicyclo[2.2.1]heptanyl]urea	
8	1-(3-cyclopropylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea	
9	1-[(2-imidazol-1-ylpyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	
10	1-[2-(cyclohexen-1-yl)ethyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
12	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-	

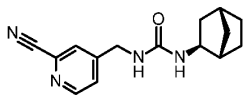
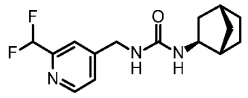
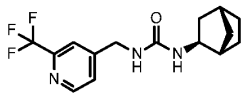
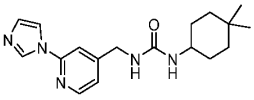
Example	Name	Structure
	bicyclo[2.2.1]heptanyl]urea	
13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
14	1-[(2-methoxypyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
15	1-[(1S,2S,4R)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
16	1-[(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-	

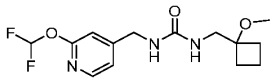
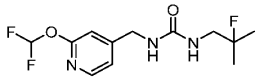
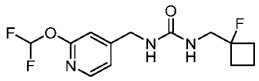
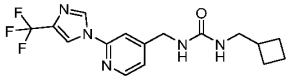
Example	Name	Structure
	ylpyridin-4-yl)methyl]urea	
17	1-(1-cyclobutylethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
18	1-(4,4-dimethylcyclohexyl)-3-[[2-(oxetan-3-yloxy)pyridin-4-yl]methyl]urea	
20	1-cyclopentyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
21	1-(cyclobutylmethyl)-3-[[2-(2,2,2-trifluoroethoxy)py	

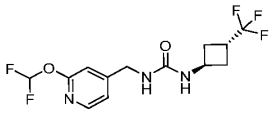
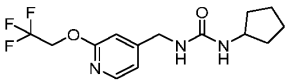
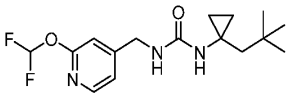
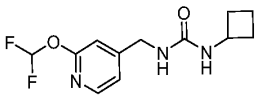
Example	Name	Structure
	ridin-4-yl]methyl]urea	
22	1-(3-chlorophenyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
23	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(4R)-3,4-dihydro-2H-chromen-4-yl]urea	
24	1-[1-(2-bicyclo[2.2.1]heptanyl)ethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
25	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,6-	

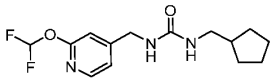
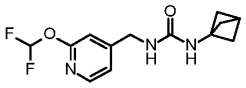
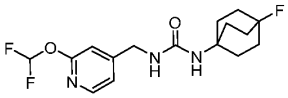
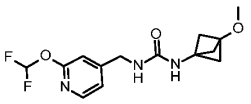
Example	Name	Structure
	dimethylcyclohexyl)urea	
26	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	
27	1-[(2-bromopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
28	1-[[2-(1,3-oxazol-5-yl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
29	1-[[2-(difluoromethoxy)pyridin-4-	

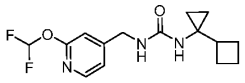
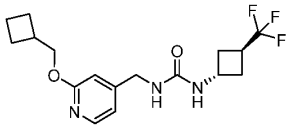
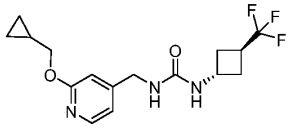
Example	Name	Structure
	yl]methyl]-3-(2,2-dimethylpropyl)urea	
31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
32	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea	
33	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	

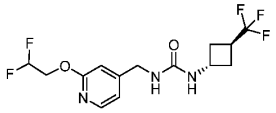
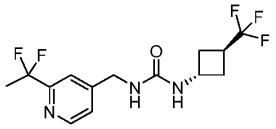
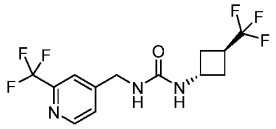
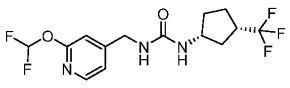
Example	Name	Structure
34	1-[(2-cyanopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
35	1-[[2-(difluoromethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
36	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	
37	1-(4,4-dimethylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea	

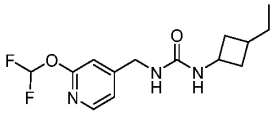
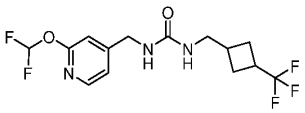
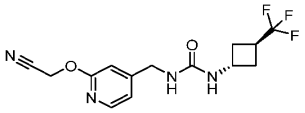
Example	Name	Structure
38	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-methoxycyclobutyl)methyl]urea	
39	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-fluoro-2-methylpropyl)urea	
40	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclobutyl)methyl]urea	
41	1-(cyclobutylmethyl)-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	

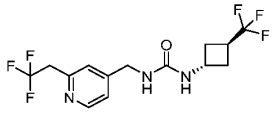
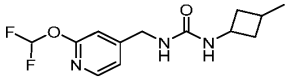
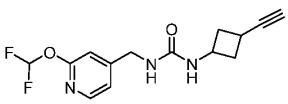
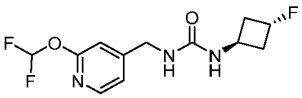
Example	Name	Structure
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
43	1-cyclopentyl-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
44	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2-dimethylpropyl)cyclopropyl]urea	
45	1-cyclobutyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

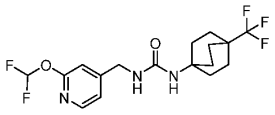
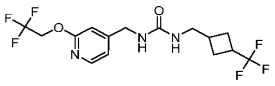
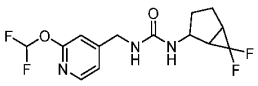
Example	Name	Structure
46	1-(cyclopentylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
47	1-(1-bicyclo[1.1.1]pentanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
49	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxy-1-	

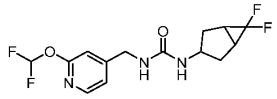
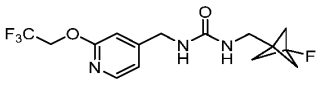
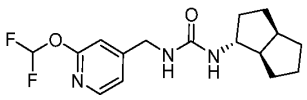
Example	Name	Structure
	bicyclo[1.1.1]pentanyl)urea	
50	1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
54	1-[[2-(cyclobutylmethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
55	1-[[2-(cyclopropylmethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-	

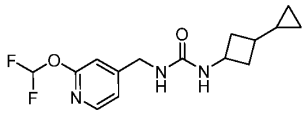
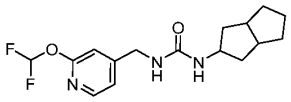
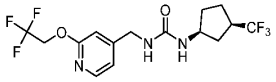
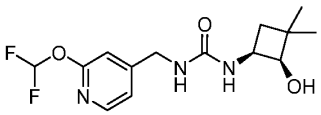
Example	Name	Structure
	(trifluoromethyl)cyclobutyl]urea	
56	1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
57	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
58	1-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	
59	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-	

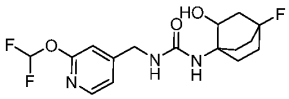
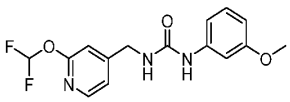
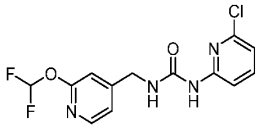
Example	Name	Structure
	(trifluoromethyl)cyclopentyl]urea	
60	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethylcyclobutyl)urea	
62	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
63	1-[[2-(cyanomethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	

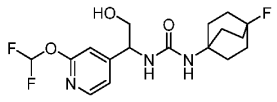
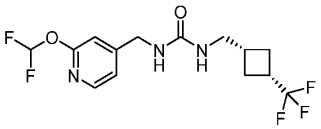
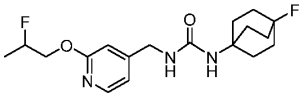
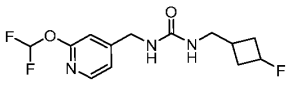
Example	Name	Structure
64	1-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
65	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylcyclobutyl)urea	
66	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethynylcyclobutyl)urea	
67	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1*r*,3*r*)-3-fluorocyclobutyl)urea	

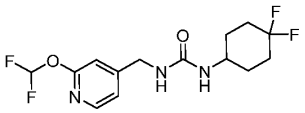
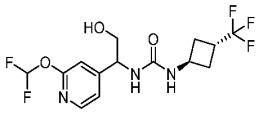
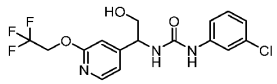
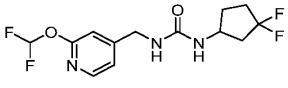
Example	Name	Structure
68	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[4-(trifluoromethyl)-1-bicyclo[2.2.2]octanyl]urea	
71	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	
73	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5R)-6,6-difluoro-2-	

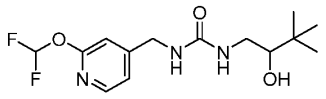
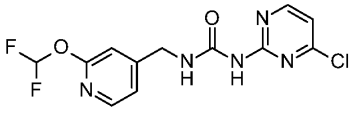
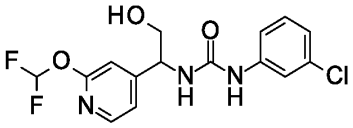
Example	Name	Structure
	bicyclo[3.1.0]hexanyl]urea	
74	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
75	1-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
76	1-[(1R,3aR,6aR)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

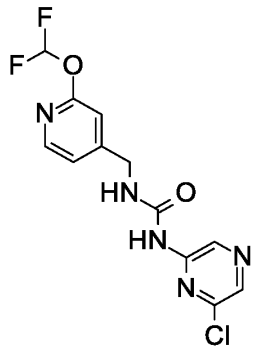
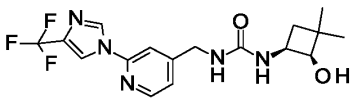
Example	Name	Structure
77	1-(3-cyclopropylcyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
78	1-(1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
79	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
81	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-	

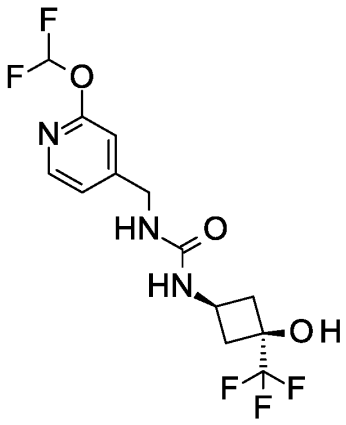
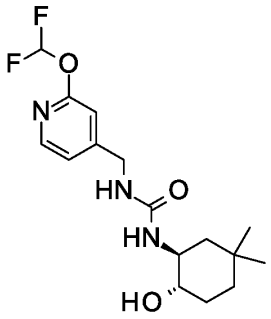
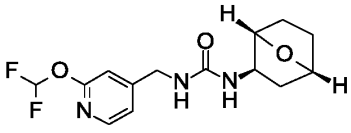
Example	Name	Structure
	(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]urea	
82	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-2-hydroxy-1-bicyclo[2.2.2]octanyl)urea	
83	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxyphenyl)urea	
84	1-(6-chloropyridin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

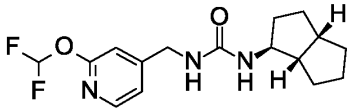
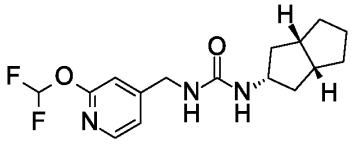
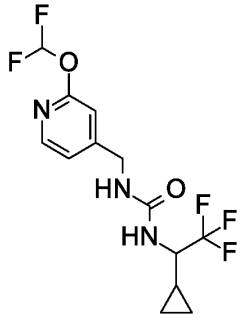
Example	Name	Structure
85	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
87	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(1r,3r)-(trifluoromethyl)cyclobutyl]methyl]urea	
88	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	
89	1-[[2-(difluoromethoxy)pyridin-4-	

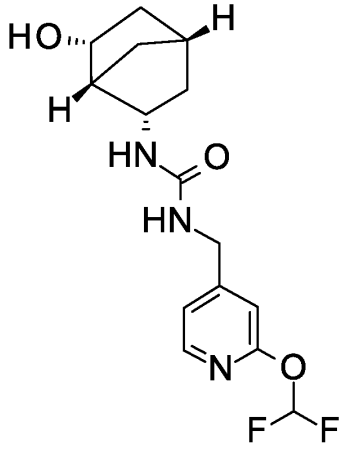
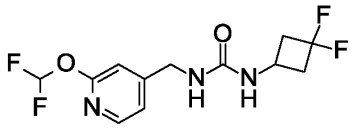
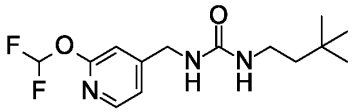
Example	Name	Structure
	yl]methyl]-3-[(3-fluorocyclobutyl) methyl]urea	
90	1-(4,4-difluorocyclohexyl)-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
91	1-[1-[2-(difluoromethoxy) pyridin-4-yl]-2-hydroxyethyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
92	1-(3-chlorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
93	1-(3,3-difluorocyclopenty	

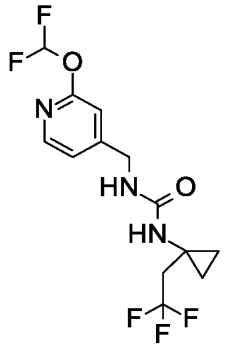
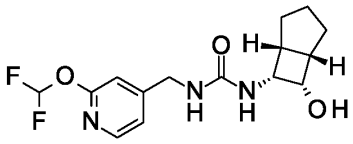
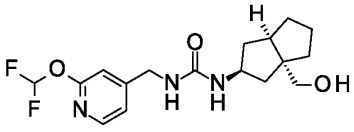
Example	Name	Structure
	l)-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
95	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea	
96	1-(4-chloropyrimidin-2-yl)-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)	

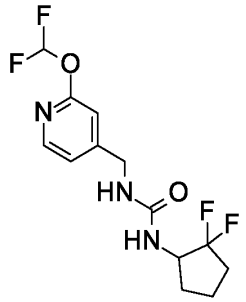
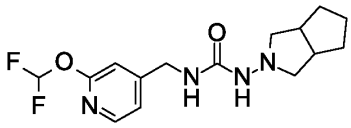
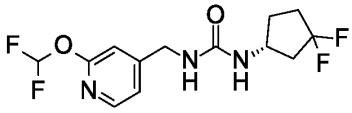
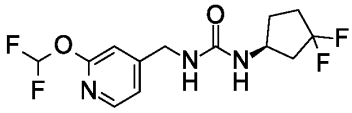
Example	Name	Structure
	pyridin-4-yl]-2-hydroxyethyl]urea	
98	1-(6-chloropyrazin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
99	1-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	

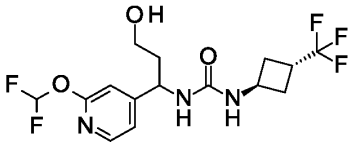
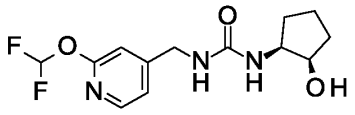
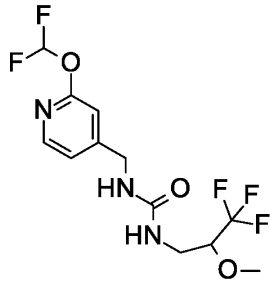
Example	Name	Structure
100	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-hydroxy-3-(trifluoromethyl)cyclobutyl]urea	
101	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-5,5-dimethylcyclohexyl]urea	
102	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S)-7-oxabicyclo[2.2.1]heptan-2-yl]urea	

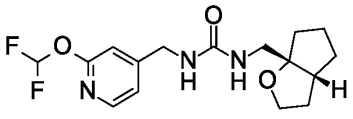
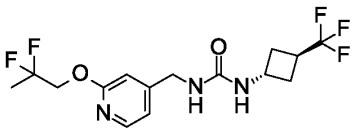
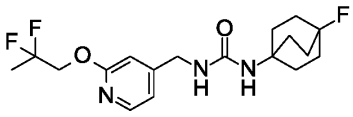
Example	Name	Structure
103	1-[(1S,3aS,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
105	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3aR,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]urea	
106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

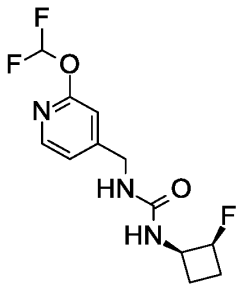
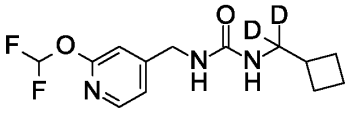
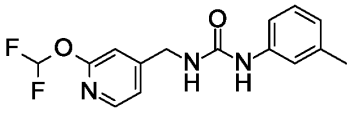
Example	Name	Structure
107	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S,6R)-6-hydroxy-2-bicyclo[2.2.1]heptanyl]urea	
108	1-(3,3-difluorocyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
109	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-dimethylbutyl)urea	

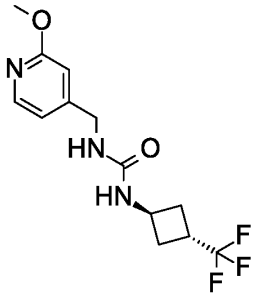
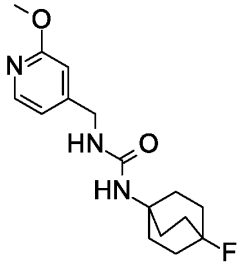
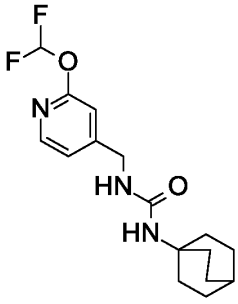
Example	Name	Structure
110	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2,2-trifluoroethyl)cyclopropyl]urea	
111	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6S,7R)-7-hydroxy-6-bicyclo[3.2.0]heptanyl]urea	
112	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(2R,3aS,6aS)-6a-(hydroxymethyl)-2,3,3a,4,5,6-hexahydro-1H-pentalen-2-yl]urea	

