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(54) Title: HETEROARYL-SUBSTITUTED UREA MODULATORS OF FATTY ACID AMIDE HYDROLASE

(57) Abstract: Certain heteroaryl-substituted piperidiny and piperaziny urea compounds are described, which are useful as FAAH inhibitors. Such compounds may be used in pharmaceutical compositions and methods for the treatment of disease states, disorders, and conditions mediated by fatty acid amide hydrolase (FAAH) activity, such as anxiety, pain, inflammation, sleep disorders, eating disorders, insulin resistance, diabetes, osteoporosis, and movement disorders (e.g., multiple sclerosis).



WO 2008/153752 A2

HETEROARYL-SUBSTITUTED UREA MODULATORS OF FATTY ACID AMIDE HYDROLASE

5 Field of the Invention

The present invention relates to certain heteroaryl-substituted piperidinyl and piperazinyl urea compounds, pharmaceutical compositions containing them, and methods of using them for the treatment of disease states, disorders, and conditions mediated by fatty acid amide hydrolase (FAAH)
10 activity.

Background of the Invention

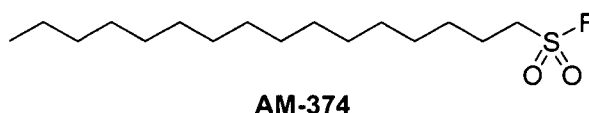
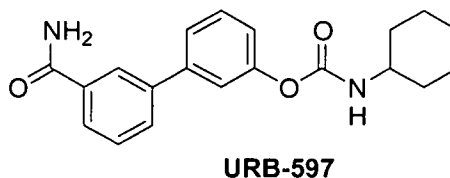
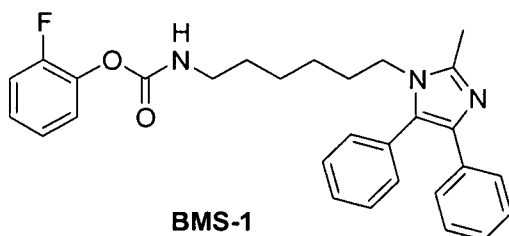
Medicinal benefits have been attributed to the cannabis plant for centuries. The primary bioactive constituent of cannabis is Δ^9 -tetrahydro-
15 cannabinol (THC). The discovery of THC eventually led to the identification of two endogenous cannabinoid receptors responsible for its pharmacological actions, namely CB₁ and CB₂ (Goya, *Exp. Opin. Ther. Patents* 2000, 10, 1529). These discoveries not only established the site of action of THC, but also inspired inquiries into the endogenous agonists of these receptors, or
20 "endocannabinoids". The first endocannabinoid identified was the fatty acid amide anandamide (AEA). AEA itself elicits many of the pharmacological effects of exogenous cannabinoids (Piomelli, *Nat. Rev. Neurosci.* 2003, 4(11), 873).

The catabolism of AEA is primarily attributable to the integral membrane
25 bound protein fatty acid amide hydrolase (FAAH), which hydrolyzes AEA to arachidonic acid. FAAH was characterized in 1996 by Cravatt and co-workers (Cravatt, *Nature* 1996, 384, 83). It was subsequently determined that FAAH is additionally responsible for the catabolism of a large number of important lipid signaling fatty acid amides including: another major endocannabinoid, 2-
30 arachidonoylglycerol (2-AG) (*Science* 1992, 258, 1946-1949); the sleep-inducing substance, oleamide (OEA) (*Science* 1995, 268, 1506); the appetite-

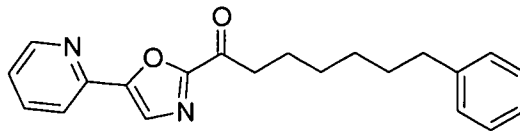
suppressing agent, N-oleoylethanolamine (Rodriguez de Fonesca, *Nature* 2001, 414, 209); and the anti-inflammatory agent, palmitoylethanolamide (PEA) (Lambert, *Curr. Med. Chem.* 2002, 9(6), 663).

Small-molecule inhibitors of FAAH should elevate the concentrations of these endogenous signaling lipids and thereby produce their associated beneficial pharmacological effects. There have been some reports of the effects of various FAAH inhibitors in pre-clinical models.

In particular, two carbamate-based inhibitors of FAAH were reported to have analgesic properties in animal models. In rats, BMS-1 (see WO 02/087569), which has the structure shown below, was reported to have an analgesic effect in the Chung spinal nerve ligation model of neuropathic pain, and the Hargraves test of acute thermal nociception. URB-597 was reported to have efficacy in the zero plus maze model of anxiety in rats, as well as analgesic efficacy in the rat hot plate and formalin tests (Kathuria, *Nat. Med.* 2003, 9(1), 76). The sulfonylfluoride AM374 was also shown to significantly reduce spasticity in chronic relapsing experimental autoimmune encephalomyelitis (CREAE) mice, an animal model of multiple sclerosis (Baker, *FASEB J.* 2001, 15(2), 300).



In addition, the oxazolopyridine ketone OL-135 is reported to be a potent inhibitor of FAAH, and has been reported to have analgesic activity in both the hot plate and tail emersion tests of thermal nociception in rats (WO 04/033652).



OL-135

Results of research on the effects of certain exogenous cannabinoids has elucidated that a FAAH inhibitor may be useful for treating various conditions, diseases, disorders, or symptoms. These include pain, 5 nausea/emesis, anorexia, spasticity, movement disorders, epilepsy and glaucoma. To date, approved therapeutic uses for cannabinoids include the relief of chemotherapy-induced nausea and emesis among patients with cancer and appetite enhancement in patients with HIV/AIDs who experience anorexia as a result of wasting syndrome. Two products are commercially 10 available in some countries for these indications, namely, dronabinol (Marinol®) and nabilone.

Apart from the approved indications, a therapeutic field that has received much attention for cannabinoid use is analgesia, i.e., the treatment of pain. Five small randomized controlled trials showed that THC is superior to 15 placebo, producing dose-related analgesia (Robson, *Br. J. Psychiatry* 2001, 178, 107-115). Atlantic Pharmaceuticals is reported to be developing a synthetic cannabinoid, CT-3, a 1,1-dimethyl heptyl derivative of the carboxylic metabolite of tetrahydrocannabinol, as an orally active analgesic and anti-inflammatory agent. A pilot phase II trial in chronic neuropathic pain with CT-3 20 was reportedly initiated in Germany in May 2002.

A number of individuals with locomotor activity-related diseases, such as multiple sclerosis have claimed a benefit from cannabis for both disease-related pain and spasticity, with support from small controlled trials (Croxford et al., *J. Neuroimmunol*, 2008, 193, 120-9; Svendsen, *Br. Med. J.* 2004, 329, 25 253). Likewise, various victims of spinal cord injuries, such as paraplegia, have reported that their painful spasms are alleviated after smoking marijuana. A report showing that cannabinoids appear to control spasticity and tremor in the CREAE model of multiple sclerosis demonstrated that these effects are mediated by CB₁ and CB₂ receptors (Baker, *Nature* 2000, 404, 84-87). Phase

3 clinical trials have been undertaken in multiple sclerosis and spinal cord injury patients with a narrow ratio mixture of tetrahydrocannabinol/cannabidiol (THC/CBD).

5 Reports of small-scale controlled trials to investigate other potential commercial uses of cannabinoids have been made. Trials in volunteers have been reported to have confirmed that oral, injected, and smoked cannabinoids produced dose-related reductions in intraocular pressure (IOP) and therefore may relieve glaucoma symptoms. Ophthalmologists have prescribed cannabis for patients with glaucoma in whom other drugs have failed to adequately
10 control intraocular pressure (Robson, 2001, *supra*).

Inhibition of FAAH using a small-molecule inhibitor may be advantageous compared to treatment with a direct-acting CB₁ agonist. Administration of exogenous CB₁ agonists may produce a range of responses, including reduced nociception, catalepsy, hypothermia, and increased feeding
15 behavior. These four in particular are termed the "cannabinoid tetrad." Experiments with FAAH -/- mice show reduced responses in tests of nociception, but did not show catalepsy, hypothermia, or increased feeding behavior (Cravatt, *Proc. Natl. Acad. Sci. USA* 2001, 98(16), 9371). Fasting caused levels of AEA to increase in rat limbic forebrain, but not in other brain
20 areas, providing evidence that stimulation of AEA biosynthesis may be anatomically regionalized to targeted CNS pathways (Kirkham, *Br. J. Pharmacol.* 2002, 136, 550). The finding that AEA increases are localized within the brain, rather than systemic, suggests that FAAH inhibition with a small molecule could enhance the actions of AEA and other fatty acid amides
25 in tissue regions where synthesis and release of these signaling molecules is occurring in a given pathophysiological condition (Piomelli, 2003, *supra*).

In addition to the effects of a FAAH inhibitor on AEA and other endocannabinoids, inhibitors of FAAH's catabolism of other lipid mediators may be used in treating certain other therapeutic indications. For example,
30 PEA has demonstrated biological effects in animal models of inflammation (Holt, et al. *Br. J. Pharmacol.* 2005, 146, 467-476), immunosuppression, analgesia, and neuroprotection (Ueda, *J. Biol. Chem.* 2001, 276(38), 35552).

Oleamide, another substrate of FAAH, induces sleep (Boger, *Proc. Natl. Acad. Sci. USA* 2000, 97(10), 5044; Mendelson, *Neuropsychopharmacology* 2001, 25, S36). Inhibition of FAAH has also been implicated in cognition (Varvel et al., *J. Pharmacol. Exp. Ther.* 2006, 317(1), 251-257) and depression (Gobbi et al., *Proc. Natl. Acad. Sci. USA* 2005, 102(51), 18620-18625).

Two additional indications for FAAH are supported by recent data indicating that FAAH substrate activated receptors are important in energy metabolism, and in bone homeostasis (Overton et al., *Br. J. Pharmacol.* 2008, in press; and Plutzky, *Diab. Vasc. Dis. Res.* 2007, 4 Suppl 3, S12-4). It has been shown that the previously mentioned lipid signaling fatty acid amides catabolized by FAAH, oleoylethanolamide (OEA), is one of the most active agonists of the recently de-orphanised GPCR 119 (GPR119) (also termed glucose dependent insulinotropic receptor). This receptor is expressed predominantly in the pancreas in humans and activation improves glucose homeostasis via glucose-dependent insulin release in pancreatic beta-cells. GPR119 agonists can suppress glucose excursions when administered during oral glucose tolerance tests, and OEA has also been shown independently to regulate food intake and body weight gain when administered to rodents, indicating a probable benefit in energy metabolism disorders, such as insulin resistance and diabetes. The FAAH substrate palmitoylethanolamide (PEA) is an agonist at the PPAR α receptor. Evidence from surrogate markers in human studies with the PPAR α agonist fenofibrate is supportive of the concept that PPAR α agonism offers the potential for inducing a coordinated PPAR α response that may improve dyslipidaemia, repress inflammation and limit atherosclerosis in patients with the metabolic syndrome or type 2 diabetes. The FAAH substrate anandamide (AEA) is an agonist at the PPAR γ receptor. Anandamide treatment induces 3T3-L1 differentiation into adipocytes, as well as triglyceride droplet accumulation and expression of adiponectin (Bouaboula et al., *E. J. Pharmacol.* 2005, 517, 174-181). Low dose cannabinoid therapy has been shown to reduce atherosclerosis in mice, further suggesting a therapeutic benefit of FAAH inhibition in dyslipidemia, liver steatosis,

steatohepatitis, obesity, and metabolic syndrome (Steffens et al., *Nature*, 2005, 434, 782-6).

Osteoporosis is one of the most common degenerative diseases. It is characterized by reduced bone mineral density (BMD) with an increased risk for bone fractures. CB₂-deficient mice have a markedly accelerated age-related trabecular bone loss and cortical expansion. A CB₂-selective agonism enhances endocortical osteoblast number and activity and restrains trabecular osteoclastogenesis and attenuates ovariectomy-induced bone loss (Ofek et al., *Proc. Natl. Acad. Sci. U.S.A.* 2006, 103, 696-701). There is a substantial genetic contribution to BMD, although the genetic factors involved in the pathogenesis of human osteoporosis are largely unknown. The applicability to human BMD is suggested by genetic studies in which a significant association of single polymorphisms and haplotypes was found encompassing the CNR2 gene on human chromosome 1p36, demonstrating a role for the peripherally expressed CB₂ receptor in the etiology of osteoporosis (Karsak et al., *Hum. Mol. Genet.*, 2005, 14, 3389-96).

Thus, small-molecule FAAH inhibitors should be useful in treating pain of various etiologies, anxiety, multiple sclerosis and other movement disorders, nausea/emesis, eating disorders, epilepsy, glaucoma, inflammation, immunosuppression, neuroprotection, depression, cognition enhancement, and sleep disorders, and potentially with fewer side effects than treatment with an exogenous cannabinoid.

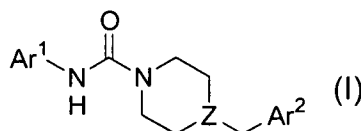
A number of heteroaryl-substituted ureas have been reported in various publications. Certain substituted thiophene ureas are described in US Patent No. 6,881,741. Certain ureido-pyrazoles are described in US Patent No. 6,387,900. Certain benzothiazole amide derivatives are described in US Patent Publication US 2003/149036. Certain ureas are reported as prenyltransferase inhibitors in WO 2003/047569. Piperidinyl ureas are described as histamine H₃ receptor antagonists in US Patent No. 6,100,279. Piperazinyl ureas are disclosed as calcitonin mimetics in US Patent Nos. 6,124,299 and 6,395,740. Various ureas are reported as small-molecule FAAH modulators in US Patent Publication Nos. US 2006/173184 and US

2007/0004741, in Intl. Patent Appl. Nos. WO 2008/023720, WO 2008/047229, and WO 2008/024139, and by Cravatt et al. (Biochemistry 2007, 46(45), 13019. Ureas are described as modulators of other targets in U.S. Pat. Appl. Publ. US 2007/270433, and in Intl. Pat. Appl. Publ. Nos. WO 2007/096251 and
 5 WO 2006/085108. However, there remains a desire for potent FAAH modulators with suitable pharmaceutical properties.

Summary of the Invention

Certain heteroaryl-substituted piperidinyl and piperazinyl urea derivatives have now been found to have FAAH-modulating activity. Thus, the
 10 invention is directed to the general and preferred embodiments defined, respectively, by the independent and dependent claims appended hereto, which are incorporated by reference herein.

In one general aspect, the invention is directed to compounds of Formula (I):



wherein:

Ar¹ is a benzo[d]isoxazol-3-yl, 6-fluorobenzo[d]isoxazol-3-yl, 3-phenyl-
 [1,2,4]thiadiazol-5-yl, 1H-tetrazol-5-yl, benzo[1,2,5]thiadiazol-4-yl,
 benzo[1,2,5]oxadiazol-4-yl, thiophen-2-yl, thiophen-3-yl, 6-chloro-pyridazin-
 3-yl, pyrazin-2-yl, isoxazol-3-yl, 1H-benzotriazol-5-yl, [1,5]naphthyridin-2-yl,
 20 quinolin-2-yl, benzothiazol-6-yl, quinolin-5-yl, 1H-pyrazol-3-yl, 5-methylpyrazin-2-yl, 3-chloropyrazin-2-yl, pyridazin-3-yl, 6-methoxypyridazin-3-yl, 5-methylisoxazol-3-yl, 1,5-dimethyl-1H-pyrazol-3-yl, 4-bromo-1-methyl-1H-pyrazol-3-yl, 2-ethyl-2H-pyrazol-3-yl, 5-methyl-1H-pyrazol-3-yl, or 5-
 25 phenyl-1H-pyrazol-3-yl group;

Z is -N- or >CH; and

Ar² is:

(i) phenyl unsubstituted or substituted with one or two R^a moieties;

where each R^a moiety is independently -C₁₋₄alkyl, -C≡C-R^d, -OC₁₋₄alkyl,
 30 halo, -CF₃, -OCF₃, -OCH₂CF₃, -SCF₃, -S(O)₀₋₂C₁₋₄alkyl, -SO₂CF₃,

-OSO₂C₁₋₄alkyl, -(CH₂)₀₋₁CO₂C₁₋₄alkyl, -CO₂H, -COC₁₋₄alkyl, -N(R^b)R^c,
 -SO₂NR^bR^c, -NR^bSO₂R^c, -C(O)NR^bR^c, -NO₂, or -(CH₂)₀₋₁CN;
 or two adjacent R^a moieties taken together form -O(CH₂)₁₋₂O- or
 -OCF₂O-;

5 where R^b and R^c are each independently -H or -C₁₋₄alkyl; and
 R^d is H, C₃₋₆cycloalkyl, or -CH₂NR^eR^f;

where R^e and R^f are each independently H or C₁₋₄alkyl;

(ii) phenyl substituted at the 3- or 4-position with -L-Ar³, unsubstituted or
 substituted with one or two R^a moieties, wherein:

10 L is a linker selected from the group consisting of -(CH₂)₁₋₃-, -CH=CH-,
 -O-, -OCH₂-, -CH₂O-, -NH-, >NC₁₋₄alkyl, -S-, -C≡C-, -C(=O)-, and
 a covalent bond; and

Ar³ is:

(a) phenyl;

15 (b) naphthyl; or

(c) a monocyclic or bicyclic heteroaryl group; or

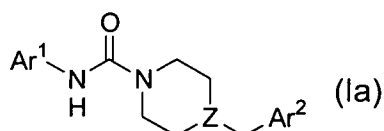
(iii) a 9- or 10-membered fused bicyclic heteroaryl group;

where when Ar¹ is 6-chloro-pyridazin-3-yl, isoxazol-3-yl, or 1H-pyrazol-3-yl,

then Ar² is not benzo[1,3]dioxol-5-yl or 2,2-difluoro-benzo[1,3]dioxol-5-yl;

20 and pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs,
 and pharmaceutically active metabolites of said compounds.

In another general aspect, the invention is directed to compounds of
 Formula (Ia):



25

wherein:

Ar¹ is a benzo[d]isoxazol-3-yl, 6-fluorobenzo[d]isoxazol-3-yl, 3-phenyl-
 [1,2,4]thiadiazol-5-yl, 1H-tetrazol-5-yl, benzo[1,2,5]thiadiazol-4-yl,
 benzo[1,2,5]oxadiazol-4-yl, thiophen-2-yl, thiophen-3-yl, 6-chloro-pyridazin-

3-yl, pyrazin-2-yl, isoxazol-3-yl, 1H-benzotriazol-5-yl, [1,5]naphthyridin-2-yl, quinolin-2-yl, benzothiazol-6-yl, quinolin-5-yl, or 1H-pyrazol-3-yl group;

Z is -N- or >CH; and

Ar² is:

- 5 (i) phenyl or 3-phenoxyphenyl substituted with one or two R^a moieties; where each R^a moiety is independently -C₁₋₄alkyl, -OC₁₋₄alkyl, halo, -CF₃, -OCF₃, -OCH₂CF₃, -SCF₃, -S(O)₀₋₂C₁₋₄alkyl, -OSO₂C₁₋₄alkyl, -CO₂C₁₋₄alkyl, -CO₂H, -COC₁₋₄alkyl, -N(R^b)R^c, -SO₂NR^bR^c, -NR^bSO₂R^c, -C(O)NR^bR^c, -NO₂, or -CN;
- 10 where R^b and R^c are each independently -H or -C₁₋₄alkyl; or
- (ii) benzo[1,3]dioxol-5-yl, 2,2-difluoro-benzo[1,3]dioxol-5-yl, or naphthyl; where when Ar¹ is 6-chloro-pyridazin-3-yl, isoxazol-3-yl, or 1H-pyrazol-3-yl, then Ar² is not benzo[1,3]dioxol-5-yl or 2,2-difluoro-benzo[1,3]dioxol-5-yl; and pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs,
- 15 and pharmaceutically active metabolites of such compounds. In especially preferred embodiments, the invention is directed to compounds described or exemplified in the detailed description below and their pharmaceutically acceptable salts.

One skilled in the art will recognize that compounds of Formula (Ia) are
20 embodiments of compounds of Formula (I). References herein to compounds of Formula (I) therefore encompass compounds of Formula (Ia) as well.

In a further general aspect, the invention relates to pharmaceutical compositions each comprising: (a) an effective amount of at least one agent selected from compounds of Formula (I), pharmaceutically acceptable salts of
25 compounds of Formula (I), pharmaceutically acceptable prodrugs of compounds of Formula (I), and pharmaceutically active metabolites of Formula (I); and (b) a pharmaceutically acceptable excipient.

In another general aspect, the invention is directed to a method of treating a subject suffering from or diagnosed with a disease, disorder, or
30 medical condition mediated by FAAH activity, comprising administering to the subject in need of such treatment an effective amount of at least one agent selected from compounds of Formula (I) and their pharmaceutically acceptable

salts, pharmaceutically active prodrugs, and pharmaceutically active metabolites. In preferred embodiments of the inventive method, the disease, disorder, or medical condition is selected from: anxiety, depression, pain, sleep disorders, eating disorders, inflammation, multiple sclerosis and other movement disorders, HIV wasting syndrome, closed head injury, stroke, learning and memory disorders, Alzheimer's disease, epilepsy, Tourette's syndrome, Niemann-Pick disease, Parkinson's disease, Huntington's chorea, optic neuritis, autoimmune uveitis, symptoms of drug withdrawal, nausea, emesis, sexual dysfunction, post-traumatic stress disorder, cerebral vasospasm, glaucoma, irritable bowel syndrome, inflammatory bowel disease, immunosuppression, gastroesophageal reflux disease, paralytic ileus, secretory diarrhea, gastric ulcer, rheumatoid arthritis, unwanted pregnancy, hypertension, cancer, hepatitis, allergic airway disease, auto-immune diabetes, intractable pruritis, and neuroinflammation.

Additional embodiments, features, and advantages of the invention will be apparent from the following detailed description and through practice of the invention.

Detailed Description of Invention and Its Preferred Embodiments

The invention may be more fully appreciated by reference to the following detailed description, including the following glossary of terms and the concluding examples. For the sake of brevity, the disclosures of the publications, including patents, cited in this specification are herein incorporated by reference.

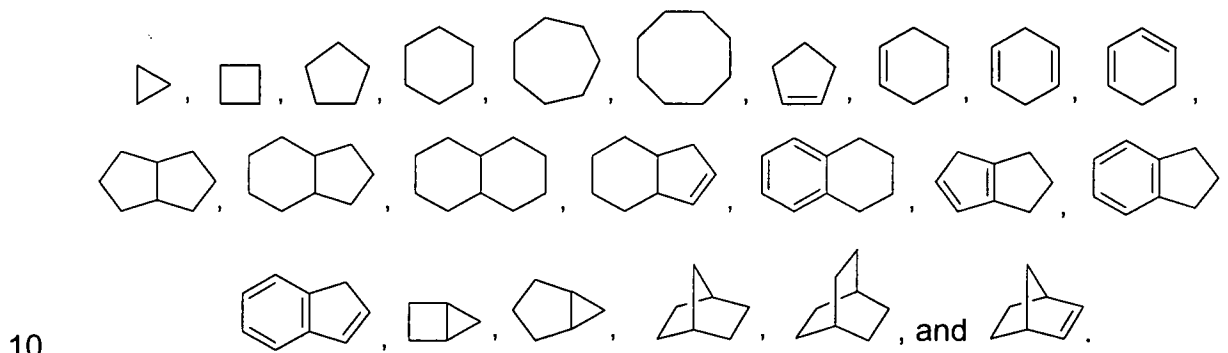
As used herein, the terms "including", "containing" and "comprising" are used in their open, non-limiting sense.

The term "alkyl" refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain. Examples of alkyl groups include methyl (Me, which also may be structurally depicted by / symbol), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and so on.

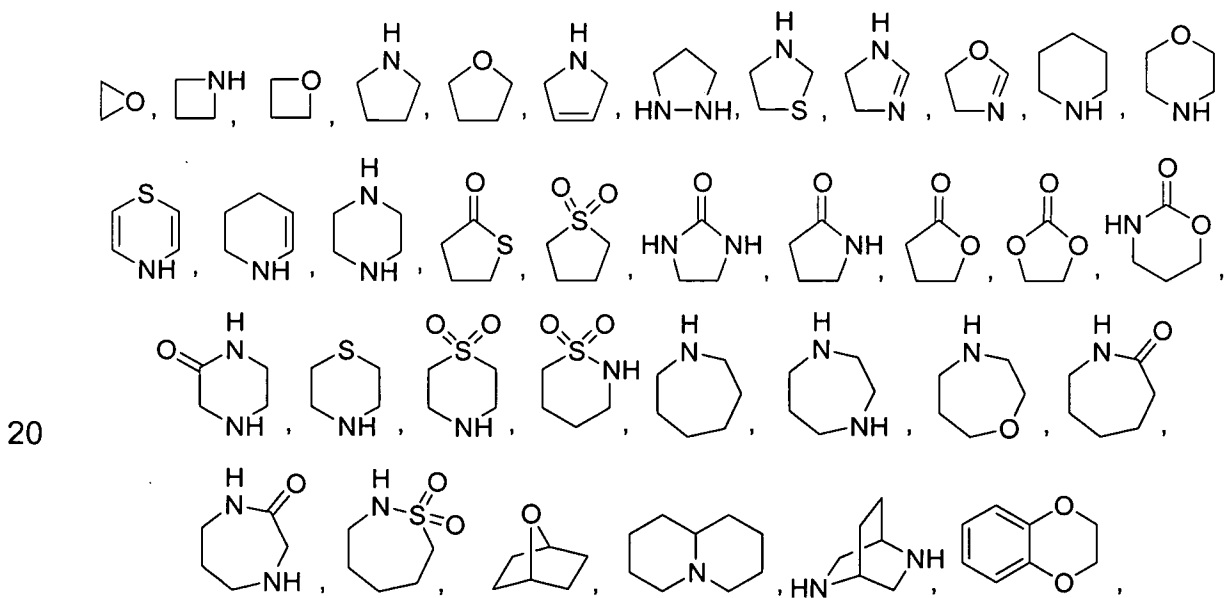
The term "alkenyl" refers to a straight- or branched-chain alkenyl group having from 2 to 12 carbon atoms in the chain. (The double bond of the

alkenyl group is formed by two sp^2 hybridized carbon atoms.) Illustrative alkenyl groups include prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, and so on.

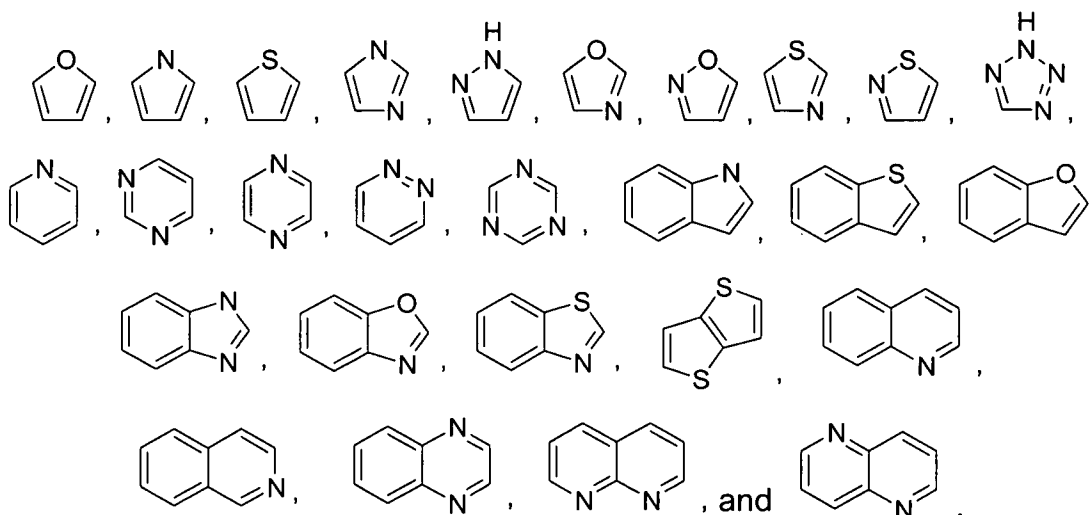
The term “cycloalkyl” refers to a saturated or partially saturated, monocyclic, fused polycyclic, or spiro polycyclic carbocycle having from 3 to 12 ring atoms per carbocycle. Illustrative examples of cycloalkyl groups include the following entities, in the form of properly bonded moieties:



A "heterocycloalkyl" refers to a monocyclic, or fused, bridged, or spiro polycyclic ring structure that is saturated or partially saturated and has from 3 to 12 ring atoms per ring structure selected from carbon atoms and up to three heteroatoms selected from nitrogen, oxygen, and sulfur. The ring structure may optionally contain up to two oxo groups on carbon or sulfur ring members. Illustrative examples of heterocycloalkyl groups include the following entities, in the form of properly bonded moieties:



The term "heteroaryl" refers to a monocyclic, fused bicyclic, or fused polycyclic aromatic heterocycle (ring structure having ring atoms selected from carbon atoms and up to four heteroatoms selected from nitrogen, oxygen, and sulfur) having from 3 to 12 ring atoms per heterocycle. Illustrative examples of heteroaryl groups include the following entities, in the form of properly bonded moieties:



The term "halogen" represents chlorine, fluorine, bromine or iodine. The term "halo" represents chloro, fluoro, bromo or iodo.

The term "substituted" means that the specified group or moiety bears one or more substituents. The term "unsubstituted" means that the specified group bears no substituents. The term "optionally substituted" means that the specified group is unsubstituted or substituted by one or more substituents. Where the term "substituted" is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system. In cases where a specified moiety or group is not expressly noted as being optionally substituted or substituted with any specified substituent, it is understood that such a moiety or group is intended to be unsubstituted.

A structural formula given herein is intended to represent compounds having structures depicted by the formula as well as equivalent variations or forms. For example, compounds encompassed by Formula (I) may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of the general formula,

and mixtures thereof, are considered within the scope of the formula. Thus, a general formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof. Furthermore, certain structures
5 may exist as geometric isomers (i.e., *cis* and *trans* isomers), as tautomers (e.g. pyrazole, benzimidazole, tetrazole, or benzotriazole tautomers), or as atropisomers, which are intended to be represented by the structural formula. Additionally, a formula given herein is intended to embrace hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

10 A structural formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated
15 into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{32}P , ^{33}P , ^{35}S , ^{18}F , ^{36}Cl , and ^{125}I , respectively. Such isotopically labeled compounds are useful in metabolic studies (preferably with ^{14}C), reaction kinetic studies (with, for example ^2H or ^3H), detection or imaging
20 techniques [such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT)], including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F - or ^{11}C -labeled compound may be preferred for PET or SPECT studies. Further, substitution with heavier isotopes such as deuterium (i.e., ^2H) may
25 afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements. Isotopically labeled compounds of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily
30 available isotopically labeled reagent for a non-isotopically labeled reagent.

When referring to any formula given herein, the selection of a particular moiety from a list of possible species for a specified variable is not intended to

define the moiety for the variable appearing elsewhere. In other words, where a formula variable appears more than once, the choice of the species from a specified list is independent of the choice of the species for the same variable elsewhere in the formula.

5 In preferred embodiments of Formula (I), Ar¹ is a benzo[d]isoxazol-3-yl, 6-fluorobenzo[d]isoxazol-3-yl, benzo[1,2,5]thiadiazol-4-yl, benzo[1,2,5]oxadiazol-4-yl, 6-chloro-pyridazin-3-yl, pyrazin-2-yl, isoxazol-3-yl, 1H-benzotriazol-5-yl, benzothiazol-6-yl, or 1H-pyrazol-3-yl group. In further preferred embodiments, Ar¹ is a benzo[d]isoxazol-3-yl group. In still further preferred
10 embodiments, Ar¹ is a pyrazin-2-yl group. In still further preferred embodiments, Ar¹ is an isoxazol-3-yl group. In still further preferred embodiments, Ar¹ is a pyridazin-3-yl group.

In preferred embodiments, Z is -N-. In other preferred embodiments, Z is >CH.

15 In preferred embodiments, Ar² is phenyl, substituted with one or two R^a moieties.

In preferred embodiments, Ar² is phenyl, substituted with one or two R^a moieties, and each R^a moiety is independently selected from the group consisting of: chloro, cyano, isobutyl, methylsulfanyl, methanesulfonyl, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, fluoro, methyl, methoxy, 20 tert-butyl, bromo, methoxycarbonyl, cyanomethyl, methoxycarbonylmethyl, trifluoromethanesulfonyl, trifluoromethanesulfanyl, and butyl; or two adjacent R^a moieties taken together form -OCH₂O- or -OCF₂O-.

In further preferred embodiments, Ar² is phenyl substituted at the 3- or 4-position with -L-Ar³, to form a -phenyl-L-Ar³ group that is unsubstituted or
25 substituted with one or two R^a moieties. In further preferred embodiments, L is -CH₂CH₂-, -O-, -OCH₂-, or -C≡C-. In still further preferred embodiments, Ar³ is phenyl. In still further preferred embodiments, Ar³ is phenyl and each R^a moiety is independently selected from the group consisting of: chloro, cyano, isobutyl, methylsulfanyl, methanesulfonyl, trifluoromethyl, trifluoromethoxy, 30 2,2,2-trifluoroethoxy, fluoro, methyl, methoxy, tert-butyl, bromo, methoxycarbonyl, cyanomethyl, methoxycarbonylmethyl,

trifluoromethanesulfonyl, trifluoromethanesulfanyl, and butyl; or two adjacent R^a moieties taken together form -OCH₂O- or -OCF₂O-.

In still further preferred embodiments, Ar³ is naphthyl. In still further preferred embodiments, Ar³ is a monocyclic or bicyclic heteroaryl group. In still further preferred embodiments, Ar³ is a thiophenyl, pyrimidinyl, pyridyl, pyrazinyl, or quinolinyl group. In still further preferred embodiments, Ar³ is naphthyl or a monocyclic or bicyclic heteroaryl group and each R^a moiety is independently selected from the group consisting of: chloro, cyano, isobutyl, methylsulfanyl, methanesulfonyl, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, fluoro, methyl, methoxy, tert-butyl, bromo, methoxycarbonyl, cyanomethyl, methoxycarbonylmethyl, trifluoromethanesulfonyl, trifluoromethanesulfanyl, and butyl; or two adjacent R^a moieties taken together form -OCH₂O- or -OCF₂O-.

In further preferred embodiments, Ar² is a 9- or 10-membered fused bicyclic heteroaryl group. In still further preferred embodiments, Ar² is a benzimidazolyl, indazolyl, benzothiophenyl, quinolinyl, indolyl, or benzofuranyl group.

In preferred embodiments of Formula (I) or (Ia), Ar¹ is a benzo[d]isoxazol-3-yl, 6-fluorobenzo[d]isoxazol-3-yl, benzo[1,2,5]thiadiazol-4-yl, benzo[1,2,5]oxadiazol-4-yl, 6-chloro-pyridazin-3-yl, pyrazin-2-yl, isoxazol-3-yl, 1H-benzotriazol-5-yl, benzothiazol-6-yl, or 1H-pyrazol-3-yl group. In further preferred embodiments, Ar¹ is a benzo[d]isoxazol-3-yl group. In still further preferred embodiments, Ar¹ is a pyrazin-2-yl group. In still further preferred embodiments, Ar¹ is an isoxazol-3-yl group. In still further preferred embodiments, Ar¹ is a pyridazin-3-yl group.

In preferred embodiments, Ar² is 3-phenoxyphenyl substituted with one or two R^a moieties independently selected from the group consisting of fluoro, chloro, bromo, -CF₃, -OCF₃, or -OCH₂CF₃. In other preferred embodiments, Ar² is naphthyl.

The invention also relates to pharmaceutically acceptable salts of the free acids or bases represented by Formula (I), preferably of the preferred embodiments described above and of the specific compounds exemplified

herein. The therapeutic compositions and methods of the invention may employ pharmaceutically acceptable salts of the free acids or bases represented by Formula (I), preferably of the preferred embodiments described above and of the specific compounds exemplified herein. A "pharmaceutically acceptable salt" is intended to mean a salt of a free acid or base of a compound represented by Formula (I) that is non-toxic, biologically tolerable, or otherwise biologically suitable for administration to the subject. See, generally, S.M. Berge, et al., "Pharmaceutical Salts", J. Pharm. Sci., 1977, 66:1-19, and *Handbook of Pharmaceutical Salts, Properties, Selection, and Use*, Stahl and Wermuth, Eds., Wiley-VCH and VHCA, Zurich, 2002.

Preferred pharmaceutically acceptable salts are those that are pharmacologically effective and suitable for contact with the tissues of patients without undue toxicity, irritation, or allergic response. A compound of Formula (I) may possess a sufficiently acidic group, a sufficiently basic group, or both types of functional groups, and accordingly react with a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Examples of pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrate, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ -hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If the compound of Formula (I) contains a basic nitrogen, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, by treatment of the free base with an inorganic

acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, boric acid, phosphoric acid, and the like; or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, 5 valeric acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, oleic acid, palmitic acid, lauric acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as mandelic acid, citric acid, or tartaric acid; an amino acid, such as aspartic acid or glutamic acid; an aromatic acid, such as benzoic acid, 2-acetoxybenzoic acid, 10 naphthoic acid, or cinnamic acid; a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, or ethanesulfonic acid; or any compatible mixture of acids such as those given as examples herein.

If the compound of Formula (I) is an acid such as a carboxylic acid or sulfonic acid, the desired pharmaceutically acceptable salt may be prepared by 15 any suitable method, for example, by treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide, alkaline earth metal hydroxide, or any compatible mixture of bases such as those given as examples herein. Illustrative examples of suitable salts include organic salts derived from amino acids, such 20 as glycine and arginine, ammonia, carbonates, bicarbonates, primary, secondary, and tertiary amines, and cyclic amines, such as benzylamines, pyrrolidines, piperidine, morpholine, and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum, and lithium.

25 The invention also relates to pharmaceutically acceptable prodrugs of the compounds of Formula (I). The term "prodrug" means a precursor of a designated compound that, following administration to a subject, yields the compound *in vivo* via a chemical or physiological process such as solvolysis or enzymatic cleavage, or under physiological conditions (e.g., a prodrug on being 30 brought to physiological pH is converted to the compound of Formula (I)). A "pharmaceutically acceptable prodrug" is a prodrug that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to

the subject. Illustrative procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Examples of prodrugs include compounds having an amino acid
5 residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues, covalently joined through an amide or ester bond to a free amino, hydroxy, or carboxylic acid group of a compound of Formula (I). Examples of amino acid residues include the twenty naturally occurring amino acids, commonly designated by three letter symbols, as well as 4-
10 hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone.

Additional types of prodrugs may be produced, for instance, by derivatizing free carboxyl groups of structures of Formula (I) as amides or alkyl
15 esters. Examples of amides include those derived from ammonia, primary C₁₋₆alkyl amines and secondary di(C₁₋₆alkyl) amines. Secondary amines include 5- or 6-membered heterocycloalkyl or heteroaryl ring moieties. Examples of amides include those that are derived from ammonia, C₁₋₃alkyl primary amines, and di(C₁₋₂alkyl)amines. Examples of esters of the invention include C₁₋₇alkyl,
20 C₅₋₇cycloalkyl, phenyl, and phenyl(C₁₋₆alkyl) esters. Preferred esters include methyl esters. Prodrugs may also be prepared by derivatizing free hydroxy groups using groups including hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, following procedures such as those outlined in Fleisher et al., *Adv. Drug Delivery Rev.*
25 1996, 19, 115-130. Carbamate derivatives of hydroxy and amino groups may also yield prodrugs. Carbonate derivatives, sulfonate esters, and sulfate esters of hydroxy groups may also provide prodrugs. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers, wherein the acyl group may be an alkyl ester, optionally substituted with one or more ether, amine, or
30 carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, is also useful to yield prodrugs. Prodrugs of this type may be prepared as described in Robinson et al., *J. Med. Chem.* 1996, 39, 10-18.

Free amines can also be derivatized as amides, sulfonamides or phosphoramidates. All of these prodrug moieties may incorporate groups including ether, amine, and carboxylic acid functionalities.

The present invention also relates to pharmaceutically active metabolites of compounds of Formula (I). A "pharmaceutically active metabolite" means a pharmacologically active product of metabolism in the body of a compound of Formula (I) or salt thereof. Prodrugs and active metabolites of a compound may be determined using routine techniques known or available in the art. See, e.g., Bertolini et al., *J. Med. Chem.* 1997, 40, 2011-2016; Shan et al., *J. Pharm. Sci.* 1997, 86 (7), 765-767; Bagshawe, *Drug Dev. Res.* 1995, 34, 220-230; Bodor, *Adv. Drug Res.* 1984, 13, 255-331; Bundgaard, *Design of Prodrugs* (Elsevier Press, 1985); and Larsen, *Design and Application of Prodrugs, Drug Design and Development* (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

The compounds of Formula (I), and their pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites (collectively, "active agents") of the present invention are useful as FAAH inhibitors in the methods of the invention. The active agents may be used in the inventive methods for the treatment of medical conditions, diseases, or disorders mediated through inhibition or modulation of FAAH, such as those described herein. Active agents according to the invention may therefore be used as an analgesic, anti-depressant, cognition enhancer, neuroprotectant, sedative, appetite stimulant, or contraceptive.

Exemplary medical conditions, diseases, and disorders mediated by FAAH activity include anxiety, depression, pain, sleep disorders, eating disorders, inflammation, multiple sclerosis and other movement disorders, HIV wasting syndrome, closed head injury, stroke, learning and memory disorders, Alzheimer's disease, epilepsy, Tourette's syndrome, epilepsy, Niemann-Pick disease, Parkinson's disease, Huntington's chorea, optic neuritis, autoimmune uveitis, symptoms of drug withdrawal, nausea, emesis, sexual dysfunction, post-traumatic stress disorder, cerebral vasospasm, diabetes, metabolic syndrome and osteoporosis.

Thus, the active agents may be used to treat subjects diagnosed with or suffering from such a disease, disorder, or condition. The term "treat" or "treating" as used herein is intended to refer to administration of an agent or composition of the invention to a subject for the purpose of effecting a therapeutic benefit through modulation of FAAH activity. Treating includes reversing, ameliorating, alleviating, inhibiting the progress of, lessening the severity of, reducing the incidence of, or preventing a disease, disorder, or condition, or one or more symptoms of such disease, disorder or condition mediated through modulation of FAAH activity. The term "subject" refers to a mammalian patient in need of such treatment, such as a human. "Modulators" include both inhibitors and activators, where "inhibitors" refer to compounds that decrease, prevent, inactivate, desensitize or down-regulate FAAH expression or activity, and "activators" are compounds that increase, activate, facilitate, sensitize, or up-regulate FAAH expression or activity.

Accordingly, the invention relates to methods of using the active agents described herein to treat subjects diagnosed with or suffering from a disease, disorder, or condition mediated through FAAH activity, such as: anxiety, pain, sleep disorders, eating disorders, inflammation, movement disorders (e.g., multiple sclerosis), energy metabolism (e.g. insulin resistance, diabetes, dyslipidemia, liver steatosis, steatohepatitis, obesity, and metabolic syndrome) and bone homeostasis (e.g. osteoporosis).

Symptoms or disease states are intended to be included within the scope of "medical conditions, disorders, or diseases." For example, pain may be associated with various diseases, disorders, or conditions, and may include various etiologies. Illustrative types of pain treatable with a FAAH-modulating agent, in one example herein a FAAH-inhibiting agent, according to the invention include cancer pain, postoperative pain, GI tract pain, spinal cord injury pain, visceral hyperalgesia, thalamic pain, headache (including stress headache and migraine), low back pain, neck pain, musculoskeletal pain, peripheral neuropathic pain, central neuropathic pain, neurodegenerative disorder related pain, and menstrual pain. HIV wasting syndrome includes associated symptoms such as appetite loss and nausea. Parkinson's disease includes, for

example, levodopa-induced dyskinesia. Treatment of multiple sclerosis may include treatment of symptoms such as spasticity, neurogenic pain, central pain, or bladder dysfunction. Symptoms of drug withdrawal may be caused by, for example, addiction to opiates or nicotine. Nausea or emesis may be due to
5 chemotherapy, postoperative, or opioid related causes. Treatment of sexual dysfunction may include improving libido or delaying ejaculation. Treatment of cancer may include treatment of glioma. Sleep disorders include, for example, sleep apnea, insomnia, and disorders calling for treatment with an agent having a sedative or narcotic-type effect. Eating disorders include, for
10 example, anorexia or appetite loss associated with a disease such as cancer or HIV infection/AIDS.

In treatment methods according to the invention, an effective amount of at least one active agent according to the invention is administered to a subject suffering from or diagnosed as having such a disease, disorder, or condition. A
15 "therapeutically effective amount" or "effective amount" means an amount or dose of a FAAH-modulating agent sufficient to generally bring about a therapeutic benefit in patients in need of treatment for a disease, disorder, or condition mediated by FAAH activity. Effective amounts or doses of the active agents of the present invention may be ascertained by routine methods such
20 as modeling, dose escalation studies or clinical trials, and by taking into consideration routine factors, e.g., the mode or route of administration or drug delivery, the pharmacokinetics of the agent, the severity and course of the disease, disorder, or condition, the subject's previous or ongoing therapy, the subject's health status and response to drugs, and the judgment of the treating
25 physician. An exemplary dose is in the range of from about 0.0001 to about 200 mg of active agent per kg of subject's body weight per day, preferably about 0.001 to 100 mg/kg/day, or about 0.01 to 35 mg/kg/day, or about 0.1 to 10 mg/kg daily in single or divided dosage units (e.g., BID, TID, QID). For a 70-kg human, an illustrative range for a suitable dosage amount is from about
30 0.05 to about 7 g/day, or about 0.2 to about 5 g/day. Once improvement of the patient's disease, disorder, or condition has occurred, the dose may be adjusted for maintenance treatment. For example, the dosage or the

frequency of administration, or both, may be reduced as a function of the symptoms, to a level at which the desired therapeutic effect is maintained. Of course, if symptoms have been alleviated to an appropriate level, treatment may cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence of symptoms.

In addition, the active agents of the invention may be used in combination with additional active ingredients in the treatment of the above conditions. The additional active ingredients may be coadministered separately with an active agent of Formula (I) or included with such an agent in a pharmaceutical composition according to the invention. In an exemplary embodiment, additional active ingredients are those that are known or discovered to be effective in the treatment of conditions, disorders, or diseases mediated by FAAH activity, such as another FAAH modulator or a compound active against another target associated with the particular condition, disorder, or disease. The combination may serve to increase efficacy (e.g., by including in the combination a compound potentiating the potency or effectiveness of an active agent according to the invention), decrease one or more side effects, or decrease the required dose of the active agent according to the invention. In one illustrative embodiment, a composition according to the invention may contain one or more additional active ingredients selected from opioids, NSAIDs (e.g., ibuprofen, cyclooxygenase-2 (COX-2) inhibitors, and naproxen), gabapentin, pregabalin, tramadol, acetaminophen, and aspirin.

The active agents of the invention are used, alone or in combination with one or more additional active ingredients, to formulate pharmaceutical compositions of the invention. A pharmaceutical composition of the invention comprises: (a) an effective amount of at least one active agent in accordance with the invention; and (b) a pharmaceutically acceptable excipient.

A "pharmaceutically acceptable excipient" refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of a agent and that is compatible therewith.

Examples of excipients include calcium carbonate, calcium phosphate, various sugars and types of starch, cellulose derivatives, gelatin, vegetable oils, and polyethylene glycols.

Delivery forms of the pharmaceutical compositions containing one or more dosage units of the active agents may be prepared using suitable pharmaceutical excipients and compounding techniques known or that become available to those skilled in the art. The compositions may be administered in the inventive methods by a suitable route of delivery, e.g., oral, parenteral, rectal, topical, or ocular routes, or by inhalation.

The preparation may be in the form of tablets, capsules, sachets, dragees, powders, granules, lozenges, powders for reconstitution, liquid preparations, or suppositories. Preferably, the compositions are formulated for intravenous infusion, topical administration, or oral administration.

For oral administration, the active agents of the invention can be provided in the form of tablets or capsules, or as a solution, emulsion, or suspension. To prepare the oral compositions, the active agents may be formulated to yield a dosage of, e.g., from about 5 mg to 5 g daily, or from about 50 mg to 5 g daily, in single or divided doses. For example, a total daily dosage of about 5 mg to 5 g daily may be accomplished by dosing once, twice, three, or four times per day.

Oral tablets may include the active ingredient(s) mixed with compatible pharmaceutically acceptable excipients such as diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservative agents. Suitable inert fillers include sodium and calcium carbonate, sodium and calcium phosphate, lactose, starch, sugar, glucose, methyl cellulose, magnesium stearate, mannitol, sorbitol, and the like. Exemplary liquid oral excipients include ethanol, glycerol, water, and the like. Starch, polyvinyl-pyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are exemplary disintegrating agents. Binding agents may include starch and gelatin. The lubricating agent, if present, may be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate to delay

absorption in the gastrointestinal tract, or may be coated with an enteric coating.

Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, active ingredient(s) may be mixed with a solid, semi-solid, or liquid diluent. Soft gelatin capsules may be prepared by mixing the active ingredient with water, an oil such as peanut oil or olive oil, liquid paraffin, a mixture of mono and di-glycerides of short chain fatty acids, polyethylene glycol 400, or propylene glycol.

Liquids for oral administration may be in the form of suspensions, solutions, emulsions or syrups or may be lyophilized or presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may optionally contain: pharmaceutically-acceptable excipients such as suspending agents (for example, sorbitol, methyl cellulose, sodium alginate, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminum stearate gel and the like); non-aqueous vehicles, e.g., oil (for example, almond oil or fractionated coconut oil), propylene glycol, ethyl alcohol, or water; preservatives (for example, methyl or propyl p-hydroxybenzoate or sorbic acid); wetting agents such as lecithin; and, if desired, flavoring or coloring agents.

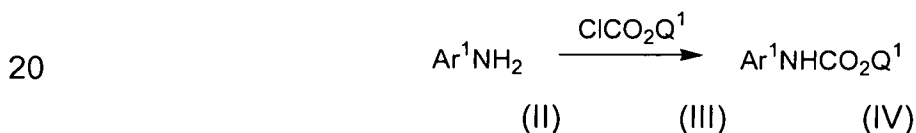
The active agents of this invention may also be administered by non-oral routes. For example, compositions may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, or subcutaneous routes, the agents of the invention may be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity or in parenterally acceptable oil. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Such forms may be presented in unit-dose form such as ampules or disposable injection devices, in multi-dose forms such as vials from which the appropriate dose may be withdrawn, or in a solid form or pre-concentrate that can be used to prepare an injectable formulation. Illustrative infusion doses range from about 1 to 1000 $\mu\text{g/kg/minute}$ of agent admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

For topical administration, the agents may be mixed with a pharmaceutical carrier at a concentration of about 0.1% to about 10% of drug to vehicle. Another mode of administering the agents of the invention may utilize a patch formulation to affect transdermal delivery.

5 Active agents may alternatively be administered in methods of this invention by inhalation, via the nasal or oral routes, e.g., in a spray formulation also containing a suitable carrier.

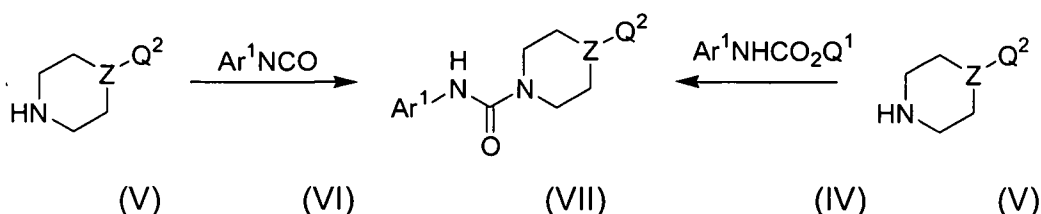
Exemplary active agents useful in methods of the invention will now be described by reference to illustrative synthetic schemes for their general
10 preparation below and the specific examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ,
15 in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Unless otherwise specified, the variables are as defined above in reference to Formula (I).

SCHEME A:



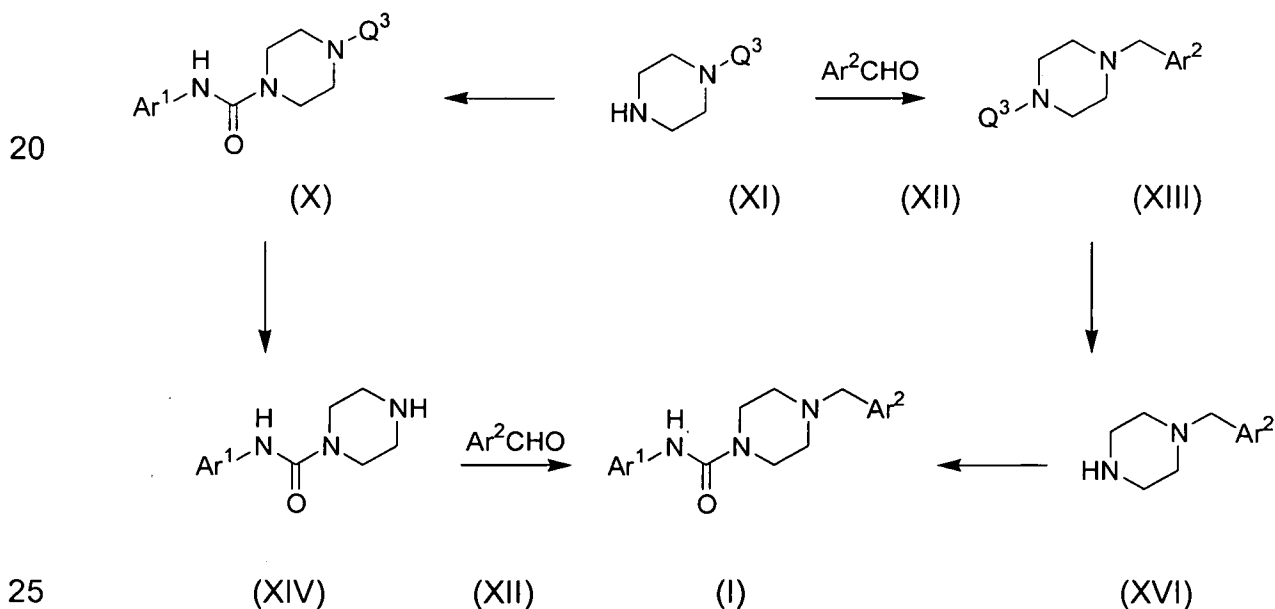
Referring to Scheme A, a carbamate of formula (IV) may be obtained by reacting a compound of formula (II) with a compound of formula (III), in which Q¹ represents an aryl group, under chloroformate condensation conditions.
25 Preferably, Q¹ is substituted or unsubstituted phenyl, and the reaction occurs with or without a base, in a solvent such as acetonitrile, at a temperature from about 0 °C to about 80 °C. More preferably, Q¹ is phenyl, and the reaction occurs in acetonitrile at about 70 °C, or in the presence of a base such as pyridine, triethylamine, or diisopropylethylamine, in dichloromethane at 0 °C
30 followed by warming to room temperature.

SCHEME B:



- Referring to Scheme B, a compound of formula (VII) is prepared from a compound of formula (V). The group Q² is CH₂Ar² or when Z is N, Q² may also be a suitable nitrogen protecting group Q³. A compound of formula (VII) is obtained by reacting a compound of formula (V) with a compound of formula (VI) under isocyanate addition conditions. In a preferred embodiment, the reaction is performed in a solvent at a temperature from 0 °C to 100 °C.
- Preferred conditions employ dichloromethane (DCM) at room temperature. Alternatively, a compound of formula (VII) is obtained by reacting a compound of formula (V) with a compound of formula (IV) under aryl carbamate condensation conditions. The reaction may preferably take place in a solvent at a temperature from about room temperature to about 120 °C. Preferably, Q¹ is phenyl, and the reaction is performed in dimethylsulfoxide (DMSO) in a microwave reactor at about 100 °C or by conventional heating from about room temperature to about 50 °C. Where Q² is CH₂Ar², compounds of formula (VII) fall within the scope of Formula (I).

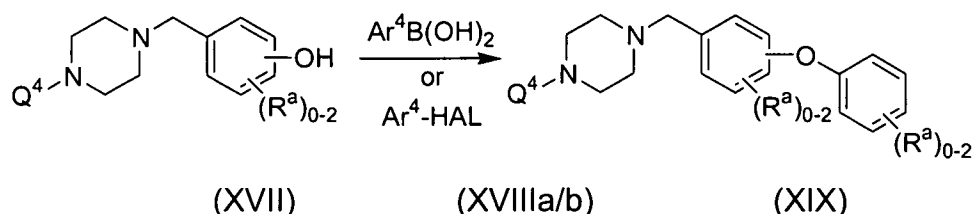
SCHEME C:



Referring to Scheme C, compounds of formula (I) are prepared from compounds of formula (XI). A suitable protecting group Q^3 compatible with the transformations in Scheme C is selected. Preferably, Q^3 is *tert*-butyl-carbamoyl (Boc). A compound of formula (X) is obtained by reacting a compound of
5 formula (XI): (a) with a compound of formula (VI); (b) with a compound of formula (IV); or (c) with a compound Ar^1NH_2 in the presence of di-(N-succinimidyl)carbonate. An amine of formula (XIV) is obtained by deprotecting a compound of formula (X) with a reagent under suitable Q^3 deprotection conditions. Boc deprotection may be preferably effected with HCl or
10 trifluoroacetic acid (TFA) in a solvent such as diethyl ether (Et_2O), DCM, or 1,4-dioxane. A compound of Formula (I) is obtained by reacting a compound of formula (XIV) with an aldehyde (XII) under reductive amination conditions in the presence of a reductant such as sodium triacetoxyborohydride, resin-supported triacetoxyborohydride (e.g., MP-B(OAc)₃H), sodium
15 cyanoborohydride, or phenylsilane in a solvent such as tetrahydrofuran (THF), 1,2-dichloroethane (DCE), DCM, methanol (MeOH), ethanol (EtOH), or Et_2O at a temperature from about 0 °C to 80 °C. The use of a promoter or catalyst with acidic character such as an organometallic complex or carboxylic acid may increase the rate of the reaction and/or reduce the formation of by-products.
20 Preferably, sodium triacetoxyborohydride in DCE is employed at room temperature. Reductive amination may also be performed using solid-supported triacetoxyborohydride in the presence of Et_3N in tetrahydrofuran (THF).

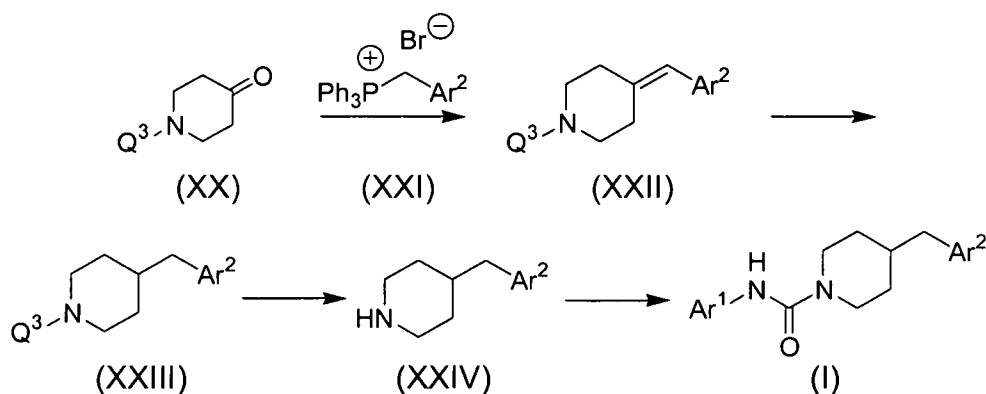
Alternatively, a compound of formula (XIII) is obtained by reacting an
25 aldehyde (XI) with a protected piperazine (XII) under reductive amination conditions as described. Deprotection of Q^3 from a compound of formula (XIII) under general deprotection conditions provides piperazines (XVI). A compound of Formula (I) is obtained by reacting a compound of formula (XVI) with either a compound of formula (IV) or with a compound of formula (VI) as
30 described in the preceding schemes.

SCHEME D:



- Referring to Scheme D, a compound of formula (XVII), where Q⁴ is -
- 5 CONR¹Ar¹ or a nitrogen protecting group Q³, is prepared as described in the preceding schemes. A compound of formula (XVII) is converted to a compound of formula (XIX) by reaction with a suitable boronic acid (XVIIIa) in the presence of a drying agent such as powdered 4Å molecular sieves, a promoter such as copper(II) acetate, optionally in the presence of air or a pure
- 10 oxygen atmosphere, and optionally in the presence of a base such as pyridine or triethylamine, in a solvent such as DCM or DCE. Where Q⁴ is -CONR¹Ar¹, compounds of formula (XIX) are within the scope of Formula (I). Alternatively, a compound of formula (XIX), where Q⁴ is a nitrogen protecting group Q³, is prepared from (XVII) by treatment with a suitable aryl halide
- 15 (XVIIIb, where HAL is chloro, bromo, or iodo) and a base such as Cs₂CO₃ in a solvent such as DMSO at temperatures ranging from about room temperature to about 120 °C.

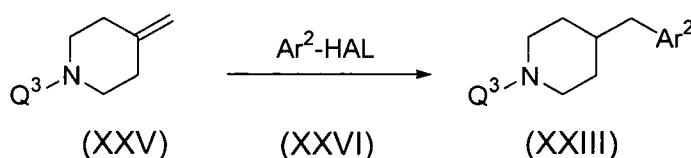
SCHEME E:



- 20 Compounds of Formula (I) are also prepared according to Scheme E. Deprotection of a Wittig reagent (XXI; obtained from a commercial source or prepared from a suitable bromide, alcohol, aldehyde, or other precursor following general techniques known in the art) with a base such as NaH, in a

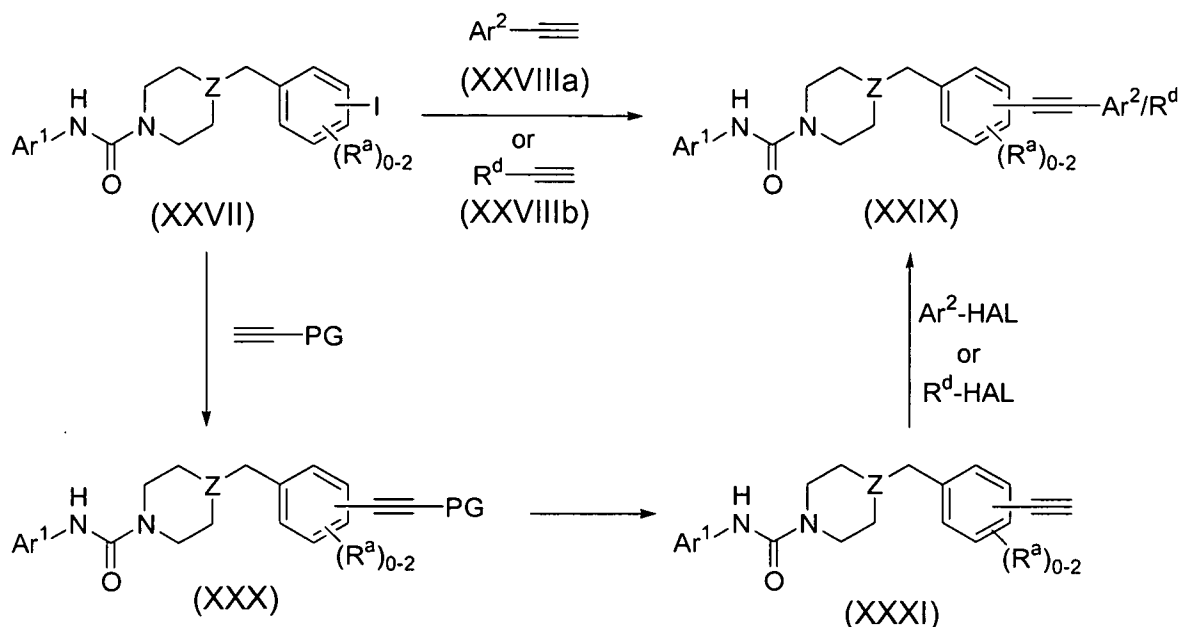
solvent such as DMSO, and subsequent treatment with a piperidone (XX), where Q^3 is a nitrogen protecting group (such as Boc or benzyl) gives a compound of formula (XXII). Reduction of the double bond with hydrogen (about 10 to 100 psi) in the presence of a catalyst such as palladium on carbon or platinum(II) oxide, in solvent such as MeOH or EtOH gives a compound of formula (XXIII). Deprotection of Q^3 is accomplished using conventional conditions to give a piperidine (XXIV). A compound of Formula (I) is prepared by reacting a compound of formula (XXIV) with either a compound of formula (IV) or a compound of formula (VI) as described in the preceding schemes.

SCHEME F:



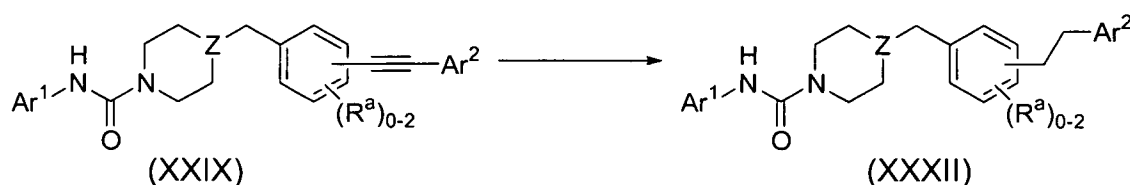
Intermediate compounds of formula (XXIII) are also prepared according to Scheme F. Hydrometallation of an alkenyl compound (XXV) gives an activated species, which is subsequently reacted with a suitable reagent Ar²-HAL (where HAL is chloride, bromide, or iodide), to provide a compound (XXIII). Preferably, hydrometallation is accomplished by hydroboration using a suitable dialkylborane reagent such as 9-borabicyclo[3.3.1]nonane (9-BBN) or diisopinocampheylborane, in a solvent such as THF. The resulting boron adduct is preferably reacted with Ar²-HAL in the presence of a suitable palladium(II) catalyst, a base such as K₂CO₃ or Cs₂CO₃, in a solvent such as N,N-dimethylformamide (DMF) or an aqueous mixture thereof. Compounds of formula (XXIII) are converted to compounds of Formula (I) using methods described in the preceding schemes.

Scheme G:



- Further embodiments of Formula (I), such as compounds (XXIX) or (XXXI) are prepared as described in Scheme G. Palladium-catalyzed coupling of compounds (XXVII, prepared as described in the preceding Schemes) with alkynes (XXVIIIa/b) provides compounds (XXIX). Preferably, reactions are run in the presence of a palladium(II) catalyst such as $Pd(PPh_3)_2Cl_2$, a copper(I) catalyst such as CuI , a base such as triethylamine, with or without an additional phosphine ligand such as triphenylphosphine, in a solvent such as THF, at a temperature from about room temperature to about 50 °C. Alternatively, iodides (XXVII) are coupled with a protected alkyne reagent, where PG is a suitable protecting group such as trimethylsilyl, to give compounds (XXX). Removal of the protecting group gives compounds (XXXI). A second palladium-catalyzed coupling reaction with suitable halides Ar^2-HAL or R^d-HAL (where HAL is chloride, bromide, or iodide) gives compounds (XXIX).

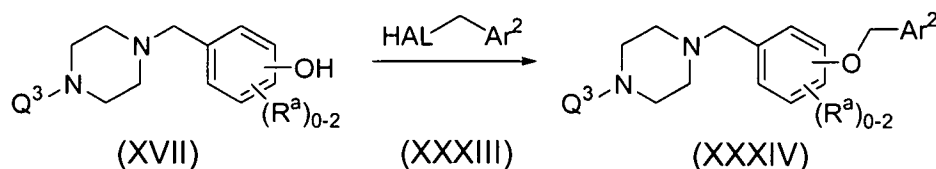
Scheme H:



Alkynes (XXIX) are optionally reduced to compounds (XXXII) using standard hydrogenation protocols. Preferably, reactions are accomplished

using hydrogen gas and a catalyst such as palladium on carbon, in a solvent such as EtOH.

Scheme I:



- 5 Further embodiments of Formula (I) are prepared as shown in Scheme I. Alkylation of a phenol (XVII) with a suitable benzyl halide (XXXIII) and a base such as K_2CO_3 in a solvent such as acetonitrile at a temperature from about room temperature to about 50 °C provides compounds (XXXIV).

- 10 Compounds of Formula (I) may be converted to their corresponding salts by applying general techniques described in the art. For example, a compound of Formula (I) may be treated with trifluoroacetic acid, HCl, or citric acid in a solvent such as Et_2O , 1,4-dioxane, DCM, THF, or MeOH to provide the corresponding salt forms.

- 15 Compounds prepared according to the schemes described above may be obtained as single enantiomers, diastereomers, or regioisomers, by enantio-, diastereo-, or regio-specific synthesis, or by resolution. Compounds prepared according to the schemes above may alternatively be obtained as racemic (1:1) or non-racemic (not 1:1) mixtures or as mixtures of diastereomers or regioisomers. Where racemic and non-racemic mixtures of enantiomers are obtained, single enantiomers may be isolated using conventional separation methods, such as chiral chromatography, recrystallization, diastereomeric salt formation, derivatization into diastereomeric adducts, biotransformation, or enzymatic transformation. Where regioisomeric or diastereomeric mixtures are obtained, single isomers may be separated using conventional methods such as chromatography or crystallization.
- 20
- 25

The following specific examples are provided to further illustrate the invention and various preferred embodiments.

EXAMPLES

Chemistry:

In preparing the examples listed below, the following general experimental and analytical methods were used.

5 Reaction mixtures were stirred under a nitrogen atmosphere at room temperature (rt) unless otherwise noted. Where solutions or mixtures are concentrated, they are typically concentrated under reduced pressure using a rotary evaporator. Where solutions are dried, they are typically dried over a drying agent such as MgSO_4 or Na_2SO_4 .

10 Normal phase flash column chromatography (FCC) was performed on silica gel columns using ethyl acetate (EtOAc)/hexanes as eluent, unless otherwise indicated.