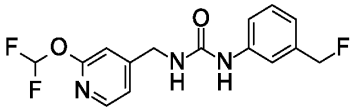
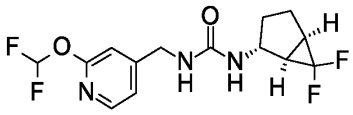
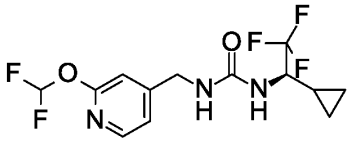
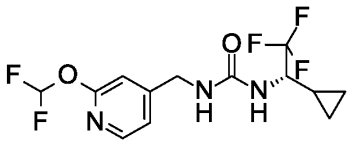
Example	Name	Structure
113	1-(2,2-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
114	1-(3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)	

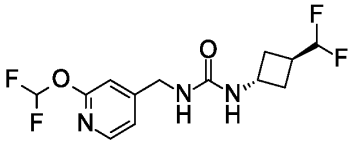
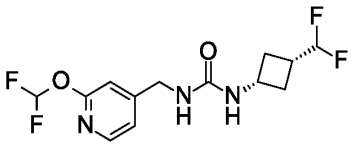
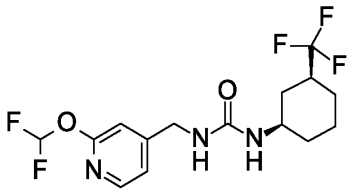
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
117	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-3-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
118	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxycyclopentyl]urea	
119	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3,3-trifluoro-2-methoxypropyl)urea	

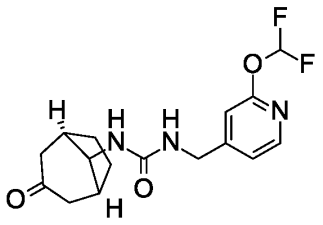
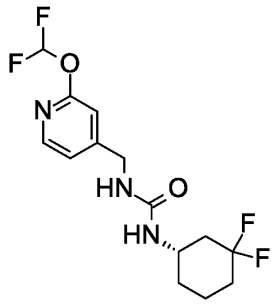
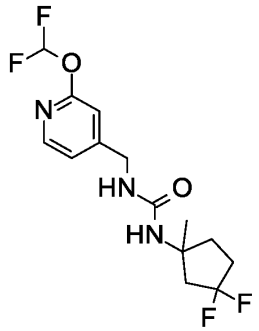
Example	Name	Structure
120	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[rac-(3aR,6aR)-2,3,3a,4,5,6-hexahydrocyclopenta[b]furan-6a-yl]methyl]urea	
121	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
122	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	

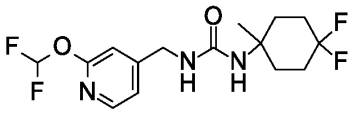
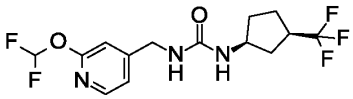
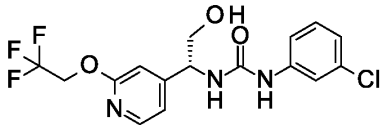
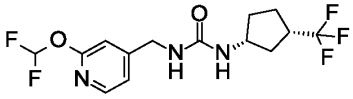
Example	Name	Structure
123	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-fluorocyclobutyl]urea	
125	1-[cyclobutyl(dideuterio)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
126	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylphenyl)urea	

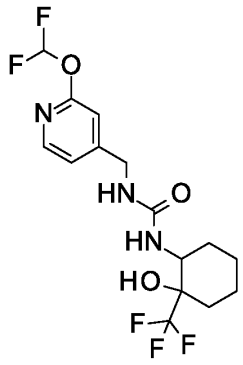
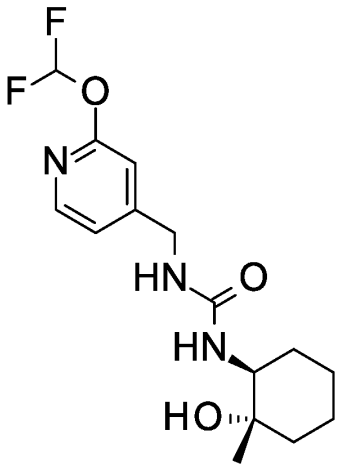
Example	Name	Structure
128	1-[(2-methoxypyridin-4-yl)methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
129	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[(2-methoxypyridin-4-yl)methyl]urea	
131	1-(1-bicyclo[2.2.2]octanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

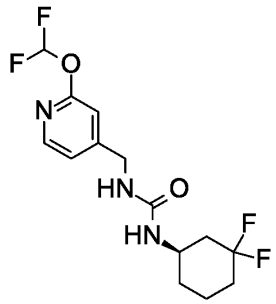
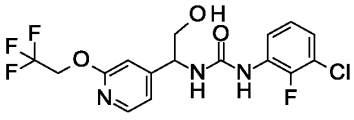
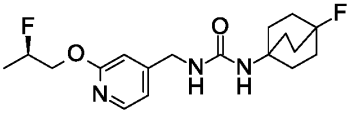
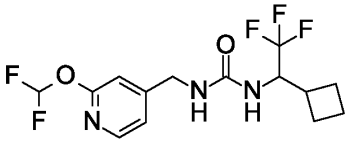
Example	Name	Structure
132	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(fluoromethyl)phenyl]urea	
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
135	1-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)	

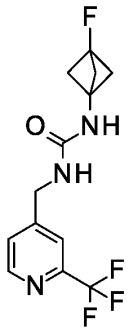
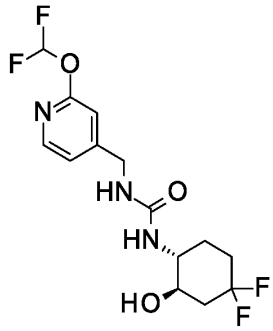
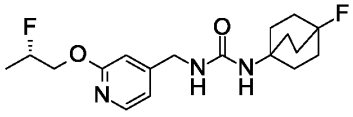
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
136	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(difluoromethyl)cyclobutyl]urea	
137	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(difluoromethyl)cyclobutyl]urea	
138	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	

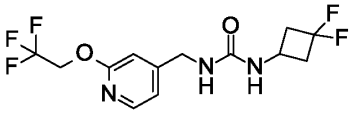
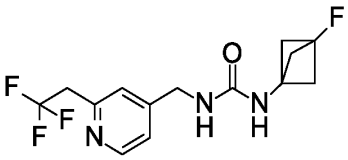
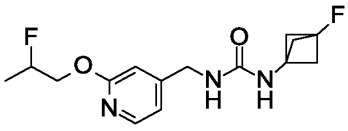
Example	Name	Structure
139	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3-oxo-8-bicyclo[3.2.1]octanyl]urea	
140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
142	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-difluoro-1-methylcyclopentyl)urea	

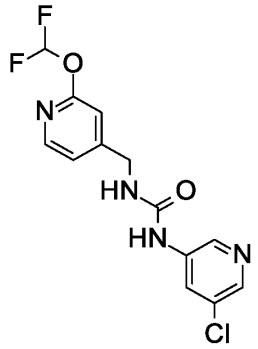
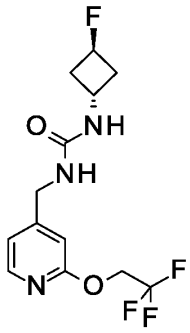
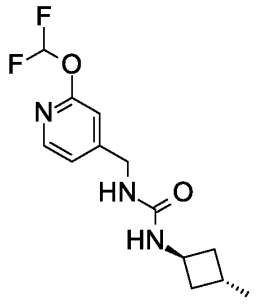
Example	Name	Structure
143	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4,4-difluoro-1-methylcyclohexyl)urea	
144	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3R)-3-(trifluoromethyl)cyclopentyl]urea	
145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
146	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-	

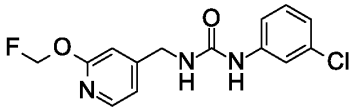
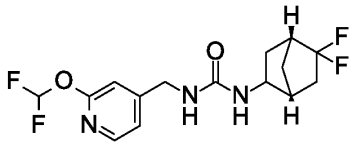
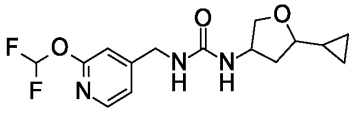
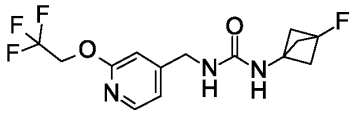
Example	Name	Structure
	(trifluoromethyl)cyclopentyl]urea	
147	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-hydroxy-2-(trifluoromethyl)cyclohexyl]urea	
148	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-2-methylcyclohexyl]urea	

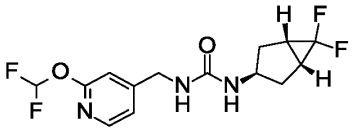
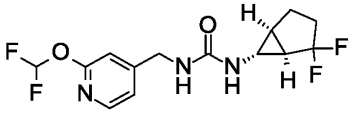
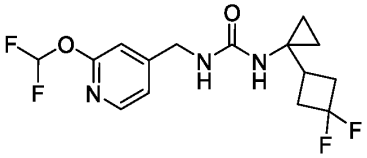
Example	Name	Structure
149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
150	1-(3-chloro-2-fluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
151	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]urea	
152	1-(1-cyclobutyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)	

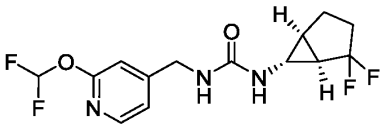
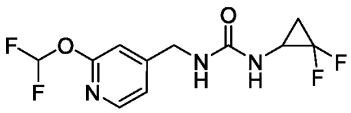
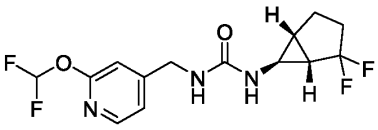
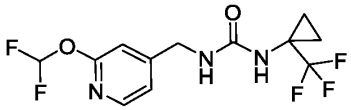
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
153	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	
154	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-4,4-difluoro-2-hydroxycyclohexyl]urea	
156	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]urea	

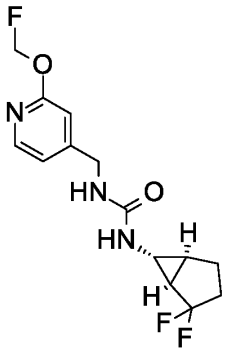
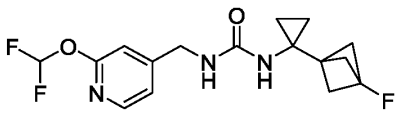
Example	Name	Structure
157	1-(3,3-difluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
159	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
160	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	

Example	Name	Structure
161	1-(5-chloropyridin-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
162	1-((1r,3r)-3-fluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
163	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1r,3r)-3-methylcyclobutyl)urea	

Example	Name	Structure
164	1-(3-chlorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
165	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,4R)-5,5-difluoro-2-bicyclo[2.2.1]heptanyl]urea	
166	1-(5-cyclopropyloxolan-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
168	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethoxy)py	

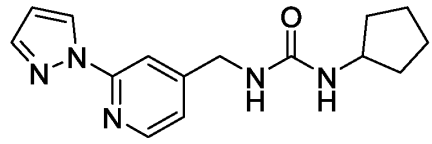
Example	Name	Structure
	ridin-4-yl]methyl]urea	
169	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
170	1-[(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
171	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

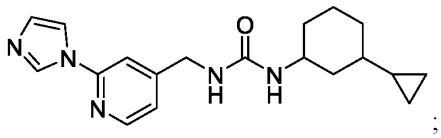
Example	Name	Structure
172	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
173	1-(2,2-difluorocyclopropyl)-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
174	1-[(1S,5R,6S)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
175	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[1-	

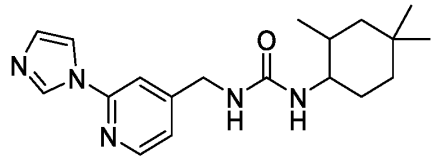
Example	Name	Structure
	(trifluoromethyl)cyclopropyl]urea	
176	1-[[2-(fluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
177	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)cyclopropyl]urea	

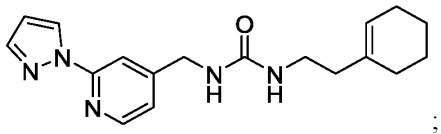
48. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 9-47, or a pharmaceutical composition according to any one of clauses 1-8, wherein R^1 is CHF_2O- and R^6 is substituted with one or two F-.

49. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 9-48, or a pharmaceutical composition according to any one of clauses 1-6 with the proviso that the compound is not one selected from:


;


;


;


;

50. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 9-49, wherein such compounds of formula (I) show Kv7.2 EC_{50} <3μM and selectivity ratio Kv7.3_7.5/Kv7.2 >10x.

51. A pharmaceutical composition according to any one of clauses 1-8, or a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof according to any one of clauses 9-50, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

52. A pharmaceutical pharmaceutical composition according to any one of clauses 1-8, or a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof according to any one of clauses 9-50, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the disorder, disease, or disability is selected from behavioral disorders, mood disorders, neurodevelopmental

disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus.

53. The pharmaceutical composition for use according to clause 52, wherein the disorder, disease, or disability is a behavioral disorder which is Attention Deficit Hyperactivity Disorder (ADHD).

54. The pharmaceutical composition for use according to clause 52, wherein the disorder, disease, or disability is a mood disorder which is depression.

55. The pharmaceutical composition for use according to clause 52, wherein the disorder, disease, or disability is a neurodevelopment disorder selected from autism spectrum disorder (ASD) and syndromic developmental disorders.

56. The pharmaceutical composition for use according to clause 52, wherein the disorder, disease, or disability is a syndromic developmental disorder selected from Dup15q syndrome (Dup15q), Fragile X syndrome (FXS) and Angelman syndrome.

57. The pharmaceutical composition for use according to clause 52, wherein the disorder, disease, or disability is an epilepsy selected from broad pediatric epilepsy, West syndrome, Ohtahara syndrome, and epileptic encephalopathy.

58. The pharmaceutical composition for use according to clause 52, wherein disorder, disease, or disability is a neurodegenerative disease selected from Alzheimer's disease, and motor neuron diseases.

59. The pharmaceutical composition for use according to any one of clauses 51-58, for systemic or local administration such as oral, nasal, parenteral (as by intravenous (both bolus and infusion), intramuscular, or subcutaneous injection), transdermal, vaginal, buccal, rectal, or topical administration modes, intracisternally, intraperitoneally, as an oral or nasal spray, or as a liquid aerosol or dry powder for inhalation.

60. A compound according to any one of clauses 9-50, or a pharmaceutical composition according to any one of clauses 1-8 for use in therapy.

61. A compound according to any one of clauses 9-50, or a pharmaceutical composition according to any one of clauses 1-8, or a pharmaceutical composition for use according to any one of clauses 51-59, for the manufacture of a medicament for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2.

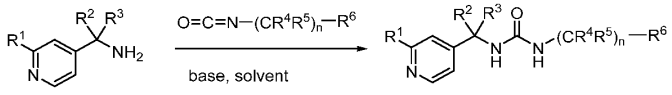
62. A method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2, which method comprises administering a therapeutically effective amount of a compound according to any one of clauses 9-50, or a pharmaceutical composition according to any one of clauses 1-8, or a pharmaceutical composition for use according to any one of clauses 51-59.

63. A kit for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 comprising:

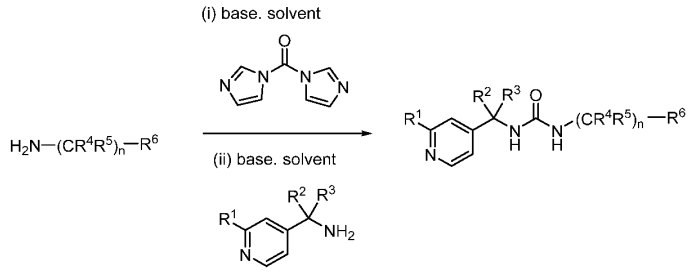
b) a compound according to any one of clauses 9-50, or a pharmaceutical composition according to any one of clauses 1-8, or a pharmaceutical composition for use according to any one of clauses 51-59; and

b) instructions for use.

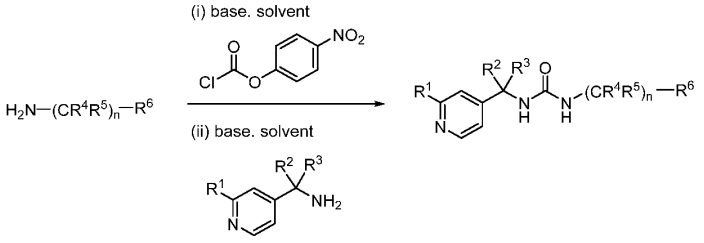
64. A process for the preparation of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 9-50, wherein the urea formation comprises the reactions:



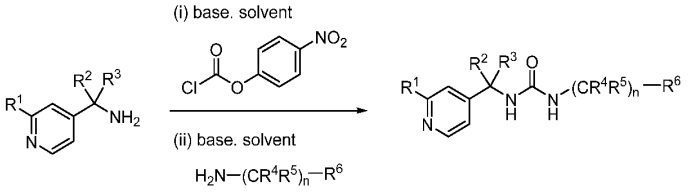
or



or



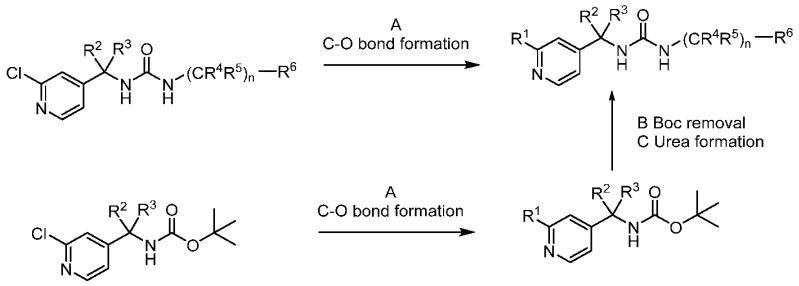
or



wherein R^1, R^2, R^3, n, R^4, R^5 and R^6 are as defined herein.

65. A process for the preparation of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 64, wherein R^1 is selected from 7-12 membered heterocycloalkyl, cyano, halogen, haloC_{1-6}alkyl, and 5 membered heteroaryl.

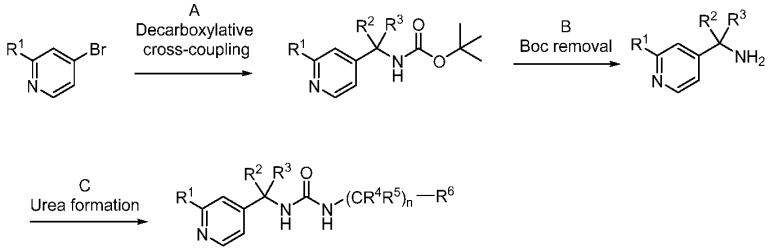
66. A process for the preparation of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 9-50, wherein the process comprises the following reaction step:



wherein R^1, R^2, R^3, n, R^4, R^5 and R^6 are as defined herein.

67. A process for the preparation of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to clause 66, wherein R^1 is selected from haloC_{1-6}alkoxy, C_{1-6}alkoxy, 4-6 membered heterocyclyloxy, and C_{3-5}cycloalkylC_{1-6}alkoxy and R^2 and R^3 are hydrogen.

68. A process for the preparation of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of clauses 9-50, wherein the process comprises the reactions of the following reaction steps:



wherein R^1, R^2, R^3, n, R^4, R^5 and R^6 are as defined herein.

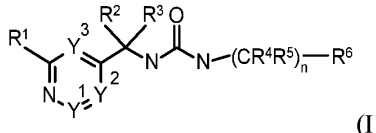
69. A process for the preparation of a compound of formula (I), or a solvate or pharmaceutically acceptable salt thereof, according to clause 68, wherein R^1 is selected from haloC_{1-6}alkoxy, C_{1-6}alkoxy, 4-6 membered heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or cyanoC_{1-6}alkoxy, and R^2 is hydroxyC_{1-6}alkyl and R^3 is hydrogen.

70. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof according to any one of clauses 9-50, when manufactured according to a process according to any one of clauses 64-69.

71. The invention as hereinbefore described.

CLAIMS

1. A pharmaceutical composition comprising a compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof:



(I')

wherein:

Y^1 is CR^a or N;

Y^2 is CR^b or N;

Y^3 is CR^c or N;

provided that only 0 or 1 of Y^1, Y^2 and Y^3 is N and the others are CR^a, CR^b, or CR^c;

R^a, R^b and R^c are each independently selected from hydrogen or halogen;

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, haloC_{1-6} alkylthio, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, 4-6 membered cycloalkyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl; wherein the 4-6 membered cycloalkyloxy is optionally substituted with one, two, or three substituents independently selected from halogen; and wherein the haloC_{1-6}alkoxy is optionally substituted with C_{1-6}alkoxy;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

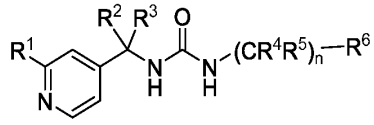
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and Si(C_{1-6}alkyl)$_3$; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl and C_{2-6} alkynyl; and

n is 0, 1, 2, or 3.

2. A pharmaceutical composition according to claim 1 comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, haloC_{1-6} alkylthio, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, 4-6 membered cycloalkyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl; wherein the 4-6 membered cycloalkyloxy is optionally substituted with one, two, or three substituents independently

selected from halogen; and wherein the haloC_{1-6}alkoxy is optionally substituted with C_{1-6}alkoxy;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

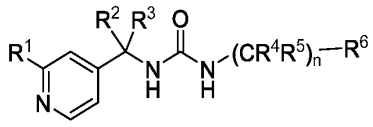
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and $Si(C_{1-6}alkyl)_3$; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl and C_{2-6} alkynyl; and

n is 0, 1, 2, or 3.

3. A pharmaceutical composition comprising a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

4. A pharmaceutical composition according to any one of claims 1 to 3 comprising a compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof:

wherein:

Y^1, Y^2 are CH

Y^3 is selected from CH or N;

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, haloC_{1-6} alkylthio, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, and hydroxyC_{1-6}alkyl;

R^4 and R^5 are independently selected from hydrogen, a saturated monocyclic 3-5 membered cycloalkyl, haloC_{1-6}alkyl and C_{1-6}alkyl, or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, $Si(C_{1-6}alkyl)_3$ and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkoxy, and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

5. A pharmaceutical composition according to any one of claims 1 to 4 comprising a compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof:

wherein:

Y^1, Y^2 are CH

Y^3 is selected from CH or N;

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, haloC_{1-6} alkylthio, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, or 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, and hydroxyC_{1-6}alkyl;

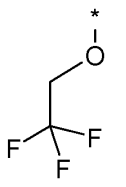
R^4 and R^5 are independently selected from hydrogen, a saturated monocyclic 3-5 membered cycloalkyl, haloC_{1-6}alkyl and hydroxyC_{1-6}alkyl,

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, $Si(C_{1-6}alkyl)_3$ and phenyl, wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, hydroxy, haloC_{1-6}alkoxy and haloC_{1-6}alkyl; and

n is 0, 1, or 2.

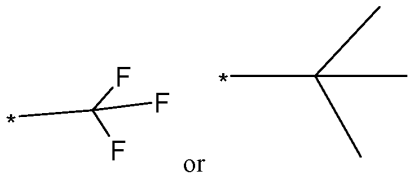
6. A pharmaceutical composition according to any one of claims 1-5, wherein the compound of formula (I') or (I) excludes compounds in which all of the following applies:

R^1 is



,

R^6 is:



or ,

n is 2, and R^4 and R^5 are (i) all hydrogen or (ii) within the first pair of R^4 and R^5 both are hydrogen and within the second pair of R^4 and R^5 one is hydrogen and the other one is hydroxy.

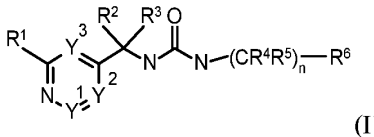
7. A pharmaceutical composition according to any one of claims 1-6, wherein the compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein n is 0 or 1.

8. A pharmaceutical composition according to any one of claims 1-7, wherein the compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from a saturated monocyclic 3-6 membered cycloalkyl, a 7-10 membered bicyclic fused cycloalkyl, a 4-10 membered bridged cycloalkyl, a saturated monocyclic 3-6 membered cycloalkyl group, a 7-10 membered bicyclic fused cycloalkyl, phenyl, $Si(C_{1-6}alkyl)_3$ and a $haloC_{1-6}alkyl$.

9. A pharmaceutical composition according to any one of claims 1-8, wherein the compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, wherein R^6 is selected from a saturated monocyclic 3-6 membered cycloalkyl, a 7-10 membered bicyclic fused cycloalkyl, a 4-10 membered bridged cycloalkyl, a saturated monocyclic 3-6 membered cycloalkyl group, and a 7-10 membered bicyclic fused cycloalkyl.

10. A pharmaceutical composition according to any one of claims 1-9, wherein the pharmaceutical composition further comprises one or more pharmaceutical excipients.

11. A compound of formula (I'), or a solvate or a pharmaceutically acceptable salt thereof:



(I')

wherein:

Y^1 is CR^a or N;

Y^2 is CR^b or N;

Y^3 is CR^c or N;

provided that only 0 or 1 of Y^1, Y^2 and Y^3 is N and the others are CR^a, CR^b, or CR^c;

R^a, R^b and R^c are each independently selected from hydrogen or halogen;

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, haloC_{1-6} alkylthio, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, 4-6 membered cycloalkyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl; wherein the 4-6 membered cycloalkyloxy is optionally substituted with one, two, or three substituents independently selected from halogen; and wherein the haloC_{1-6}alkoxy is optionally substituted with C_{1-6}alkoxy;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

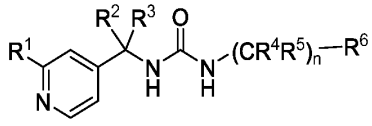
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and $Si(C_{1-6}alkyl)_3$; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl and C_{2-6} alkynyl; and

n is 0, 1, 2, or 3.

12. A compound according to claim 11 wherein the compound is of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, haloC_{1-6} alkylthio, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, 4-6 membered cycloalkyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl; wherein the 4-6 membered cycloalkyloxy is optionally substituted with one, two, or three substituents independently selected from halogen; and wherein the haloC_{1-6}alkoxy is optionally substituted with C_{1-6}alkoxy;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

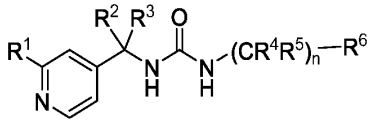
R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy and Si(C_{1-6}alkyl)$_3$; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, haloC_{1-6}alkyl and C_{2-6} alkynyl; and

n is 0, 1, 2, or 3.

13. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is selected from a 4-6 membered heterocycloalkyl, cyano, haloC_{1-6}alkoxy, C_{1-6}alkoxy, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, and 5 membered heteroaryl; wherein the heterocycloalkyl, heterocyclyloxy, and heteroaryl are optionally substituted with one C_{1-6}alkyl, or haloC_{1-6}alkyl;

R^2 and R^3 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, and hydroxyC_{1-6}alkyl; or

R^2 and R^3 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^4 and R^5 are independently selected from hydrogen, deuterium, C_{1-6}alkyl, saturated monocyclic 3-5 membered cycloalkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, and hydroxy; or

R^4 and R^5 together with the one carbon atom to which they are attached form a saturated monocyclic 3-5 membered cycloalkyl;

R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 4-10 membered cycloalkyl, phenyl, C_{1-6}alkyl, and haloC_{1-6}alkyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl; and

n is 0, 1, 2, or 3.

14. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11 to 13 wherein:

Y^1, Y^2 are CH;

Y^3 is selected from CH or N.

15. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11 to 14, wherein R^1 is selected from cyano, haloC_{1-6}alkoxy, haloC_{1-6} alkylthio, a 4-6 membered heterocyclyloxy, halogen, haloC_{1-6}alkyl, C_{3-5}cycloalkylC_{1-6}alkoxy, and cyanoC_{1-6}alkoxy; wherein the heterocyclyloxy and cycloakylalkoxy are optionally substituted with one C_{1-6}alkyl or haloC_{1-6}alkyl.

16. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11 to 15, wherein R^1 is selected from cyano, haloC_{1-6}alkoxy, haloC_{1-6} alkylthio, and haloC_{1-6}alkyl.

17. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11 to 15, wherein R^1 is selected from cyano, CHF_2O-, CHF_2S-, CH_3CF_2O-, CH_3CFHCH_2O-, CF_3CH_2O-, CH_3CF_2-, CHF_2-, and CF_3-.

18. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 17, wherein R^1 is selected from CHF_2O-, CHF_2S-, CH_3CF_2O-, CH_3CFHCH_2O-, and CF_3CH_2O-.

19. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 17 or 18, wherein R^1 is CHF_2O- or CH_3CF_2O-.

20. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11 to 14, wherein R^1 is 5 membered heteroaryl selected from pyrazolyl and imidazolyl which are optionally substituted with one, two, or three substituents independently selected from halogen or halo$C_{1\text{-}6}$alkyl.

21. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 20, wherein R^1 is unsubstituted pyrazolyl or unsubstituted imidazolyl.

22. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof according to any one of claims 11 to 21, wherein (i) both R^2 and R^3 are hydrogen, or (ii) one of R^2 and R^3 is hydrogen and the other one is hydroxy$C_{1\text{-}6}$alkyl.

23. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 22, wherein one of R^2 and R^3 is hydrogen and the other one is hydroxy$C_{1\text{-}6}$alkyl selected from $HOCH_2$-, $HOCH_2CH_2$-, $HOCH_2CH_2CH_2$-, and $HOCH_2CH_2CH_2CH_2$-.

24. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 23, wherein the hydroxy$C_{1\text{-}6}$alkyl is $HOCH_2$- or $HOCH_2CH_2$-.

25. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 22, wherein both R^2 and R^3 are hydrogen.

26. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11 to 25, wherein n is 0 or 1.

27. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 26, wherein n is 0.

28. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 26, wherein n is 1.

29. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 28, wherein n is 1 and (i) both R^4 and R^5 are hydrogen, (ii) one of R^4 and R^5 is hydrogen and the other one is C_{1-6}alkyl, haloC_{1-6}alkyl, a saturated monocyclic 3-5 membered cycloalkyl, or C_{1-6}alkoxy.

30. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 29, wherein one of R^4 and R^5 is hydrogen and the other one is a methyl (CH_3-) or methoxy (CH_3O-).

31. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 29, wherein one of R^4 and R^5 is hydrogen and the other one is a trifluoromethyl (-CF_3) or difluoromethyl (-CHF_2).

32. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 29, wherein the saturated monocyclic 3-5 membered cycloalkyl is unsubstituted cyclopropyl.

33. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 29, wherein n is 1 and both R^4 and R^5 are hydrogen.

34. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11-29, wherein R^4 and R^5, together with the one carbon atom to which they are attached, form cyclopropyl.

35. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof according to any one of claims 11-34, wherein R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, a 3-10 membered cycloalkyl, C_{1-6}alkyl, haloC_{1-6}alkyl, $Si(C_{1-6}alkyl)_3$ and phenyl; wherein the heterocycloalkyl, heteroaryl, cycloalkyl, or phenyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

36. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof according to any one of claims 11-35, wherein R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 3-10 membered cycloalkyl; wherein the heterocycloalkyl, heteroaryl, or cycloalkyl are optionally substituted with one, two, or three substituents independently selected from halogen, C_{1-6} alkyl, C_{3-6}cycloalkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyano, oxo, hydroxy, hydroxyC_{1-6}alkyl, and haloC_{1-6}alkyl.

37. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 36, wherein R^6 is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CH_2F-, CF_3-, $(CH_3)_2CF$-, cyclopropyl, and CH_3O-, CF_3O-, CHF_2O-, cyano, and hydroxy.

38. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 37, wherein R^6 is optionally substituted with one, two, or three substituents independently selected from Cl-, F-, CH_3-, CF_3-, cyclopropyl, CH_3O-, CF_3O- and CHF_2O- .

39. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 37 or 38, wherein R^6 is optionally substituted with one, two, or three substituents independently selected from F-, CF_3-, CF_3O- and CHF_2O-.

40. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 35-39, wherein R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl;

c) a 3-10 membered cycloalkyl selected from a saturated monocyclic 3-6 membered cycloalkyl, a 6 membered cycloalkenyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings;

d) phenyl;

e) C_{1-6}alkyl;

f) haloC_{1-6}alkyl;

g) Si(C_{1-6}alkyl)$_3$; and

optionally substituted according to any one of claims 35-39.

41. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 40, wherein R^6 is selected from:

a) a 5-12 membered heterocycloalkyl, which heterocycloalkyl is selected from a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom; a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom; and a 7-10 membered bridged heterocycloalkyl, wherein the bridge comprises an O-atom;

b) a 6 membered heteroaryl; and

c) a 3-10 membered cycloalkyl selected from a saturated monocyclic 3-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings.