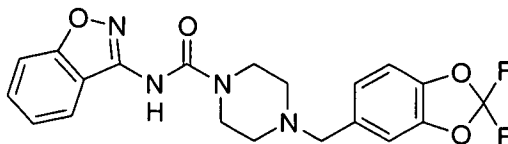
Reversed-Phase high performance liquid chromatography (HPLC) was performed using: 1) a Gilson® instrument with a YMC-Pack ODS-A, 5 μm ,
15 75x30 mm column, a flow rate of 25 mL/min, detection at 220 and 254 nm, with a 15% to 99% acetonitrile/water/0.05% TFA gradient; or 2) Shimadzu instrument with a Phenomenex Gemini column 5 μm C18 (150 x 21.2 mm) or Waters Xterra RP18 OBD column 5 μm (100 x 30 mm), a gradient of 95:5 to 0:100 water (0.05% TFA)/ CH_3CN (0.05% TFA), a flow rate of 30 mL/min, and
20 detection at 254 nm.

Mass spectra were obtained on an Agilent series 1100 MSD using electrospray ionization (ESI) in positive mode unless otherwise indicated.

NMR spectra were obtained on either a Bruker model DPX400 (400 MHz), DPX500 (500 MHz), DRX600 (600 MHz) spectrometer. The format of
25 the ^1H NMR data below is: chemical shift in ppm down field of the tetramethylsilane reference (multiplicity, coupling constant J in Hz, integration).

Chemical names were generated using ChemDraw Ultra 6.0.2 (CambridgeSoft Corp., Cambridge, MA) or ACD/Name Version 9 (Advanced Chemistry Development, Toronto, Ontario, Canada).

Example 1: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.



Step A: Benzo[d]isoxazol-3-yl-carbamic acid phenyl ester. A mixture of

5 benzo[d]isoxazol-3-ylamine (3.0 g) and ClCO_2Ph (0.94 mL) in dry CH_3CN (30 mL) was stirred for 23 h at 70 °C. The reaction mixture was poured into de-ionized water, stirred for 30 min and filtered. The isolated solid was rinsed thoroughly with water and then dried under high vacuum to give 1.90 g (100%) of the title compound. MS: 255.1.

Step B: 1-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine.

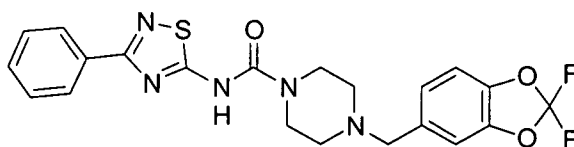
10 A 0 °C solution of piperazine-1-carboxylic acid tert-butyl ester (20.0 g) and 2,2-difluoro-benzo[1,3]dioxole-5-carbaldehyde (14.8 mL) in DCE (208 mL) was treated with $\text{NaB}(\text{OAc})_3\text{H}$ (31.8 g). The mixture was allowed to warm to rt and was stirred for 16 h. The resulting mixture was
15 cooled in an ice bath and treated with 10% aq. KOH (200 mL). After 1 h, the resulting mixture was extracted with DCM (3x200 mL). The combined organic extracts were dried and concentrated, giving a white solid (37.6 g). This solid was dissolved in MeOH (850 mL) and treated with HCl (2 M in Et_2O ; 159 mL). After 16 h, the resulting mixture was
20 treated with Et_2O (850 mL). A white precipitate was filtered off and washed with Et_2O (2x140 mL), giving a white solid (27.6 g). This solid (27.5 g) was suspended in DCM (200 mL) and treated with 10% aq. KOH (200 mL). The organic phase was extracted with DCM (2x150 mL). The combined organic extracts were dried and concentrated, giving the
25 title compound as a white solid (20.8 g). MS: 257.1.

Step C: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt. To a Smith Process vial were added a spin vane, benzo[d]isoxazol-3-yl-carbamic acid phenyl ester (51.2 mg), 1-(2,2-difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine (76.5 mg) and DMSO (0.5 mL). The vial was
30

purged with N₂, capped and heated via microwave irradiation for 15 min at 100 °C. The reaction mixture was then directly purified by reverse-phase HPLC to give 62.4 mg (58%) of the desired product as the TFA salt. MS: 417.2. ¹H NMR (d₄-MeOH): 7.88 (d, *J* = 7.8, 1H), 7.60-7.57 (m, 1H), 7.52 (d, *J* = 8.4, 1H), 7.43 (d, *J* = 1.8, 1H), 7.35-7.34 (dd, *J* = 1.5, 8.1, 1H), 7.32-7.30 (m, 2H), 4.53-3.54 (br hump, 4H), 4.43 (s, 2H), 3.40 (br s, 4H).

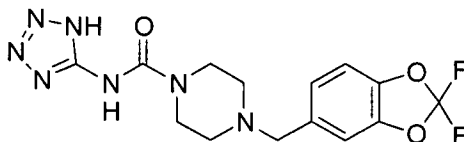
The compounds in Examples 2-8 were prepared using methods analogous to those described in Example 1.

10 Example 2: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid (3-phenyl-[1,2,4]thiadiazol-5-yl)-amide trifluoroacetic acid salt.



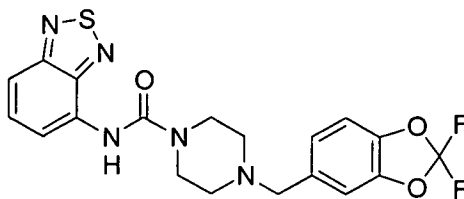
MS: 460.5. ¹H NMR (CDCl₃): 10.66 (br s, 1H), 8.10-8.08 (m, 2H), 7.46-7.43 (m, 3H), 7.00 (s, 1H), 6.96 (d, *J* = 8.4, 1H), 6.91-6.89 (dd, *J* = 1.2, 7.8, 1H), 3.33 (br s, 6H), 2.15 (br s, 4H).

15 Example 3: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid (1H-tetrazol-5-yl)-amide trifluoroacetic acid salt.



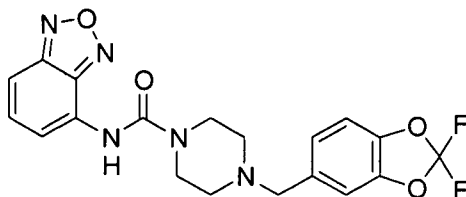
MS: 368.5. ¹H NMR (d₆-DMSO): 15.51 (s, 1H), 10.98 (s, 1H), 7.54 (s, 2H), 7.33-7.32 (m, 1H), 4.29 (br s, 4H), 3.58-2.86 (m, 6H).

20 Example 4: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide trifluoroacetic acid salt.



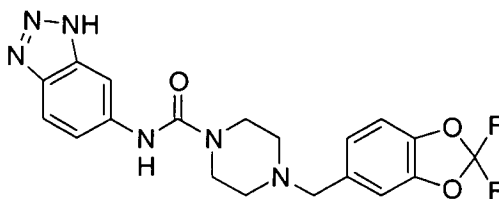
MS: 434.5. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.94-7.93 (dd, $J = 1.2, 7.2, 1\text{H}$), 7.63-7.57 (m, 2H), 7.26 (s, 1H), 7.14 (d, $J = 0.6, 2\text{H}$), 3.64 (t, $J = 4.8, 4\text{H}$), 2.54 (t, $J = 4.8, 4\text{H}$).

- 5 Example 5: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid benzo[1,2,5]oxadiazol-4-ylamide trifluoroacetic acid salt.



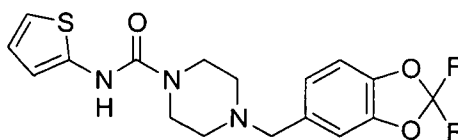
MS: 418.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.62 (d, $J = 7.2, 1\text{H}$), 7.57 (d, $J = 9.0, 1\text{H}$), 7.48-7.45 (m, 2H), 7.38-7.34 (m, 2H), 4.44 (s, 2H), 4.28-3.63 (br hump, 4H), 3.39 (br s, 4H).

- 10 Example 6: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid (3H-benzotriazol-5-yl)-amide trifluoroacetic acid salt.



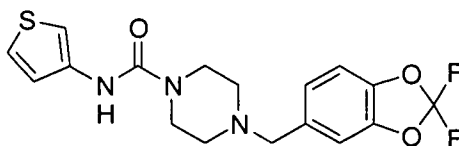
- MS: 417.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.00 (s, 1H), 7.79 (d, $J = 9.0, 1\text{H}$), 7.44 (s, 1H), 7.42-7.40 (dd, $J = 1.8, 9.0, 1\text{H}$), 7.37-7.33 (m, 2H), 4.44 (s, 2H), 4.50-3.20 (br hump, 4H), 3.37 (br s, 4H).

- Example 7: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid thiophen-2-ylamide.



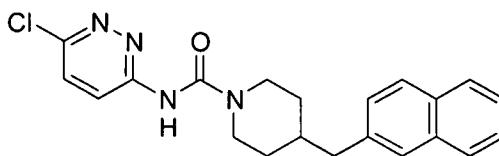
- MS: 382.1. ^1H NMR (CDCl_3): 7.11 (s, 1H), 7.05 (s, 1H), 7.02-6.97 (m, 2H), 6.83-6.77 (m, 2H), 6.54-6.51 (m, 1H), 3.52-3.48 (m, 6H), 2.49-2.43 (m, 4H).

- Example 8: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid thiophen-3-ylamide.



MS: 382.1. ^1H NMR (CDCl_3): 7.27-7.25 (m, 1H), 7.21-7.17 (m, 1H), 7.11 (s, 1H), 7.01-6.94 (m, 3H), 6.69 (s, 1H), 3.51-3.45 (m, 6H), 2.48-2.42 (m, 4H).

5 Example 9: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide.



Step A: Naphthalen-2-ylmethyl-triphenyl-phosphonium bromide.

A flask containing a mixture of 2-bromomethyl-naphthalene (25.0 g) and triphenylphosphine (31.3 g) in xylenes (230 mL) was fitted with a reflux condenser, purged with N_2 , and heated to 135 °C for 24 h. The resulting white solid was isolated by filtration, washed with toluene, and dried under high vacuum.

Step B: 4-Naphthalen-2-ylmethylene-piperidine-1-carboxylic acid

15 tert-butyl ester. A 0 °C suspension of NaH (95%, 3.30 g) in dry DMSO (300 mL) was stirred for 10 min and then treated with a hot solution of naphthalen-2-ylmethyl-triphenyl-phosphonium bromide (52.4 g) in DMSO (100 mL) via cannula over 20 min (heating the DMSO solution was necessary to dissolve the phosphonium salt). The resultant bright red mixture was allowed to stir at 0 °C for 10 min before adding a solution of N-Boc-piperidinone (26.3 g) in DMSO (100 mL) via cannula over 20 min. After stirring for 1 h at 0 °C, 3 h at rt and 50 °C for 18 h, the mixture was diluted with 1-L water and extracted with Et_2O (500 mLx4). The organic extracts were washed with water (x2), dried, and concentrated to give a yellow heterogeneous mixture. The crude material was suspended in hot hexanes (700 mL) and the solid removed by filtration. Concentration of the filtrate gave an oily residue that was

purified by FCC to give 28.1 g (80%) of the title compound as a colorless oil.

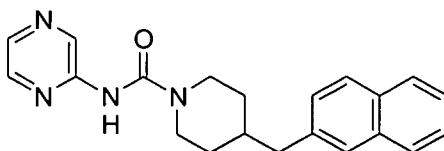
5 Step C: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid tert-butyl ester. A flask containing a suspension of 4-naphthalen-2-ylmethylene-piperidine-1-carboxylic acid tert-butyl ester (22.7 g) and 10% Pd/C (6.3 g) in EtOH (350 mL) was evacuated and then affixed with a H₂ balloon. After 18 h, the H₂ was evacuated from the flask and replaced with N₂. The reaction mixture was filtered twice through diatomaceous earth and then through a Zapcap. The filtrate was
10 concentrated to give 21.9 g (96%) of the title compound as a pale-yellow oil. MS: 348.5 (M+Na)⁺.

Step D: 4-Naphthalen-2-ylmethyl-piperidine. A mixture of 4-naphthalen-2-ylmethyl-piperidine-1-carboxylic acid tert-butyl ester (21.4 g) and TFA (75 mL) was stirred at rt for 18 h. The mixture was
15 concentrated, diluted with DCM, and washed with 1 N NaOH. The organic layer was dried and concentrated to give 14.8 g (100%) of the title compound as a pale-yellow oil that crystallized upon standing. MS: 226.2.

Step E: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide. The title compound was prepared using methods
20 analogous to those described in Example 1, Step C. MS: 481.5. ¹H NMR (CDCl₃): 8.46 (br s, 1H), 8.31 (br s, 1H), 7.81 (d, J = 7.5, 1H), 7.78 (d, J = 8.5, 2H), 7.58 (s, 1H), 7.48-7.39 (m, 3H), 7.30-7.28 (dd, J = 1.5, 8.5, 1H), 4.17 (d, J = 13.5, 2H), 2.87 (t, J = 12.5, 2H), 2.73 (d, J = 7.0, 2H), 1.94-1.83 (m, 1H), 1.76
25 (d, J = 13, 2H), 1.36-1.25 (m, 2H).

The compounds in Examples 10-27 were prepared using methods analogous to those described in Example 9.

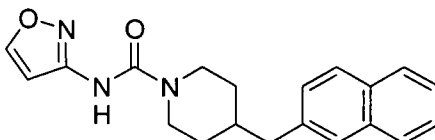
Example 10: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid pyrazin-2-ylamide trifluoroacetic acid salt.



30

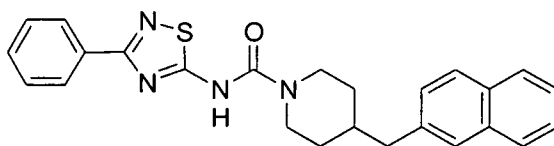
MS: 347.5. ^1H NMR (CDCl_3): 9.42 (d, $J = 1.5$, 1H), 8.27 (d, $J = 2.5$, 1H), 8.15-8.14 (dd, $J = 1.5$, 2.5, 1H), 7.84-7.79 (m, 3H), 7.60 (s, 1H), 7.48-7.43 (m, 2H), 7.32-7.30 (m, 1H), 4.13 (d, $J = 13$, 2H), 2.94-2.88 (dt, $J = 3.0$, 12.5, 2H), 2.76 (d, $J = 7.5$, 2H), 1.92-1.87 (m, 1H), 1.81 (d, $J = 13.0$, 2H), 1.39-1.30 (m, 2H).

Example 11: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid isoxazol-3-ylamide.



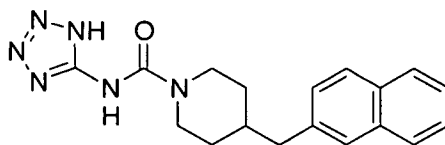
MS: 336.5. ^1H NMR (d_6 -acetone): 8.71 (s, 1H), 8.16 (s, 1H), 7.81 (d, $J = 8.4$, 1H), 7.78 (d, $J = 8.4$, 2H), 7.58 (s, 1H), 7.48-7.42 (m, 2H), 7.30-7.28 (dd, $J = 1.8$, 9, 1H), 7.00 (s, 1H), 4.17 (d, $J = 13.2$, 2H), 2.86 (t, $J = 12.6$, 2H), 2.72 (d, $J = 7.2$, 2H), 1.90-1.83 (m, 1H), 1.75 (d, $J = 12.6$, 2H), 1.33-1.25 (m, 2H).

Example 12: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (3-phenyl-[1,2,4]thiadiazol-5-yl)-amide.



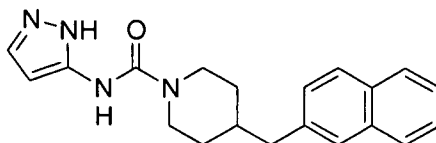
MS: 429.5. ^1H NMR (CDCl_3): 8.13-8.12 (m, 2H), 7.82 (d, $J = 7.8$, 1H), 7.79 (d, $J = 8.4$, 2H), 7.56 (s, 1H), 7.50-7.43 (m, 5H), 7.28-7.26 (m, 1H), 4.16 (br s, 1H), 2.86 (t, $J = 12.6$, 2H), 2.70 (d, $J = 7.2$, 2H), 1.90-1.83 (m, 1H), 1.76 (d, $J = 13.2$, 2H), 1.28-1.21 (m, 2H).

Example 13: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (1H-tetrazol-5-yl)-amide.



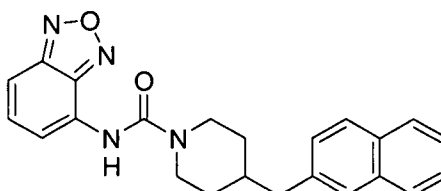
MS: 337.5. ^1H NMR (d_6 -DMSO): 15.36 (s, 1H), 10.67 (s, 1H), 7.88-7.84 (m, 3H), 7.68 (s, 1H), 7.50-7.44 (m, 2H), 7.38-7.37 (dd, $J = 1.8$, 8.4, 1H), 4.15 (d, $J = 13.2$, 2H), 2.83-2.79 (m, 2H), 2.70 (d, $J = 7.2$, 2H), 1.91-1.85 (m, 1H), 1.64-1.61 (m, 2H), 1.20-1.13 (m, 3H).

Example 14: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (2H-pyrazol-3-yl)-amide.



MS: 335.5. ¹H NMR (CDCl₃): 7.79 (d, *J* = 7.8, 1H), 7.76 (d, *J* = 7.8, 2H), 7.63 (br s, 1H), 7.56 (s, 1H), 7.46-7.40 (m, 2H), 7.37 (s, 1H), 7.28-7.26 (m, 1H), 6.37 (br s 1H), 4.05 (d, *J* = 12.6, 2H), 2.78-2.74 (m, 2H), 2.68 (d, *J* = 7.2, 2H), 1.83-1.77 (m, 1H), 1.68 (d, *J* = 12.6, 2H), 1.29-1.21 (m, 2H).

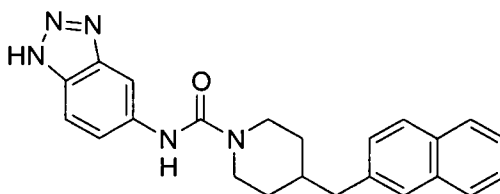
Example 15: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid benzo[1,2,5]oxadiazol-4-ylamide.



10

MS: 387.3. ¹H NMR (CDCl₃): 7.97-7.96 (m, 1H), 7.82 (d, *J* = 15.6, 1H), 7.80-7.81 (m, 2H), 7.60 (s, 1H), 7.49-7.43 (m, 2H), 7.40-7.39 (m, 2H), 7.36 (s, 1H), 7.30 (d, *J* = 8.4, 1H), 4.13 (d, *J* = 13.2, 2H), 2.98-2.94 (m, 2H), 2.76 (d, *J* = 7.2, 2H), 1.96-1.88 (m, 1H), 1.85-1.82 (m, 2H), 1.40-1.33 (m, 2H).

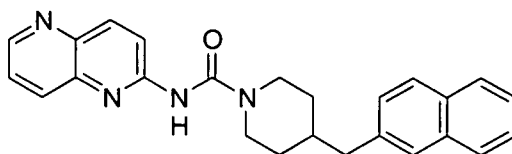
Example 16: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (1H-benzotriazol-5-yl)-amide.



MS: 386.3. ¹H NMR (CDCl₃): 8.19 (br s, 1H), 7.80-7.76 (m, 3H), 7.64 (br s, 1H), 7.56 (s, 1H), 7.46-7.40 (m, 2H), 7.36 (br s, 1H), 6.91 (br s, 1H), 4.14 (d, *J* = 11.4, 2H), 2.91-2.87 (m, 2H), 2.69 (d, *J* = 6.6, 2H), 1.90 (br s, 1H), 1.77 (d, *J* = 12.6, 2H), 1.34-1.28 (m, 2H).

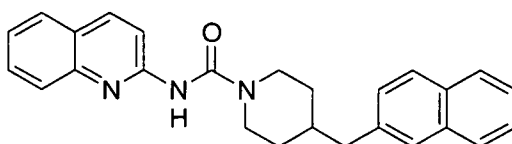
20

Example 17: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid [1,5]naphthyridin-2-ylamide trifluoroacetic acid salt.



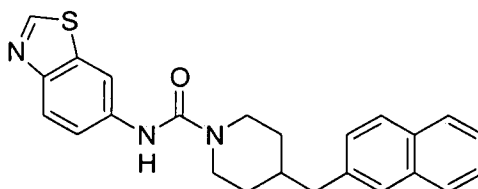
MS: 397.3. ^1H NMR (CDCl_3): 9.00 (d, $J = 3.6$, 1H), 8.65 (d, $J = 9.6$, 1H), 8.49 (d, $J = 9.6$, 1H), 8.41 (d, $J = 8.4$, 1H), 7.82-7.78 (m, 4H), 7.59 (s, 1H), 7.48-7.42 (m, 2H), 7.31-7.29 (dd, $J = 1.2$, 8.4, 1H), 4.32-4.30 (m, 2H), 2.96 (br s, 2H), 2.76 (d, $J = 7.2$, 2H), 1.96-1.88 (m, 1H), 1.84 (d, $J = 13.2$, 2H), 1.41-1.34 (m, 2H).

Example 18: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid quinolin-2-ylamide trifluoroacetic acid salt.



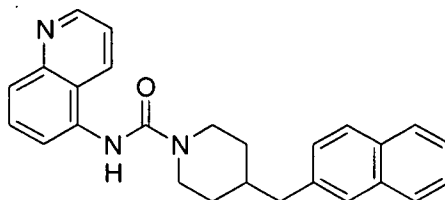
MS: 396.3. ^1H NMR (d_6 -acetone): 8.72 (d, $J = 9.6$, 1H), 8.23 (d, $J = 9.0$, 1H), 8.12-8.09 (m, 2H), 7.99-7.96 (m, 1H), 7.87-7.83 (m, 3H), 7.73-7.70 (m, 2H), 7.49-7.43 (m, 2H), 7.41-7.40 (dd, $J = 1.2$, 8.4, 1H), 4.35 (d, $J = 13.8$, 2H), 2.99 (br s, 2H), 2.78 (d, $J = 7.2$, 2H), 2.09-1.98 (m, 1H), 1.80-1.77 (m, 2H), 1.41-1.34 (m, 2H).

Example 19: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid benzothiazol-6-ylamide.



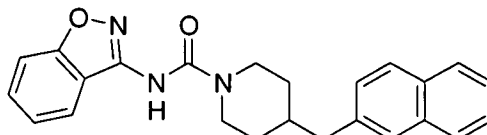
MS: 402.2. ^1H NMR (CDCl_3): 9.01 (s, 1H), 8.31 (s, 1H), 8.03 (d, $J = 8.4$, 1H), 7.83-7.78 (m, 3H), 7.59 (s, 1H), 7.49-7.43 (m, 2H), 7.30 (d, $J = 8.4$, 1H), 7.25-7.23 (m, 1H), 6.70 (s, 1H), 4.08 (d, $J = 13.8$, 2H), 2.91-2.86 (m, 2H), 2.75 (d, $J = 7.2$, 2H), 1.93-1.85 (m, 1H), 1.78 (d, $J = 12.6$, 2H), 1.37-1.30 (m, 2H).

Example 20: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid quinolin-5-ylamide trifluoroacetic acid salt.



MS: 396.3. ¹H NMR (CDCl₃): 8.72 (d, *J* = 7.8, 2H), 7.95 (s, 1H), 7.85-7.80 (m, 4H), 7.66-7.62 (m, 3H), 7.52-7.44 (m, 3H), 7.32 (d, *J* = 8.4, 1H), 4.24 (d, *J* = 13.8, 2H), 2.93 (t, *J* = 12.6, 2H), 2.78 (d, *J* = 6.6, 2H), 1.96-1.87 (m, 1H), 1.82 (d, *J* = 12.6, 2H), 1.41-1.34 (m, 2H).

Example 21: 4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.

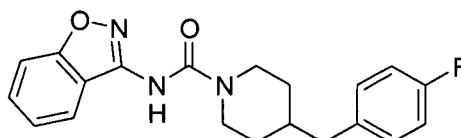


10

MS: 386.3. ¹H NMR (CDCl₃/d₄-MeOH mix): 7.84 (d, *J* = 7.8, 1H), 7.79-7.75 (m, 3H), 7.58 (s, 1H), 7.52-7.49 (m, 1H), 7.44-7.38 (m, 3H), 7.31-7.29 (dd, *J* = 1.5, 15.9, 1H), 7.24 (br t, *J* = 7.5, 1H), 4.18 (d, *J* = 13.2, 2H), 2.91-2.87 (m, 2H), 2.73 (d, *J* = 7.2, 2H), 1.95-1.85 (m, 1H), 1.75 (d, *J* = 12.6, 2H), 1.36-1.29 (m, 2H).

15

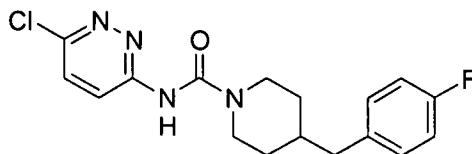
Example 22: 4-(4-Fluoro-benzyl)-piperidine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.



MS: 354.2. ¹H NMR (CDCl₃): 8.79 (s, 1H), 8.06 (d, *J* = 8.5, 1H), 7.54-7.51 (m, 1H), 7.43-7.42 (m, 1H), 7.29-7.26 (m, 1H), 7.11-7.08 (m, 2H), 7.00-6.96 (m, 2H), 4.27 (d, *J* = 13.0, 2H), 2.93 (t, *J* = 12.0, 2H), 2.55 (d, *J* = 7.0, 2H), 1.74 (d, *J* = 9.5, 3H), 1.33-1.24 (m, 2H).

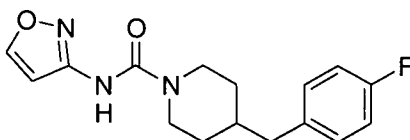
20

Example 23: 4-(4-Fluoro-benzyl)-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide.



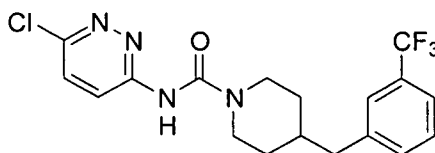
MS: 349.2. ^1H NMR (CDCl_3): 8.45 (s, 1H), 8.29 (d, $J = 9.5$, 1H), 7.42
5 (d, $J = 9.5$, 1H), 7.11-7.08 (m, 2H), 6.99-6.96 (m, 2H), 4.18 (d, $J = 13.5$, 2H),
2.90-2.89 (m, 2H), 2.55 (d, $J = 6.5$, 2H), 1.77-1.71 (m, 3H), 1.29-1.21 (m, 2H).

Example 24: 4-(4-Fluoro-benzyl)-piperidine-1-carboxylic acid isoxazol-3-ylamide.



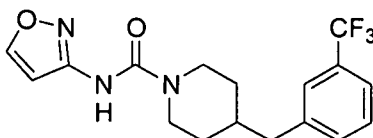
MS: 304.2. ^1H NMR (CDCl_3): 9.04 (s, 1H), 8.17 (d, $J = 1.5$, 1H), 7.10-
10 7.08 (m, 2H), 7.01 (d, $J = 2.0$, 1H), 6.99-6.96 (m, 2H), 4.21 (m, $J = 13.5$, 2H),
2.88-2.83 (m, 2H), 2.33 (d, $J = 7.0$, 2H), 1.74-1.70 (m, 3H), 1.28-1.93 (m, 2H).

Example 25: 4-(3-Trifluoromethyl-benzyl)-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide.



MS: 399.1. ^1H NMR (CDCl_3): 8.46 (d, $J = 9.5$, 1H), 7.57 (d, $J = 9.5$,
15 1H), 7.48 (d, $J = 8.0$, 1H), 7.43-7.40 (m, 2H), 7.33 (d, $J = 7.5$, 1H), 4.22 (d, $J =$
13.5, 2H), 2.90 (t, $J = 12.0$, 2H), 2.64 (d, $J = 7.0$, 2H), 1.86-1.74 (m, 3H), 1.33-
1.25 (m, 2H).

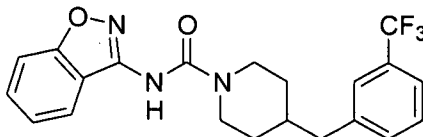
20 Example 26: 4-(3-Trifluoromethyl-benzyl)-piperidine-1-carboxylic acid isoxazol-3-ylamide.



MS: 354.2. ^1H NMR (CDCl_3): 9.11 (s, 1H), 8.17 (d, $J = 2.0$, 1H), 7.48
(d, $J = 7.5$, 1H), 7.43-7.40 (m, 2H), 7.33 (d, $J = 7.5$, 1H), 7.02 (d, $J = 2.0$, 1H),

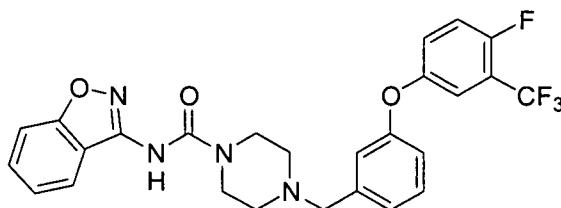
4.22 (d, $J = 13.5$, 2H), 2.90-2.84 (m, 2H), 2.63 (d, $J = 7.0$, 2H), 1.82-1.76 (m, 1H), 1.72 (d, $J = 13.5$, 2H), 1.27 (m, 2H).

Example 27: 4-(3-Trifluoromethyl-benzyl)-piperidine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.



MS: 404.2. ^1H NMR (CDCl_3): 9.09 (s, 1H), 8.06 (d, $J = 8.0$, 1H), 7.54-7.48 (m, 2H), 7.42-7.39 (m, 3H), 7.32 (d, $J = 7.5$, 1H), 7.29-7.26 (m, 1H), 4.30 (d, $J = 13.0$, 2H), 2.93 (t, $J = 12.5$, 2H), 2.63 (d, $J = 7.0$, 2H), 1.84-1.78 (m, 1H), 1.74 (d, $J = 14.0$, 2H), 1.35-1.27 (m, 2H).

Example 28: 4-[3-(4-Fluoro-3-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.



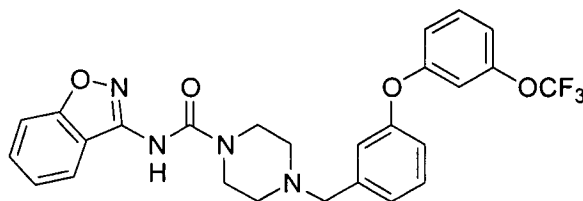
Step A: 4-(3-Hydroxy-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide. The title compound was prepared using methods analogous to those described in Example 1. MS: 353.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.84-7.81 (m, 1H), 7.59-7.54 (m, 1H), 7.53-7.50 (m, 1H), 7.32-7.27 (m, 1H), 7.16-7.11 (m, 1H), 6.82-6.80 (m, 2H), 6.71-6.68 (m, 1H), 3.64-3.61 (m, 4H), 3.52-3.50 (m, 2H), 2.55-2.51 (m, 4H).

Step B: 4-[3-(4-Fluoro-3-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt. A mixture of 4-fluoro-3-(trifluoromethyl)phenylboronic acid (124.7 mg), pyridine (122 μL), 4 Å powdered molecular sieves (181 mg), and $\text{Cu}(\text{OAc})_2$ (51.5 mg) in DCM (3 mL) was stirred, open to air, for 48 h at rt. Additional DCM was added as the mixture dried up. The reaction mixture was filtered through a pad of diatomaceous earth and passed through a pad of silica gel ($\text{NH}_3/\text{MeOH}/\text{DCM}$). The filtrate was concentrated and the residue was purified by reverse-phase HPLC to give 45.1 mg (24%) of the desired product as the TFA salt. MS:

515.2. ^1H NMR (CDCl_3): 9.75 (s, 1H), 7.93 (d, $J = 8.0$, 1H), 7.51-7.48 (m, 1H), 7.35-7.32 (m, 2H), 7.24 (t, $J = 8.0$, 1H), 7.19-7.17 (m, 1H), 7.15-7.10 (m, 3H), 7.03 (t, $J = 2.0$, 1H), 6.99-6.97 (m, 1H), 4.17 (s, 2H), 4.39-3.50 (br s, 4H), 3.45-2.82 (br s, 4H).

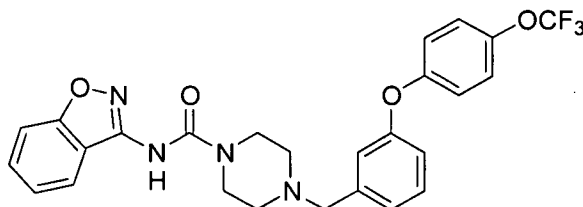
- 5 The compounds in Examples 29-35 were prepared using methods analogous to those described in Example 28.

Example 29: 4-[3-(3-Trifluoromethoxy-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.

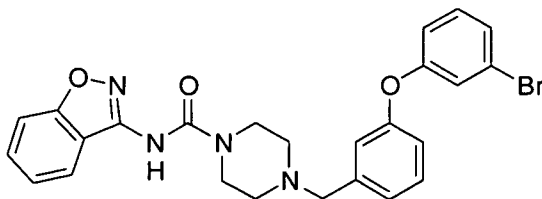


- 10 MS: 513.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.87 (d, $J = 8.0$, 1H), 7.62-7.59 (m, 1H), 7.56-7.52 (m, 2H), 7.47 (t, $J = 8.0$, 1H), 7.36-7.30 (m, 2H), 7.27 (s, 1H), 7.21-7.18 (m, 1H), 7.08-7.07 (m, 1H), 7.04-7.01 (m, 1H), 6.94 (s, 1H), 4.42 (s, 2H), 4.09-3.50 (br s, 4H), 3.39 (s, 4H).

Example 30: 4-[3-(4-Trifluoromethoxy-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.

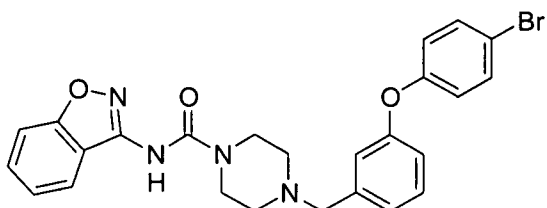


- 15 MS: 513.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.87 (d, $J = 8.0$, 1H), 7.61-7.58 (m, 1H), 7.55-7.52 (m, 2H), 7.33-7.30 (m, 4H), 7.24-7.23 (m, 1H), 7.19-7.17 (m, 1H), 7.14-7.11 (m, 2H), 4.41 (s, 2H), 4.15-3.55 (br s, 4H), 3.38 (s, 4H).
- 20 Example 31: 4-[3-(3-Bromo-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.



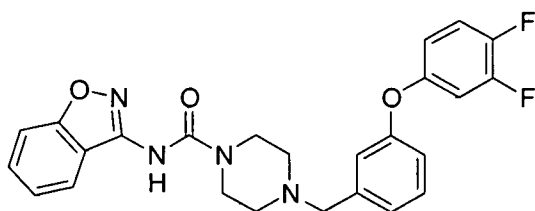
MS: 507.1. ^1H NMR (CDCl_3): 9.72 (s, 1H), 7.93 (d, $J = 8.0$, 1H), 7.52-7.49 (m, 1H), 7.36-7.32 (m, 2H), 7.26-7.23 (m, 2H), 7.17 (t, $J = 8.0$, 1H), 7.12 (d, $J = 8.0$, 1H), 7.10 (t, $J = 2.0$, 1H), 7.02-7.01 (m, 2H), 6.90-6.88 (m, 1H), 4.15 (s, 2H), 4.35-3.55 (br s, 4H), 3.55-2.89 (br s, 4H).