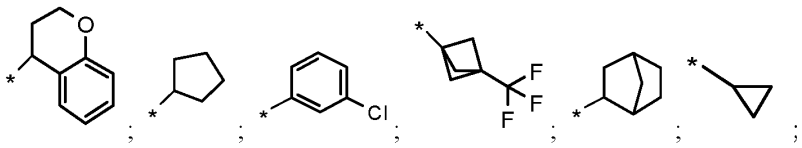
42. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 35-41, wherein R^6 is selected from:

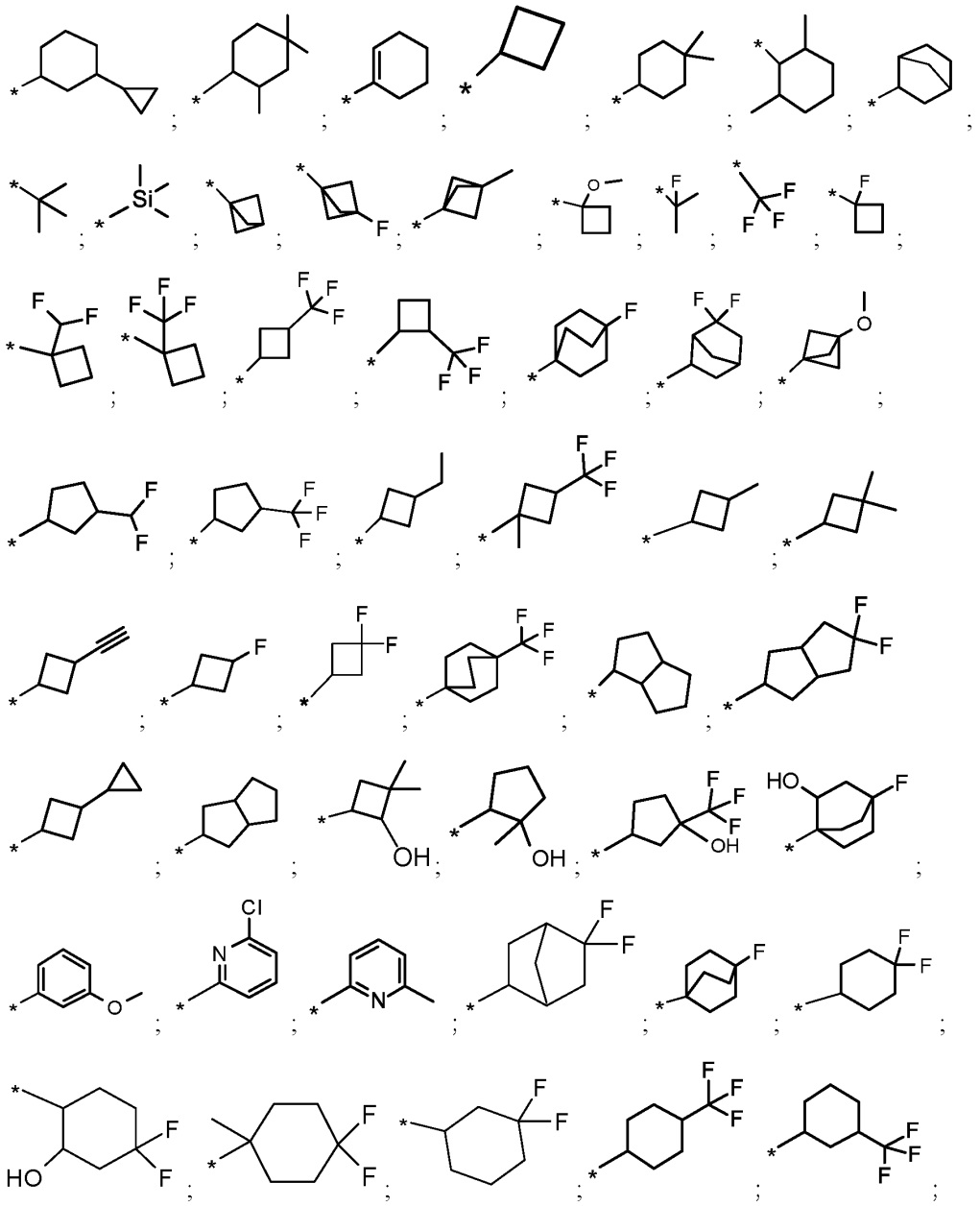
dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, tert-butyl, bicyclo[2.2.2]octanyl, $(CH_3)_2CF$-, CHF_2-, $Si(CH_3)_3$, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyridinyl, and pyrimidinyl.

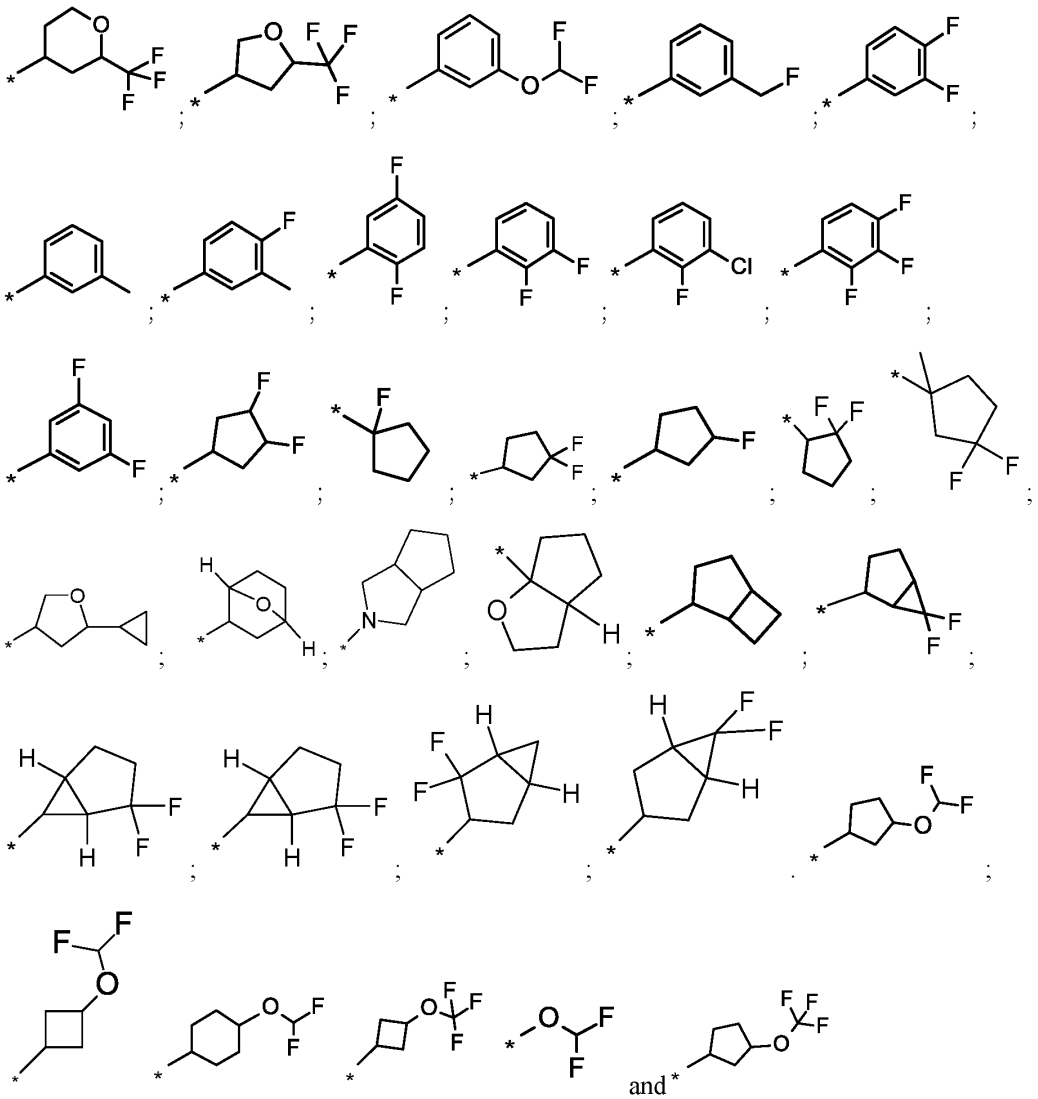
43. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 35-42, wherein R^6 is selected from:

dihydrochromenyl, cyclopentyl, phenyl, cyclohexyl, bicyclo[1.1.1]pentanyl, bicyclo[2.2.1]heptanyl, cyclohexenyl, cyclobutyl, bicyclo[2.2.2]octanyl, bicyclo[3.1.0]hexanyl, oxolanyl, octahydropentalenyl, hexahydrocyclopenta[b]furanyl, pyrazinyl, pyridinyl, and pyrimidinyl.

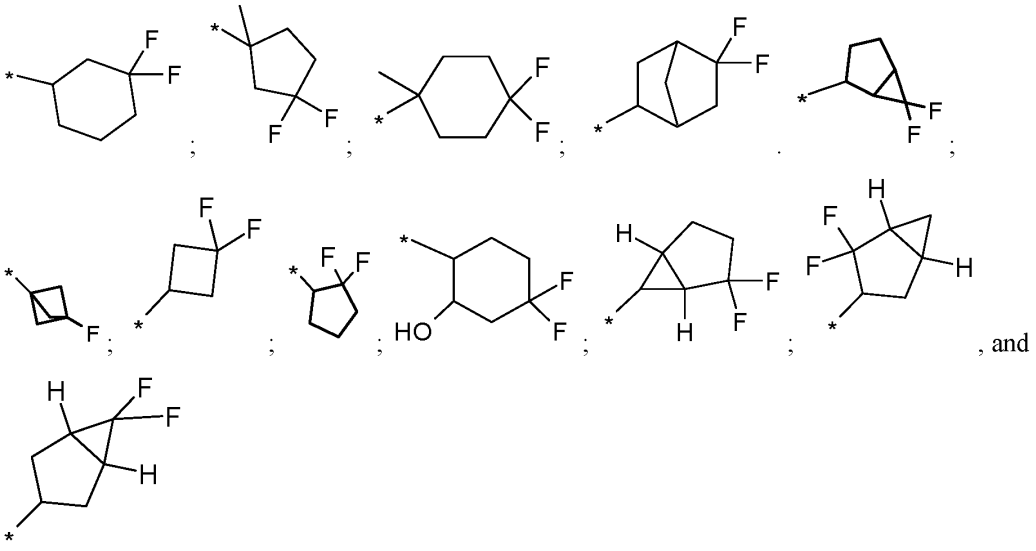
44. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 35-43, wherein R^6 is selected from:







45. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 44, wherein R^6 is selected from:



46. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 35-45, wherein R^1 is selected from CHF_2O-, unsubstituted pyrazolyl, unsubstituted imidazolyl, CH_3O-, $(CH_3)CF_2$-, CN-, CHF_2-, CF_3-, CF_3CH_2O-, CH_3CFHCH_2O-, CF_2H-S-, R^2 and R^3 are hydrogen, n is 0 or 1, (i) R^4 and R^5 are hydrogen, or (ii) one of R^4 and R^5 is hydrogen and the other is cyclopropyl, or (iii) one of R^4 and R^5 is hydrogen and the other is selected from CF_3-, CHF_2, and CH_2F or (iv) R^4 and R^5 together with the one carbon atom to which they are attached, form cyclopropyl, and R^6 is selected from a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, a 7-10 membered bridged heterosystem, wherein the bridge comprises an O-atom, a 6 membered heteroaryl; and a 3-10 membered cycloalkyl selected from cyclopropyl, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, all optionally substituted according to any one of claims 35-39 and 44-45.

47. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 46, wherein R^1 is selected from CF_3CH_2O-, CHF_2O- or unsubstituted imidazolyl, R^2 and R^3 are hydrogen, n is 0 or 1, (i) R^4 and R^5 are hydrogen, or (ii) one of R^4 and R^5 are hydrogen and the other is cyclopropyl, or (iii) one of R^4 and R^5 is hydrogen and the other is selected from CF_3-, CHF_2, and CH_2F, or (iii) R^4 and R^5 together with the one carbon atom to which they are attached, form cyclopropyl, and R^6 is selected from a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, a 7-10 membered bridged heterosystem, wherein the bridge comprises an O-atom; a 6 membered heteroaryl; and a 3-10 membered cycloalkyl selected from cyclopropyl, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings, all optionally substituted according to any one of claims 34-38 and 43-44.

48. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 46 or 47, wherein R^1 is selected from CF_3CH_2O-, CHF_2O- and unsubstituted imidazolyl, R^2 and R^3 are hydrogen, n is 0; and R^6 is selected from a 5-12 membered heterocycloalkyl which heterocycloalkyl is a bicyclic edge-to-edge fused heterocycloalkyl comprising one aliphatic and one aromatic ring, wherein one ring comprises one O-atom, a 7-10 membered bicyclic edge-to-edge fused heterocycloalkyl comprising two aliphatic rings, wherein the one ring comprises one O-atom or one N-atom, a 7-10 membered bridged heterosystem, wherein the bridge comprises an O-atom; a 6 membered heteroaryl; and a 3-10 membered cycloalkyl selected from cyclopropyl, a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings; all optionally substituted according to any one of claims 34-38 and 43-44.

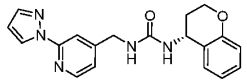
49. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 46-48, wherein R^1 is CF_3CH_2O-, or CHF_2O- and R^6 is substituted with one or two F- or CF_3-, or R^6 is CF_3-.

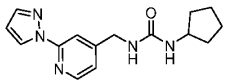
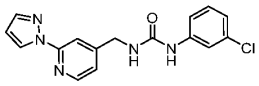
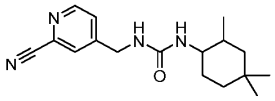
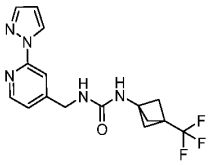
50. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 49, wherein R^1 is CHF_2O- and R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings; all substituted with one or two F- or CF_3-.

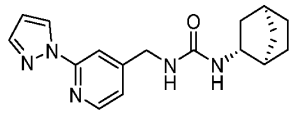
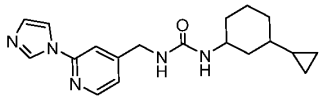
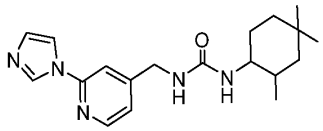
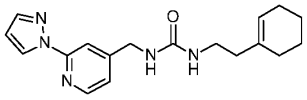
51. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 35-49 wherein R^1 is CHF_2O-, n is 0 or 1, and R^6 is selected from a 5-12 membered heterocycloalkyl, a 6 membered heteroaryl, and a 4-10 membered cycloalkyl; all substituted with substituted with one or two F- or CF_3-.

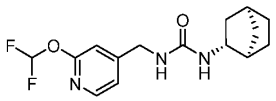
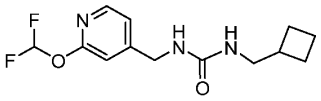
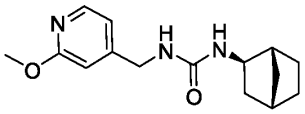
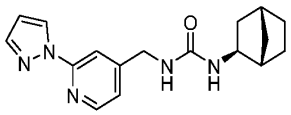
52. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to 51, wherein R^6 is selected from a saturated monocyclic 4-6 membered cycloalkyl, a 4-10 membered bridged cycloalkyl, and a 7-10 membered bicyclic edge-to-edge fused cycloalkyl comprising two aliphatic rings; all substituted with one or two F- or CF_3-.

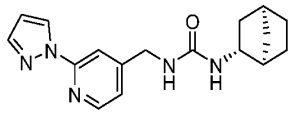
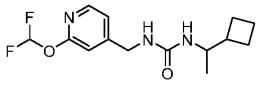
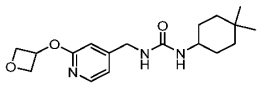
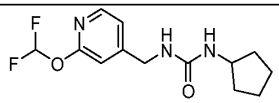
53. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11-52, or a pharmaceutical composition according to any one of claims 1-9, wherein the compound is selected from:

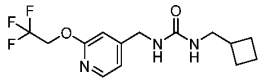
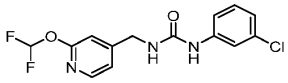
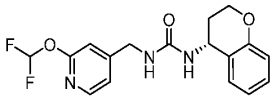
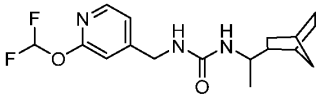
Example	Name	Structure
1	1-[(4R)-3,4-dihydro-2H-chromen-4-yl]-3-[(2-pyrazol-1-	

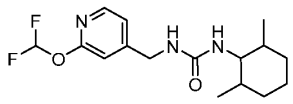
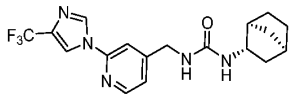
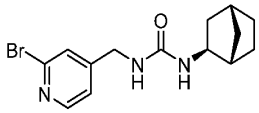
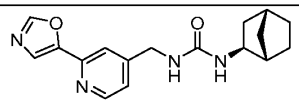
Example	Name	Structure
	ylpyridin-4-yl)methyl]urea	
2	1-cyclopentyl-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
4	1-(3-chlorophenyl)-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
5	1-[(2-cyanopyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	
6	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[3-(trifluoromethyl)-1-	

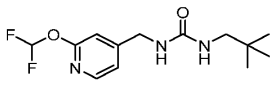
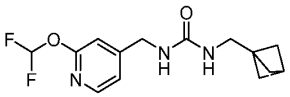
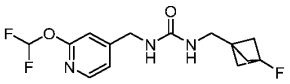
Example	Name	Structure
	bicyclo[1.1.1]pentanyl]urea	
7	1-[(2-pyrazol-1-ylpyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
8	1-(3-cyclopropylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea	
9	1-[(2-imidazol-1-ylpyridin-4-yl)methyl]-3-(2,4,4-trimethylcyclohexyl)urea	
10	1-[2-(cyclohexen-1-yl)ethyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	

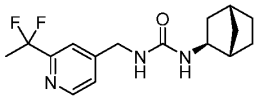
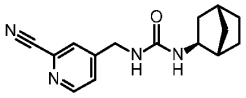
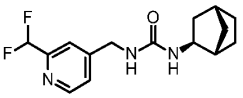
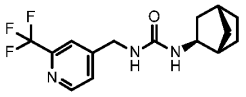
Example	Name	Structure
12	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
13	1-(cyclobutylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
14	1-[(2-methoxypyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
15	1-[(1S,2S,4R)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-	

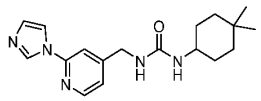
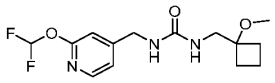
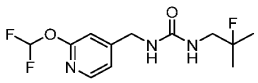
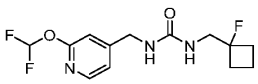
Example	Name	Structure
	ylpyridin-4-yl)methyl]urea	
16	1-[(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[(2-pyrazol-1-ylpyridin-4-yl)methyl]urea	
17	1-(1-cyclobutylethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
18	1-(4,4-dimethylcyclohexyl)-3-[[2-(oxetan-3-yloxy)pyridin-4-yl]methyl]urea	
20	1-cyclopentyl-3-[[2-(difluoromethoxy)	

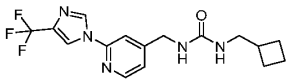
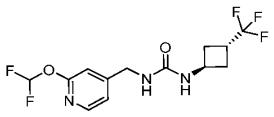
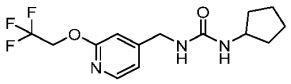
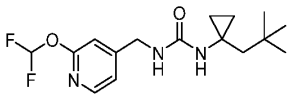
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
21	1-(cyclobutylmethyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
22	1-(3-chlorophenyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
23	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(4R)-3,4-dihydro-2H-chromen-4-yl]urea	
24	1-[1-(2-bicyclo[2.2.1]heptanyl)ethyl]-3-[[2-(difluoromethoxy)	

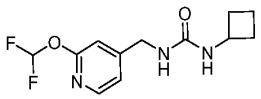
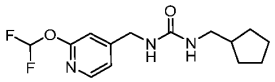
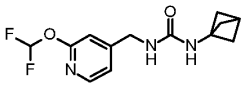
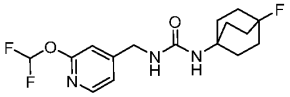
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
25	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,6-dimethylcyclohexyl)urea	
26	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	
27	1-[(2-bromopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
28	1-[[2-(1,3-oxazol-5-yl)pyridin-4-yl]methyl]-3-[rac-	

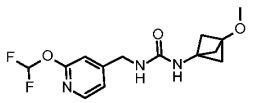
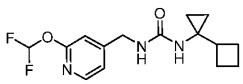
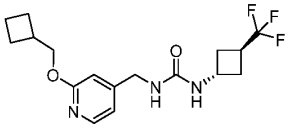
Example	Name	Structure
	(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
29	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,2-dimethylpropyl)urea	
31	1-(1-bicyclo[1.1.1]pentanylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
32	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]urea	

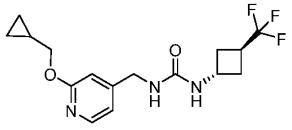
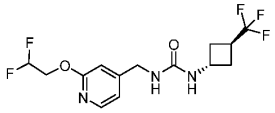
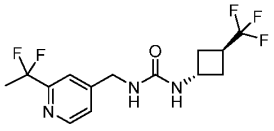
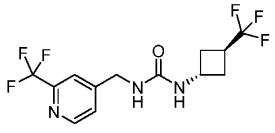
Example	Name	Structure
33	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
34	1-[(2-cyanopyridin-4-yl)methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
35	1-[[2-(difluoromethyl)pyridin-4-yl]methyl]-3-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]urea	
36	1-[rac-(1R,2R,4S)-2-bicyclo[2.2.1]heptanyl]-3-[[2-(trifluoromethyl)p	

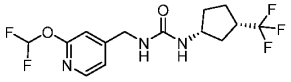
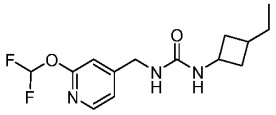
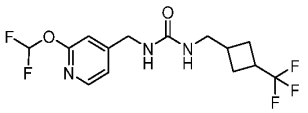
Example	Name	Structure
	yridin-4-yl]methyl]urea	
37	1-(4,4-dimethylcyclohexyl)-3-[(2-imidazol-1-ylpyridin-4-yl)methyl]urea	
38	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-methoxycyclobutyl)methyl]urea	
39	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-fluoro-2-methylpropyl)urea	
40	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclobutyl)methyl]urea	

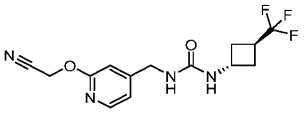
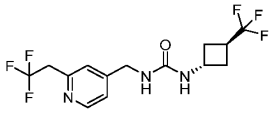
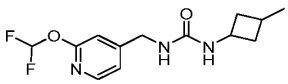
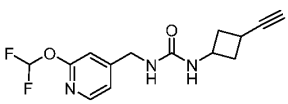
Example	Name	Structure
41	1-(cyclobutylmethyl)-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	
42	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
43	1-cyclopentyl-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
44	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2-	

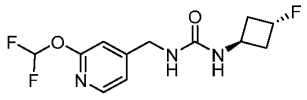
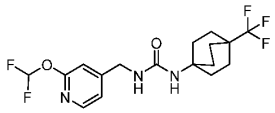
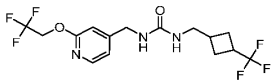
Example	Name	Structure
	dimethylpropyl)cyclopropyl]urea	
45	1-cyclobutyl-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
46	1-(cyclopentylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
47	1-(1-bicyclo[1.1.1]pentanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
48	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-	

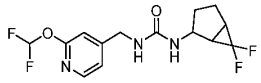
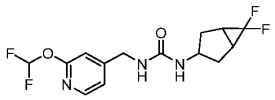
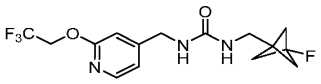
Example	Name	Structure
	bicyclo[2.2.2]octanyl)urea	
49	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxy-1-bicyclo[1.1.1]pentanyl)urea	
50	1-(1-cyclobutylcyclopropyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
54	1-[[2-(cyclobutylmethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-	

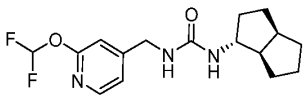
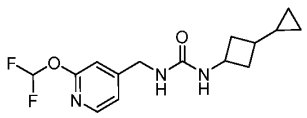
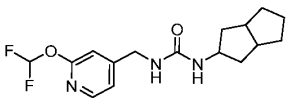
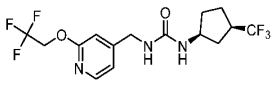
Example	Name	Structure
	(trifluoromethyl)cyclobutyl]urea	
55	1-[[2-(cyclopropylmethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
56	1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
57	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
58	1-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(trifluoromethyl)p	

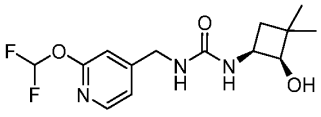
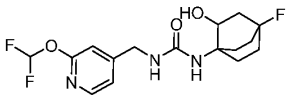
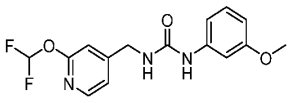
Example	Name	Structure
	yridin-4-yl]methyl]urea	
59	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea	
60	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethylcyclobutyl)urea	
62	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	

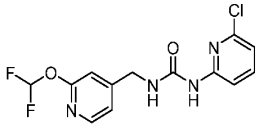
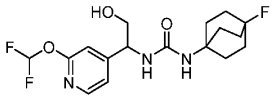
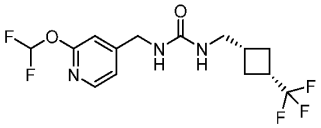
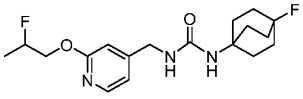
Example	Name	Structure
63	1-[[2-(cyanomethoxy)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
64	1-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
65	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylcyclobutyl)urea	
66	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-ethynylcyclobutyl)urea	

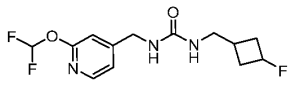
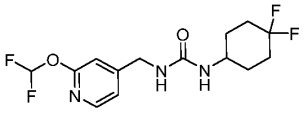
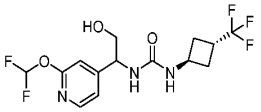
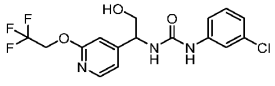
Example	Name	Structure
67	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1*r*,3*r*)-3-fluorocyclobutyl)urea	
68	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[4-(trifluoromethyl)-1-bicyclo[2.2.2]octanyl]urea	
71	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[3-(trifluoromethyl)cyclobutyl]methyl]urea	

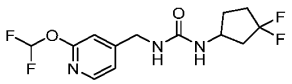
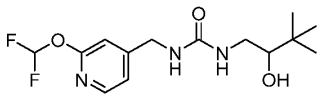
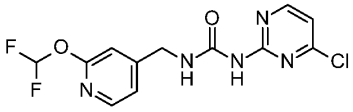
Example	Name	Structure
73	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]urea	
74	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
75	1-[(3-fluoro-1-bicyclo[1.1.1]pentanyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

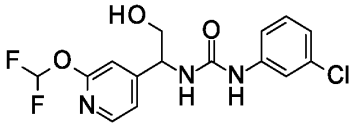
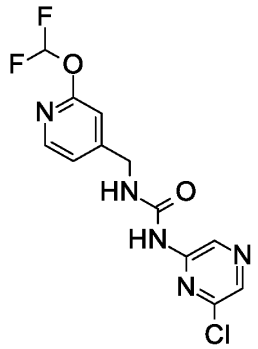
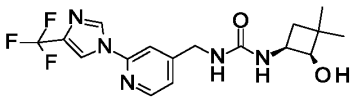
Example	Name	Structure
76	1-[(1R,3aR,6aR)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
77	1-(3-cyclopropylcyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
78	1-(1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
79	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]-3-[[2-(2,2,2-trifluoroethoxy)py	

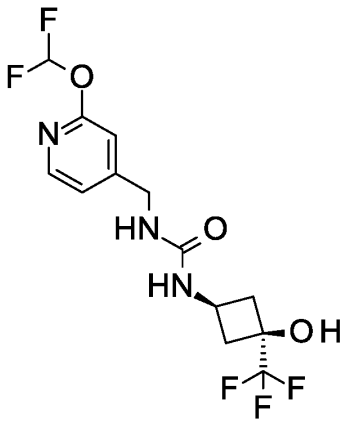
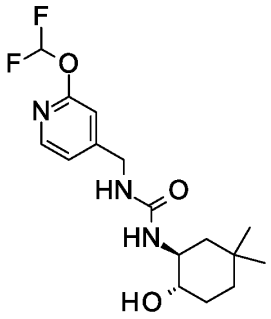
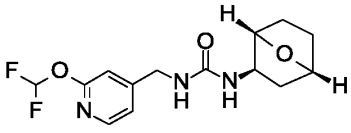
Example	Name	Structure
	ridin-4-yl]methyl]urea	
81	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]urea	
82	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-2-hydroxy-1-bicyclo[2.2.2]octanyl)urea	
83	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methoxyphenyl)urea	

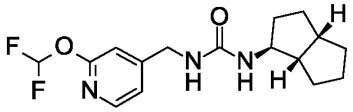
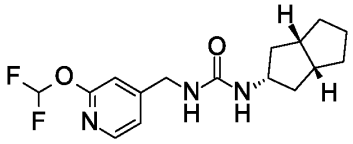
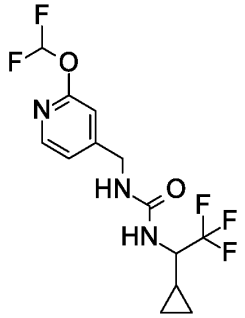
Example	Name	Structure
84	1-(6-chloropyridin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
85	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
87	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[3-(1r,3r)-(trifluoromethyl)cyclobutyl]methyl]urea	
88	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2-	

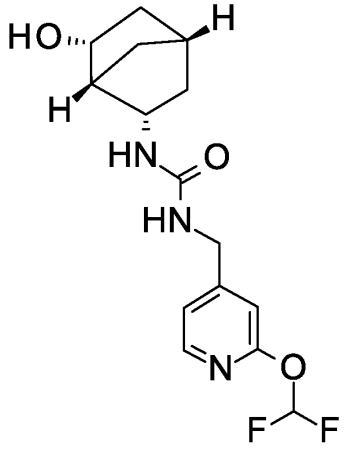
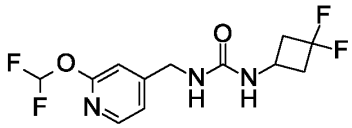
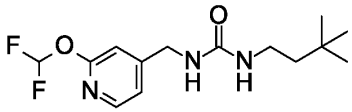
Example	Name	Structure
	fluoropropoxy)pyridin-4-yl]methyl]urea	
89	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3-fluorocyclobutyl)methyl]urea	
90	1-(4,4-difluorocyclohexyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
91	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(1*r*,3*r*)-3-(trifluoromethyl)cyclobutyl]urea	
92	1-(3-chlorophenyl)-3-[2-hydroxy-1-[2-	

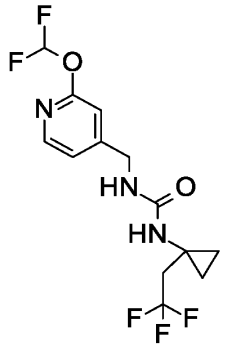
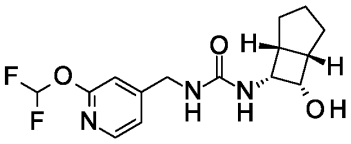
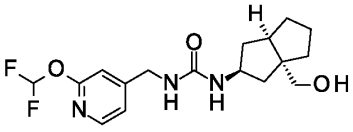
Example	Name	Structure
	(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
93	1-(3,3-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
95	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-hydroxy-3,3-dimethylbutyl)urea	
96	1-(4-chloropyrimidin-2-yl)-3-[[2-(difluoromethoxy)	

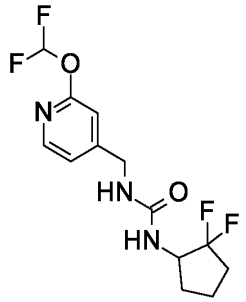
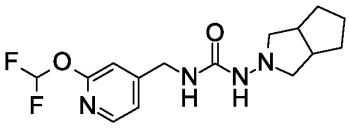
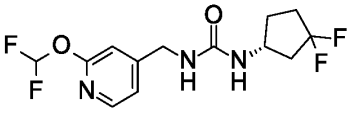
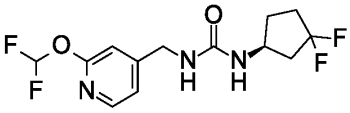
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
97	1-(3-chlorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
98	1-(6-chloropyrazin-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
99	1-[rac-(1R,2S)-2-hydroxy-3,3-dimethylcyclobutyl]-3-[[2-[4-(trifluoromethyl)imidazol-1-yl]pyridin-4-yl]methyl]urea	

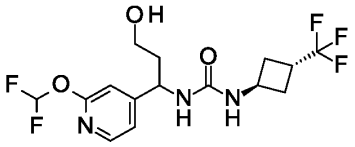
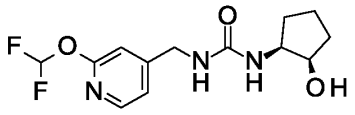
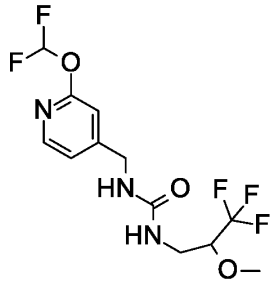
Example	Name	Structure
100	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-hydroxy-3-(trifluoromethyl)cyclobutyl]urea	
101	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-5,5-dimethylcyclohexyl]urea	
102	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S)-7-oxabicyclo[2.2.1]heptan-2-yl]urea	

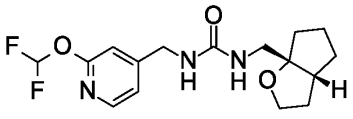
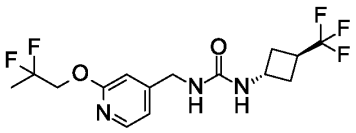
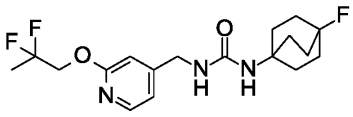
Example	Name	Structure
103	1-[(1S,3aS,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-1-yl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
105	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(3aR,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]urea	
106	1-(1-cyclopropyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

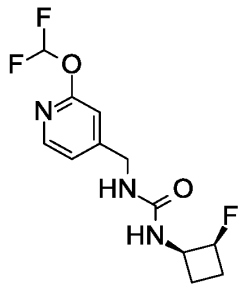
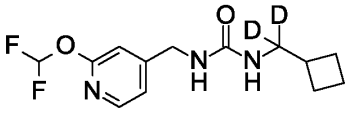
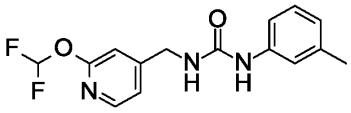
Example	Name	Structure
107	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S,6R)-6-hydroxy-2-bicyclo[2.2.1]heptanyl]urea	
108	1-(3,3-difluorocyclobutyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
109	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-dimethylbutyl)urea	

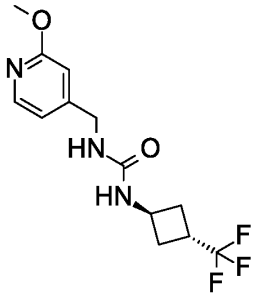
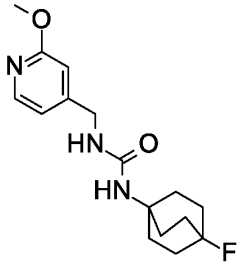
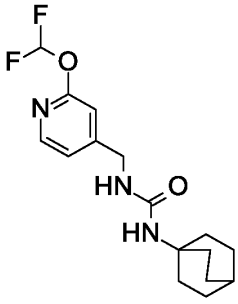
Example	Name	Structure
110	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(2,2,2-trifluoroethyl)cyclopropyl]urea	
111	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6S,7R)-7-hydroxy-6-bicyclo[3.2.0]heptanyl]urea	
112	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(2R,3aS,6aS)-6a-(hydroxymethyl)-2,3,3a,4,5,6-hexahydro-1H-pentalen-2-yl]urea	