5 Example 32: 4-[3-(4-Bromo-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.



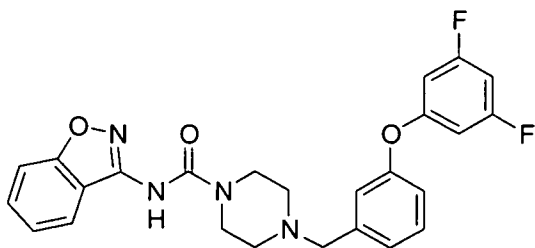
MS: 507.1. ^1H NMR (CDCl_3): 9.70 (s, 1H), 7.93 (d, $J = 8.0$, 1H), 7.50 (t, $J = 8.0$, 1H), 7.43-7.40 (m, 2H), 7.36-7.31 (m, 2H), 7.27-7.24 (m, 1H), 7.09 (d, $J = 7.5$, 1H), 7.00-6.99 (m, 2H), 6.85-6.82 (m, 2H), 4.15 (s, 2H), 4.31-3.35 (br s, 4H), 3.45-2.70 (br s, 4H).

10 Example 33: 4-[3-(3,4-Difluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.



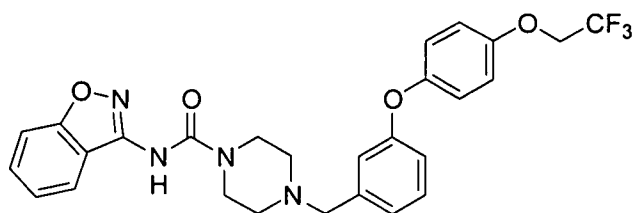
15 MS: 465.2. ^1H NMR ($d_4\text{-MeOH}$): 9.78 (s, 1H), 7.92 (d, $J = 6.8$, 1H), 7.49 (t, $J = 6.4$, 1H), 7.34-7.31 (m, 2H), 7.23 (t, $J = 6.0$, 1H), 7.11-7.07 (m, 2H), 7.01-6.98 (m, 2H), 6.80-6.76 (m, 1H), 6.70-6.67 (m, 1H), 4.14 (s, 2H), 4.30-3.50 (br s, 4H), 3.35-2.85 (br s, 4H).

20 Example 34: 4-[3-(3,5-Difluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.



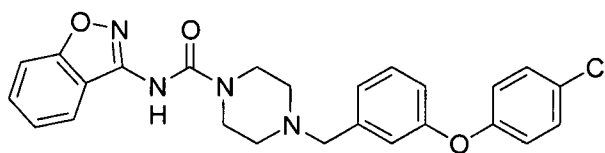
MS: 465.2. ^1H NMR (CDCl_3): 9.75 (s, 1H), 7.92 (d, $J = 8.0$, 1H), 7.51-7.47 (m, 1H), 7.38-7.33 (m, 2H), 7.24 (t, $J = 8.0$, 1H), 7.17 (d, $J = 7.5$, 1H), 7.07-7.05 (m, 2H), 6.56-6.51 (m, 1H), 6.46-6.41 (m, 2H), 4.147 (s, 2H), 4.28-3.55 (br s, 4H), 3.40-2.90 (br s, 4H).

- 5 Example 35: 4-{3-[4-(2,2,2-Trifluoro-ethoxy)-phenoxy]-benzyl}-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.



- MS: 527.2. ^1H NMR (CDCl_3): 8.41 (s, 1H), 8.07 (d, $J = 8.0$, 1H), 7.54-7.50 (m, 1H), 7.44 (d, $J = 8.5$, 1H), 7.28 (d, $J = 8.0$, 2H), 7.06 (d, $J = 7.5$, 1H),
 10 7.01-6.98 (m, 3H), 6.95-6.92 (m, 2H), 6.87-6.85 (m, 1H), 4.36-4.31 (m, 2H), 3.66-3.64 (m, 4H), 3.54 (s, 2H), 2.55-2.53 (m, 4H).

Example 36: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.



- 15 Step A: 4-(Benzo[d]isoxazol-3-ylcarbamoyl)-piperazine-1-carboxylic acid tert-butyl ester. A mixture of benzo[d]isoxazol-3-yl-carbamic acid phenyl ester (1.072 g) and piperazine-1-carboxylic acid tert-butyl ester (942 mg) in DMSO (8 mL) was stirred at 50 °C for 20 h, and then was diluted with water (400 mL), mixed thoroughly and filtered.
- 20 The collected solid was dissolved in DCM and washed with water (x1) and satd. aq. NaHCO_3 (x1), dried and concentrated to give a brown solid. Purification by FCC gave 1.10 g (79%) of the product as a white crystalline solid.

Step B: Piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.

- 25 A mixture of 4-(benzo[d]isoxazol-3-ylcarbamoyl)-piperazine-1-carboxylic acid tert-butyl ester (1.10 g) and TFA (2.5 mL) in DCM (32 mL) was

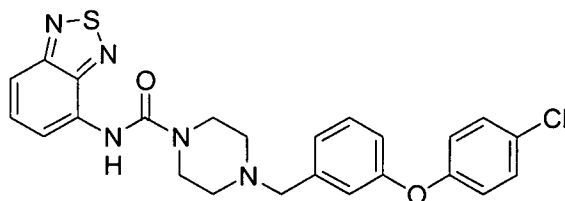
stirred for 2.5 h and then concentrated to give 1.15 g (100%) of the title compound as a pale-yellow viscous oil. MS: 247.2.

Step C: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide. A mixture of piperazine-1-carboxylic

5 acid benzo[d]isoxazol-3-ylamide (60.5 mg), 3-(4-chlorophenoxy)-benzaldehyde (88.4 mg), Et₃N (0.1 mL), and MP-B(OAc)₃H (235 mg; resin loading = 2.33 mmol/g) in THF (2.0 mL) was mixed on a shaker table for 19 h. The mixture was filtered and the filtrate was concentrated. The residue was purified by reverse-phase HPLC to give
10 44.6 mg (46%) of the title compound as the TFA salt. MS: 463.2. ¹H NMR (d₄-MeOH): 7.88 (d, *J* = 7.8, 1H), 7.60-7.58 (m, 1H), 7.54-7.48 (m, 2H), 7.38-7.35 (m, 2H), 7.33-7.28 (m, 2H), 7.202-7.196 (m, 1H), 7.14-7.12 (dd, *J* = 1.8, 8.4, 1H), 7.03-7.01 (m, 2H), 4.66-2.69 (br hump, 4H), 4.40 (s, 2H), 3.38 (br hump, 4H).

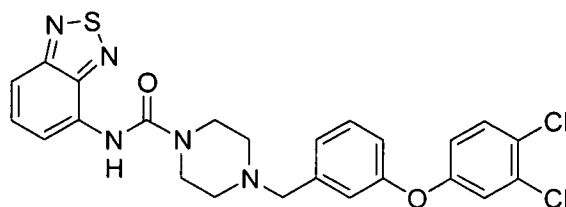
15 The compounds in Examples 37-57 were prepared using methods analogous to those described in Example 36.

Example 37: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide trifluoroacetic acid salt.



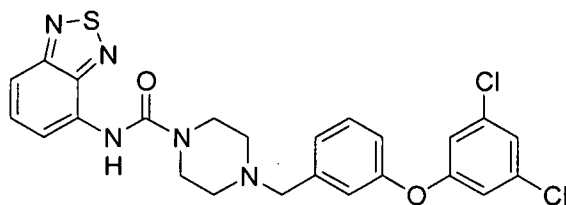
20 MS: 480.2. ¹H NMR (d₄-MeOH): 7.92-7.90 (dd, *J* = 0.6, 7.2, 1H), 7.66-7.65 (d, *J* = 9.0, 1H), 7.60-7.57 (dd, *J* = 9.0, 7.8, 1H), 7.51-7.48 (t, *J* = 8.4, 1H), 7.38-7.36 (m, 2H), 7.29 (br d, *J* = 7.8, 1H), 7.21-7.20 (br m, 1H), 7.14-7.12 (dd, *J* = 1.8, 7.8, 1H), 7.04-7.02 (m, 2H), 4.40 (s, 2H), 3.80-3.01 (br hump, 8H).

25 Example 38: 4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide trifluoroacetic acid salt.



MS: 514.1. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.92-7.91 (dd, $J = 1.2, 7.8$, 1H), 7.67-7.65 (dd, $J = 1.2, 9.0$, 1H), 7.61-7.58 (dd, $J = 7.2, 9.0$, 1H), 7.55-7.52 (t, $J = 7.8$, 1H), 7.50 (d, $J = 9.0$, 1H), 7.35 (d, $J = 7.2$, 1H), 7.25 (br m, 1H), 7.21 (d, $J = 2.4$, 1H), 7.20-7.18 (dd, $J = 2.4, 8.4$, 1H), 6.99-6.97 (dd, $J = 3.0, 9.0$, 1H), 4.58-4.22 (br hump, 4H), 4.42 (s, 2H), 3.72-3.01 (br hump, 4H).

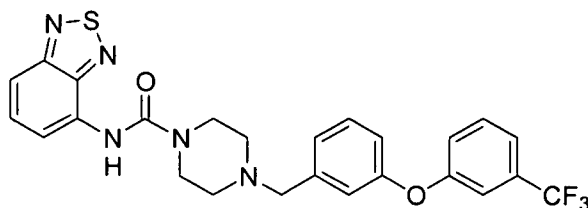
Example 39: 4-[3-(3,5-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide trifluoroacetic acid salt.



10

MS: 514.1. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.94-7.93 (dd, $J = 0.6, 7.2$, 1H), 7.70-7.68 (dd, $J = 1.2, 9.0$, 1H), 7.63-7.56 (m, 2H), 7.40 (d, $J = 7.8$, 1H), 7.30-7.29 (m, 1H), 7.24-7.23 (m, 2H), 7.02 (d, $J = 1.8$, 2H), 4.83-2.94 (br hump, 4H), 4.40 (s, 2H), 3.41 (br s, 4H).

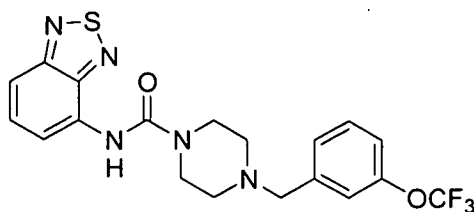
Example 40: 4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide trifluoroacetic acid salt.



MS: 514.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.92-7.91 (dd, $J = 1.2, 7.2$, 1H), 7.67-7.65 (dd, $J = 1.2, 9.0$, 1H), 7.61-7.53 (m, 3H), 7.45 (d, $J = 7.8$, 1H), 7.36 (d, $J = 7.8$, 1H), 7.31-7.28 (m, 3H), 7.20-7.18 (m, 1H), 4.85-2.94 (br hump, 4H), 4.43 (s, 2H), 3.41 (br hump, 4H).

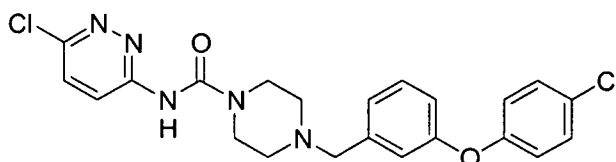
20

Example 41: 4-(3-Trifluoromethoxy-benzyl)-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide trifluoroacetic acid salt.



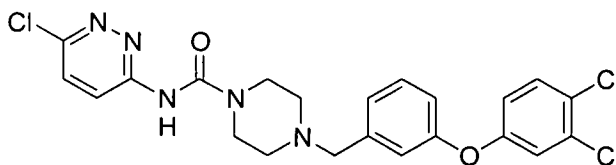
MS: 438.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.93-7.92 (dd, $J = 7.2, 0.6$, 1H), 7.69-7.67 (1.2, 9.0, 1H), 7.64-7.60 (m, 2H), 7.57-7.55 (m, 2H), 7.47-7.45 (m, 1H), 4.48 (s, 2H), 4.33-3.66 (br hump, 4H), 3.42 (br s, 4H).

Example 42: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide trifluoroacetic acid salt.



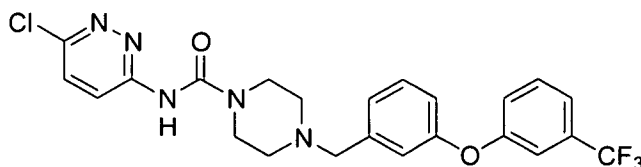
MS: 413.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.47 (s, 1H), 7.48 (t, $J = 8.4$, 1H), 7.38-7.36 (m, 2H), 7.28 (d, $J = 7.2$, 1H), 7.18 (t, $J = 1.8$, 1H), 7.14-7.12 (dd, $J = 2.4, 7.8$, 1H), 7.03-7.01 (m, 2H), 6.73 (s, 1H), 4.70-2.85 (br hump, 4H), 4.37 (s, 2H), 3.36 (br hump, 4H).

Example 43: 4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide trifluoroacetic acid salt.



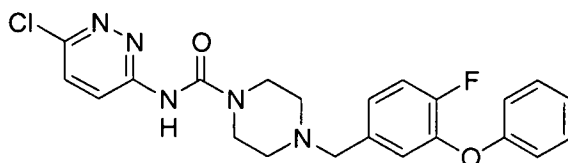
MS: 447.1. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.46 (s, 1H), 7.53-7.50 (s, 2H), 7.33 (d, $J = 7.8$, 1H), 7.23 (t, $J = 1.8$, 1H), 7.20 (d, $J = 3.0$, 1H), 7.19-7.17 (m, 1H), 6.98-6.96 (dd, $J = 2.4, 8.4$, 1H), 6.73 (s, 1H), 4.74-2.66 (br hump, 4H), 4.39 (s, 2H), 3.36 (br hump, 4H).

Example 44: 4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide trifluoroacetic acid salt.



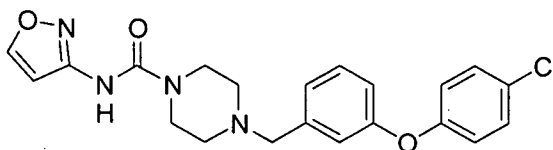
MS: 447.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.61 (br s, 1H), 7.57 (t, $J = 8.4$, 1H), 7.53 (t, $J = 7.8$, 1H), 7.45 (d, $J = 7.8$, 1H), 7.34 (d, $J = 7.8$, 1H), 7.29-7.25 (m, 3H), 7.18-7.17 (dd, $J = 1.8$, 7.8, 1H), 6.84 (br s, 1H), 4.77-2.89 (br hump, 4H), 4.40 (s, 2H), 3.35 (br hump, 4H).

5 Example 45: 4-(4-Fluoro-3-phenoxy-benzyl)-piperazine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide trifluoroacetic acid salt.



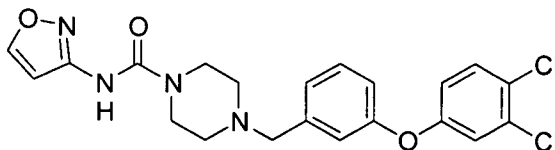
MS: 397.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.44 (d, $J = 1.8$, 1H), 7.38-7.31 (m, 4H), 7.28-7.27 (dd, $J = 1.8$, 7.8, 1H), 7.15-7.12 (m, 1H), 7.009-6.995 (m, 1H), 6.71 (d, $J = 1.8$, 1H), 4.75-2.84 (br hump, 4H), 4.34 (s, 2H), 3.33 (br hump, 4H).

10 Example 46: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide trifluoroacetic acid salt.



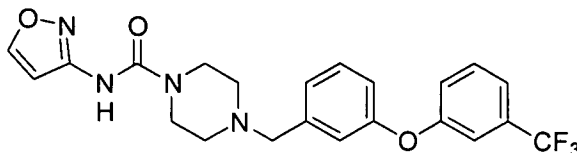
15 MS: 458.1. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.12 (d, $J = 9.0$, 1H), 7.67 (d, $J = 9.6$, 1H), 7.49 (t, $J = 7.8$, 1H), 7.38-7.35 (m, 2H), 7.28 (d, $J = 7.8$, 1H), 7.19 (t, $J = 1.8$, 1H), 7.14-7.12 (dd, $J = 1.8$, 7.8, 1H), 7.03-7.01 (m, 2H), 4.79-2.86 (br hump, 4H), 4.39 (s, 2H), 3.38 (br hump, 4H).

20 Example 47: 4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide trifluoroacetic acid salt.



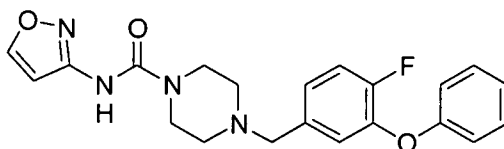
MS: 490.1. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.14 (d, $J = 9.6$, 1H), 7.68 (d, $J = 9.0$, 1H), 7.55-7.51 (m, 2H), 7.34 (d, $J = 7.8$, 1H), 7.24 (t, $J = 2.4$, 1H), 7.21 (d, $J = 2.4$, 1H), 7.20-7.18 (m, 1H), 7.00-6.98 (dd, $J = 3.0$, 9.0, 1H), 4.72-2.72 (br hump, 4H), 4.40 (s, 2H), 3.38 (br hump, 4H).

Example 48: 4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide trifluoroacetic acid salt.



MS: 492.2. ¹H NMR (d₄-MeOH): 8.21 (br s, 1H), 7.72 (br s, 1H),
 5 7.59-7.53 (m, 2H), 7.45 (d, *J* = 7.8, 1H), 7.35 (d, *J* = 7.8, 1H), 7.30-7.27
 (m, 3H), 7.20-7.18 (dd, *J* = 1.8, 7.8, 1H), 4.70-2.82 (br hump, 4H), 4.41
 (s, 2H), 3.39 (br hump, 4H).

Example 49: 4-(4-Fluoro-3-phenoxy-benzyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide trifluoroacetic acid salt.

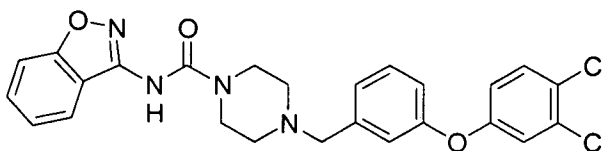


10

MS: 442.2. ¹H NMR (d₄-MeOH): 8.13 (br s, 1H), 7.67 (d, *J* =
 9.0, 1H), 7.39-7.32 (m, 4H), 7.30-7.28 (dd, *J* = 2.4, 7.8, 1H), 7.15-7.12
 (m, 1H), 7.02-7.00 (dd, *J* = 1.2, 9.0, 1H), 4.76-2.55 (br hump, 4H), 4.35
 (s, 2H), 3.34 (br hump, 4H).

15

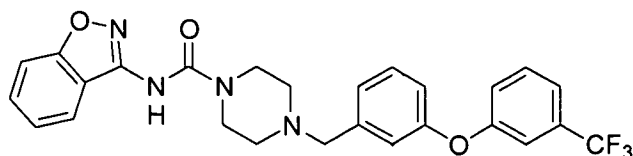
Example 50: 4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.



20

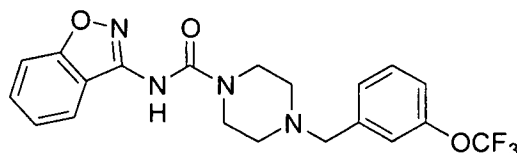
MS: 497.1. ¹H NMR (d₄-MeOH): 7.87 (d, *J* = 2.4, 1H), 7.61-7.59
 (m, 1H), 7.55-7.50 (m, 3H), 7.35-7.30 (m, 2H), 7.25-7.24 (m, 1H), 7.21
 (d, *J* = 3.0, 1H), 7.20-7.18 (m, 1H), 6.99-6.97 (dd, *J* = 2.4, 8.4, 1H), 4.55-
 2.93 (br hump, 4H), 4.42 (s, 2H), 3.40 (br hump, 4H).

Example 51: 4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.



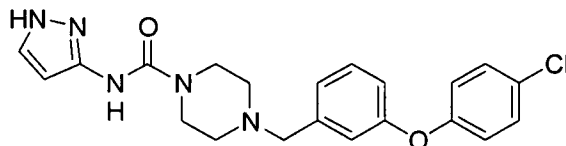
MS: 497.2. ¹H NMR (d₄-MeOH): 7.88 (d, *J* = 7.8, 1H), 7.60-7.52 (m, 4H), 7.45 (d, *J* = 7.8, 1H), 7.35 (d, *J* = 7.8, 1H), 7.32-7.27 (m, 4H), 7.19-7.17 (dd, *J* = 2.4, 7.8, 1H), 4.69-2.98 (br hump, 4H), 4.42 (s, 2H), 3.40 (br hump, 4H).

Example 52: 4-(3-Trifluoromethoxy-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.



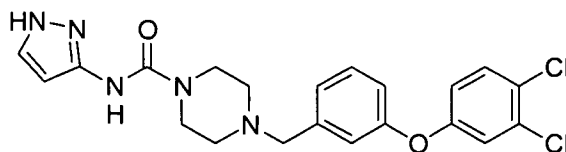
MS: 421.2. ¹H NMR (d₄-MeOH): 7.88 (d, *J* = 7.8, 1H), 7.63-7.58 (m, 2H), 7.55-7.50 (m, 3H), 7.43 (d, *J* = 7.2, 1H), 7.32 (t, *J* = 7.8, 1H), 4.61-2.99 (br hump, 4H), 4.47 (s, 2H), 3.42 (br hump, 4H).

Example 53: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide trifluoroacetic acid salt.



MS: 412.2. ¹H NMR (d₄-MeOH): 7.89 (br hump, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.39-7.36 (m, 2H), 7.28 (d, *J* = 7.8, 1H), 7.19 (t, *J* = 1.8, 1H), 7.15-7.13 (dd, *J* = 1.8, 7.8, 1H), 7.04-7.02 (m, 2H), 6.38 (br hump, 1H), 4.50-2.95 (br hump, 4H), 3.35 (br hump, 4H).

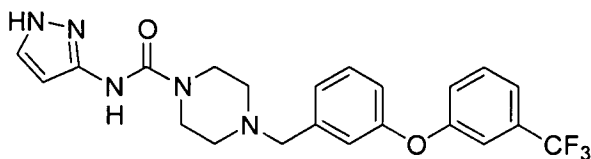
Example 54: 4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide trifluoroacetic acid salt.



MS: 446.1. ¹H NMR (d₄-MeOH): 7.91 (br hump, 1H), 7.55-7.52 (m, 2H), 7.34 (d, *J* = 7.8, 1H), 7.25 (t, *J* = 1.8, 1H), 7.22 (d, *J* = 3.0, 1H),

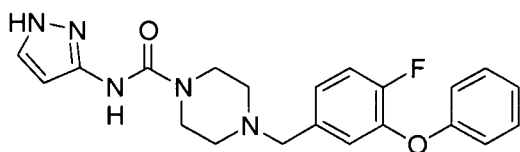
7.20-7.18 (dd; $J = 2.4, 7.8, 1\text{H}$), 7.01-6.99 (dd, $J = 3.0, 9.0, 1\text{H}$), 6.44 (br hump, 1H), 4.6-2.85 (br hump, 4H), 4.40 (s, 2H), 3.37 (br hump, 4H).

Example 55: 4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide trifluoroacetic acid salt.



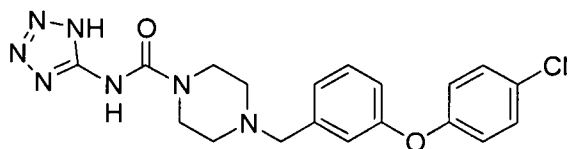
MS: 446.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.98 (br hump, 1H), 7.61-7.55 (m, 2H), 7.47 (d, $J = 7.8, 1\text{H}$), 7.36 (d, $J = 7.8, 1\text{H}$), 7.31-7.27 (m, 3H), 7.22-7.20 (dd, $J = 2.4, 7.8, 1\text{H}$), 4.60-2.89 (br hump, 4H), 4.41 (s, 2H), 3.36 (br hump, 4H).

Example 56: 4-(4-Fluoro-3-phenoxy-benzyl)-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide trifluoroacetic acid salt.



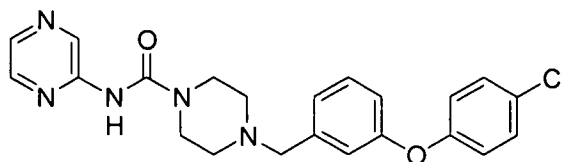
MS: 396.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.89 (br hump, 1H), 7.41-7.33 (m, 4H), 7.31-7.29 (dd, $J = 1.8, 7.8, 1\text{H}$), 7.16 (t, $J = 7.2, 1\text{H}$), 7.03 (d, $J = 7.8, 1\text{H}$), 6.43 (br hump, 1H), 4.60-2.71 (br hump, 4H), 4.35 (s, 2H), 3.35 (br hump, 4H).

Example 57: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-tetrazol-5-yl)-amide trifluoroacetic acid salt.



MS: 414.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.51 (t, $J = 7.8, 1\text{H}$), 7.40-7.39 (m, 2H), 7.28 (d, $J = 7.8, 1\text{H}$), 7.19 (br s, 1H), 7.16-7.14 (dd, $J = 1.8, 7.8, 1\text{H}$), 7.05-7.03 (m, 2H), 4.36 (s, 2H), 4.10-3.60 (br hump, 4H), 3.44-3.21 (br hump, 4H).

Example 58: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide trifluoroacetic acid salt.



Step A: 4-(Pyrazin-2-ylcarbamoyl)-piperazine-1-carboxylic acid tert-butyl ester. To a mixture of aminopyrazine (530 mg) in DCM (52 mL) was added di(N-succinimidyl)carbonate (1.43 g). The

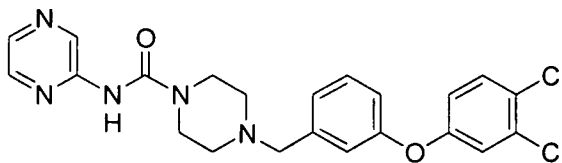
5 heterogeneous mixture was stirred for 21 h and then was treated with N-Boc-piperazine (1.62 g). After 8 h, the mixture was concentrated and the residue purified by FCC (NH₃/MeOH/DCM) to give 1.07 g (63%) of the title compound as a white solid. MS: 308.2.

Step B: Piperazine-1-carboxylic acid pyrazin-2-ylamide. The title
10 compound was prepared using methods analogous to those described in Example 36, Step B. MS: 208.2.

Step C: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide. The title compound was prepared a the TFA salt using methods analogous to those described in Example 36, Step
15 C. MS: 424.2. ¹H NMR (d₄-MeOH): 9.18 (br s, 1H), 8.34 (br s, 2H), 7.50 (t, J = 7.8, 1H), 7.39-7.36 (m, 2H), 7.29 (d, J = 7.2, 1H), 7.201-7.195 (m, 1H), 7.15-7.13 (m, 1H), 7.04-7.02 (m, 2H), 4.58-2.83 (br hump, 4H), 4.38 (s, 2H), 3.37 (br hump, 4H).

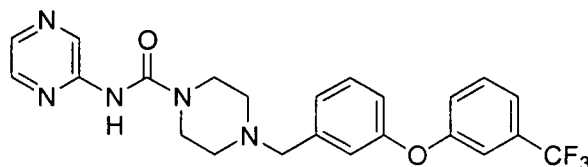
The compounds in Examples 59-61 were prepared using methods
20 analogous to those described in Example 58.

Example 59: 4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide trifluoroacetic acid salt.



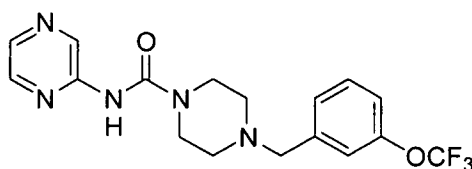
MS: 458.1. ¹H NMR (d₄-MeOH): 9.06 (s, 1H), 8.31 (s, 1H), 8.21 (s,
25 1H), 7.55-7.51 (m, 2H), 7.34 (d, 1H), 7.24-7.18 (m, 3H), 7.00-6.98 (dd, J = 2.4, 8.4, 1H), 4.57-2.85 (br hump, 4H), 4.40 (s, 2H), 3.36 (br hump, 4H).

Example 60: 4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide trifluoroacetic acid salt.



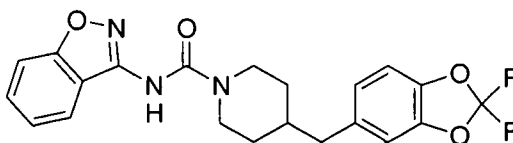
MS: 458.2. ¹H NMR (d₄-MeOH): 9.22 (br s, 1H), 8.36 (br s, 2H), 7.59-7.53 (m, 2H), 7.45 (d, *J* = 7.8, 1H), 7.35 (d, *J* = 7.8, 1H), 7.30-7.26 (m, 3H), 7.20-7.18 (m, 1H), 4.80-2.94 (br hump, 4H), 4.41 (s, 2H), 3.37 (br hump, 4H).

Example 61: 4-(3-Trifluoromethoxy-benzyl)-piperazine-1-carboxylic acid pyrazin-2-ylamide trifluoroacetic acid salt.



MS: 382.2. ¹H NMR (d₄-MeOH): 9.06 (s, 1H), 8.32 (s, 1H), 8.21 (s, 1H), 7.61 (t, *J* = 7.8, 1H), 7.56-7.53 (m, 2H), 7.45-7.44 (m, 1H), 4.62-2.89 (br hump, 4H), 4.46 (s, 2H), 3.38 (br hump, 4H).

Example 62: N-1,2-Benzisoxazol-3-yl-4-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]piperidine-1-carboxamide.



15

Step A: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester. 1-Boc-4-methylene piperidine (454.6 mg) was degassed (neat) for 15 min, and then treated with a THF solution of 9-borabicyclo[3.3.1]nonane (BBN; 0.5 M in THF, 4.7 mL). The reaction mixture was refluxed for 3.5 h, then cooled to rt. The reaction mixture was then added, via cannula, to a preformed solution consisting of 5-bromo-2,2-difluoro-1,3-benzodioxole (502.3 mg), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (Pd(dppf)Cl₂), complex with DCM (45.9 mg), and potassium carbonate (369.6 mg) in DMF/H₂O (10 mL/1 mL). The resultant mixture was heated at 60 °C for 18 h, cooled to rt,

20

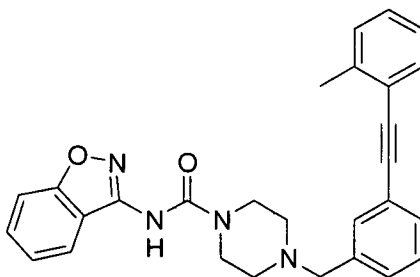
25

poured into water, basified to pH 11 with 10% NaOH, and extracted with EtOAc (3x). The organic layers were combined, dried (Na₂SO₄), and concentrated. The crude residue was purified (FCC) to give 4-(2,2-difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperidine-1-carboxylic acid tert-butyl ester (608.2 mg, 81%).

5 Step B: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperidine. The title compound was prepared using methods analogous to those described in Example 9, Step D.

10 Step C: N-1,2-Benzisoxazol-3-yl-4-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]piperidine-1-carboxamide. The title compound was prepared using methods analogous to those described in Example 1, Step C. MS: 414.4. ¹H NMR (d₄-MeOH): 7.83-7.80 (m, 1H), 7.59-7.54 (m, 1H), 7.53-7.50 (m, 1H), 7.31-7.27 (m, 1H), 7.11-7.07 (m, 2H), 7.00-6.97 (m, 1H), 4.24-4.17 (m, 2H), 2.98-2.90 (m, 2H), 2.64 (d, J = 7.2, 2H), 1.89-1.81 (m, 1H), 1.75-1.70 (m, 2H), 1.33-1.24 (m, 2H).

15 Example 63: 4-(3-o-Tolyethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.



20 Step A: 1-(3-Iodo-benzyl)-piperazine. The title compound was prepared using methods analogous to those described in Example 1, Step B. MS: 403.1.

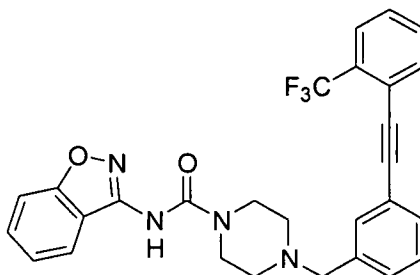
Step B: 4-(3-Iodo-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide. The title compound was prepared using methods analogous to those described in Example 1, Step C. MS: 463.1.

25 Step C: 4-(3-o-Tolyethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide. To a solution of Pd(PPh₃)₂Cl₂ (7.2 mg) in THF/Et₃N (1 mL each) was added 4-(3-iodo-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide (100.0 mg). The solution was degassed for

15 min, then copper(I) iodide (4.6 mg) and 2-ethynyltoluene (37.8 mg) were added. The reaction mixture was stirred at rt for 10 min, then poured into water and extracted with EtOAc (3x). The organic layers were combined, washed with NH₄OH, dried (Na₂SO₄), and concentrated. The crude residue was
5 purified (FCC) to afford the title compound (89.3 mg, 92%). MS: 451.2. ¹H NMR (d₄-MeOH): 7.88-7.83 (m, 1H), 7.62-7.51 (m, 3H), 7.50-7.44 (m, 2H), 7.42-7.36 (m, 2H), 7.34-7.24 (m, 3H), 7.22-7.17 (m, 1H), 3.71-3.60 (m, 6H), 2.61-2.55 (m, 4H), 2.53 (s, 3H).

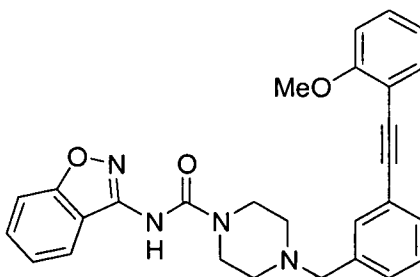
The compounds in Examples 64-80 were prepared using methods
10 analogous to those described in Example 63.

Example 64: N-1,2-Benzisoxazol-3-yl-4-(3-{[2-(trifluoromethyl)-phenyl]-ethynyl}benzyl)-piperazine-1-carboxamide.



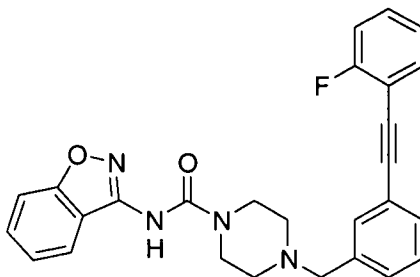
MS: 505.2. ¹H NMR (d₄-MeOH): 7.86 (d, *J* = 8.1, 1H), 7.78-7.72 (m,
15 2H), 7.67-7.62 (m, 1H), 7.61-7.52 (m, 4H), 7.49-7.39 (m, 3H), 7.34-7.29 (m, 1H), 3.71-3.60 (m, 6H), 2.62-2.52 (m, 4H).

Example 65: N-1,2-Benzisoxazol-3-yl-4-{3-[(2-methoxyphenyl)-ethynyl]-benzyl}-piperazine-1-carboxamide.



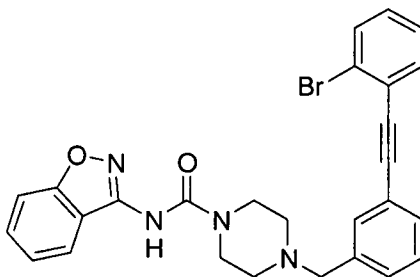
20 MS: 467.2. ¹H NMR (d₄-MeOH): 7.88-7.83 (m, 1H), 7.61-7.51 (m, 3H), 7.47-7.42 (m, 2H), 7.39-7.29 (m, 4H), 7.04 (d, *J* = 8.4, 1H), 6.98-6.93 (m, 1H), 3.93 (s, 3H), 3.69-3.64 (m, 4H), 3.62 (s, 2H), 2.61-2.55 (m, 4H).

Example 66: N-1,2-Benzisoxazol-3-yl-4-{3-[(2-fluorophenyl)ethynyl]-benzyl}-piperazine-1-carboxamide.



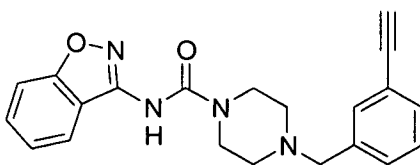
MS: 455.2. ¹H NMR (d₄-MeOH): 7.88-7.83 (m, 1H), 7.62-7.51 (m, 4H),
 5 7.50-7.46 (m, 1H), 7.45-7.37 (m, 3H), 7.34-7.29 (m, 1H), 7.24-7.15 (m, 2H),
 3.71-3.59 (m, 6H), 2.61-2.54 (m, 4H).

Example 67: N-1,2-Benzisoxazol-3-yl-4-{3-[(2-bromophenyl)-ethynyl]benzyl}-piperazine-1-carboxamide.



10 MS: 515.1. ¹H NMR (CDCl₃): 8.11-8.07 (m, 1H), 7.66-7.63 (m, 1H),
 7.60-7.57 (m, 2H), 7.56-7.51 (m, 2H), 7.50-7.47 (m, 1H), 7.42-7.28 (m, 5H),
 7.23-7.19 (m, 1H), 3.66-3.62 (m, 4H), 3.60 (s, 2H), 2.60-2.55 (m, 4H).

Example 68: 4-(3-Ethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.



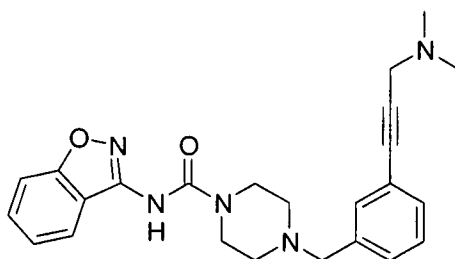
15

Step A: 4-(3-Trimethylsilanylethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide. The title compound was prepared using methods analogous to those described in Example 63, Step C. MS: 433.2.

Step B: 4-(3-Ethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide. To a solution of 4-(3-trimethylsilanylethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide (396.2 mg) in
 20

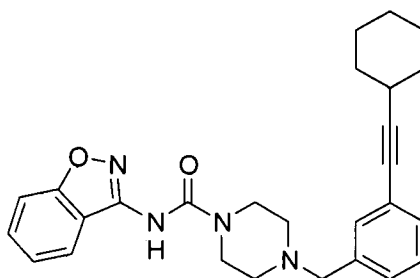
MeOH (10 mL) was added potassium carbonate (500 mg). The reaction mixture was stirred at rt for 2 h, then filtered through diatomaceous earth and concentrated. The crude residue was purified (FCC) to give the title compound (291.7 mg, 88%). MS: 361.2. ¹H NMR (CDCl₃): 8.11-8.08 (m, 1H), 7.88 (s, 1H), 7.57-7.50 (m, 2H), 7.49-7.46 (m, 1H), 7.45-7.42 (m, 1H), 7.37-7.29 (m, 3H), 3.68-3.62 (m, 4H), 3.56 (s, 2H), 3.10 (s, 1H), 2.58-2.53 (m, 4H).

Example 69: N-1,2-Benzisoxazol-3-yl-4-[3-[3-(dimethylamino)prop-1-yn-1-yl]benzyl]-piperazine-1-carboxamide.



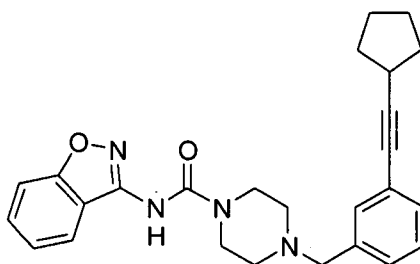
MS: 418.2. ¹H NMR (d₄-MeOH): 7.87-7.83 (m, 1H), 7.61-7.56 (m, 1H), 7.56-7.52 (m, 1H), 7.49-7.46 (m, 1H), 7.39-7.29 (m, 4H), 3.67-3.62 (m, 4H), 3.59 (s, 2H), 3.51 (s, 2H), 2.58-2.51 (m, 4H), 2.40 (s, 6H).

Example 70: N-1,2-Benzisoxazol-3-yl-4-[3-(cyclohexylethynyl)benzyl]-piperazine-1-carboxamide.



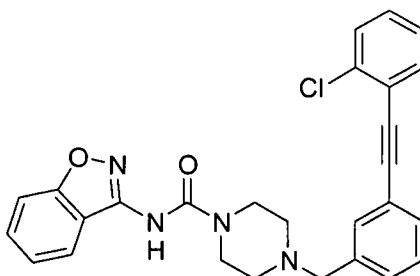
MS: 443.2. ¹H NMR (d₆-DMSO): 8.00-7.96 (m, 1H), 7.60-7.55 (m, 1H), 7.53-7.51 (m, 1H), 7.41-7.38 (m, 1H), 7.34-7.26 (m, 4H), 3.70-3.64 (m, 4H), 3.55 (s, 2H), 2.65-2.60 (m, 1H), 2.54-2.49 (m, 4H), 1.91-1.85 (m, 2H), 1.79-1.72 (m, 2H), 1.58-1.48 (m, 3H), 1.43-1.35 (m, 3H).

Example 71: N-1,2-Benzisoxazol-3-yl-4-[3-(cyclopentylethynyl)benzyl]-piperazine-1-carboxamide.



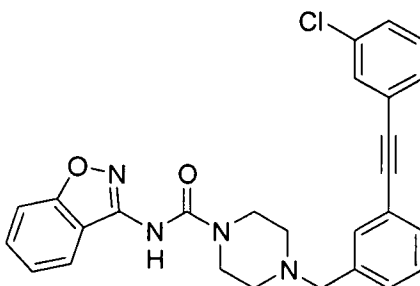
MS: 429.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.87-7.83 (m, 1H), 7.61-7.57 (m, 1H),
 7.55-7.52 (m, 1H), 7.40-7.37 (m, 1H), 7.34-7.26 (m, 4H), 3.68-3.62 (m, 4H),
 3.57 (s, 2H), 2.90-2.83 (m, 1H), 2.57-2.52 (m, 4H), 2.07-1.98 (m, 2H), 1.84-
 5 1.77 (m, 2H), 1.74-1.62 (m, 4H).

Example 72: N-1,2-Benzisoxazol-3-yl-4-{3-[(2-chlorophenyl)-ethynyl]benzyl}-piperazine-1-carboxamide.



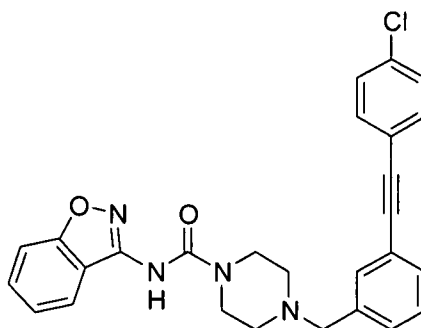
MS: 471.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.87-7.84 (m, 1H), 7.63-7.56 (m, 3H),
 10 7.55-7.47 (m, 3H), 7.45-7.29 (m, 5H), 3.69-3.61 (m, 6H), 2.61-2.55 (m, 4H).

Example 73: N-1,2-Benzisoxazol-3-yl-4-{3-[(3-chlorophenyl)ethynyl]benzyl}-piperazine-1-carboxamide.



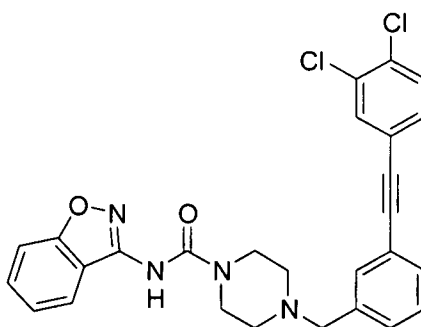
MS: 471.2. ^1H NMR (CDCl_3): 8.12-8.08 (m, 1H), 7.69 (s, 1H), 7.57-
 15 7.51 (m, 3H), 7.50-7.45 (m, 2H), 7.45-7.42 (m, 1H), 7.37-7.28 (m, 5H), 3.68-
 3.63 (m, 4H), 3.59 (s, 2H), 2.60-2.54 (m, 4H).

Example 74: N-1,2-Benzisoxazol-3-yl-4-{3-[(4-chlorophenyl)ethynyl]benzyl}-piperazine-1-carboxamide.



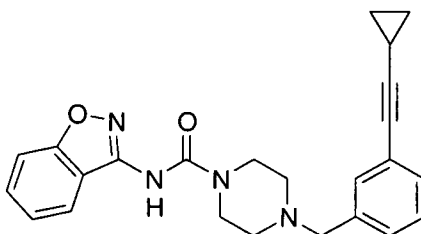
MS: 471.2. ^1H NMR (CDCl_3): 8.11-8.08 (m, 1H), 7.76 (s, 1H), 7.57-7.51 (m, 2H), 7.50-7.45 (m, 4H), 7.38-7.33 (m, 4H), 7.31-7.28 (m, 1H), 3.68-3.63 (m, 4H), 3.59 (s, 2H), 2.61-2.52 (m, 4H).

- 5 Example 75: N-1,2-Benzisoxazol-3-yl-4-[3-[(3,4-dichlorophenyl)ethynyl]benzyl]-piperazine-1-carboxamide.



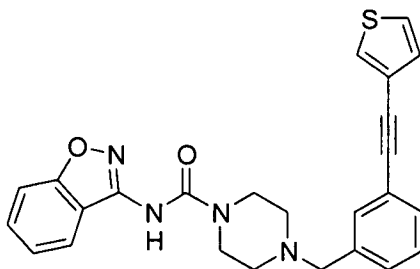
MS: 505.1. ^1H NMR (CDCl_3): 8.11-8.08 (m, 1H), 7.69 (s, 1H), 7.65 (d, $J = 1.9$, 1H), 7.56-7.52 (m, 2H), 7.49-7.43 (m, 3H), 7.39-7.35 (m, 3H), 7.32-7.28 (m, 1H), 3.67-3.64 (m, 4H), 3.59 (s, 2H), 2.60-2.55 (m, 4H).

- 10 Example 76: N-1,2-Benzisoxazol-3-yl-4-[3-(cyclopropylethynyl)benzyl]-piperazine-1-carboxamide.



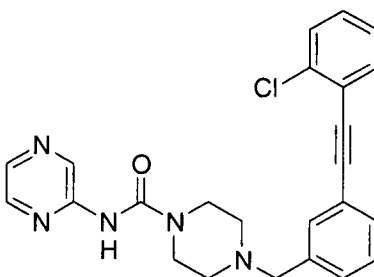
- MS: 401.2. ^1H NMR (CDCl_3): 8.09 (d, $J = 8.1$, 1H), 7.57-7.51 (m, 1H), 7.49-7.46 (m, 1H), 7.40-7.38 (m, 1H), 7.33-7.23 (m, 5H), 3.66-3.60 (m, 4H), 3.53 (s, 2H), 2.57-2.51 (m, 4H), 1.51-1.44 (m, 1H), 0.92-0.87 (m, 2H), 0.85-0.81 (m, 2H).

Example 77: N-1,2-Benzisoxazol-3-yl-4-[3-(thiophen-3-ylethynyl)benzyl]-piperazine-1-carboxamide.



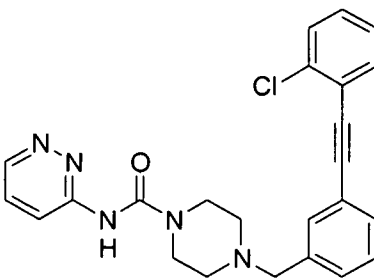
MS: 443.2. ¹H NMR (d₄-MeOH): 7.86-7.81 (m, 1H), 7.64-7.49 (m, 4H),
5 7.46-7.27 (m, 5H), 7.21-7.16 (m, 1H), 3.69-3.56 (m, 6H), 2.60-2.50 (m, 4H).

Example 78: 4-{3-[(2-Chlorophenyl)ethynyl]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide hydrochloride salt.



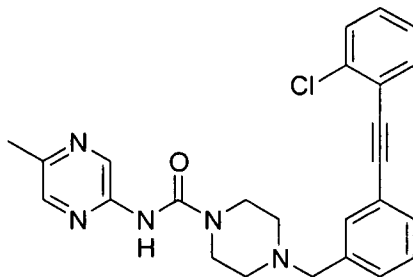
MS: 431.2. ¹H NMR (d₆-DMSO): 9.83-9.82 (m, 1H), 9.03-9.02 (m, 1H),
10 8.34-8.32 (m, 1H), 8.25 (d, *J* = 2.6, 1H), 7.84-7.82 (m, 1H), 7.71-7.65 (m, 3H),
7.64-7.61 (m, 1H), 7.60-7.55 (m, 1H), 7.50-7.41 (m, 2H), 4.43-4.39 (m, 2H),
4.32-4.25 (m, 2H), 3.41-3.25 (m, 4H), 3.14-3.03 (m, 2H).

Example 79: 4-{3-[(2-Chlorophenyl)ethynyl]benzyl}-N-pyridazin-3-ylpiperazine-1-carboxamide.



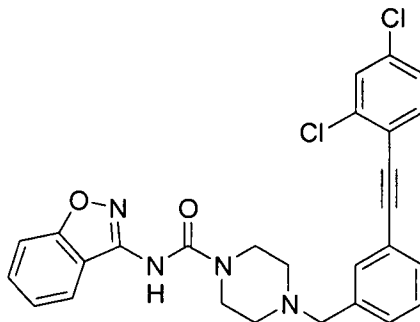
MS: 432.2. ¹H NMR (d₄-MeOH): 8.82-8.76 (m, 1H), 8.15-8.08 (m, 1H),
15 7.62-7.56 (m, 3H), 7.50-7.46 (m, 2H), 7.43-7.29 (m, 4H), 3.67-3.58 (m, 6H),
2.60-2.50 (m, 4H).

Example 80: 4-{3-[(2-Chlorophenyl)ethynyl]benzyl}-N-(5-methylpyrazin-2-yl)piperazine-1-carboxamide.



MS: 446.2. ¹H NMR (d₄-MeOH): 8.89 (d, *J* = 1.5, 1H), 8.19-8.16 (m, 1H), 7.61-7.56 (m, 2H), 7.50-7.45 (m, 2H), 7.42-7.29 (m, 4H), 3.62-3.56 (m, 6H), 2.55-2.50 (m, 4H), 2.46 (s, 3H).

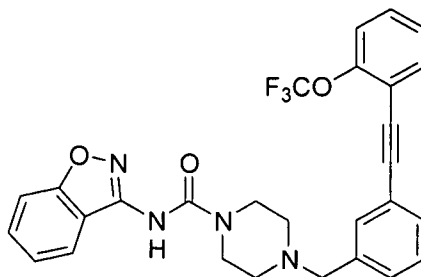
Example 81: N-1,2-Benzisoxazol-3-yl-4-{3-[(2,4-dichlorophenyl)ethynyl]benzyl}-piperazine-1-carboxamide.



To a solution of Pd(PPh₃)₂Cl₂ (7.2 mg) in THF/Et₃N (1 mL each) was added 1,3-dichloro-4-iodobenzene (60.3 mg). The solution was degassed for 15 min, then copper(I) iodide (4.3 mg) and 4-(3-ethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide (75.6 mg) were added. The reaction mixture was stirred at rt for 3 h, then poured into water, and extracted with EtOAc (3x). The organic layers were combined, washed with NH₄OH, dried (Na₂SO₄), and concentrated. The crude residue was purified (FCC) to give the title compound (70.8 mg, 67%). MS: 505.1. ¹H NMR (d₄-MeOH): 7.87-7.83 (m, 1H), 7.61-7.56 (m, 4H), 7.55-7.52 (m, 1H), 7.51-7.47 (m, 1H), 7.46-7.36 (m, 3H), 7.34-7.29 (m, 1H), 3.69-3.60 (m, 6H), 2.61-2.53 (m, 4H).

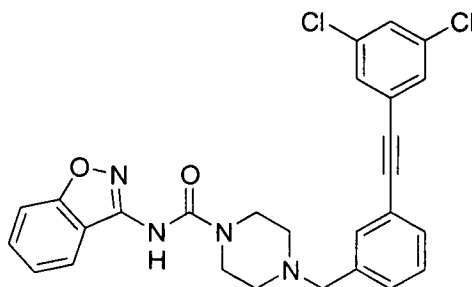
The compounds in Examples 82-93 were prepared using methods analogous to those described in Example 81.

Example 82: N-1,2-Benzisoxazol-3-yl-4-(3-{[2-(trifluoromethoxy)phenyl]-ethynyl}benzyl)-piperazine-1-carboxamide.



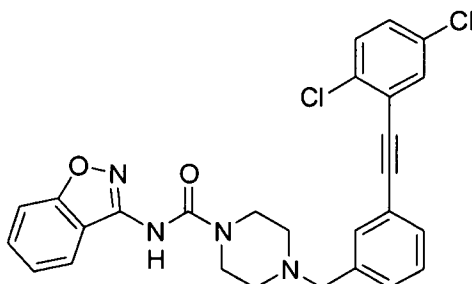
MS: 521.2. ¹H NMR (CDCl₃): 8.12-8.08 (m, 1H), 7.64-7.59 (m, 1H),
 5 7.57-7.52 (m, 2H), 7.51-7.47 (m, 2H), 7.43-7.35 (m, 4H), 7.34-7.29 (m, 3H),
 3.66-3.61 (m, 4H), 3.60 (s, 2H), 2.62-2.53 (m, 4H).

Example 83: N-1,2-Benzisoxazol-3-yl-4-{3-[(3,5-dichlorophenyl)ethynyl]benzyl}-piperazine-1-carboxamide.



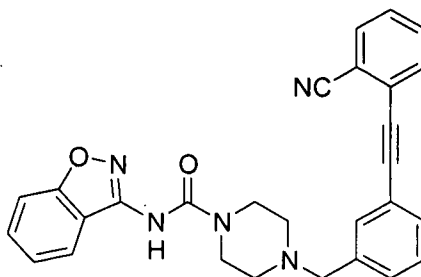
10 MS: 505.1. ¹H NMR (d₄-MeOH): 7.87-7.83 (m, 1H), 7.62-7.56 (m, 2H),
 7.56-7.52 (m, 1H), 7.52-7.47 (m, 4H), 7.46-7.43 (m, 1H), 7.43-7.38 (m, 1H),
 7.34-7.29 (m, 1H), 3.69-3.64 (m, 4H), 3.63 (s, 2H), 2.60-2.54 (m, 4H).

Example 84: N-1,2-Benzisoxazol-3-yl-4-{3-[(2,5-dichlorophenyl)ethynyl]benzyl}-piperazine-1-carboxamide.



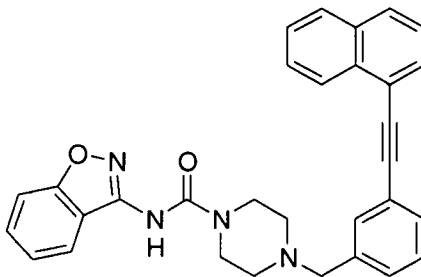
15 MS: 505.1. ¹H NMR (CDCl₃): 8.11-8.08 (m, 1H), 7.59-7.56 (m, 2H),
 7.56-7.47 (m, 4H), 7.40-7.36 (m, 3H), 7.32-7.24 (m, 2H), 3.67-3.62 (m, 4H),
 3.60 (s, 2H), 2.62-2.55 (m, 4H).

Example 85: N-1,2-Benzisoxazol-3-yl-4-{3-[(2-cyanophenyl)ethynyl]benzyl}-piperazine-1-carboxamide.



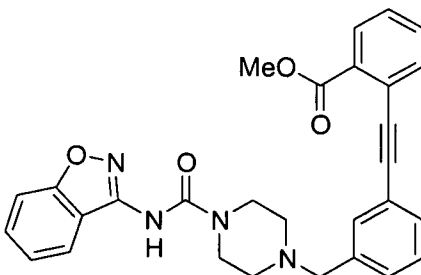
MS: 462.2. ¹H NMR (d₄-MeOH): 7.87-7.84 (m, 1H), 7.82-7.79 (m, 1H),
 5 7.75-7.68 (m, 2H), 7.67-7.63 (m, 1H), 7.61-7.51 (m, 4H), 7.49-7.41 (m, 2H),
 7.34-7.29 (m, 1H), 3.70-3.60 (m, 6H), 2.63-2.52 (m, 4H).

Example 86: N-1,2-Benzisoxazol-3-yl-4-[3-(naphthalen-1-ylethynyl)benzyl]piperazine-1-carboxamide.



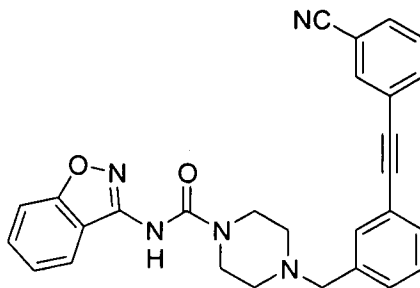
10 MS: 487.2. ¹H NMR (CDCl₃): 8.48-8.43 (m, 1H), 8.10-8.06 (m, 1H),
 7.90-7.84 (m, 2H), 7.79-7.76 (m, 1H), 7.66-7.44 (m, 8H), 7.42-7.36 (m, 2H),
 7.30-7.27 (m, 1H), 3.67-3.59 (m, 6H), 2.62-2.54 (m, 4H).

Example 87: Methyl 2-[(3-{[4-(1,2-benzisoxazol-3-ylcarbamoyl)piperazin-1-yl]methyl}phenyl)ethynyl]benzoate.



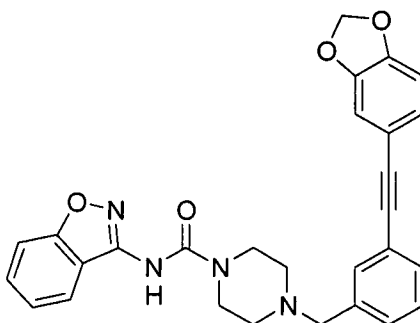
15 MS: 495.2. ¹H NMR (d₄-MeOH): 7.99-7.95 (m, 1H), 7.87-7.84 (m, 1H),
 7.70-7.66 (m, 1H), 7.62-7.57 (m, 3H), 7.56-7.45 (m, 3H), 7.44-7.38 (m, 2H),
 7.34-7.30 (m, 1H), 3.98 (s, 3H), 3.69-3.62 (m, 6H), 2.61-2.56 (m, 4H).

Example 88: N-1,2-Benzisoxazol-3-yl-4-{3-[(3-cyanophenyl)ethynyl]benzyl}piperazine-1-carboxamide.



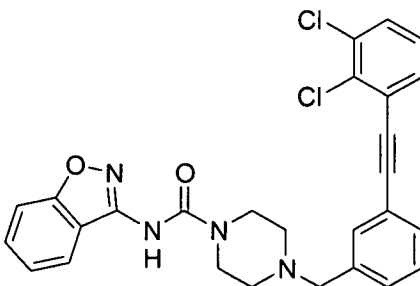
MS: 462.2. ¹H NMR (d₄-MeOH): 7.90-7.88 (m, 1H), 7.85-7.80 (m, 2H),
 5 7.74-7.71 (m, 1H), 7.60-7.55 (m, 3H), 7.52 (d, *J* = 8.5, 1H), 7.49-7.47 (m, 1H),
 7.44-7.42 (m, 1H), 7.39 (t, *J* = 7.6, 1H), 7.30 (t, *J* = 7.5, 1H), 3.66-3.63 (m, 4H),
 3.62 (s, 2H), 2.58-2.54 (m, 4H).

Example 89: N-1,2-Benzisoxazol-3-yl-4-[3-(1,3-benzodioxol-5-ylethynyl)benzyl]-piperazine-1-carboxamide.



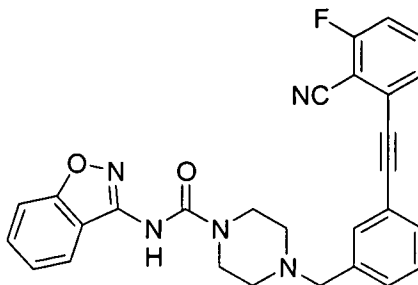
10 MS: 481.2. ¹H NMR (d₄-MeOH): 7.88-7.84 (m, 1H), 7.63-7.53 (m, 3H),
 7.45-7.30 (m, 4H), 7.09-7.05 (dd, *J* = 8.0, 1.6, 1H), 6.99-6.98 (m, 1H), 6.87-
 6.84 (m, 1H), 6.01 (s, 2H), 3.69-3.65 (m, 4H), 3.62 (s, 2H), 2.61-2.55 (m, 4H).

15 Example 90: N-1,2-Benzisoxazol-3-yl-4-{3-[(2,3-dichlorophenyl)ethynyl]benzyl}-piperazine-1-carboxamide.



MS: 505.1. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.87-7.84 (m, 1H), 7.64-7.50 (m, 6H), 7.48-7.40 (m, 2H), 7.36-7.30 (m, 2H), 3.71-3.62 (m, 6H), 2.63-2.54 (m, 4H).

Example 91: N-1,2-Benzisoxazol-3-yl-4-{3-[(2-cyano-3-fluorophenyl)ethynyl]-benzyl}piperazine-1-carboxamide.

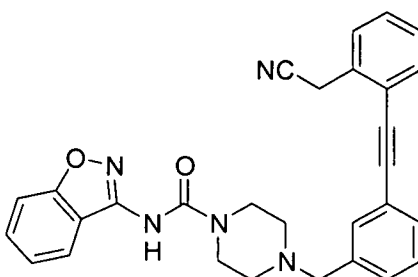


5

MS: 480.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.85-7.82 (m, 1H), 7.76-7.69 (m, 1H), 7.67-7.64 (m, 1H), 7.60-7.35 (m, 7H), 7.33-7.27 (m, 1H), 3.68-3.62 (m, 6H), 2.61-2.53 (m, 4H).

Example 92: N-1,2-Benzisoxazol-3-yl-4-(3-{[2-(cyanomethyl)phenyl]ethynyl}-benzyl)piperazine-1-carboxamide.

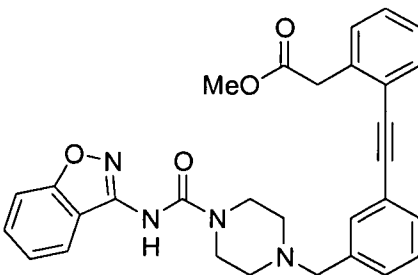
10



MS: 476.2. ^1H NMR ($\text{d}_6\text{-DMSO}$): 9.89 (s, 1H), 7.82-7.79 (m, 1H), 7.65-7.61 (m, 2H), 7.61-7.58 (m, 2H), 7.56-7.53 (m, 2H), 7.50-7.46 (m, 1H), 7.46-7.41 (m, 3H), 7.32-7.29 (m, 1H), 4.21 (s, 2H), 3.60-3.51 (m, 6H), 2.46-2.42 (m, 4H).

15

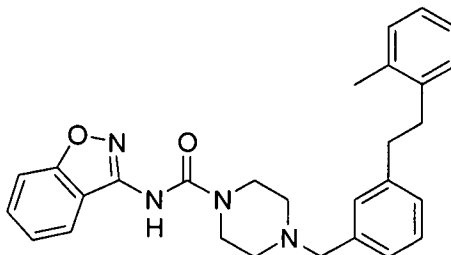
Example 93: Methyl {2-[(3-{[4-(1,2-benzisoxazol-3-ylcarbamoyl)piperazin-1-yl]methyl}phenyl)ethynyl]phenyl}acetate.



MS: 509.2. ^1H NMR ($\text{d}_6\text{-DMSO}$): 9.88 (s, 1H), 7.82-7.79 (m, 1H), 7.65-7.53 (m, 3H), 7.51-7.48 (m, 1H), 7.45-7.27 (m, 7H), 3.93 (s, 2H), 3.63 (s, 3H), 3.58-3.52 (m, 6H), 2.47-2.41 (m, 4H).

Example 94: 4-[3-(2-o-Tolyl-ethyl)-benzyl]-piperazine-1-carboxylic acid

5 benzo[d]isoxazol-3-ylamide hydrochloride salt.



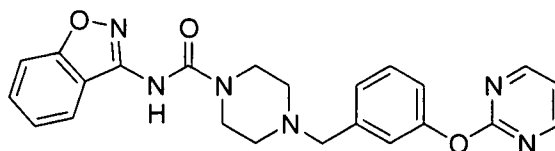
Step A: 4-(3-o-Tolylethynyl-benzyl)-piperazine-1-carboxylic acid tert-butyl ester. The title compound was prepared using methods analogous to those described in Example 63, Step C. MS: 391.3.

10 Step B: 4-[3-(2-o-Tolyl-ethyl)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester. To a solution of 4-(3-o-tolylethynyl-benzyl)-piperazine-1-carboxylic acid tert-butyl ester (489.4 mg) in EtOH (20 mL) was added 10% Pd/C (139 mg). The flask was purged with N_2 , and then fitted with a H_2 balloon. The mixture was stirred at rt for 2 h under 1 atm of H_2 , then filtered through
15 diatomaceous earth and concentrated to give 4-[3-(2-o-tolyl-ethyl)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester (480.2 mg, 97%). MS: 395.3.

Step C: 1-[3-(2-o-Tolyl-ethyl)-benzyl]-piperazine. The title compound was prepared using methods analogous to those described in Example 1, Step B. MS: 295.2.

20 Step D: 4-[3-(2-o-Tolyl-ethyl)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide hydrochloride salt. The title compound was prepared using methods analogous to those described in Example 1, Step C. MS: 455.3. ^1H NMR ($\text{d}_6\text{-DMSO}$): 7.87-7.83 (m, 1H), 7.68-7.60 (m, 2H), 7.46-7.30 (m, 5H), 7.16-7.07 (m, 4H), 4.37-4.25 (m, 4H), 3.47-3.25 (br hump, 2H),
25 3.13-3.02 (m, 2H), 2.90-2.85 (m, 4H), 2.27 (s, 3H).

Example 95: 4-[3-(Pyrimidin-2-yloxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.



Step A: 4-[3-(Pyrimidin-2-yloxy)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester. To a solution of 4-(3-hydroxy-benzyl)-piperazine-1-carboxylic acid tert-butyl ester (500.2 mg) in DMSO (5 mL) were added cesium carbonate (1.10 g) and 2-chloropyrimidine (236.2 mg). The reaction mixture was heated at 60 °C for 18 h, then was cooled to rt, poured into H₂O, and extracted with EtOAc (3x). The organic layers were combined, dried (Na₂SO₄), and concentrated. The crude residue was purified (FCC) to give 4-[3-(pyrimidin-2-yloxy)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester (452.8 mg, 71%).

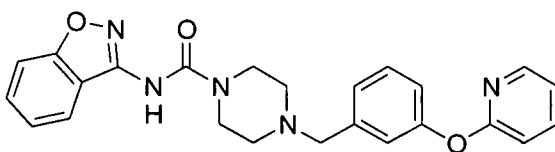
MS: 371.5.

Step B: 2-(3-Piperazin-1-ylmethyl-phenoxy)-pyrimidine. The title compound was prepared using methods analogous to those described in Example 1, Step B. MS: 271.2.

Step C: 4-[3-(Pyrimidin-2-yloxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide. The title compound was prepared using methods analogous to those described in Example 1, Step C. MS: 431.5. ¹H NMR (d₄-MeOH): 8.61 (d, *J* = 4.8, 2H), 7.87-7.82 (m, 1H), 7.62-7.57 (m, 1H), 7.55-7.53 (m, 1H), 7.43 (t, *J* = 7.8, 1H), 7.34-7.28 (m, 2H), 7.25-7.22 (m, 2H), 7.14-7.10 (m, 1H), 3.69-3.63 (m, 6H), 2.64-2.54 (m, 4H).

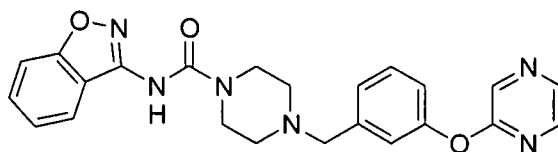
The compounds in Examples 96-97 were prepared using methods analogous to those described in Example 95.

Example 96: N-1,2-Benzisoxazol-3-yl-4-[3-(pyridin-2-yloxy)benzyl]piperazine-1-carboxamide.



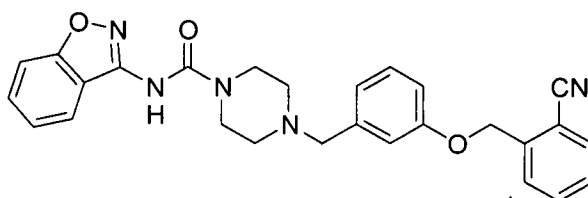
MS: 430.5. ¹H NMR (d₄-MeOH): 8.19-8.14 (m, 1H), 7.88-7.83 (m, 2H), 7.62-7.57 (m, 1H), 7.56-7.53 (m, 1H), 7.43-7.39 (m, 1H), 7.34-7.30 (m, 1H), 7.27-7.24 (m, 1H), 7.19-7.13 (m, 2H), 7.07-7.03 (m, 1H), 6.99-6.95 (m, 1H), 3.69-3.61 (m, 6H), 2.63-2.54 (m, 4H).

Example 97: N-1,2-Benzisoxazol-3-yl-4-[3-(pyrazin-2-yloxy)benzyl]piperazine-1-carboxamide.



MS: 431.5. ¹H NMR (d₄-MeOH): 8.42 (d, *J* = 1.3, 1H), 8.29 (d, *J* = 2.7, 1H), 8.15-8.14 (m, 1H), 7.85-7.82 (m, 1H), 7.59-7.55 (m, 1H), 7.53-7.51 (m, 1H), 7.42 (t, *J* = 7.9, 1H), 7.32-7.26 (m, 2H), 7.23-7.21 (m, 1H), 7.11-7.08 (m, 1H), 3.67-3.60 (m, 6H), 2.60-2.54 (m, 4H).

Example 98: 4-[3-(2-Cyano-benzyloxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.