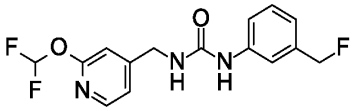
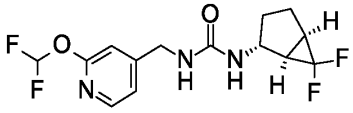
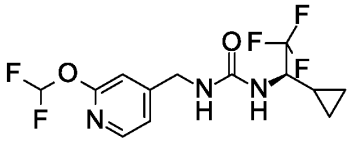
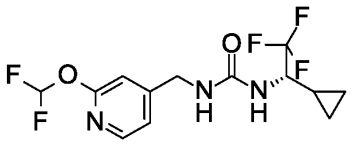
Example	Name	Structure
113	1-(2,2-difluorocyclopentyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
114	1-(3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrol-2-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
115	1-[(1R)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
116	1-[(1S)-3,3-difluorocyclopentyl]-3-[[2-(difluoromethoxy)	

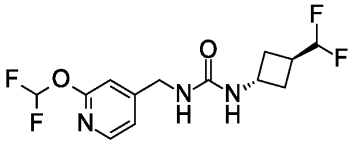
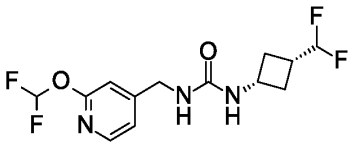
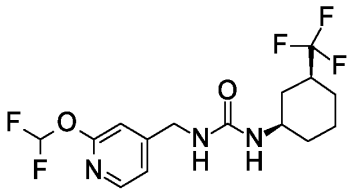
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
117	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-3-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
118	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-hydroxycyclopentyl]urea	
119	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3,3-trifluoro-2-methoxypropyl)urea	

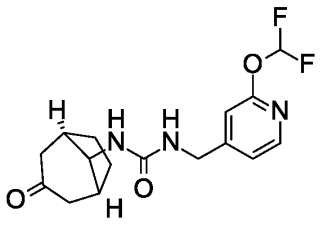
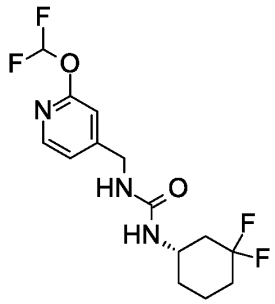
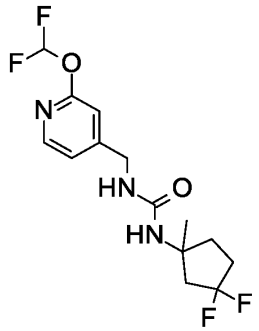
Example	Name	Structure
120	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[rac-(3aR,6aR)-2,3,3a,4,5,6-hexahydrocyclopenta[b]furan-6a-yl]methyl]urea	
121	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
122	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	

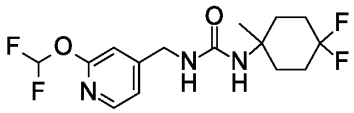
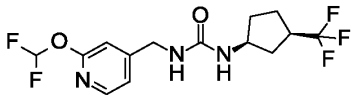
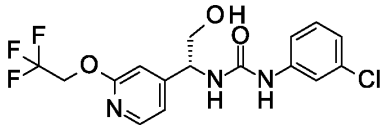
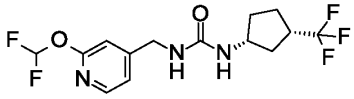
Example	Name	Structure
123	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-fluorocyclobutyl]urea	
125	1-[cyclobutyl(dideuterio)methyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
126	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methylphenyl)urea	

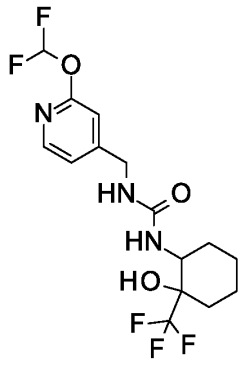
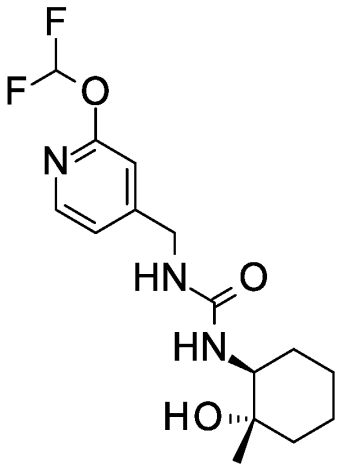
Example	Name	Structure
128	1-[(2-methoxypyridin-4-yl)methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
129	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[(2-methoxypyridin-4-yl)methyl]urea	
131	1-(1-bicyclo[2.2.2]octanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

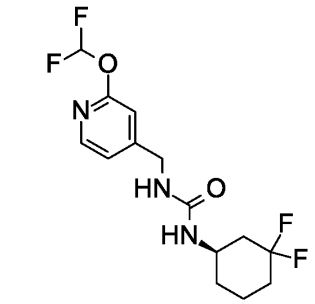
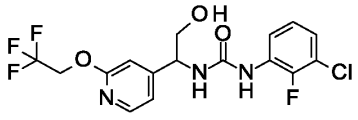
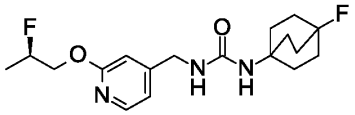
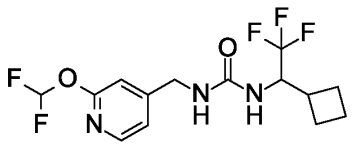
Example	Name	Structure
132	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(fluoromethyl)phenyl]urea	
133	1-[(1R,2R,5R)-6,6-difluoro-2-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
134	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
135	1-[(1S)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)	

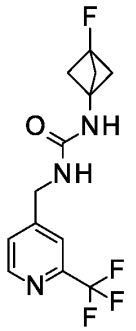
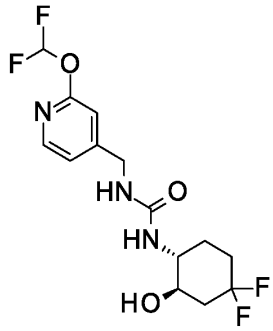
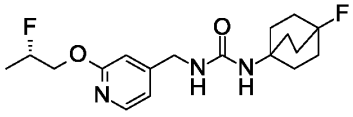
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
136	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(difluoromethyl)cyclobutyl]urea	
137	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,3s)-3-(difluoromethyl)cyclobutyl]urea	
138	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	

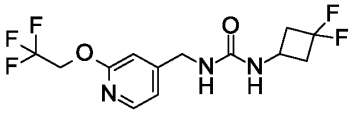
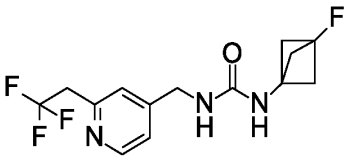
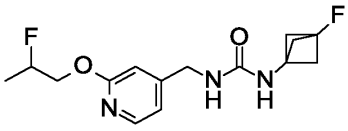
Example	Name	Structure
139	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3-oxo-8-bicyclo[3.2.1]octanyl]urea	
140	1-[(1S)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
142	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-difluoro-1-methylcyclopentyl)urea	

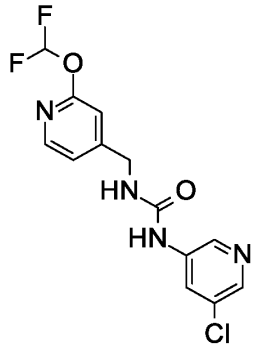
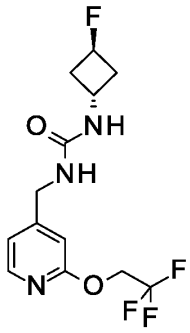
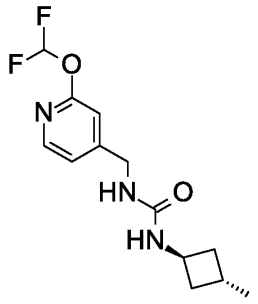
Example	Name	Structure
143	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4,4-difluoro-1-methylcyclohexyl)urea	
144	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3R)-3-(trifluoromethyl)cyclopentyl]urea	
145	1-(3-chlorophenyl)-3-[(1R)-2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
146	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-	

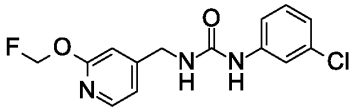
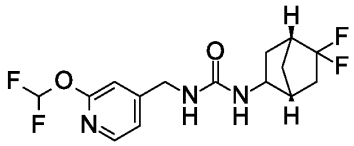
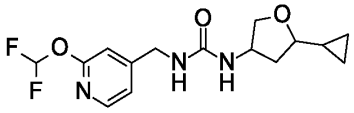
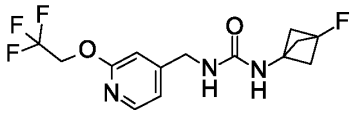
Example	Name	Structure
	(trifluoromethyl)cyclopentyl]urea	
147	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-hydroxy-2-(trifluoromethyl)cyclohexyl]urea	
148	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-2-hydroxy-2-methylcyclohexyl]urea	

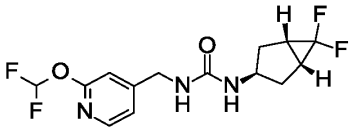
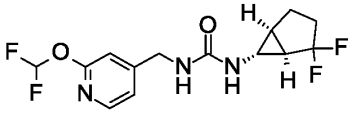
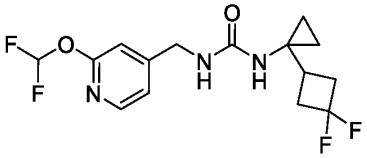
Example	Name	Structure
149	1-[(1R)-3,3-difluorocyclohexyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
150	1-(3-chloro-2-fluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
151	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]urea	
152	1-(1-cyclobutyl-2,2,2-trifluoroethyl)-3-[[2-(difluoromethoxy)	

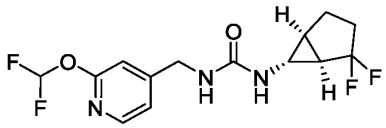
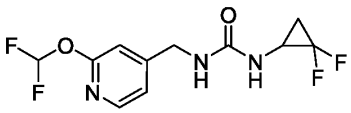
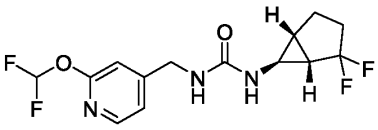
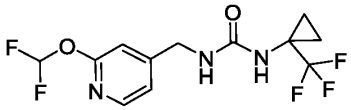
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
153	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(trifluoromethyl)pyridin-4-yl]methyl]urea	
154	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2R)-4,4-difluoro-2-hydroxycyclohexyl]urea	
156	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]urea	

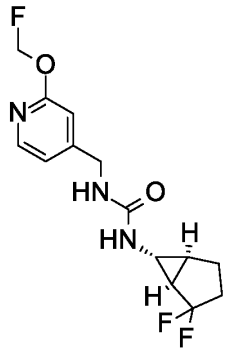
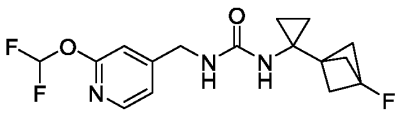
Example	Name	Structure
157	1-(3,3-difluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
159	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
160	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]urea	

Example	Name	Structure
161	1-(5-chloropyridin-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
162	1-((1r,3r)-3-fluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
163	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-((1r,3r)-3-methylcyclobutyl)urea	

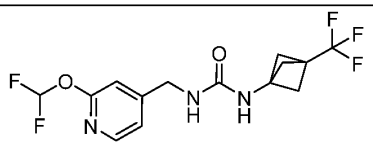
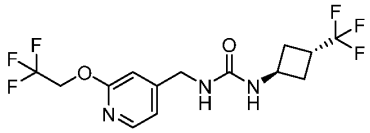
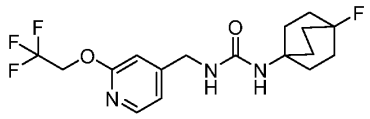
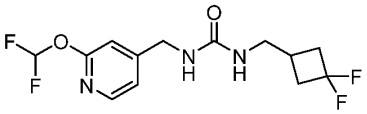
Example	Name	Structure
164	1-(3-chlorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
165	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,4R)-5,5-difluoro-2-bicyclo[2.2.1]heptanyl]urea	
166	1-(5-cyclopropyloxolan-3-yl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
168	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(2,2,2-trifluoroethoxy)py	

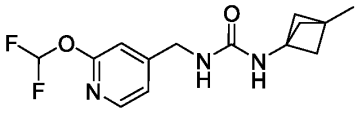
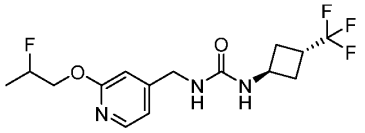
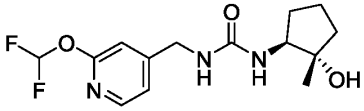
Example	Name	Structure
	ridin-4-yl]methyl]urea	
169	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
170	1-[(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
171	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

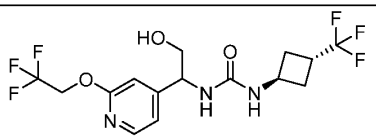
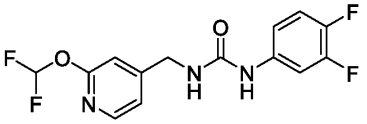
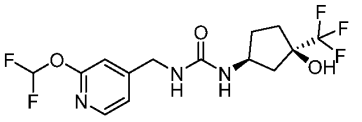
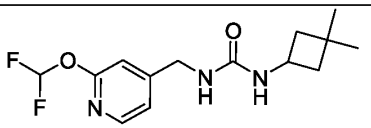
Example	Name	Structure
172	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
173	1-(2,2-difluorocyclopropyl)-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
174	1-[(1S,5R,6S)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
175	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[1-	

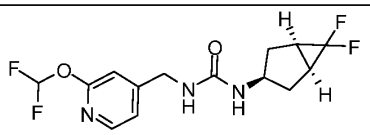
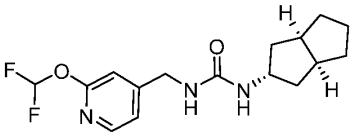
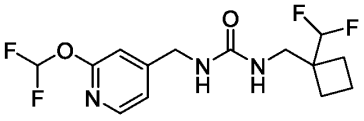
Example	Name	Structure
	(trifluoromethyl)cyclopropyl]urea	
176	1-[[2-(fluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-2,2-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
177	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)cyclopropyl]urea	

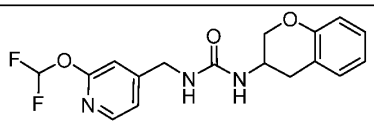
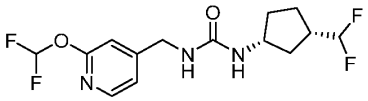
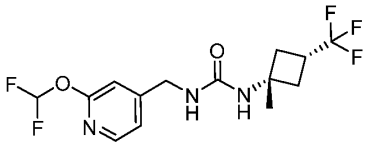
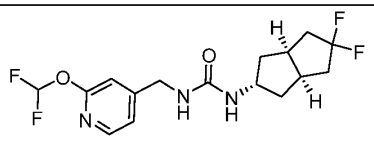
54. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11-52, or a pharmaceutical composition according to any one of claims 1-9, wherein the compound is selected from:

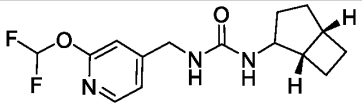
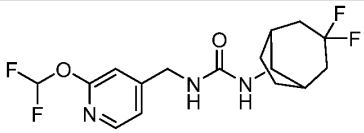
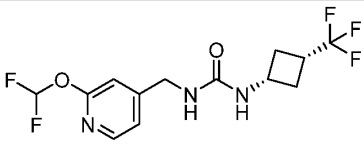
Example	Name	Structure
178	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3-(trifluoromethyl)-1-bicyclo[1.1.1]pentanyl]urea	
179	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
180	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
181	1-[(3,3-difluorocyclobutyl)methyl]-3-[[2-(difluoromethoxy)	

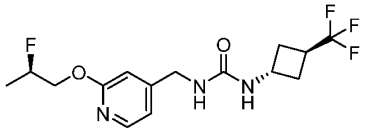
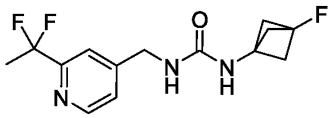
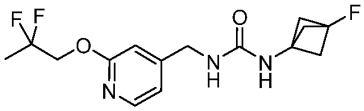
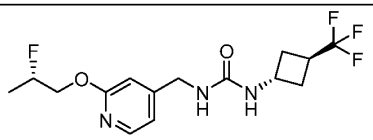
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
182	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3-methyl-1-bicyclo[1.1.1]pentanyl)urea	
183	1-[[2-(2-fluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
184	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,2S)-2-hydroxy-2-methylcyclopentyl]urea	

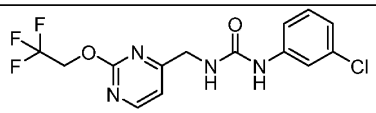
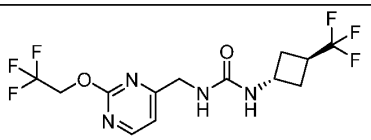
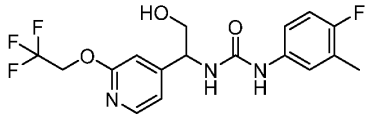
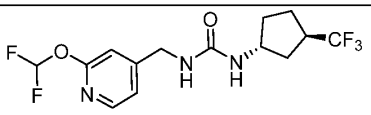
Example	Name	Structure
185	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
186	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-difluorophenyl)urea	
187	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-hydroxy-3-(trifluoromethyl)cyclopentyl]urea	
188	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,3-	