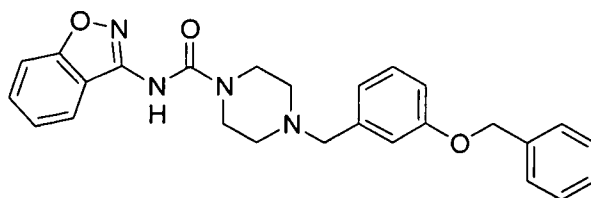


10

To a solution of 4-(3-hydroxy-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide (100.2 mg) in acetonitrile (1 mL) were added potassium carbonate (75.6 mg) and α-bromo-o-tolunitrile (62.9 mg). The reaction mixture was heated at 50 °C for 18 h, then was cooled to rt, poured into H₂O, and extracted with EtOAc (3x). The organic layers were combined, dried (Na₂SO₄), and concentrated. The crude residue was purified (FCC) to give the title compound (41.3 mg, 31%). MS: 468.2. ¹H NMR (d₄-MeOH): 7.84-7.81 (m, 1H), 7.80-7.78 (m, 1H), 7.72-7.68 (m, 2H), 7.60-7.56 (m, 1H), 7.54-7.50 (m, 2H), 7.32-7.26 (m, 2H), 7.09-7.07 (m, 1H), 7.00-6.95 (m, 2H), 5.29-5.26 (m, 2H), 3.64-3.60 (m, 4H), 3.59-3.57 (m, 2H), 2.55-2.50 (m, 4H).

20

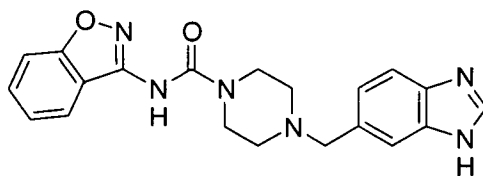
Example 99: N-1,2-Benzisoxazol-3-yl-4-[3-(benzyloxy)benzyl]piperazine-1-carboxamide.



The title compound was prepared using methods analogous to those described in Example 98. MS: 443.2. ¹H NMR (d₄-MeOH): 7.84-7.81 (m, 1H), 7.59-7.56 (m, 1H), 7.54-7.51 (m, 1H), 7.45-7.42 (m, 2H), 7.38-7.34 (m, 2H), 7.32-7.28 (m, 2H), 7.26-7.23 (m, 1H), 7.03-7.01 (m, 1H), 6.95-6.90 (m, 2H), 5.10 (s, 2H), 3.63-3.59 (m, 4H), 3.56 (s, 2H), 2.54-2.47 (m, 4H).

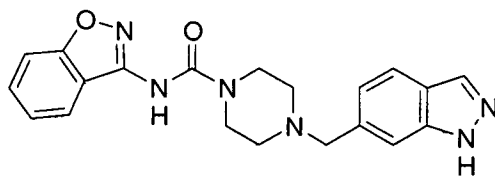
The compounds in Examples 100-203 were prepared using methods analogous to those described in Example 1.

Example 100: 4-(1H-Benzimidazol-6-ylmethyl)-N-1,2-benzisoxazol-3-ylpiperazine-1-carboxamide.



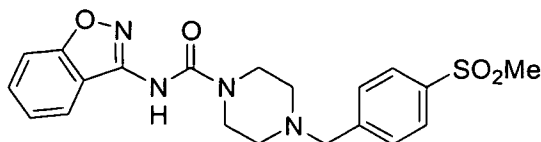
MS: 377.5. ¹H NMR (d₆-DMSO): 8.18 (s, 1H), 7.81-7.78 (td, *J* = 8.0, 1.0, 1H), 7.61-7.50 (m, 4H), 7.28-7.24 (m, 1H), 7.19-7.16 (dd, *J* = 8.2, 1.4, 1H), 3.62 (s, 2H), 3.55-3.50 (m, 4H), 2.44-2.40 (m, 4H).

Example 101: N-1,2-Benzisoxazol-3-yl-4-(1H-indazol-6-ylmethyl)piperazine-1-carboxamide.



MS: 377.4. ¹H NMR (d₆-DMSO): 13.00 (s, 1H), 9.85 (s, 1H), 8.03 (d, *J* = 0.8, 1H), 7.79 (d, *J* = 8.0, 1H), 7.66 (s, 1H), 7.61-7.55 (m, 2H), 7.50 (d, *J* = 8.5, 1H), 7.37-7.33 (dd, *J* = 8.6, 1.4, 1H), 7.27 (t, *J* = 7.9, 1H), 3.61 (s, 2H), 3.55-3.50 (m, 4H), 2.45-2.40 (m, 4H).

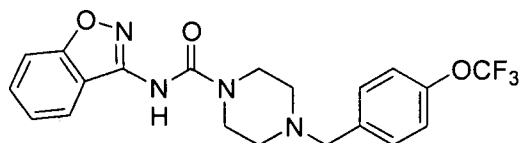
Example 102: N-1,2-Benzisoxazol-3-yl-4-[4-(methylsulfonyl)benzyl]piperazine-1-carboxamide.



MS: 415.4. ^1H NMR (d_6 -DMSO): 9.88 (s, 1H), 7.91 (d, $J = 8.4$, 1H), 7.81 (d, $J = 8.0$, 1H), 7.64-7.56 (m, 4H), 7.31-7.27 (m, 1H), 3.65 (s, 2H), 3.57-3.53 (m, 4H), 3.22 (s, 3H), 2.46-2.41 (m, 4H).

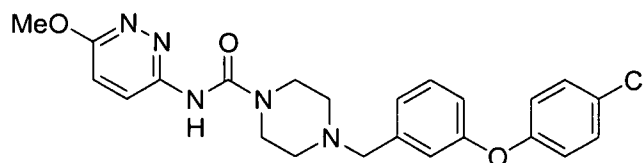
Example 103: N-1,2-Benzisoxazol-3-yl-4-[4-

5 (trifluoromethoxy)benzyl]piperazine-1-carboxamide.



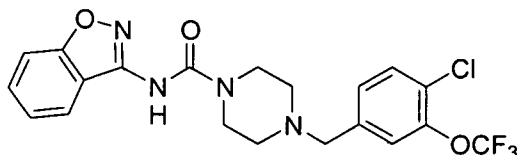
MS: 421.4. ^1H NMR (d_6 -DMSO): 9.83 (s, 1H), 7.82-7.79 (td, $J = 8.1$, 0.9, 2H), 7.63-7.56 (m, 2H), 7.47 (d, $J = 8.7$, 1H), 7.35-7.27 (m, 3H), 3.56 (s, 2H), 3.55-3.51 (m, 4H), 2.44-2.40 (m, 4H).

10 Example 104: 4-[3-(4-Chlorophenoxy)benzyl]-N-(6-methoxypyridazin-3-yl)piperazine-1-carboxamide.



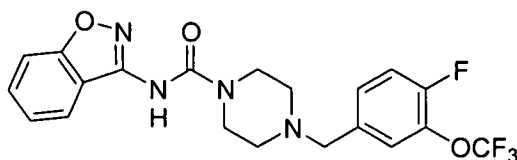
MS: 454.2. ^1H NMR (d_6 -DMSO): 8.10 (d, $J = 9.6$, 1H), 7.41 (d, $J = 8.9$, 2H), 7.38 (t, $J = 7.8$, 1H), 7.19 (d, $J = 7.5$, 1H), 7.11-7.09 (m, 1H), 7.06-7.03 (m, 3H), 6.96-6.93 (dd, $J = 7.9$, 2.3, 1H), 3.99 (s, 3H), 3.63-3.59 (m, 4H), 3.58 (s, 2H), 2.52-2.47 (m, 4H).

Example 105: N-1,2-Benzisoxazol-3-yl-4-[4-chloro-3-(trifluoromethoxy)benzyl]-piperazine-1-carboxamide.



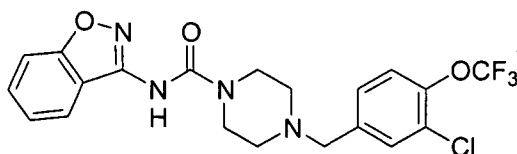
20 MS: 455.4. ^1H NMR (d_6 -DMSO): 9.87 (s, 1H), 7.80 (d, $J = 8.0$, 1H), 7.67 (d, $J = 8.2$, 1H), 7.64-7.57 (m, 2H), 7.52 (s, 1H), 7.44-7.41 (dd, $J = 8.3$, 1.8, 1H), 7.31-7.27 (m, 1H), 3.60 (s, 2H), 3.56-3.52 (m, 4H), 2.46-2.40 (m, 4H).

Example 106: N-1,2-Benzisoxazol-3-yl-4-[4-fluoro-3-(trifluoromethoxy)benzyl]-piperazine-1-carboxamide.



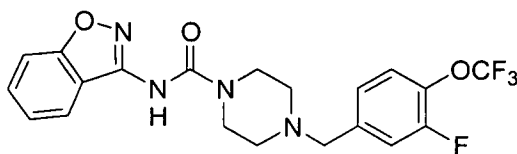
MS: 439.4. ^1H NMR (d_6 -DMSO): 9.83 (s, 1H), 7.82-7.79 (td, $J = 8.1$, 1.0, 1H), 7.64-7.56 (m, 2H), 7.52-7.40 (m, 3H), 7.32-7.27 (m, 1H), 3.57 (s, 2H), 3.56-3.51 (m, 4H), 2.46-2.40 (m, 4H).

- 5 Example 107: N-1,2-Benzisoxazol-3-yl-4-[3-chloro-4-(trifluoromethoxy)benzyl]-piperazine-1-carboxamide.



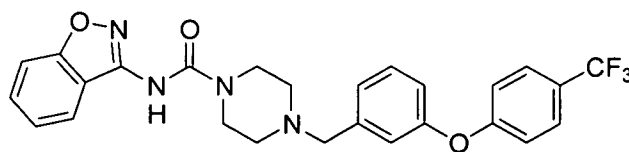
MS: 455.4. ^1H NMR (d_6 -DMSO): 9.88 (s, 1H), 7.81 (d, $J = 8.0$, 1H), 7.67-7.52 (m, 4H), 7.47-7.43 (dd, $J = 8.4$, 2.0, 1H), 7.32-7.28 (m, 1H), 3.58 (s, 2H), 3.57-3.51 (m, 4H), 2.46-2.41 (m, 4H).

- 10 Example 108: N-1,2-Benzisoxazol-3-yl-4-[3-fluoro-4-(trifluoromethoxy)benzyl]-piperazine-1-carboxamide.



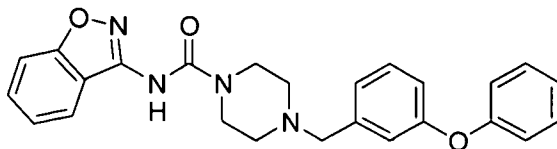
MS: 439.4. ^1H NMR (d_6 -DMSO): 9.88 (s, 1H), 7.81 (d, $J = 8.0$, 1H), 7.64-7.58 (m, 2H), 7.54 (t, $J = 8.2$, 1H), 7.49-7.45 (dd, $J = 11.4$, 1.8, 1H), 7.33-7.28 (m, 2H), 3.58 (s, 2H), 3.57-3.51 (m, 4H), 2.45-2.42 (m, 4H).

- 15 Example 109: N-1,2-Benzisoxazol-3-yl-4-[3-[4-(trifluoromethyl)phenoxy]benzyl]-piperazine-1-carboxamide.



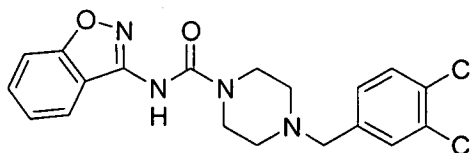
20 MS: 497.5. ^1H NMR (CDCl_3): 8.08 (d, $J = 8.1$, 1H), 7.87 (s, 1H), 7.60 (d, $J = 8.9$, 2H), 7.56-7.52 (m, 1H), 7.47 (d, $J = 8.5$, 1H), 7.37 (t, $J = 7.9$, 1H), 7.32-7.28 (m, 1H), 7.19 (d, $J = 7.4$, 1H), 7.12-7.10 (m, 1H), 7.07 (d, $J = 8.4$, 2H), 7.00-6.97 (m, 1H), 3.69-3.62 (m, 4H), 3.59 (s, 2H), 2.60-2.53 (m, 4H).

Example 110: N-1,2-Benzisoxazol-3-yl-4-(3-phenoxybenzyl)piperazine-1-carboxamide.



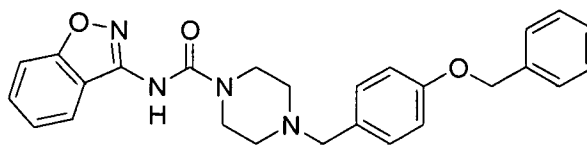
MS: 429.5. ^1H NMR (CDCl_3): 8.09 (d, $J = 8.1$, 1H), 7.80 (s, 1H), 7.57-7.52 (m, 1H), 7.48 (d, $J = 8.5$, 1H), 7.39-7.29 (m, 4H), 7.16-7.01 (m, 5H), 6.96-6.92 (m, 1H), 3.67-3.60 (m, 4H), 3.57 (s, 2H), 2.60-2.51 (m, 4H).

Example 111: N-1,2-Benzisoxazol-3-yl-4-(3,4-dichlorobenzyl)piperazine-1-carboxamide.



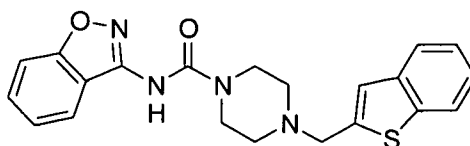
MS: 405.4. ^1H NMR (CDCl_3): 8.08 (d, $J = 8.0$, 1H), 7.94 (s, 1H), 7.57-7.53 (m, 1H), 7.50-7.46 (m, 2H), 7.43 (d, $J = 8.2$, 1H), 7.32-7.28 (m, 1H), 7.22-7.19 (dd, $J = 8.2$, 2.0, 1H), 3.68-3.63 (m, 4H), 3.53 (s, 2H), 2.59-2.52 (m, 4H).

Example 112: N-1,2-Benzisoxazol-3-yl-4-[4-(benzyloxy)benzyl]piperazine-1-carboxamide.



MS: 443.5. ^1H NMR (CDCl_3): 8.09 (d, $J = 8.1$, 1H), 7.80 (s, 1H), 7.57-7.52 (m, 1H), 7.50-7.25 (m, 9H), 6.97 (d, $J = 8.6$, 2H), 5.09 (s, 2H), 3.66-3.61 (m, 4H), 3.52 (s, 2H), 2.58-2.50 (m, 4H).

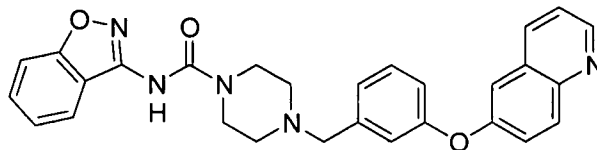
Example 113: N-1,2-Benzisoxazol-3-yl-4-(1-benzothiophen-2-ylmethyl)piperazine-1-carboxamide.



MS: 393.4. ^1H NMR (CDCl_3): 8.08 (d, $J = 8.1$, 1H), 7.83 (d, $J = 8.1$, 1H), 7.77 (s, 1H), 7.73 (d, $J = 8.0$, 1H), 7.56-7.52 (m, 1H), 7.47 (d, $J = 8.5$, 1H),

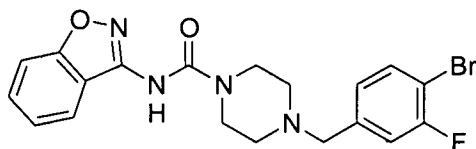
7.38-7.29 (m, 3H), 7.20 (s, 1H), 3.88 (s, 2H), 3.71-3.63 (m, 4H), 2.69-2.62 (m, 4H).

Example 114: N-1,2-Benzisoxazol-3-yl-4-[3-(quinolin-6-yloxy)benzyl]piperazine-1-carboxamide.



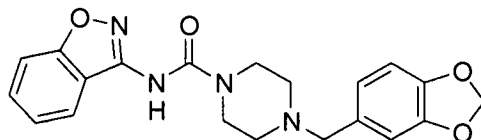
MS: 480.5. ¹H NMR (CDCl₃): 8.88-8.85 (dd, *J* = 4.2, 1.7, 1H), 8.12 (d, *J* = 9.2, 1H), 8.08 (d, *J* = 8.1, 1H), 8.04 (d, *J* = 8.2, 1H), 7.64 (s, 1H), 7.56-7.50 (m, 2H), 7.48 (d, *J* = 8.5, 1H), 7.42-7.35 (m, 2H), 7.31-7.26 (m, 2H), 7.18 (d, *J* = 7.7, 1H), 7.16-7.13 (m, 1H), 7.05-7.01 (m, 1H), 3.66-3.58 (m, 6H), 2.62-2.53 (m, 4H).

Example 115: N-1,2-Benzisoxazol-3-yl-4-(4-bromo-3-fluorobenzyl)piperazine-1-carboxamide.



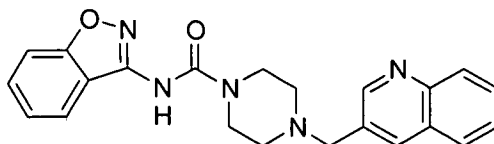
MS: 433.4. ¹H NMR (CDCl₃): 8.08 (d, *J* = 8.0, 1H), 7.91 (s, 1H), 7.58-7.46 (m, 3H), 7.32-7.29 (m, 1H), 7.21-7.17 (dd, *J* = 9.4, 1.8, 1H), 7.05-7.02 (dd, *J* = 8.1, 1.4, 1H), 3.69-3.61 (m, 4H), 3.54 (s, 2H), 2.59-2.51 (m, 4H).

Example 116: N-1,2-Benzisoxazol-3-yl-4-(1,3-benzodioxol-5-ylmethyl)piperazine-1-carboxamide.



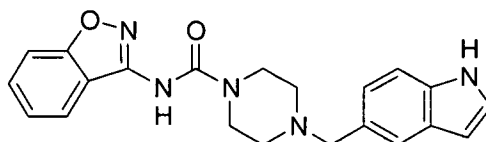
MS: 381.4. ¹H NMR (CDCl₃): 8.13-8.06 (m, 2H), 7.57-7.52 (m, 1H), 7.47 (d, *J* = 8.5, 1H), 7.32-7.28 (m, 1H), 6.90 (s, 1H), 6.80-6.76 (m, 2H), 5.98 (s, 2H), 3.69-3.62 (m, 4H), 3.49 (s, 2H), 2.57-2.50 (m, 4H).

Example 117: N-1,2-Benzisoxazol-3-yl-4-(quinolin-3-ylmethyl)piperazine-1-carboxamide.



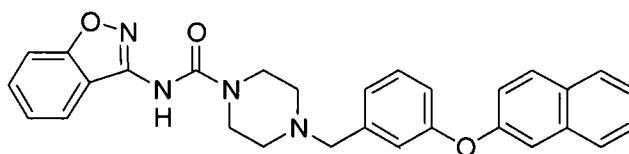
MS: 388.5. ^1H NMR (CDCl_3): 8.94 (d, $J = 2.1$, 1H), 8.62 (s, 1H), 8.15-8.04 (m, 3H), 7.82 (d, $J = 9.2$, 1H), 7.74-7.69 (m, 1H), 7.59-7.48 (m, 2H), 7.41 (d, $J = 8.5$, 1H), 7.29-7.24 (m, 1H), 3.75 (s, 2H), 3.72-3.67 (m, 4H), 2.65-2.56 (m, 4H).

Example 118: N-1,2-Benzisoxazol-3-yl-4-(1H-indol-5-ylmethyl)piperazine-1-carboxamide.



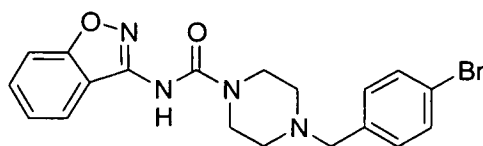
MS: 376.5. ^1H NMR (CDCl_3): 8.18 (s, 1H), 8.08 (d, $J = 8.0$, 1H), 7.99 (s, 1H), 7.58 (s, 1H), 7.54-7.49 (m, 1H), 7.44 (d, $J = 8.5$, 1H), 7.37 (d, $J = 8.3$, 1H), 7.29-7.24 (m, 1H), 7.23-7.17 (m, 2H), 6.56-6.51 (m, 1H), 3.67 (s, 2H), 3.65-3.60 (m, 4H), 2.61-2.53 (m, 4H).

Example 119: N-1,2-Benzisoxazol-3-yl-4-[3-(naphthalen-2-yloxy)benzyl]piperazine-1-carboxamide.



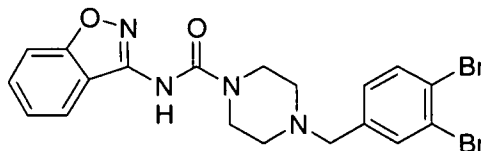
MS: 479.5. ^1H NMR (CDCl_3): 8.11-8.04 (m, 2H), 7.85-7.80 (m, 2H), 7.70 (d, $J = 8.1$, 1H), 7.53-7.38 (m, 4H), 7.35-7.24 (m, 4H), 7.11 (d, $J = 7.5$, 1H), 7.00-6.96 (m, 1H), 3.66-3.60 (m, 4H), 3.56 (s, 2H), 2.58-2.51 (m, 4H).

Example 120: N-1,2-Benzisoxazol-3-yl-4-(4-bromobenzyl)piperazine-1-carboxamide.



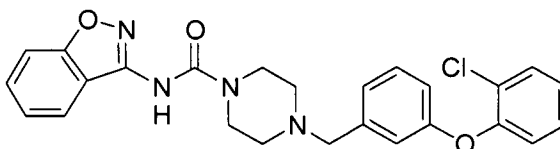
MS: 415.4. ^1H NMR (CDCl_3): 8.68 (s, 1H), 8.07 (d, $J = 8.0$, 1H), 7.55-7.40 (m, 4H), 7.30-7.20 (m, 3H), 3.70-3.62 (m, 4H), 3.50 (s, 2H), 2.56-2.47 (m, 4H).

Example 121: N-1,2-Benzisoxazol-3-yl-4-(3,4-dibromobenzyl)piperazine-1-carboxamide.



MS: 493.3. ¹H NMR (CDCl₃): 8.73 (s, 1H), 8.07 (d, *J* = 8.1, 1H), 7.63
5 (d, *J* = 2.0, 1H), 7.57 (d, *J* = 8.2, 1H), 7.55-7.50 (m, 1H), 7.43 (d, *J* = 8.5, 1H),
7.30-7.25 (m, 1H), 7.17-7.13 (m, 1H), 3.71-3.64 (m, 4H), 3.48 (s, 2H), 2.56-
2.48 (m, 4H).

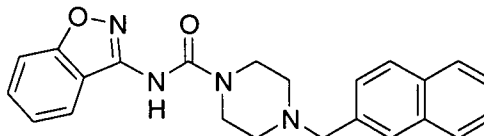
Example 122: N-1,2-Benzisoxazol-3-yl-4-[3-(2-chlorophenoxy)benzyl]piperazine-1-carboxamide.



10

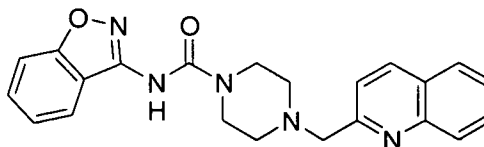
MS: 463.5. ¹H NMR (d₆-DMSO): 9.86 (s, 1H), 7.80 (d, *J* = 8.0, 1H),
7.65-7.57 (m, 3H), 7.40-7.28 (m, 3H), 7.26-7.21 (m, 1H), 7.13-7.09 (m, 2H),
6.94 (s, 1H), 6.86-6.83 (m, 1H), 3.55-3.47 (m, 6H), 2.44-2.37 (m, 4H).

Example 123: 4-Naphthalen-2-ylmethyl-piperazine-1-carboxylic acid
15 benzo[d]isoxazol-3-ylamide.



MS: 387.5. ¹H NMR (CDCl₃): 8.07 (d, *J* = 8.4, 1H), 7.85-7.82 (m, 3H),
7.76 (s, 1H), 7.53-7.45 (m, 6H), 7.28-7.26 (m, 1H), 3.73 (s, 2H), 3.63 (t, *J* = 4.8,
4H), 2.59 (t, *J* = 4.8, 4H).

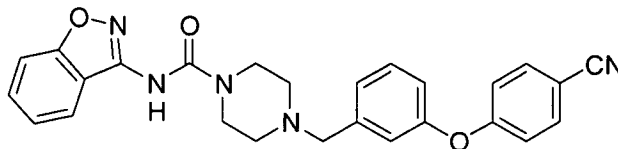
20 Example 124: 4-Quinolin-2-ylmethyl-piperazine-1-carboxylic acid
benzo[d]isoxazol-3-ylamide.



MS: 388.5. ¹H NMR (CDCl₃): 8.17 (d, *J* = 8.4, 1H), 8.10-8.07 (m, 2H),
7.83 (d, *J* = 7.8, 1H), 7.74-7.71 (m, 1H), 7.64 (d, *J* = 8.4, 1H), 7.56-7.51 (m,

3H), 7.46 (d, $J = 7.8$, 1H), 7.29-7.26 (m, 1H), 3.92 (s, 2H), 3.66 (t, $J = 4.8$, 4H), 2.67 (t, $J = 4.8$, 4H).

Example 125: 4-[3-(4-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.

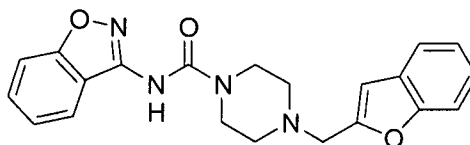


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MS: 454.5. ^1H NMR (CDCl_3): 8.07 (d, $J = 7.8$, 1H), 7.91 (s, 1H), 7.62-7.60 (m, 2H), 7.54-7.51 (m, 1H), 7.45 (d, $J = 8.4$, 1H), 7.38 (t, $J = 7.8$, 1H), 7.29-7.26 (m, 1H), 7.21 (d, $J = 7.2$, 1H), 7.10-7.09 (m, 1H), 7.03-7.01 (m, 2H), 6.99-6.97 (dd, $J = 1.8, 7.2$, 1H), 3.64 (t, $J = 4.8$, 4H), 3.58 (s, 2H), 2.55 (t, $J = 4.8$, 4H).

10

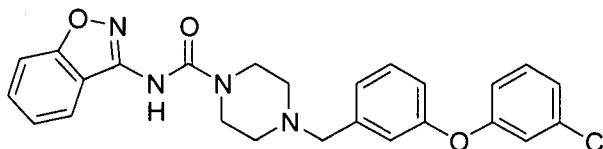
Example 126: 4-Benzofuran-2-ylmethyl-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.



MS: 377.4. ^1H NMR (CDCl_3): 8.07 (d, $J = 7.8$, 1H), 8.05 (s, 1H), 7.56-7.50 (m, 3H), 7.45 (d, $J = 8.4$, 1H), 7.30-7.27 (m, 2H), 7.25-7.22 (m, 1H), 6.65 (s, 1H), 3.78 (s, 2H), 3.70 (t, $J = 4.8$, 4H), 2.67 (t, $J = 4.8$, 4H).

15

Example 127: N-1,2-Benzisoxazol-3-yl-4-[3-(3-chlorophenoxy)benzyl]piperazine-1-carboxamide.

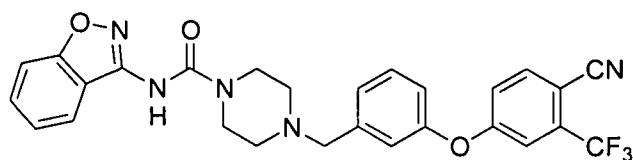


20

MS: 463.5. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.85-7.82 (m, 1H), 7.59-7.55 (m, 1H), 7.53-7.51 (m, 1H), 7.39-7.35 (m, 1H), 7.34-7.28 (m, 2H), 7.19-7.17 (m, 1H), 7.12-7.07 (m, 2H), 6.97-6.94 (m, 2H), 6.93-6.91 (m, 1H), 3.65-3.58 (m, 6H), 2.57-2.51 (m, 4H).

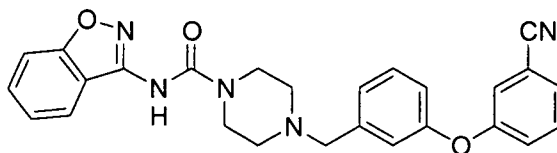
Example 128: N-1,2-Benzisoxazol-3-yl-4-[3-[4-cyano-3-(trifluoromethyl)phenoxy]benzyl]piperazine-1-carboxamide.

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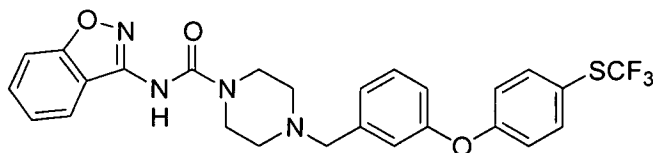
MS: 522.2. ¹H NMR (d₄-MeOH): 7.94 (d, *J* = 8.6, 1H), 7.84-7.82 (m, 1H), 7.59-7.55 (m, 1H), 7.53-7.51 (m, 1H), 7.48 (t, *J* = 7.9, 1H), 7.42 (d, *J* = 2.4, 1H), 7.35-7.26 (m, 3H), 7.22-7.20 (m, 1H), 7.10-7.07 (m, 1H), 3.65-3.61 (m, 6H), 2.58-2.53 (m, 4H).

Example 129: N-1,2-Benzisoxazol-3-yl-4-([3-(3-cyanophenoxy)benzyl]piperazine-1-carboxamide.



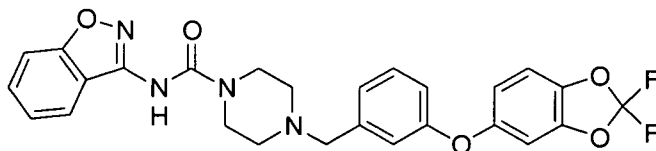
¹H NMR (d₆-DMSO): 9.94-9.75 (m, 1H), 7.89-7.68 (m, 1H), 7.67-7.54 (m, 4H), 7.53-7.49 (m, 1H), 7.43-7.38 (m, 1H), 7.37-7.33 (m, 1H), 7.32-7.28 (m, 1H), 7.21-7.17 (m, 1H), 7.08-7.05 (m, 1H), 7.00-6.96 (m, 1H), 3.59-3.46 (m, 6H), 2.46-2.39 (m, 4H).

Example 130: N-1,2-Benzisoxazol-3-yl-4-([3-(4-[(trifluoromethyl)sulfanyl]phenoxy]benzyl]piperazine-1-carboxamide.



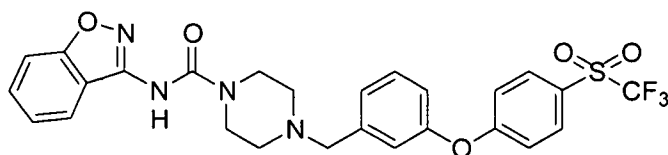
MS: 529.2. ¹H NMR (d₄-MeOH): 7.89-7.81 (m, 1H), 7.70-7.64 (m, 2H), 7.62-7.56 (m, 1H), 7.55-7.52 (m, 1H), 7.44-7.38 (m, 1H), 7.35-7.28 (m, 1H), 7.26-7.22 (m, 1H), 7.17-7.13 (m, 1H), 7.09-7.05 (m, 2H), 7.04-7.01 (m, 1H), 3.69-3.58 (m, 6H), 2.64-2.49 (m, 4H).

Example 131: N-1,2-Benzisoxazol-3-yl-4-([3-[(2,2-difluoro-1,3-benzodioxol-5-yl)oxy]benzyl]piperazine-1-carboxamide.



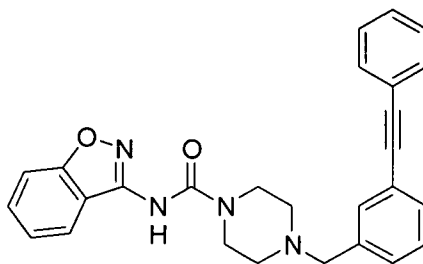
MS: 509.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 7.87-7.83 (m, 1H), 7.62-7.56 (m, 1H), 7.55-7.52 (m, 1H), 7.39-7.29 (m, 2H), 7.21-7.14 (m, 2H), 7.08-7.05 (m, 1H), 6.97-6.92 (m, 2H), 6.84-6.77 (m, 1H), 3.69-3.61 (m, 4H), 3.61-3.59 (m, 2H), 2.63-2.47 (m, 4H).

5 Example 132: N-1,2-Benzisoxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}benzyl)piperazine-1-carboxamide.



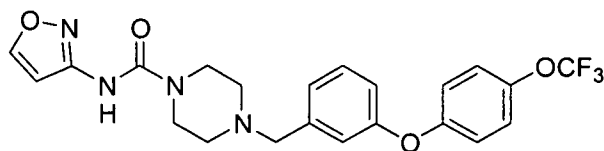
MS: 561.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.10-8.02 (m, 2H), 7.87-7.81 (m, 1H), 7.62-7.56 (m, 1H), 7.56-7.47 (m, 2H), 7.38-7.28 (m, 2H), 7.29-7.23 (m, 3H), 7.15-7.09 (m, 1H), 3.80-3.45 (m, 6H), 2.67-2.47 (m, 4H).

10 Example 133: N-1,2-Benzisoxazol-3-yl-4-{3-(phenylethynyl)phenyl}methylpiperazine-1-carboxamide.



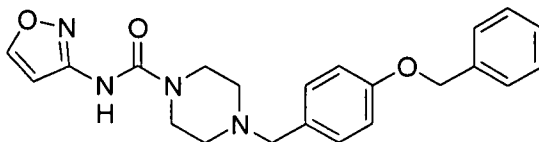
MS: 437.2. ^1H NMR (CDCl_3): 8.14-7.98 (m, 1H), 7.62-7.33 (m, 12H), 3.75-3.48 (m, 6H), 2.68-2.48 (m, 4H).

15 Example 134: N-Isoxazol-3-yl-4-{3-[4-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide.



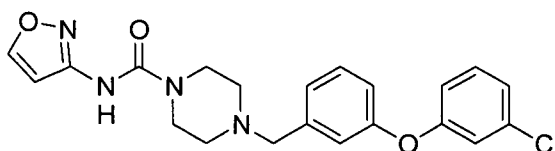
MS: 463.2. ^1H NMR ($\text{d}_6\text{-DMSO}$): 9.99-9.91 (m, 1H), 8.66-8.63 (m, 1H), 7.50-7.44 (m, 1H), 7.39-7.34 (m, 2H), 7.27-7.15 (m, 2H), 7.14-7.09 (m, 3H), 6.72-6.70 (m, 1H), 4.36-4.26 (m, 2H), 4.22-4.13 (m, 2H), 3.35-3.24 (m, 2H), 3.16-2.94 (m, 4H).

Example 135: 4-[4-(Benzyloxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide.