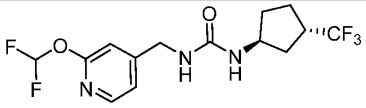
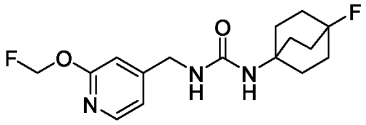
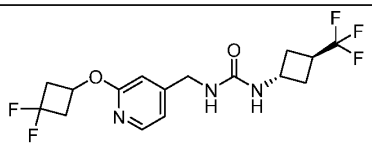
Example	Name	Structure
	dimethylcyclobutyl)urea	
189	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3r,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]urea	
190	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2s,3aR,6aS)-1,2,3,3a,4,5,6,6a-octahydropentalen-2-yl]urea	
191	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(difluoromethyl)cyclobutyl]methyl]urea	

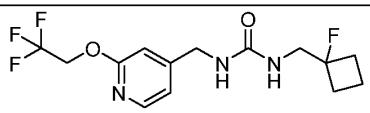
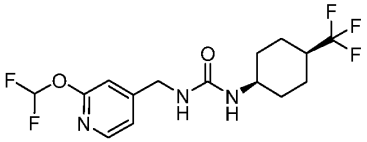
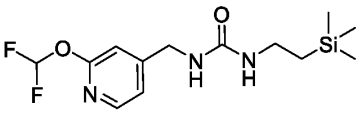
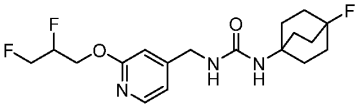
Example	Name	Structure
192	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(3,4-dihydro-2H-chromen-3-yl)urea	
193	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(difluoromethyl)cyclopentyl]urea	
194	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-1-methyl-3-(trifluoromethyl)cyclobutyl]urea	
195	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2r,3aR,6aS)-5,5-	

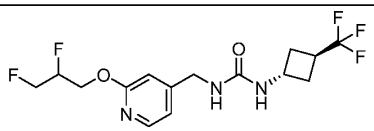
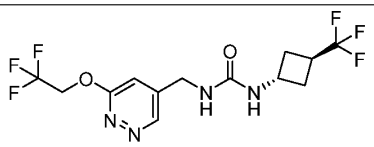
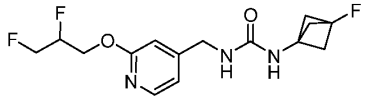
Example	Name	Structure
	difluoro-2,3,3a,4,6,6a-hexahydro-1H-pentalen-2-yl]urea	
196	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[rac-(1R,5R)-2-bicyclo[3.2.0]heptanyl]urea	
197	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[rac-(1R,5S)-3,3-difluoro-8-bicyclo[3.2.1]octanyl]urea	
198	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[(1s,3s)-3-	

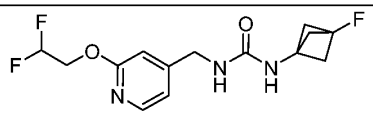
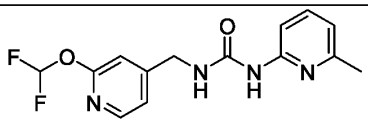
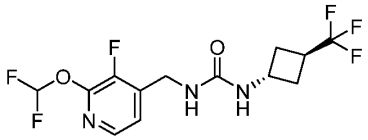
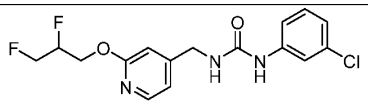
Example	Name	Structure
	(trifluoromethyl)cyclobutyl]urea	
199	1-[[2-[(2R)-2-fluoropropoxy]pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
200	1-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
201	1-[[2-(2,2-difluoropropoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
202	1-[[2-[(2S)-2-fluoropropoxy]pyridin-4-yl]methyl]-3-[(1r,3r)-3-	

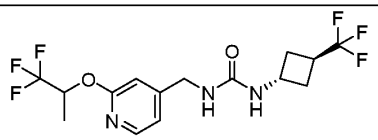
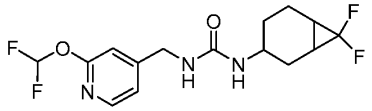
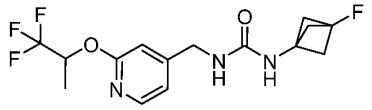
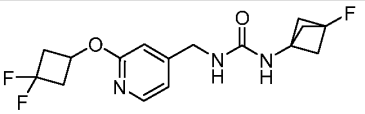
Example	Name	Structure
	(trifluoromethyl)cyclobutyl]urea	
203	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]urea	
204	1-[[2-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
205	1-(4-fluoro-3-methylphenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
206	1-[[2-(difluoromethoxy)pyridin-4-	

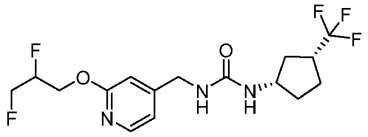
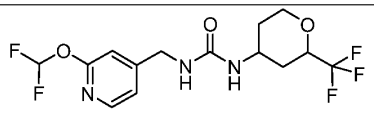
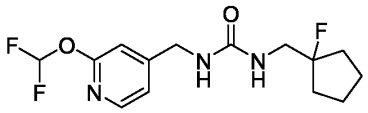
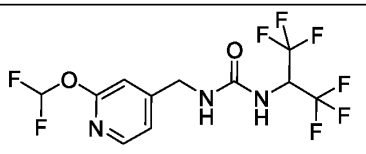
Example	Name	Structure
	yl]methyl]-3-[(1R,3R)-3-(trifluoromethyl)cyclopentyl]urea	
207	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1S,3S)-3-(trifluoromethyl)cyclopentyl]urea	
208	1-(4-fluoro-1-bicyclo[2.2.2]octanyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
209	1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

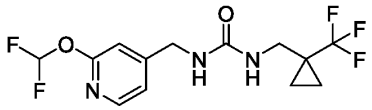
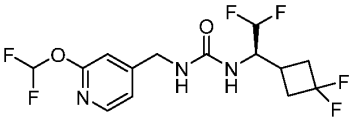
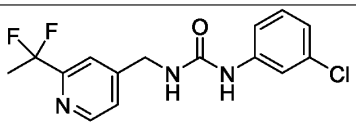
Example	Name	Structure
210	1-[(1-fluorocyclobutyl)methyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
211	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1s,4s)-4-(trifluoromethyl)cyclohexyl]urea	
212	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2-trimethylsilylethyl)urea	
213	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-	

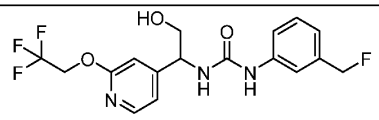
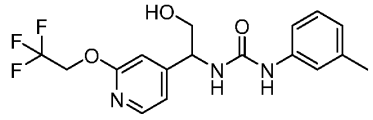
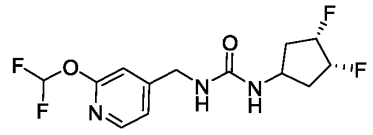
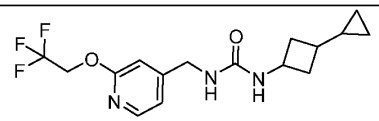
Example	Name	Structure
	bicyclo[2.2.2]octanyl)urea	
214	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
215	1-[[6-(2,2,2-trifluoroethoxy)pyridazin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
216	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	

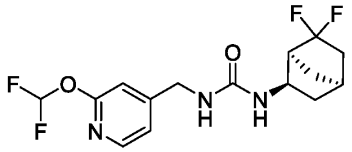
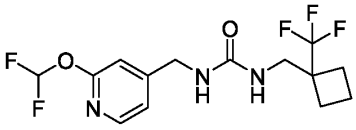
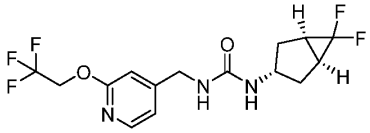
Example	Name	Structure
217	1-[[2-(2,2-difluoroethoxy)pyridin-4-yl]methyl]-3-(3-fluoro-1-bicyclo[1.1.1]pentanyl)urea	
218	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(6-methylpyridin-2-yl)urea	
219	1-[[2-(difluoromethoxy)-3-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
220	1-(3-chlorophenyl)-3-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]urea	

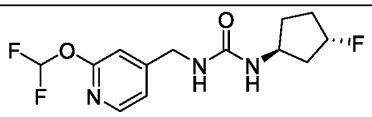
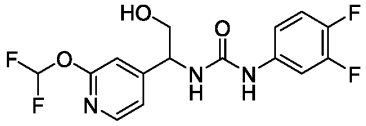
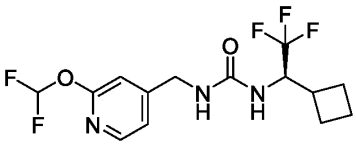
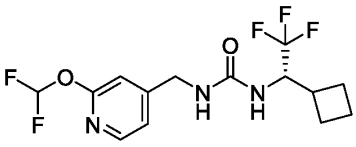
Example	Name	Structure
221	1-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]-3-[[2-(1,1,1-trifluoropropan-2-yloxy)pyridin-4-yl]methyl]urea	
222	1-(7,7-difluoro-3-bicyclo[4.1.0]heptanyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
223	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[[2-(1,1,1-trifluoropropan-2-yloxy)pyridin-4-yl]methyl]urea	
224	1-[[2-(3,3-difluorocyclobutyl)oxypyridin-4-yl]methyl]-3-(3-fluoro-1-	

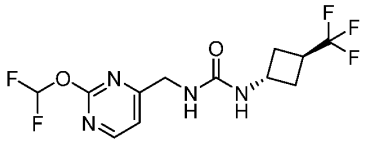
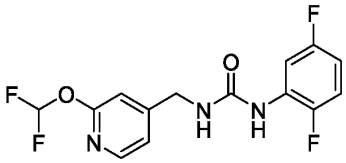
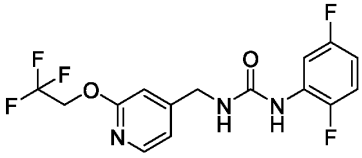
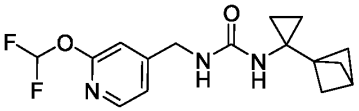
Example	Name	Structure
	bicyclo[1.1.1]pentanyl)urea	
225	1-[[2-(2,3-difluoropropoxy)pyridin-4-yl]methyl]-3-[rac-(1R,3S)-3-(trifluoromethyl)cyclopentyl]urea	
226	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(trifluoromethyl)oxan-4-yl]urea	
227	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1-fluorocyclopentyl)methyl]urea	
228	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-	

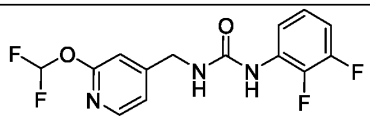
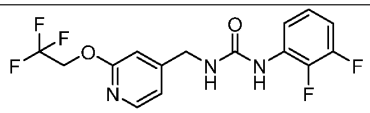
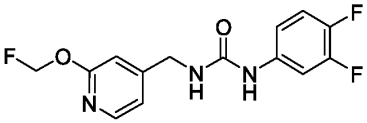
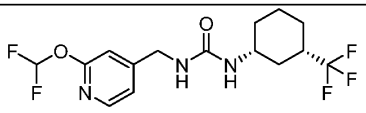
Example	Name	Structure
	(1,1,1,3,3,3-hexafluoropropan-2-yl)urea	
229	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
230	1-[(1R)-1-(3,3-difluorocyclobutyl)-2,2-difluoroethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
231	1-(3-chlorophenyl)-3-[[2-(1,1-difluoroethyl)pyridin-4-yl]methyl]urea	

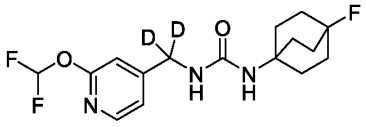
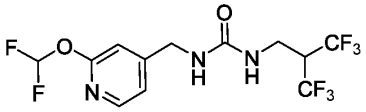
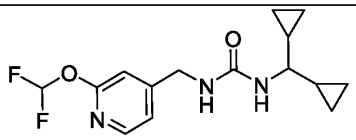
Example	Name	Structure
232	1-[3-(fluoromethyl)phenyl]-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
233	1-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]-3-(3-methylphenyl)urea	
234	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(3R,4S)-3,4-difluorocyclopentyl]urea	
235	1-(3-cyclopropylcyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)py	

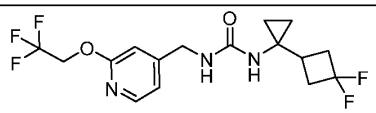
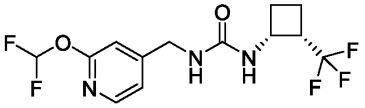
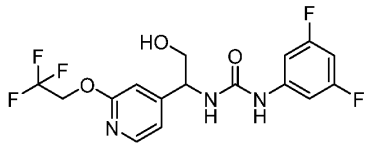
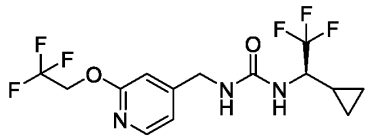
Example	Name	Structure
	ridin-4-yl]methyl]urea	
236	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S,4S)-6,6-difluoro-2-bicyclo[2.2.1]heptanyl]urea	
237	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclobutyl]methyl]urea	
238	1-[(1R,3s,5S)-6,6-difluoro-3-bicyclo[3.1.0]hexanyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	

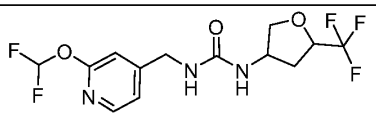
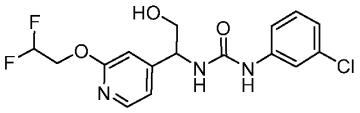
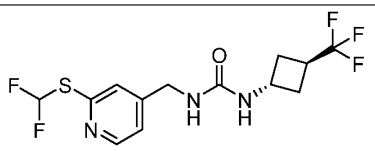
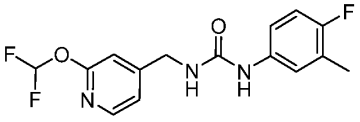
Example	Name	Structure
239	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[(1S,3S)-3-fluorocyclopentyl] urea	
240	1-[1-[2-(difluoromethoxy) pyridin-4-yl]-2-hydroxyethyl]-3-(3,4-difluorophenyl)urea	
241	1-[(1R)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
242	1-[(1S)-1-cyclobutyl-2,2,2-trifluoroethyl]-3-[[2-(difluoromethoxy)	

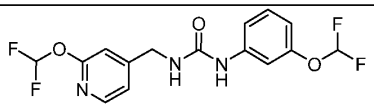
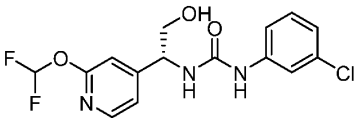
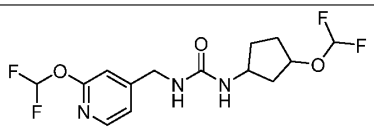
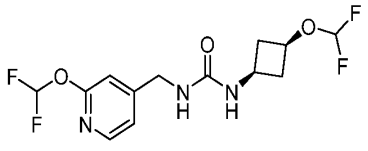
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
243	1-[[2-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
244	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,5-difluorophenyl)urea	
245	1-(2,5-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
246	1-[1-(1-bicyclo[1.1.1]pentanyl)cyclopropyl]-3-[[2-	

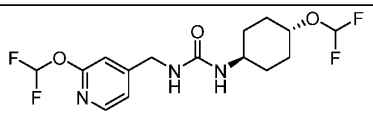
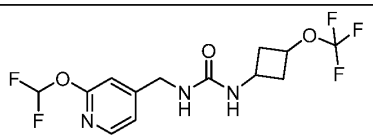
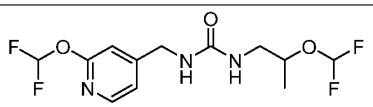
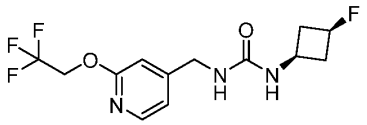
Example	Name	Structure
	(difluoromethoxy) pyridin-4-yl]methyl]urea	
247	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-(2,3-difluorophenyl)urea	
248	1-(2,3-difluorophenyl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
249	1-(3,4-difluorophenyl)-3-[[2-(fluoromethoxy)pyridin-4-yl]methyl]urea	
250	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-	

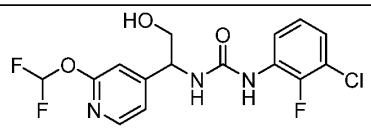
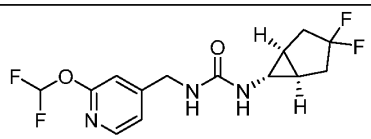
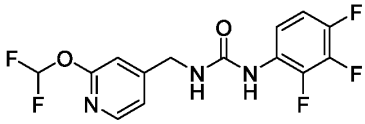
Example	Name	Structure
	[(1R,3S)-3-(trifluoromethyl)cyclohexyl]urea	
251	1-[dideuterio-[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-fluoro-1-bicyclo[2.2.2]octanyl)urea	
252	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]urea	
253	1-(dicyclopropylmethyl)-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	