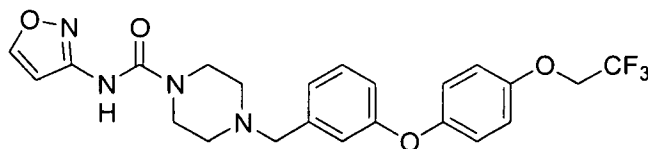
MS: 393.5. ^1H NMR (CDCl_3): 8.22 (d, $J = 1.6$, 1H), 7.85 (s, 1H), 7.48-7.32 (m, 5H), 7.25 (d, $J = 8.6$, 2H), 6.99 (d, $J = 1.8$, 1H), 6.96 (d, $J = 8.7$, 2H), 5.08 (s, 2H), 3.58-3.52 (m, 4H), 3.50 (s, 2H), 2.54-2.44 (m, 4H).

Example 136: 4-[3-(3-Chlorophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide.



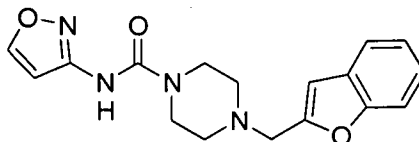
MS: 413.4. ^1H NMR (CDCl_3): 8.23 (d, $J = 1.7$, 1H), 7.81 (s, 1H), 7.34 (t, $J = 7.8$, 1H), 7.29-7.25 (m, 1H), 7.15-7.04 (m, 3H), 7.01-6.98 (m, 2H), 6.96-6.90 (m, 2H), 3.58-3.53 (m, 6H), 2.55-2.47 (m, 4H).

Example 137: N-Isloxazol-3-yl-4-{3-[4-(2,2,2-trifluoroethoxy)phenoxy]benzyl}piperazine-1-carboxamide.



MS: 477.5. ^1H NMR (CDCl_3): 8.22 (d, $J = 1.7$, 1H), 8.07 (s, 1H), 7.31-7.25 (m, 1H), 7.06 (d, $J = 7.8$, 1H), 7.03-6.98 (m, 4H), 6.95 (d, $J = 9.2$, 2H), 6.88-6.85 (dd, $J = 8.1$, 1.8, 1H), 4.39-4.33 (q, $J = 8.1$, 2H), 3.60-3.55 (m, 4H), 3.53 (s, 2H), 2.55-2.43 (m, 4H).

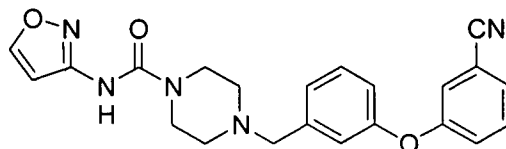
Example 138: 4-(1-Benzofuran-2-ylmethyl)-N-isoxazol-3-ylpiperazine-1-carboxamide.



MS: 327.4. ^1H NMR (CDCl_3): 8.23 (s, 1H), 8.21 (d, $J = 1.8$, 1H), 7.56 (d, $J = 7.5$, 1H), 7.51 (d, $J = 8.1$, 1H), 7.31-7.27 (m, 1H), 7.26-7.22 (dt, $J = 7.5$,

1.0, 1H), 6.99 (d, $J = 1.7$, 1H), 6.64 (s, 1H), 3.76 (s, 2H), 3.66-3.60 (m, 4H), 2.66-2.59 (m, 4H).

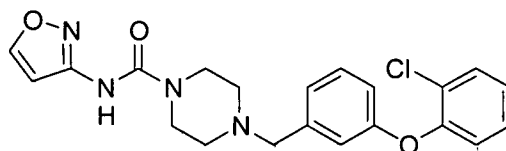
Example 139: 4-[3-(3-Cyanophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide.



5

MS: 404.5. ^1H NMR (d_6 -DMSO): 9.72 (s, 1H), 8.66 (d, $J = 1.7$, 1H), 7.62-7.57 (m, 2H), 7.51-7.49 (m, 1H), 7.42-7.38 (m, 1H), 7.36-7.33 (m, 1H), 7.17 (d, $J = 7.6$, 1H), 7.04 (s, 1H), 6.99-6.96 (m, 1H), 6.76 (d, $J = 1.7$, 1H), 3.52 (s, 2H), 3.46-3.43 (m, 4H), 2.39-2.34 (m, 4H).

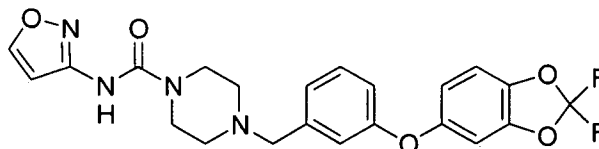
10 Example 140: 4-[3-(2-Chlorophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide.



MS: 413.4. ^1H NMR (d_6 -DMSO): 9.72 (s, 1H), 8.66 (d, $J = 1.7$, 1H), 7.63-7.58 (m, 1H), 7.40-7.32 (m, 2H), 7.25-7.21 (m, 1H), 7.13-7.07 (m, 2H), 6.92 (s, 1H), 6.85-6.82 (m, 1H), 6.76 (d, $J = 1.7$, 1H), 3.49 (s, 2H), 3.46-3.41 (m, 4H), 2.37-2.33 (m, 4H).

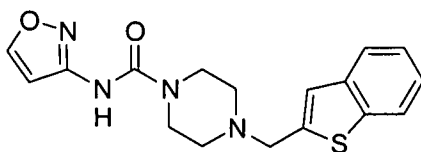
15

Example 141: 4-{3-[(2,2-Difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}-N-isoxazol-3-ylpiperazine-1-carboxamide.



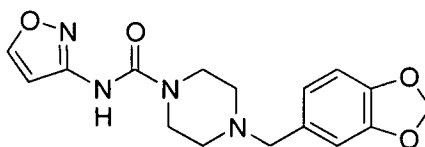
20 MS: 459.5. ^1H NMR (d_6 -DMSO): 9.72 (s, 1H), 8.66 (d, $J = 1.6$, 1H), 7.42 (d, $J = 8.8$, 1H), 7.37-7.32 (m, 1H), 7.27 (d, $J = 2.4$, 1H), 7.10 (d, $J = 7.6$, 1H), 6.98 (s, 1H), 6.91-6.88 (m, 1H), 6.87-6.83 (m, 1H), 6.76 (d, $J = 1.7$, 1H), 3.49 (s, 2H), 3.47-3.42 (m, 4H), 2.39-2.32 (m, 4H).

25 Example 142: 4-(1-Benzothiophen-2-ylmethyl)-N-isoxazol-3-ylpiperazine-1-carboxamide.



MS: 343.4. ^1H NMR (d_6 -DMSO): 9.75 (s, 1H), 8.66 (d, $J = 1.8$, 1H), 7.90 (d, $J = 7.7$, 1H), 7.76 (d, $J = 7.2$, 1H), 7.36-7.28 (m, 3H), 6.77 (d, $J = 1.8$, 1H), 3.82 (s, 2H), 3.53-3.44 (m, 4H), 2.48-2.44 (m, 4H).

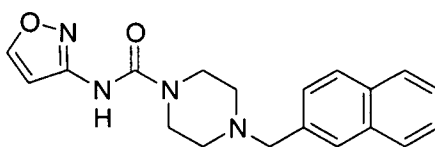
5 Example 143: 4-(1,3-Benzodioxol-5-ylmethyl)-N-isoxazol-3-ylpiperazine-1-carboxamide.



MS: 331.4. ^1H NMR (d_6 -DMSO): 9.73 (s, 1H), 8.66 (d, $J = 1.7$, 1H), 6.88-6.83 (m, 2H), 6.77-6.74 (m, 2H), 5.99 (s, 2H), 3.49-3.41 (m, 4H), 3.40 (s, 2H), 2.35-2.31 (m, 4H).

10

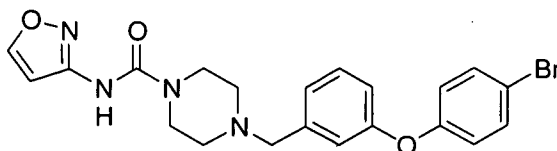
Example 144: N-Isloxazol-3-yl-4-(naphthalen-2-ylmethyl)piperazine-1-carboxamide.



MS: 337.4. ^1H NMR (d_6 -DMSO): 9.73 (s, 1H), 8.66 (d, $J = 1.7$, 1H), 7.91-7.87 (m, 3H), 7.81 (s, 1H), 7.54-7.46 (m, 3H), 6.77 (d, $J = 1.6$, 1H), 3.66 (s, 2H), 3.51-3.44 (m, 4H), 2.43-2.39 (m, 4H).

15

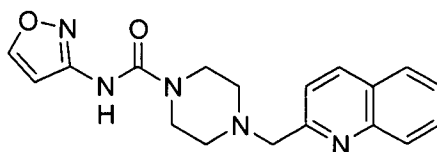
Example 145: 4-[3-(4-Bromophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide.



MS: 457.4. ^1H NMR (CDCl_3): 8.22-8.17 (m, 2H), 7.43 (d, $J = 9.0$, 2H), 7.32-7.28 (m, 1H), 7.09 (d, $J = 7.6$, 1H), 7.01 (s, 1H), 6.99 (d, $J = 1.7$, 1H), 6.91-6.87 (m, 3H), 3.58-3.51 (m, 6H), 2.52-2.46 (m, 4H).

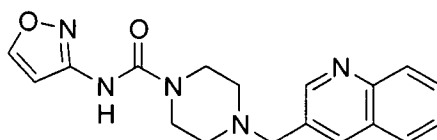
20

Example 146: 4-Quinolin-2-ylmethyl-piperazine-1-carboxylic acid isloxazol-3-ylamide.



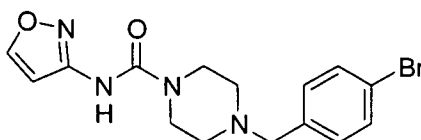
MS: 338.4. ^1H NMR (CDCl_3): 8.19 (d, $J = 1.2$, 1H), 8.15 (d, $J = 8.4$, 1H), 8.08 (d, $J = 8.4$, 1H), 7.92 (br hump, 1H), 7.82-7.81 (m, 1H), 7.73-7.70 (m, 1H), 7.63 (d, $J = 8.4$, 1H), 7.55-7.52 (m, 1H), 6.97 (d, $J = 1.2$, 1H), 3.89 (s, 2H),
 5 3.59 (t, $J = 4.8$, 4H), 2.62 (t, $J = 4.8$, 4H).

Example 147: 4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid isoxazol-3-ylamide.



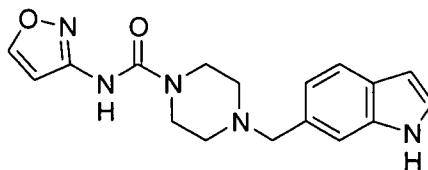
MS: 338.4. ^1H NMR (CDCl_3): 8.92 (d, $J = 2.4$, 1H), 8.21 (d, $J = 1.8$, 1H),
 10 8.11 (d, $J = 9.0$, 1H), 8.07 (d, $J = 1.2$, 1H), 7.83-7.81 (m, 1H), 7.73-7.70 (m, 1H), 7.58-7.55 (m, 1H), 7.48 (br hump, 1H), 6.96 (d, $J = 1.8$, 1H), 3.74 (s, 2H), 3.55 (t, $J = 4.8$, 4H), 2.56 (t, $J = 4.8$, 4H).

Example 148: 4-(4-Bromo-benzyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide.



MS: 363.3. ^1H NMR (CDCl_3): 8.19 (d, $J = 1.2$, 1H), 7.46-7.45 (m, 2H),
 15 7.21 (d, $J = 8.4$, 2H), 6.99 (d, $J = 1.8$, 1H), 3.57 (t, $J = 4.8$, 4H), 3.48 (s, 2H), 2.48 (t, $J = 4.8$, 4H).

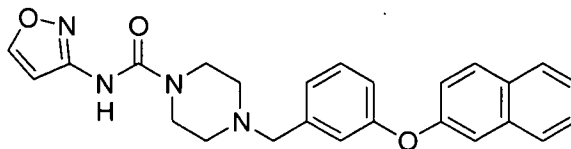
Example 149: 4-(1H-Indol-6-ylmethyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide.



MS: 326.4. ^1H NMR (CDCl_3): 8.19 (d, $J = 1.8$, 1H), 8.16 (br s, 1H),
 20 7.73 (br s, 1H), 7.56 (s, 1H), 7.36 (d, $J = 8.4$, 1H), 7.225-7.216 (m, 1H), 7.19-

7.17 (dd, $J = 1.2, 8.4$, 1H), 6.96 (d, $J = 1.8$, 1H), 6.54-6.53 (m, 1H), 3.64 (s, 2H), 3.53 (t, $J = 4.8$, 4H), 2.52 (t, $J = 4.8$, 4H).

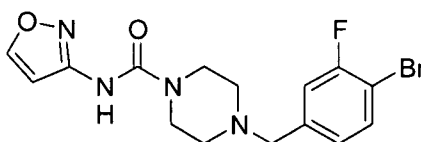
Example 150: 4-[3-(Naphthalen-2-yloxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide.



5

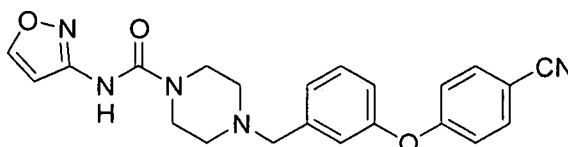
MS: 429.5. ^1H NMR (CDCl_3): 8.19 (d, $J = 1.2$, 1H), 7.88 (br hump, 1H), 7.83 (m, 2H), 7.70 (d, $J = 9.0$, 1H), 7.47-7.46 (m, 1H), 7.45-7.40 (m, 1H), 7.33-7.31 (m, 2H), 7.28-7.24 (m, 1H), 7.11-7.08 (m, 2H), 6.99-6.97 (m, 2H), 3.54-3.49 (m, 6H), 2.50 (br hump, 4H).

10 Example 151: 4-(4-Bromo-3-fluoro-benzyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide.



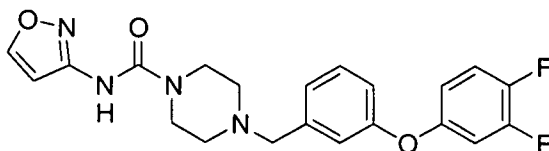
MS: 381.3. ^1H NMR (CDCl_3): 8.20 (d, $J = 1.8$, 1H), 8.13 (br s, 1H), 7.50-7.48 (dd, $J = 7.2, 7.8$, 1H), 7.17-7.15 (dd, $J = 1.8, 9.0$, 1H), 7.01-6.99 (dd, $J = 1.2, 8.4$, 1H), 6.98 (d, $J = 1.2$, 1H), 3.56 (t, $J = 4.8$, 4H), 3.49 (s, 2H), 2.49 (t, $J = 4.8$, 4H).

15 Example 152: 4-[3-(4-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide.



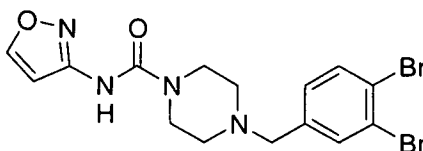
20 MS: 404.5. ^1H NMR (CDCl_3): 8.20 (d, $J = 1.2$, 1H), 8.07 (br s, 1H), 7.62-.760 (m, 2H), 7.61 (t, $J = 7.8$, 1H), 7.19 (d, $J = 7.8$, 1H), 7.08 (s, 1H), 7.01 (d, $J = 9.0$, 2H), 6.98-6.96 (m, 2H), 3.56-3.55 (m, 6H), 2.50 (t, $J = 4.8$, 4H).

Example 153: 4-[3-(3,4-Difluorophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide.



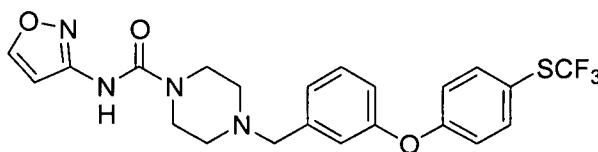
MS: 415.5. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.42 (d, $J = 1.7$, 1H), 7.35 (t, $J = 7.9$, 1H), 7.29-7.21 (m, 1H), 7.17-7.13 (m, 1H), 7.06-7.03 (m, 1H), 6.96-6.89 (m, 2H), 6.81-6.76 (m, 1H), 6.73 (d, $J = 1.7$, 1H), 3.58-3.51 (m, 6H), 2.52-2.45 (m, 4H).

Example 154: 4-(3,4-Dibromobenzyl)-N-isoxazol-3-ylpiperazine-1-carboxamide.



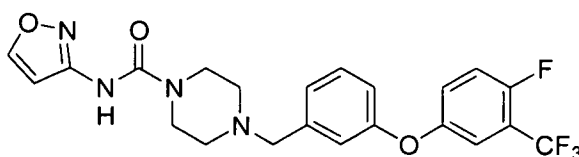
MS: 445.3. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.43 (d, $J = 1.8$, 1H), 7.71 (d, $J = 1.9$, 1H), 7.64 (d, $J = 8.2$, 1H), 7.27-7.23 (dd, $J = 8.2$, 2.0, 1H), 6.73 (d, $J = 1.8$, 1H), 3.58-3.49 (m, 6H), 2.52-2.43 (m, 4H).

Example 155: N-isoxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfanyl]phenoxy}benzyl)-piperazine-1-carboxamide.



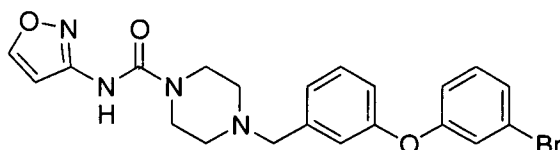
MS: 479.5. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.42 (d, $J = 1.8$, 1H), 7.68-7.63 (m, 2H), 7.39 (t, $J = 7.9$, 1H), 7.23-7.19 (m, 1H), 7.12-7.10 (m, 1H), 7.07-7.02 (m, 2H), 7.02-6.98 (m, 1H), 6.73 (d, $J = 1.8$, 1H), 3.59-3.52 (m, 6H), 2.53-2.45 (m, 4H).

Example 156: 4-{3-[4-Fluoro-3-(trifluoromethyl)phenoxy]benzyl}-N-isoxazol-3-ylpiperazine-1-carboxamide.



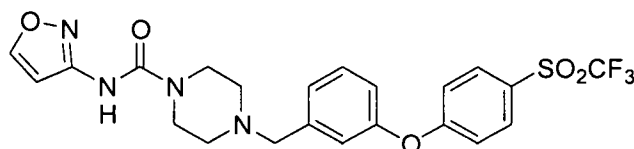
MS: 465.5. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.43 (d, $J = 1.8$, 1H), 7.41-7.24 (m, 4H), 7.20-7.16 (m, 1H), 7.09-7.06 (m, 1H), 6.98-6.94 (m, 1H), 6.73 (d, $J = 1.8$, 1H), 3.62-3.52 (m, 6H), 2.59-2.47 (m, 4H).

Example 157: 4-[3-(3-Bromophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide.



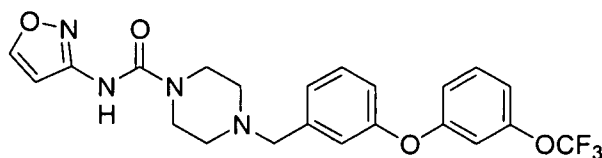
MS: 457.4. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.42 (d, $J = 1.7$, 1H), 7.36 (t, $J = 7.9$, 1H), 7.28-7.24 (m, 2H), 7.17-7.15 (m, 1H), 7.11-7.10 (m, 1H), 7.06-7.05 (m, 1H), 6.97-6.93 (m, 2H), 6.73 (d, $J = 1.7$, 1H), 3.58-3.52 (m, 6H), 2.50-2.47 (m, 4H):

Example 158: N-Isloxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}benzyl)-piperazine-1-carboxamide.



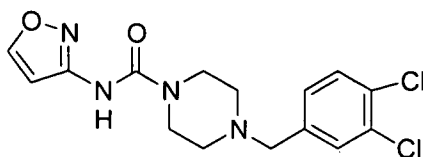
MS: 511.1. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.42 (d, $J = 1.8$, 1H), 8.05-8.01 (m, 2H), 7.49-7.44 (m, 1H), 7.33-7.29 (m, 1H), 7.26-7.22 (m, 2H), 7.21-7.19 (m, 1H), 7.10-7.07 (m, 1H), 6.73 (d, $J = 1.8$, 1H), 3.61 (s, 2H), 3.57-3.53 (m, 4H), 2.53-2.46 (m, 4H).

Example 159: N-Isloxazol-3-yl-4-{3-[3-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide.



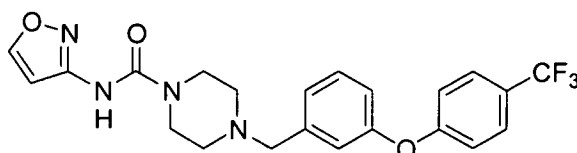
MS: 463.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.42 (d, $J = 1.8$, 1H), 7.45-7.35 (m, 2H), 7.20-7.16 (m, 1H), 7.10-7.06 (m, 1H), 7.03-6.93 (m, 3H), 6.86-6.82 (m, 1H), 6.73 (d, $J = 1.8$, 1H), 3.60-3.50 (m, 6H), 2.53-2.45 (m, 4H).

Example 160: 4-(3,4-Dichlorobenzyl)-N-isloxazol-3-ylpiperazine-1-carboxamide.



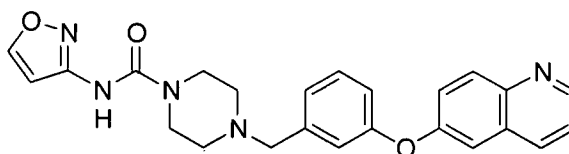
MS: 442.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.45 (d, $J = 1.6$, 1H), 7.58-7.54 (m, 1H), 7.50 (d, $J = 8.2$, 1H), 6.76-6.73 (m, 1H), 4.70-4.53 (m, 6H), 3.59-3.56 (m, 4H).

5 Example 161: N-Isloxazol-3-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide.



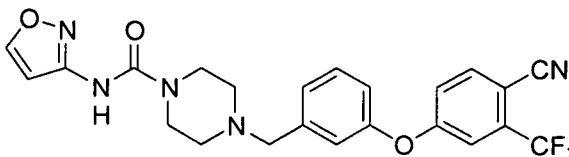
MS: 447.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.33-8.31 (dd, $J = 7.1$, 2.1, 1H), 7.65-7.58 (m, 1H), 7.57-7.51 (m, 1H), 7.50-7.45 (m, 1H), 7.44-7.39 (m, 1H), 7.35-7.28 (m, 2H), 7.26-7.21 (m, 1H), 7.15-7.10 (m, 1H), 7.03-6.97 (m, 1H), 6.55-6.44 (m, 1H), 3.76-3.66 (m, 4H), 3.65-3.60 (m, 2H), 2.68-2.45 (m, 4H).

10 Example 162: N-Isloxazol-3-yl-4-[3-(quinolin-6-yloxy)benzyl]piperazine-1-carboxamide.



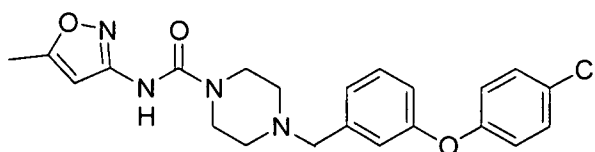
15 MS: 430.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.82-8.73 (m, 1H), 8.46-8.41 (m, 1H), 8.27-8.22 (m, 1H), 8.09-8.03 (m, 1H), 7.59-7.55 (dd, $J = 9.2$, 2.7, 1H), 7.53-7.50 (dd, $J = 8.3$, 4.3, 1H), 7.45-7.39 (m, 1H), 7.37-7.34 (m, 1H), 7.22 (d, $J = 7.6$, 1H), 7.18-7.15 (m, 1H), 7.08-7.04 (m, 1H), 6.74 (d, $J = 1.8$, 1H), 3.63-3.58 (m, 2H), 3.58-3.53 (m, 4H), 2.59-2.44 (m, 4H).

20 Example 163: 4-{3-[4-Cyano-3-(trifluoromethyl)phenoxy]benzyl}-N-isloxazol-3-ylpiperazine-1-carboxamide.



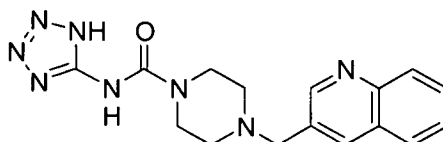
MS: 472.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.47-8.41 (m, 1H), 8.00-7.93 (m, 1H), 7.52-7.45 (m, 1H), 7.45-7.41 (m, 1H), 7.36-7.27 (m, 2H), 7.23-7.19 (m, 1H), 7.13-7.08 (m, 1H), 6.77-6.72 (m, 1H), 3.66-3.59 (m, 2H), 3.59-3.55 (m, 4H), 2.59-2.44 (m, 4H).

5 Example 164: 4-[3-(4-Chlorophenoxy)benzyl]-N-(5-methylisoxazol-3-yl)piperazine-1-carboxamide.



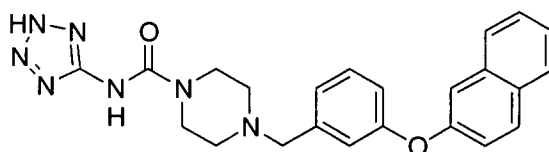
MS: 427.2. ^1H NMR ($\text{d}_6\text{-acetone}$): 9.01 (s, 1H), 7.51-7.44 (m, 1H), 7.42-7.36 (m, 3H), 7.32-7.28 (m, 1H), 7.14-7.10 (m, 1H), 7.08-7.03 (m, 2H),
10 6.52 (s, 1H), 4.48 (s, 2H), 4.22-3.69 (m, 4H), 3.49-3.29 (m, 4H), 2.34 (s, 3H).

Example 165: 4-(Quinolin-3-ylmethyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide.



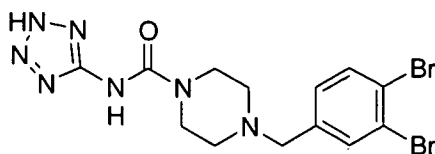
MS: 339.4. ^1H NMR ($\text{d}_6\text{-DMSO}$): 10.66 (s, 1H), 8.88 (d, $J = 2.1$, 1H),
15 8.25 (d, $J = 1.3$, 1H), 8.04-7.96 (m, 2H), 7.77-7.72 (m, 1H), 7.63-7.59 (m, 1H), 3.74 (s, 2H), 3.58-3.50 (m, 4H), 2.48-2.44 (m, 4H).

Example 166: 4-[3-(Naphthalen-2-yloxy)benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide.



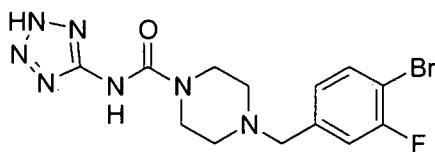
20 MS: 430.5. ^1H NMR ($\text{d}_6\text{-DMSO}$): 10.65 (s, 1H), 7.98 (d, $J = 8.9$, 1H), 7.92 (d, $J = 7.9$, 1H), 7.82 (d, $J = 8.0$, 1H), 7.52-7.39 (m, 3H), 7.38 (d, $J = 7.9$, 1H), 7.32-7.28 (dd, $J = 8.9$, 2.5, 1H), 7.13 (d, $J = 7.7$, 1H), 7.05 (s, 1H), 7.01-6.97 (dd, $J = 8.1$, 1.8, 1H), 3.52 (s, 2H), 3.51-3.47 (m, 4H), 2.41-2.37 (m, 4H).

25 Example 167: 4-(3,4-Dibromobenzyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide.



MS: 444.3. ^1H NMR (d_6 -DMSO): 10.63 (s, 1H), 7.72 (d, $J = 8.2$, 1H), 7.70 (d, $J = 1.9$, 1H), 7.29-7.26 (dd, $J = 8.2$, 1.9, 1H), 3.53-3.50 (m, 4H), 3.49 (s, 2H), 2.41-2.36 (m, 4H).

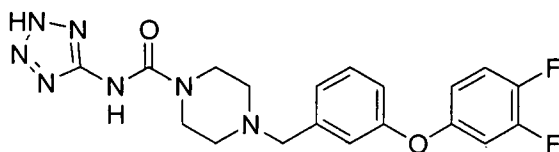
5 Example 168: 4-(4-Bromo-3-fluorobenzyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide.



MS: 384.4. ^1H NMR (d_6 -DMSO): 10.69 (s, 1H), 7.66 (t, $J = 7.8$, 1H), 7.34-7.31 (dd, $J = 9.9$, 1.6, 1H), 7.16-7.12 (dd, $J = 8.2$, 1.5, 1H), 3.56-3.48 (m, 6H), 2.42-2.37 (m, 4H).

10

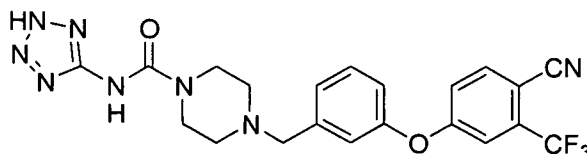
Example 169: 4-[3-(3,4-Difluorophenoxy)benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide.



MS: 416.5. ^1H NMR (d_6 -DMSO): 10.37 (s, 1H), 7.50-7.42 (dd, $J = 19.5$, 9.3, 1H), 7.37 (t, $J = 7.9$, 1H), 7.24-7.16 (m, 1H), 7.13 (d, $J = 7.6$, 1H), 7.00 (s, 1H), 6.95-6.91 (m, 1H), 6.88-6.83 (m, 1H), 3.54-3.46 (m, 6H), 2.41-2.34 (m, 4H).

15

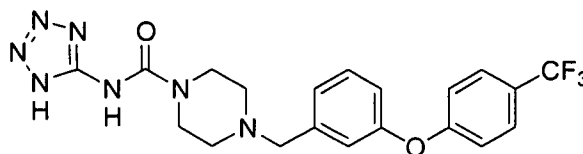
Example 170: 4-[3-[4-Cyano-3-(trifluoromethyl)phenoxy]benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide.



MS: 473.5. ^1H NMR (d_6 -DMSO): 8.14 (d, $J = 8.7$, 1H), 7.53 (s, 1H), 7.48 (t, $J = 7.8$, 1H), 7.33 (d, $J = 7.6$, 1H), 7.28 (d, $J = 7.4$, 1H), 7.17 (s, 1H), 7.13 (d, $J = 8.2$, 1H), 3.60-3.46 (m, 6H), 2.43-2.36 (m, 4H).

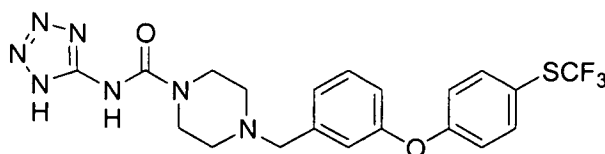
20

Example 171: N-1H-Tetrazol-5-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide.



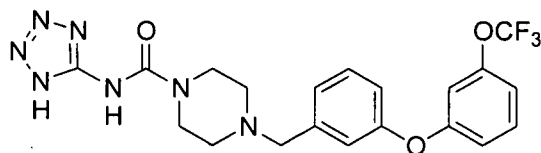
MS: 448.5. ¹H NMR (d₆-DMSO): 15.39 (s, 1H), 10.64 (s, 1H), 7.74 (d, *J* = 8.6, 2H), 7.45-7.40 (m, 1H), 7.21 (d, *J* = 7.6, 1H), 7.15 (d, *J* = 8.6, 2H), 7.10-7.08 (m, 1H), 7.05-7.02 (m, 1H), 3.56-3.48 (m, 6H), 2.43-2.35 (m, 4H).

Example 172: N-1H-Tetrazol-5-yl-4-{3-[4-(trifluoromethyl)sulfanyl]phenoxy]benzyl}-piperazine-1-carboxamide.



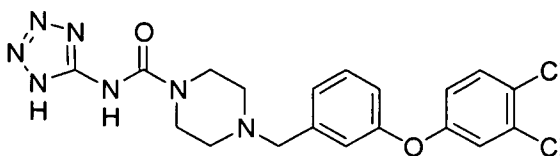
MS: 480.5. ¹H NMR (d₆-DMSO): 15.35 (s, 1H), 10.48 (s, 1H), 7.72 (d, *J* = 8.7, 2H), 7.45-7.40 (m, 1H), 7.20 (d, *J* = 7.6, 1H), 7.12-7.08 (m, 3H), 7.04-7.01 (m, 1H), 3.56-3.46 (m, 6H), 2.42-2.35 (m, 4H).

Example 173: N-1H-Tetrazol-5-yl-4-{3-[3-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide.



MS: 464.5. ¹H NMR (d₆-DMSO): 15.37 (s, 1H), 10.60 (s, 1H), 7.54-7.48 (m, 1H), 7.42-7.38 (m, 1H), 7.17 (d, *J* = 7.6, 1H), 7.13 (d, *J* = 8.3, 1H), 7.06-6.97 (m, 4H), 3.55-3.46 (m, 6H), 2.40-2.36 (m, 4H).

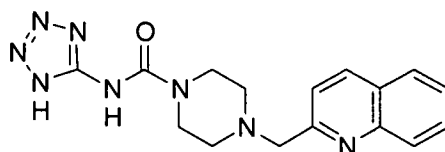
Example 174: 4-[3-(3,4-Dichlorophenoxy)benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide.



MS: 448.4. ^1H NMR (d_6 -DMSO): 15.44 (s, 1H), 10.77 (s, 1H), 7.64 (d, $J = 8.9$, 1H), 7.46-7.39 (m, 1H), 7.31 (s, 1H), 7.22-7.17 (m, 1H), 7.12-6.99 (m, 3H), 3.73-3.36 (m, 6H), 2.47-2.25 (m, 4H).

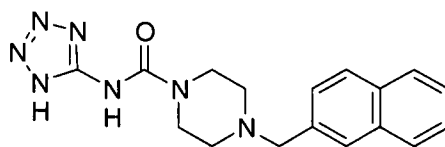
Example 175: 4-(Quinolin-2-ylmethyl)-N-1H-tetrazol-5-ylpiperazine-1-

5 carboxamide.



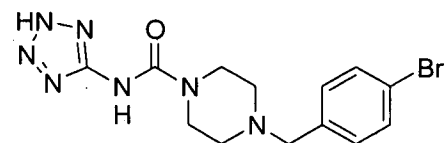
MS: 339.4. ^1H NMR (d_6 -DMSO): 15.40 (s, 1H), 10.72 (s, 1H), 8.35 (d, $J = 8.5$, 1H), 8.00-7.95 (m, 2H), 7.77-7.72 (m, 1H), 7.67 (d, $J = 8.5$, 1H), 7.61-7.57 (m, 1H), 3.82 (s, 2H), 3.60-3.52 (m, 4H), 2.50-2.46 (m, 4H).

10 Example 176: 4-(Naphthalen-2-ylmethyl)-N-1H-tetrazol-5-ylpiperazine-1-
carboxamide.



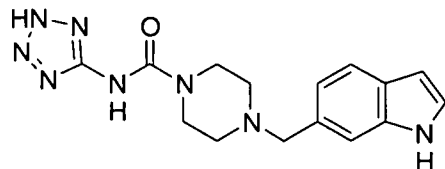
MS: 338.4. ^1H NMR (d_6 -DMSO): 10.57 (s, 1H), 7.93-7.87 (m, 3H), 7.81 (s, 1H), 7.53-7.46 (m, 3H), 3.67 (s, 2H), 3.57-3.50 (m, 4H), 2.46-2.39 (m, 4H).