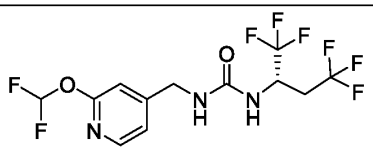
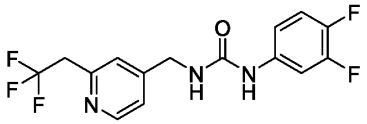
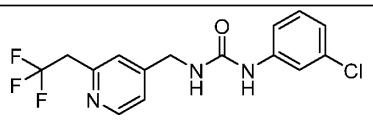
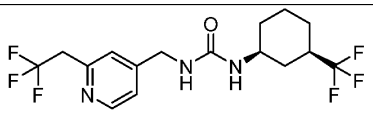
Example	Name	Structure
254	1-[1-(3,3-difluorocyclobutyl)cyclopropyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
255	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,2S)-2-(trifluoromethyl)cyclobutyl]urea	
256	1-(3,5-difluorophenyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]ethyl]urea	
257	1-[(1R)-1-cyclopropyl-2,2,2-trifluoroethyl]-3-[[2-(2,2,2-trifluoroethoxy)py	

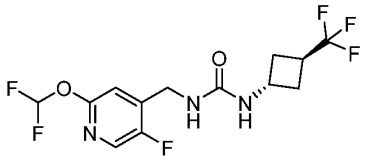
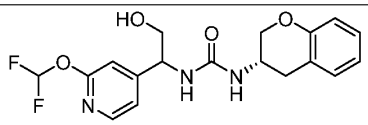
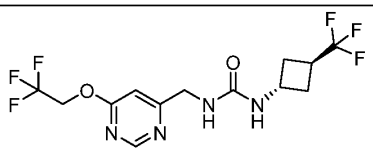
Example	Name	Structure
	ridin-4-yl]methyl]urea	
258	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[5-(trifluoromethyl)oxolan-3-yl]urea	
259	1-(3-chlorophenyl)-3-[1-[2-(2,2-difluoroethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
260	1-[[2-(difluoromethylsulfanyl)pyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
261	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(4-	

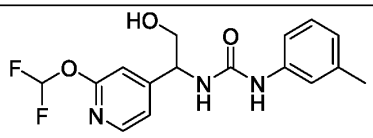
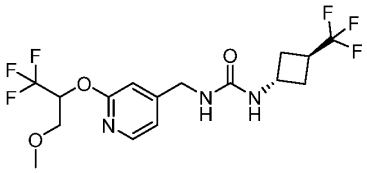
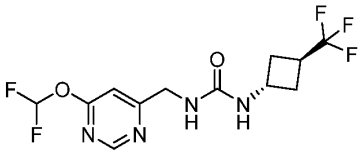
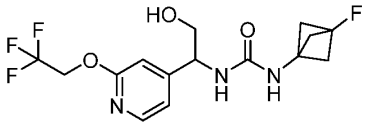
Example	Name	Structure
	fluoro-3-methylphenyl)urea	
262	1-[3-(difluoromethoxy)phenyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
263	rel-1-(3-chlorophenyl)-3-[(1R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
264	1-[3-(difluoromethoxy)cyclopentyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
265	1-[(1s,3s)-3-(difluoromethoxy)cyclobutyl]-3-[[2-(difluoromethoxy)	

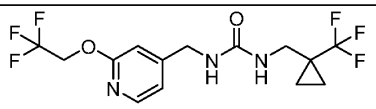
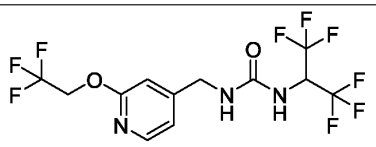
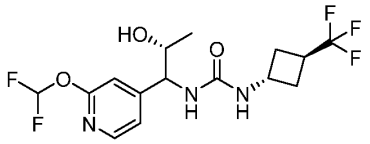
Example	Name	Structure
	pyridin-4-yl]methyl]urea	
266	1-[(1r,4r)-4-(difluoromethoxy) cyclohexyl]-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
267	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[3-(trifluoromethoxy) cyclobutyl]urea	
268	1-[2-(difluoromethoxy) propyl]-3-[[2-(difluoromethoxy) pyridin-4-yl]methyl]urea	
269	1-((1s,3s)-3-fluorocyclobutyl)-3-[[2-(2,2,2-trifluoroethoxy)py	

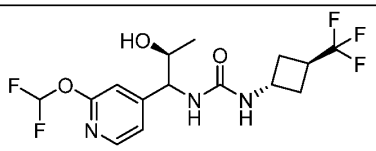
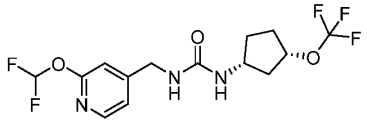
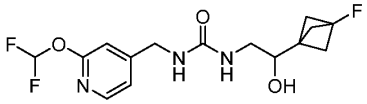
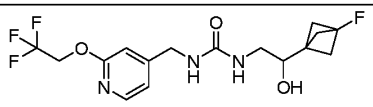
Example	Name	Structure
	ridin-4-yl]methyl]urea	
270	1-(3-chloro-2-fluorophenyl)-3-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]urea	
271	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[rac-(1R,5S,6R)-3,3-difluoro-6-bicyclo[3.1.0]hexanyl]urea	
272	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-(2,3,4-trifluorophenyl)urea	

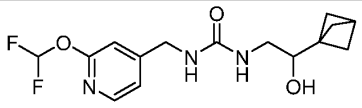
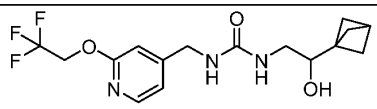
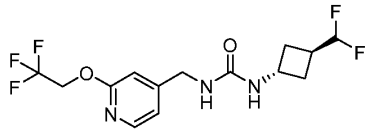
Example	Name	Structure
273	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(2S)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	
274	1-(3,4-difluorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
275	1-(3-chlorophenyl)-3-[[2-(2,2,2-trifluoroethyl)pyridin-4-yl]methyl]urea	
276	1-[rac-(1R,3S)-3-(trifluoromethyl)cyclohexyl]-3-[[2-(2,2,2-trifluoroethyl)pyri	

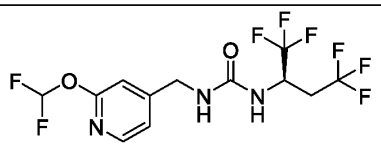
Example	Name	Structure
	din-4-yl]methyl]urea	
277	1-[[2-(difluoromethoxy)-5-fluoropyridin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
278	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-[(3S)-3,4-dihydro-2H-chromen-3-yl]urea	
279	1-[[6-(2,2,2-trifluoroethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

Example	Name	Structure
280	1-[1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxyethyl]-3-(3-methylphenyl)urea	
281	1-[[2-(1,1,1-trifluoro-3-methoxypropan-2-yl)oxypyridin-4-yl]methyl]-3-[3-(trifluoromethyl)cyclobutyl]urea	
282	1-[[6-(difluoromethoxy)pyrimidin-4-yl]methyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
283	1-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-3-[2-hydroxy-1-[2-(2,2,2-trifluoroethoxy)py	

Example	Name	Structure
	ridin-4-yl]ethyl]urea	
284	1-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]-3-[[1-(trifluoromethyl)cyclopropyl]methyl]urea	
285	1-(1,1,1,3,3,3-hexafluoropropan-2-yl)-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
286	1-[(2R)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	

Example	Name	Structure
287	1-[(2S)-1-[2-(difluoromethoxy)pyridin-4-yl]-2-hydroxypropyl]-3-[(1r,3r)-3-(trifluoromethyl)cyclobutyl]urea	
288	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[(1R,3S)-3-(trifluoromethoxy)cyclopentyl]urea	
289	1-[[2-(difluoromethoxy)pyridin-4-yl]methyl]-3-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]urea	
290	1-[2-(3-fluoro-1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-	

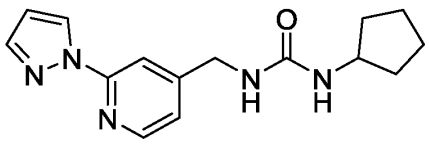
Example	Name	Structure
	[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
291	1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(difluoromethoxy)pyridin-4-yl]methyl]urea	
292	1-[2-(1-bicyclo[1.1.1]pentanyl)-2-hydroxyethyl]-3-[[2-(2,2,2-trifluoroethoxy)pyridin-4-yl]methyl]urea	
293	1-[(1r,3r)-3-(difluoromethyl)cyclobutyl]-3-[[2-(2,2,2-trifluoroethoxy)py	

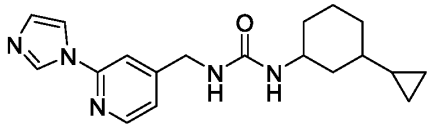
Example	Name	Structure
	ridin-4-yl]methyl]urea	
294	1-[[2-(difluoromethoxy) pyridin-4-yl]methyl]-3-[(2R)-1,1,1,4,4,4-hexafluorobutan-2-yl]urea	

55. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11-54, or a pharmaceutical composition according to any one of claims 1-10, wherein R^1 is CHF_2O- and R^6 is substituted with one or two F-.

56. A compound as set out in any one of Tables 1-9 herein or a solvate or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition comprising a compound as set out in any one of Tables 1-9 herein or a solvate or a pharmaceutically acceptable salt thereof.

57. A compound of formula (I') or (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11-56, or a pharmaceutical composition according to any one of claims 1-10 with the proviso that the compound is not one selected from:


;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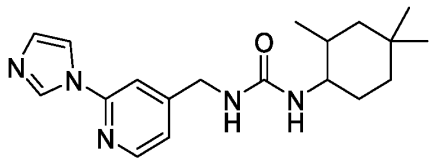
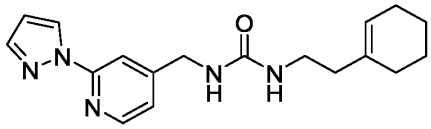

;


;

58. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11-57, wherein such compounds of formula (I) show Kv7.2 EC_{50} <3μM and selectivity ratio Kv7.3_7.5/Kv7.2 >10x.

59. A pharmaceutical composition according to any one of claims 1-10, or a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof according to any one of claims 11-58, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof.

60. A pharmaceutical pharmaceutical composition according to any one of claims 1-10, or a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof according to any one of claims 11-58, for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 in a subject in need thereof, wherein the disorder, disease, or disability is selected from behavioral disorders, mood disorders, neurodevelopmental disorders, intellectual disability, epilepsies, neurodegenerative diseases, pain, migraine, and tinnitus.

61. The pharmaceutical composition for use according to claim 60, wherein the disorder, disease, or disability is a behavioral disorder which is Attention Deficit Hyperactivity Disorder (ADHD).

62. The pharmaceutical composition for use according to claim 60, wherein the disorder, disease, or disability is a mood disorder which is depression.

63. The pharmaceutical composition for use according to claim 60, wherein the disorder, disease, or disability is a neurodevelopment disorder selected from autism spectrum disorder (ASD) and syndromic developmental disorders.

64. The pharmaceutical composition for use according to claim 60, wherein the disorder, disease, or disability is a syndromic developmental disorder selected from Dup15q syndrome (Dup15q), Fragile X syndrome (FXS) and Angelman syndrome.

65. The pharmaceutical composition for use according to claim 60, wherein the disorder, disease, or disability is an epilepsy selected from broad pediatric epilepsy, West syndrome, Ohtahara syndrome, and epileptic encephalopathy.

66. The pharmaceutical composition for use according to claim 60, wherein disorder, disease, or disability is a neurodegenerative disease selected from Alzheimer's disease, and motor neuron diseases.

67. The pharmaceutical composition for use according to any one of claims 59-66, for systemic or local administration such as oral, nasal, parenteral (as by intravenous (both bolus and infusion), intramuscular, or subcutaneous injection), transdermal, vaginal, buccal, rectal, or topical administration modes, intracisternally, intraperitoneally, as an oral or nasal spray, or as a liquid aerosol or dry powder for inhalation.

68. A compound according to any one of claims 11-58, or a pharmaceutical composition according to any one of claims 1-10 for use in therapy.

69. A compound according to any one of claims 11-58, or a pharmaceutical composition according to any one of claims 1-10, or a pharmaceutical composition for use according to any one of claims 59-67, for the manufacture of a medicament for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2.

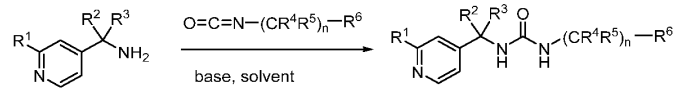
70. A method for the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2, which method comprises administering a therapeutically effective amount of a compound according to any one of claims 11-58, or a pharmaceutical composition according to any one of claims 1-10, or a pharmaceutical composition for use according to any one of claims 59-67.

71. A kit for use in the therapeutic and/or prophylactic treatment of a disorder, disease, or disability associated with Kv7.2 comprising:

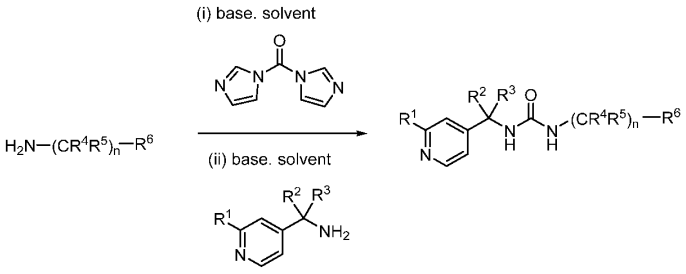
a) a compound according to any one of claims 11-58, or a pharmaceutical composition according to any one of claims 1-10, or a pharmaceutical composition for use according to any one of claims 59-67; and

b) instructions for use.

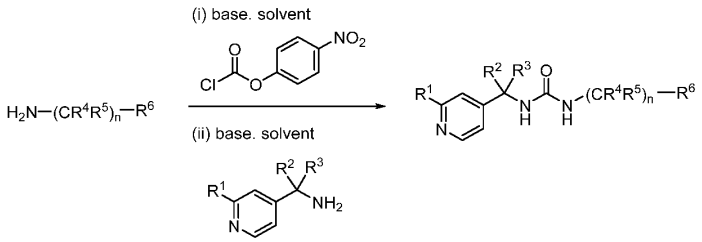
72. A process for the preparation of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11-58, wherein the urea formation comprises the reactions:



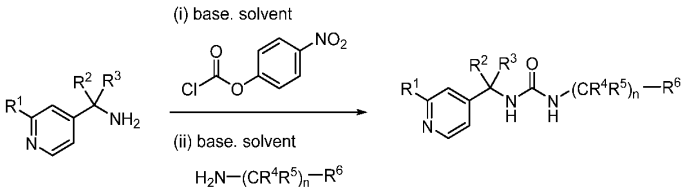
or



or



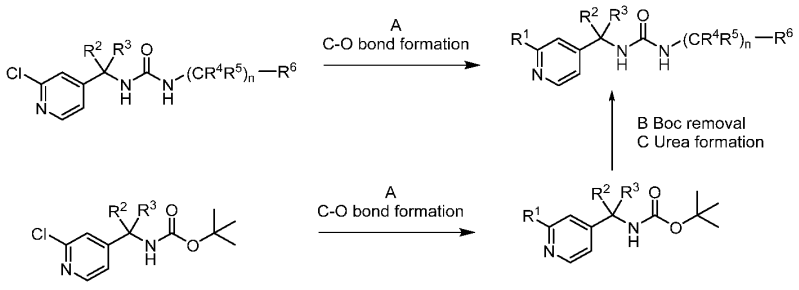
or



wherein R^1, R^2, R^3, n, R^4, R^5 and R^6 are as defined herein.

73. A process for the preparation of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 72, wherein R^1 is selected from 7-12 membered heterocycloalkyl, cyano, halogen, haloC_{1-6}alkyl, and 5 membered heteroaryl.

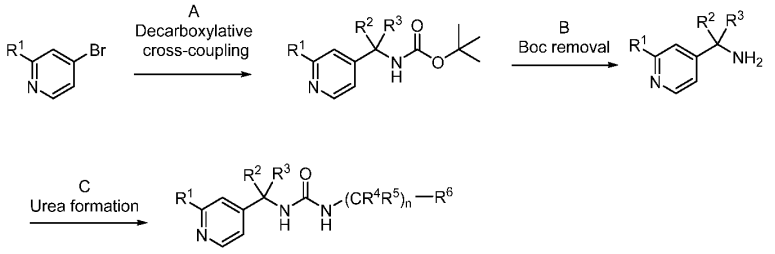
74. A process for the preparation of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11-58, wherein the process comprises the following reaction step:



wherein R^1, R^2, R^3, n, R^4, R^5 and R^6 are as defined herein.

75. A process for the preparation of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to claim 74, wherein R^1 is selected from haloC_{1-6}alkoxy, C_{1-6}alkoxy, 4-6 membered heterocyclyloxy, and C_{3-5}cycloalkylC_{1-6}alkoxy and R^2 and R^3 are hydrogen.

76. A process for the preparation of a compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof, according to any one of claims 11-58, wherein the process comprises the reactions of the following reaction steps:



wherein R^1, R^2, R^3, n, R^4, R^5 and R^6 are as defined herein.

77. A process for the preparation of a compound of formula (I), or a solvate or pharmaceutically acceptable salt thereof, according to claim 76, wherein R^1 is selected from haloC_{1-6}alkoxy, C_{1-6}alkoxy, 4-6 membered heterocyclyloxy, C_{3-5}cycloalkylC_{1-6}alkoxy, or cyanoC_{1-6}alkoxy, and R^2 is hydroxyC_{1-6}alkyl and R^3 is hydrogen.

78. A compound of formula (I), or a solvate or a pharmaceutically acceptable salt thereof according to any one of claims 11-58, when manufactured according to a process according to any one of claims 72-77.

71. The invention as hereinbefore described.