15 Example 177: 4-(4-Bromo-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-
yl)-amide.



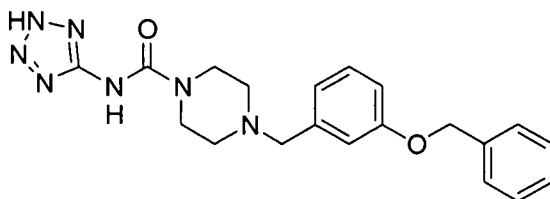
MS: 366.3. ^1H NMR (d_6 -DMSO): 7.52 (d, $J = 8.4$, 2H), 7.28 (d, $J = 8.4$, 2H), 3.51 (t, $J = 4.8$, 4H), 3.48 (s, 2H), 2.37 (t, $J = 4.8$, 4).

20 Example 178: 4-(1H-Indol-6-ylmethyl)-piperazine-1-carboxylic acid (2H-
tetrazol-5-yl)-amide.



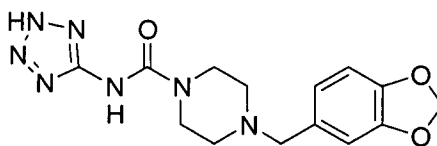
MS: 327.4. ^1H NMR (d_6 -DMSO): 11.02 (s, 1H), 10.59 (br s, 1H), 7.44 (s, 1H), 7.34-7.30 (m, 2H), 7.05 (d, $J = 8.4$, 1H), 6.38 (s, 1H), 3.56 (s, 2H), 3.50 (br s, 4H), 2.39 (br t, $J = 5.4$, 4H).

Example 179: 4-(3-Benzyloxy-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide.



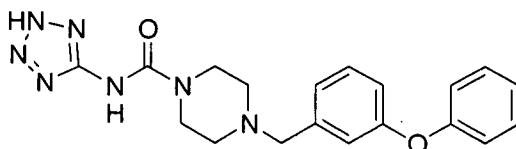
MS: 394.5. ^1H NMR (d_6 -DMSO): 15.35 (br s, 1H), 10.65 (s, 1H), 7.45 (d, $J = 7.8$, 2H), 7.39 (t, $J = 7.8$, 2H), 7.32 (t, $J = 7.2$, 1H), 7.24 (t, $J = 7.8$, 1H), 6.96 (m, 1H), 6.92-6.88 (m, 2H), 5.10 (s, 2H), 3.50-3.48 (m, 6H), 3.33 (s, 2H), 2.36 (t, $J = 4.8$, 4H).

Example 180: 4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide.



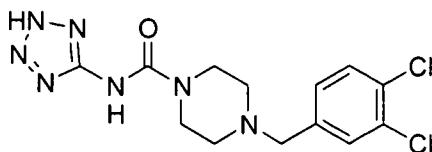
MS: 332.4. ^1H NMR (d_6 -DMSO): 15.34 (br s, 1H), 10.66 (s, 1H), 6.87 (s, 1H), 6.85 (d, $J = 7.8$, 1H), 6.75 (d, $J = 7.2$, 1H), 5.99 (s, 2H), 3.50 (br s, 4H), 3.41 (s, 2H), 2.36 (t, $J = 4.8$, 4H).

Example 181: 4-(3-Phenoxy-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide.



MS: 380.5. ^1H NMR (d_6 -DMSO): 10.23 (br s, 1H), 7.39 (t, $J = 7.8$, 2H), 7.34 (t, $J = 7.8$, 1H), 7.14 (t, $J = 7.2$, 1H), 7.08 (d, $J = 7.2$, 1H), 7.01 (d, $J = 7.8$, 2H), 6.98 (s, 1H), 6.90-6.88 (m, 1H), 3.50-3.48 (m, 6H), 2.37 (br s, 4H).

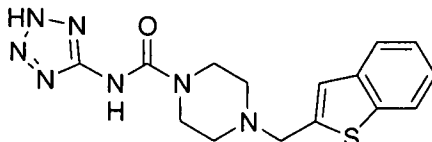
Example 182: 4-(3,4-Dichloro-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide.



^1H NMR (d_6 -DMSO): 10.56 (br s, 1H), 7.60-7.57 (m, 2H), 7.33-7.32 (dd, $J = 1.8, 8.4, 1\text{H}$), 3.52-3.51 (m, 6H), 2.39 (t, $J = 4.8, 4\text{H}$).

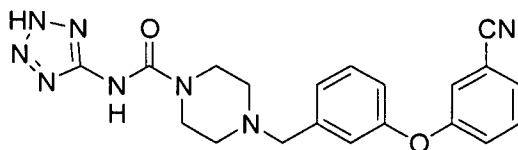
Example 183: 4-Benzo[b]thiophen-2-ylmethyl-piperazine-1-carboxylic acid

5 (2H-tetrazol-5-yl)-amide.



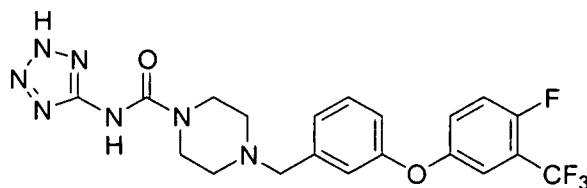
MS: 344.4. ^1H NMR (d_6 -DMSO): 15.22 (br s, 1H), 10.67 (br s, 1H), 7.89 (d, $J = 7.8, 1\text{H}$), 7.76 (d, $J = 7.2, 1\text{H}$), 7.35-7.29 (m, 3H), 3.83 (s, 2H), 3.54 (t, $J = 4.8, 4\text{H}$), 2.52-2.48 (m, 4H).

10 Example 184: 4-[3-(3-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid
(2H-tetrazol-5-yl)-amide.



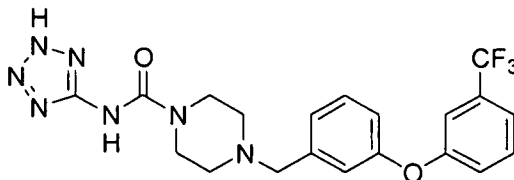
MS: 405.5. ^1H NMR (d_6 -DMSO): 15.38 (br s, 1H), 10.67 (s, 1H), 7.61-7.57 (m, 2H), 7.49 (t, $J = 1.2, 1\text{H}$), 7.40 (t, $J = 7.8, 1\text{H}$), 7.35-7.33 (m, 1H), 7.17 (d, $J = 7.8, 1\text{H}$), 7.04 (br s, 1H), 6.98-6.97 (dd, $J = 1.8, 8.4, 1\text{H}$), 3.53 (s, 2H), 3.51 (br t, $J = 4.2, 4\text{H}$), 2.39 (t, $J = 4.8, 4\text{H}$).

Example 185: 4-{3-[4-Fluoro-3-(trifluoromethyl)phenoxy]benzyl}-N-2H-tetrazol-5-ylpiperazine-1-carboxamide.



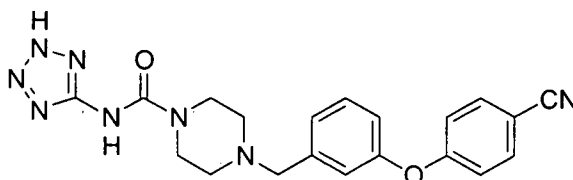
20 MS: 466.2. ^1H NMR (d_6 -DMSO): 10.45-9.75 (m, 1H), 7.50-7.24 (m, 1H), 7.22-7.14 (m, 3H), 6.98-6.92 (m, 1H), 6.85-6.82 (m, 1H), 6.79-6.73 (m, 1H), 3.37-3.21 (m, 6H), 2.23-2.09 (m, 4H).

Example 186: N-2H-Tetrazol-5-yl-4-{3-[3-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide.



MS: 448.2. ¹H NMR (d₆-DMSO): 10.84-10.43 (m, 1H), 7.66-7.59 (m, 1H), 7.52-7.47 (m, 1H), 7.43-7.38 (m, 1H), 7.34-7.27 (m, 2H), 7.20-7.15 (m, 1H), 7.08-7.04 (m, 1H), 7.02-6.98 (m, 1H), 3.58-3.45 (m, 6H), 2.45-2.30 (m, 4H).

Example 187: 4-[3-(4-Cyanophenoxy)benzyl]-N-2H-tetrazol-5-ylpiperazine-1-carboxamide.

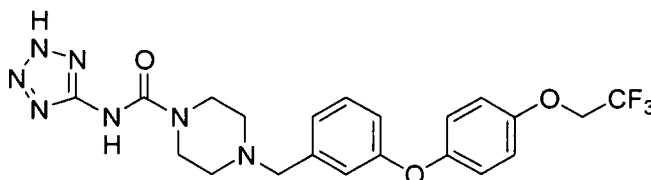


10

MS: 405.2. ¹H NMR (d₆-DMSO): 10.84-10.41 (m, 1H), 7.95-7.67 (m, 2H), 7.48-7.38 (m, 2H), 7.26-7.19 (m, 1H), 7.13-7.08 (m, 2H), 7.07-7.03 (m, 1H), 3.62-3.41 (m, 6H), 2.43-2.31 (m, 4H).

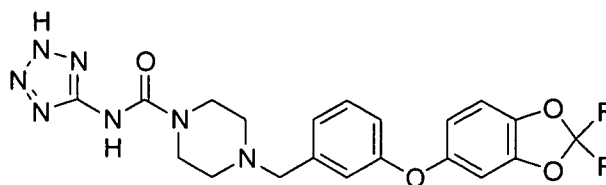
Example 188: N-2H-Tetrazol-5-yl-4-{3-[4-(2,2,2-trifluoroethoxy)phenoxy]benzyl}-piperazine-1-carboxamide.

15



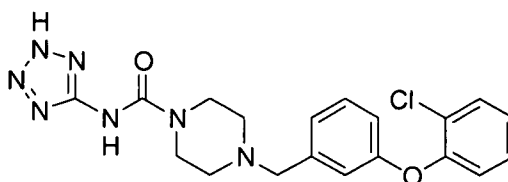
MS: 478.2. ¹H NMR (d₆-DMSO): 10.76-10.52 (m, 1H), 7.35-7.28 (m, 1H), 7.13-7.07 (m, 2H), 7.07-7.01 (m, 3H), 6.94-6.90 (m, 1H), 6.85-6.80 (m, 1H), 4.76-4.74 (q, *J* = 8.9, 2H), 3.58-3.41 (m, 6H), 2.44-2.25 (m, 4H).

20 Example 189: 4-{3-[(2,2-Difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}-N-2H-tetrazol-5-ylpiperazine-1-carboxamide.



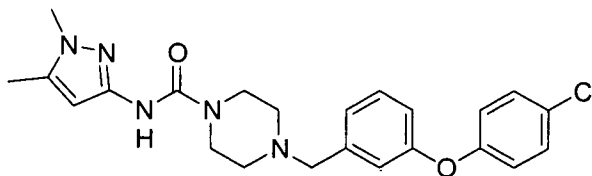
MS: 460.2. ^1H NMR (d_6 -DMSO): 10.84-10.18 (m, 1H), 7.42 (d, $J = 8.8$, 1H), 7.37-7.32 (m, 1H), 7.26 (d, $J = 2.4$, 1H), 7.13-7.08 (m, 1H), 7.01-6.96 (m, 1H), 6.92-6.87 (m, 1H), 6.87-6.83 (dd, $J = 8.8$, 2.4, 1H), 3.60-3.43 (m, 6H),
 5 2.44-2.30 (m, 4H).

Example 190: 4-[3-(2-Chlorophenoxy)benzyl]-N-2H-tetrazol-5-ylpiperazine-1-carboxamide.



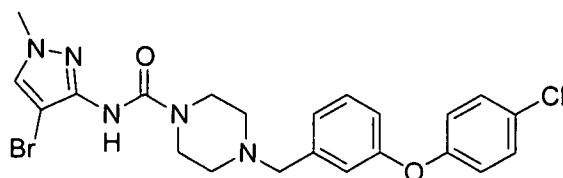
MS: 414.2. ^1H NMR (d_6 -DMSO): 10.87-10.51 (m, 1H), 7.62-7.59 (dd, $J = 8.0$, 1.6, 1H), 7.41-7.30 (m, 2H), 7.25-7.21 (dt, $J = 7.7$, 1.5, 1H), 7.13-7.07 (m, 2H), 6.95-6.91 (m, 1H), 6.86-6.82 (m, 1H), 3.54-3.48 (m, 6H), 2.44-2.30 (m, 4H).
 10

Example 191: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1,5-dimethyl-1H-pyrazol-3-yl)-amide trifluoroacetic acid salt.



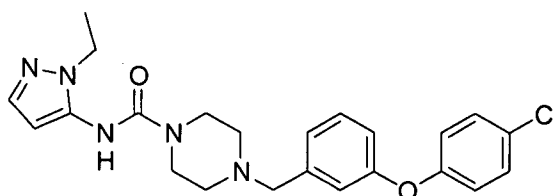
MS: 440.2. ^1H NMR (d_6 -acetone): 10.03 (s, 1H), 7.49, (t, $J = 7.8$, 1H), 7.41-7.38 (m, 3H), 7.31 (t, $J = 1.8$, 1H), 7.14-7.12 (m, 1H), 7.08-7.05 (m, 2H), 6.46 (d, $J = 2.4$, 1H), 4.50 (s, 2H), 3.80 (d, $J = 1.8$, 3H), 4.55-3.05 (br hump, 8H), 2.36 (s, 3H).
 15

20 Example 192: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (4-bromo-1-methyl-1H-pyrazol-3-yl)-amide trifluoroacetic acid salt.



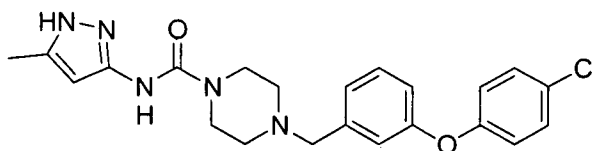
MS: 504.1. ¹H NMR (d₆-acetone): 7.66 (s, 1H), 7.50 (t, *J* = 7.8, 1H), 7.41-7.39 (m, 3H), 7.31 (t, *J* = 2.4, 1H), 7.15-7.13 (dd, *J* = 2.4, 7.8, 1H), 7.08-7.06 (m, 2H), 4.52 (s, 2H), 4.33 (br hump, 2H), 3.79 (s, 3H), 3.52 (br hump, 6H).

Example 193: 4-[3-(4-Chlorophenoxy)-benzyl]-piperazine-1-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide trifluoroacetic acid salt.



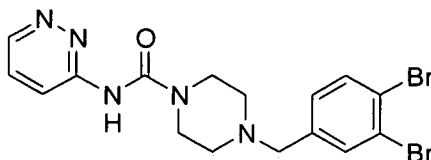
MS: 440.2. ¹H NMR (d₆-acetone): 7.51-7.48 (m, 2H), 7.41-7.39 (m, 3H), 7.30 (t, *J* = 2.4, 1H), 7.15-7.13 (m, 1H), 7.08-7.06 (m, 2H), 4.53 (s, 2H), 4.30 (br hump, 2H), 4.09-4.05 (m, 2H), 3.51 (br hump, 6H), 1.34 (t, *J* = 7.2, 3H).

Example 194: 4-[3-(4-Chlorophenoxy)benzyl]-N-(5-methyl-1H-pyrazol-3-yl)piperazine-1-carboxamide.



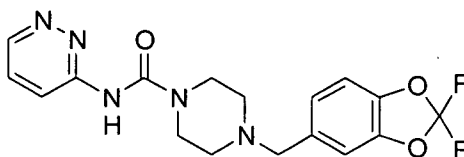
MS: 426.2. ¹H NMR (d₆-acetone): 7.51-7.38 (m, 5H), 7.35-7.31 (m, 1H), 7.15-7.11 (m, 1H), 7.09-7.06 (m, 2H), 4.48 (s, 2H), 4.24-3.66 (m, 4H), 3.50-3.35 (m, 4H), 2.32 (s, 3H).

Example 195: 4-(3,4-Dibromobenzyl)-N-pyridazin-3-ylpiperazine-1-carboxamide.



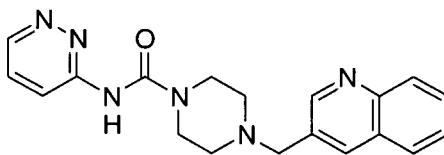
MS: 454.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.81-8.76 (m, 1H), 8.11 (d, $J = 9.0$, 1H), 7.71 (d, $J = 1.9$, 1H), 7.64 (d, $J = 8.2$, 1H), 7.60-7.57 (m, 1H), 7.27-7.24 (dd, $J = 8.2$, 1.9, 1H), 3.63-3.59 (m, 4H), 3.53 (s, 2H), 2.54-2.47 (m, 4H).

Example 196: 4-[(2,2-Difluoro-1,3-benzodioxol-5-yl)methyl]-N-pyridazin-3-ylpiperazine-1-carboxamide.



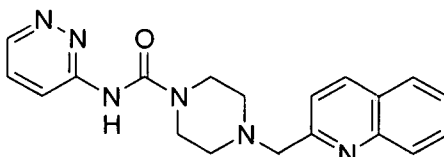
MS: 378.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.81-8.76 (m, 1H), 8.11 (d, $J = 8.8$, 1H), 7.60-7.57 (dd, $J = 9.1$, 4.7, 1H), 7.27-7.24 (m, 1H), 7.15-7.13 (m, 2H), 3.63-3.59 (m, 4H), 3.58 (s, 2H), 2.53-2.49 (m, 4H).

Example 197: N-Pyridazin-3-yl-4-(quinolin-3-ylmethyl)piperazine-1-carboxamide.



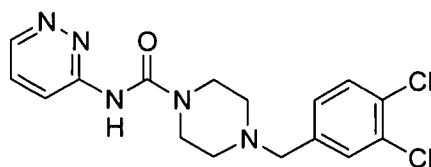
MS: 349.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.90-8.87 (m, 1H), 8.80-8.77 (m, 1H), 8.31-8.29 (m, 1H), 8.13-8.09 (m, 1H), 8.04 (d, $J = 8.5$, 1H), 7.95 (d, $J = 8.1$, 1H), 7.79-7.75 (m, 1H), 7.65-7.61 (m, 1H), 7.60-7.57 (m, 1H), 3.81 (s, 2H), 3.66-3.62 (m, 4H), 2.62-2.57 (m, 4H).

Example 198: N-Pyridazin-3-yl-4-(quinolin-2-ylmethyl)piperazine-1-carboxamide.



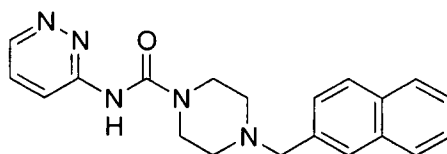
MS: 349.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 8.81-8.77 (m, 1H), 8.34 (d, $J = 8.5$, 1H), 8.12 (d, $J = 9.1$, 1H), 8.03 (d, $J = 8.5$, 1H), 7.94-7.91 (m, 1H), 7.78-7.73 (m, 2H), 7.61-7.56 (m, 2H), 3.89 (s, 2H), 3.67-3.62 (m, 4H), 2.66-2.59 (m, 4H).

Example 199: 4-(3,4-Dichlorobenzyl)-N-pyridazin-3-ylpiperazine-1-carboxamide.



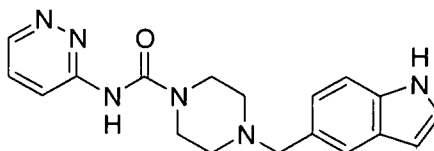
MS: 366.1. ¹H NMR (d₄-MeOH): 8.82-8.76 (m, 1H), 8.15-8.07 (m, 1H),
 7.61-7.58 (dd, *J* = 9.1, 4.7, 1H), 7.56 (d, *J* = 1.9, 1H), 7.48 (d, *J* = 8.2, 1H),
 7.32-7.28 (dd, *J* = 8.2, 2.0, 1H), 3.64-3.59 (m, 4H), 3.55 (s, 2H), 2.56-2.47 (m,
 5 4H).

Example 200: 4-(Naphthalen-2-ylmethyl)-N-pyridazin-3-ylpiperazine-1-
carboxamide.



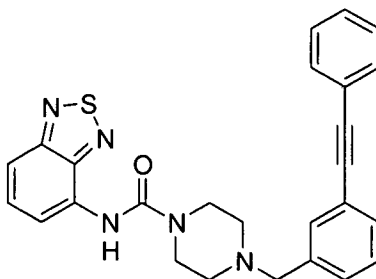
MS: 348.4. ¹H NMR (d₄-MeOH): 8.80-8.76 (m, 1H), 8.10 (d, *J* = 9.0,
 10 1H), 7.87-7.81 (m, 3H), 7.80-7.78 (m, 1H), 7.61-7.57 (dd, *J* = 9.1, 4.7, 1H),
 7.55-7.52 (dd, *J* = 8.5, 1.6, 1H), 7.50-7.43 (m, 2H), 3.74 (s, 2H), 3.65-3.59 (m,
 4H), 2.61-2.53 (m, 4H).

Example 201: 4-(1H-Indol-5-ylmethyl)-N-pyridazin-3-ylpiperazine-1-
carboxamide.



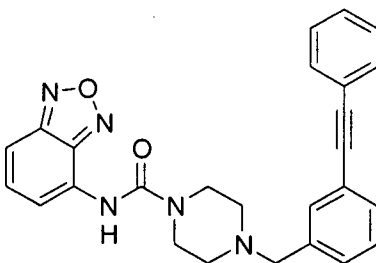
MS: 337.2. ¹H NMR (d₄-MeOH): 8.80-8.75 (m, 1H), 8.10 (d, *J* = 9.1,
 15 1H), 7.60-7.55 (m, 1H), 7.52-7.50 (m, 1H), 7.37-7.34 (m, 1H), 7.23-7.20 (m,
 1H), 7.13-7.10 (m, 1H), 6.43-6.40 (m, 1H), 3.65 (s, 2H), 3.62-3.58 (m, 4H),
 2.58-2.52 (m, 4H).

20 Example 202: N-2,1,3-Benzothiadiazol-4-yl-4-([3-
(phenylethynyl)phenyl]methyl)-piperazine-1-carboxamide.



MS: 454.2. ^1H NMR (CDCl_3): 8.28-8.22 (m, 1H), 7.88 (s, 1H), 7.59-7.56 (m, 2H), 7.55-7.51 (m, 3H), 7.47-7.44 (m, 1H), 7.38-7.30 (m, 5H), 3.67-3.62 (m, 4H), 3.57 (s, 2H), 2.61-2.52 (m, 4H).

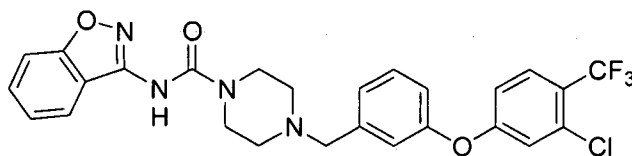
- 5 Example 203: N-2,1,3-Benzoxadiazol-4-yl-4-([3-(phenylethynyl)phenyl]methyl)-piperazine-1-carboxamide.



MS: 438.2. ^1H NMR (CDCl_3): 8.07-8.01 (m, 1H), 7.60-7.51 (m, 3H), 7.50-7.45 (m, 1H), 7.44-7.31 (m, 7H), 3.72-3.51 (m, 6H), 2.66-2.46 (m, 4H).

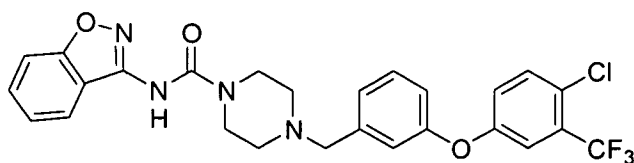
- 10 The compounds in Examples 204-209 were prepared using methods analogous to those described in Example 28.

Example 204: 4-[3-(3-Chloro-4-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.



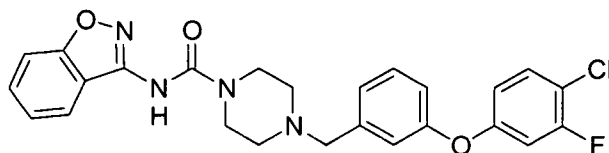
- 15 ^1H NMR (CDCl_3): 9.68 (s, 1H), 7.92 (d, $J = 8.0$, 1H), 7.51 (t, $J = 7.0$, 1H), 7.42 (t, $J = 8.0$, 1H), 7.36 (d, $J = 8.5$, 1H), 7.27-7.22 (m, 2H), 7.12-7.10 (m, 2H), 7.05 (d, $J = 2.5$, 1H), 6.90-6.88 (dd, $J = 2.5, 8.5$, 1H), 4.18 (s, 2H), 3.93 (br hump, 4H), 3.22 (br hump, 4H).

- 20 Example 205: 4-[3-(4-Chloro-3-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide trifluoroacetic acid salt.



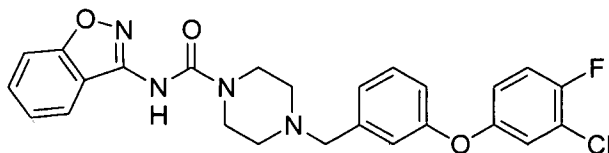
^1H NMR (CDCl_3): 9.62 (s, 1H), 7.94 (d, $J = 8.5$, 1H), 7.54-7.51 (m, 1H), 7.44 (d, $J = 8.5$, 1H), 7.41-7.37 (m, 2H), 7.30-7.26 (m, 2H), 7.17 (d, $J = 7.5$, 1H), 7.08-7.04 (m, 3H), 4.18 (s, 2H), 3.93 (br hump, 4H), 3.21 (br hump, 4H).

5 Example 206: 4-[3-(4-Chloro-3-fluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.



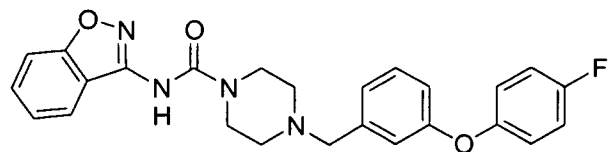
^1H NMR (CDCl_3): 8.24 (s, 1H), 8.08 (d, $J = 8.5$, 1H), 7.55-7.52 (m, 1H), 7.45 (d, $J = 8.5$, 1H), 7.36-7.29 (m, 3H), 7.16 (d, $J = 7.5$, 1H), 7.07 (s, 1H), 6.96-6.94 (dd, $J = 2.0, 7.5$, 1H), 6.82-6.79 (dd, $J = 2.5, 10.0$, 1H), 6.77-6.75 (m, 1H), 3.66 (t, $J = 5.0$, 4H), 3.57 (s, 2H), 2.56 (t, $J = 5.0$, 4H).

10 Example 207: 4-[3-(3-Chloro-4-fluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.



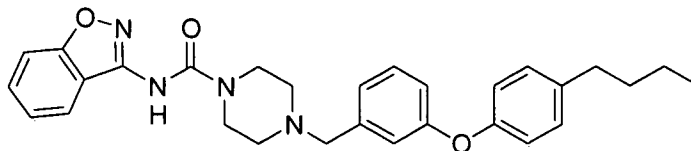
15 ^1H NMR (CDCl_3): 8.67 (s, 1H), 8.08 (d, $J = 8.0$, 1H), 7.55-7.52 (m, 1H), 7.44 (d, $J = 8.0$, 1H), 7.32-7.28 (m, 2H), 7.08-7.04 (m, 4H), 6.92-6.88 (m, 2H), 3.67 (t, $J = 4.5$, 4H), 3.56 (s, 2H), 2.56 (t, $J = 5.0$, 4H).

Example 208: 4-[3-(4-Fluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.



20 ^1H NMR (CDCl_3): 8.69 (s, 1H), 8.08 (d, $J = 8.0$, 1H), 7.55-7.51 (m, 1H), 7.44 (d, $J = 8.5$, 1H), 7.31-7.27 (m, 2H), 7.04-6.98 (m, 6H), 6.89-6.87 (dd, $J = 2.0, 8.0$, 1H), 3.68 (br s, 4H), 3.55 (s, 2H), 2.55 (br s, 4H).

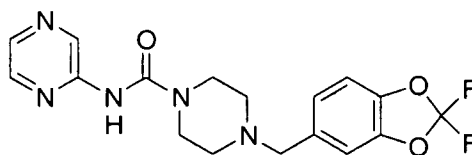
Example 209: 4-[3-(4-Butyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide.



¹H NMR (CDCl₃): 8.53 (br s, 1H), 8.08 (d, *J* = 8.0, 1H), 7.54-7.51 (m, 1H), 7.45 (d, *J* = 8.5, 1H), 7.29 (d, *J* = 8.0, 1H), 7.15 (d, *J* = 8.5, 2H), 7.07 (br d, *J* = 7.0, 1H), 7.04 (br s, 1H), 6.96-6.93 (m, 2H), 6.91-6.89 (dd, *J* = 2.0, 8.0, 1H), 3.68 (br s, 4H), 3.56 (s, 2H), 2.61 (t, *J* = 7.5, 2H), 2.56 (br s, 4H), 1.64-1.58 (m, 2H), 1.42-1.34 (m, 2H), 0.95 (t, *J* = 7.5, 3H).

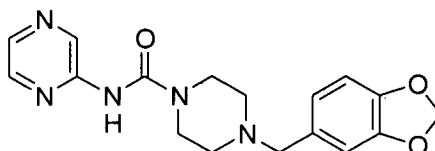
The compounds in Examples 210-244 were prepared using methods analogous to those described in Example 58.

Example 210: 4-[(2,2-Difluoro-1,3-benzodioxol-5-yl)methyl]-N-pyrazin-2-ylpiperazine-1-carboxamide.



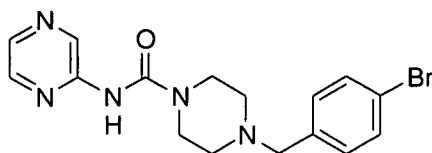
MS: 378.4. ¹H NMR (CDCl₃): 9.38 (d, *J* = 1.5, 1H), 8.26 (d, *J* = 2.6, 1H), 8.17-8.16 (dd, *J* = 2.6, 1.6, 1H), 7.14 (s, 1H), 7.11 (s, 1H), 7.03-7.01 (m, 2H), 3.60-3.55 (m, 4H), 3.54 (s, 2H), 2.55-2.47 (m, 4H).

Example 211: 4-(1,3-Benzodioxol-5-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide.



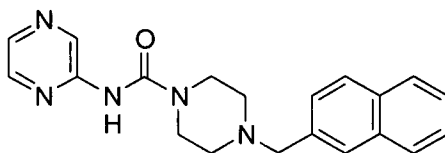
MS: 342.4. ¹H NMR (CDCl₃): 9.38 (d, *J* = 1.5, 1H), 8.26 (d, *J* = 2.6, 1H), 8.17-8.15 (dd, *J* = 2.6, 1.6, 1H), 7.10 (s, 1H), 6.88 (d, *J* = 0.9, 1H), 6.80-6.74 (m, 2H), 5.97 (s, 2H), 3.59-3.53 (m, 4H), 3.47 (s, 2H), 2.53-2.48 (m, 4H).

Example 212: 4-(4-Bromobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide.



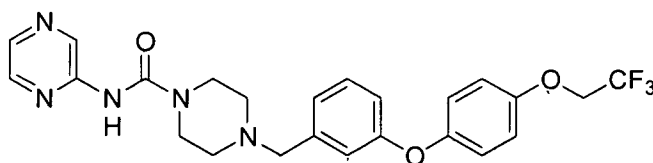
MS: 376.4. ^1H NMR (CDCl_3): 9.38 (d, $J = 1.5$, 1H), 8.26 (d, $J = 2.6$, 1H), 8.17-8.16 (dd, $J = 2.6$, 1.6, 1H), 7.48 (d, $J = 8.4$, 2H), 7.23 (d, $J = 8.4$, 2H), 7.10 (s, 1H), 3.61-3.53 (m, 4H), 3.51 (s, 2H), 2.54-2.47 (m, 4H).

5 Example 213: 4-(Naphthalen-2-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide.



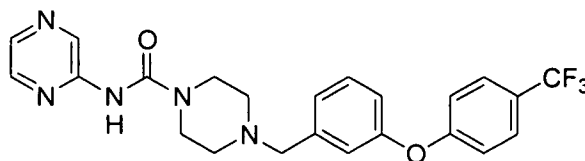
MS: 348.5. ^1H NMR (CDCl_3): 9.38 (d, $J = 1.4$, 1H), 8.26 (d, $J = 2.6$, 1H), 8.17-8.15 (dd, $J = 2.6$, 1.6, 1H), 7.88-7.82 (m, 3H), 7.76 (s, 1H), 7.55-7.46 (m, 3H), 7.07 (s, 1H), 3.73 (s, 2H), 3.62-3.55 (m, 4H), 2.61-2.53 (m, 4H).

10 Example 214: N-Pyrazin-2-yl-4-{3-[4-(2,2,2-trifluoroethoxy)phenoxy]benzyl}-piperazine-1-carboxamide.



MS: 488.5. ^1H NMR (CDCl_3): 9.38 (d, $J = 1.4$, 1H), 8.26 (d, $J = 2.6$, 1H), 8.18-8.16 (dd, $J = 2.6$, 1.6, 1H), 7.31-7.26 (m, 1H), 7.09-6.93 (m, 7H), 6.88-6.85 (dd, $J = 8.0$, 2.1, 1H), 4.40-4.33 (q, $J = 8.1$, 2H), 3.60-3.51 (m, 6H), 2.57-2.47 (m, 4H).

15 Example 215: N-Pyrazin-2-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide.

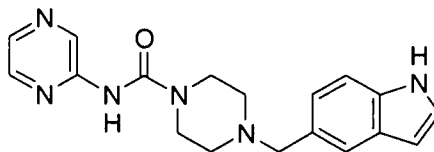


MS: 458.5. ^1H NMR (CDCl_3): 9.38 (d, $J = 1.5$, 1H), 8.26 (d, $J = 2.6$, 1H), 8.18-8.15 (dd, $J = 2.6$, 1.6, 1H), 7.60 (d, $J = 8.9$, 2H), 7.37 (t, $J = 7.8$, 1H),

7.17 (d, $J = 7.6$, 1H), 7.11-7.04 (m, 4H), 7.00-6.96 (dd, $J = 8.0$, 1.7, 1H), 3.61-3.52 (m, 6H), 2.56-2.50 (m, 4H).

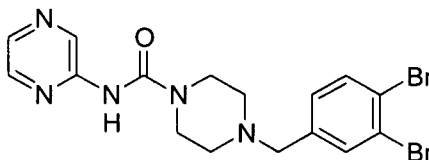
Example 216: 4-(1H-Indol-5-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide.

5



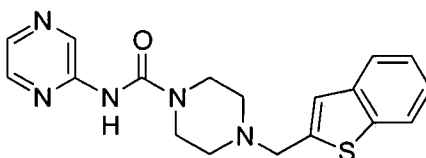
MS: 337.5. ^1H NMR (CDCl_3): 9.38 (d, $J = 1.5$, 1H), 8.25 (d, $J = 2.6$, 1H), 8.19 (s, 1H), 8.17-8.15 (dd, $J = 2.6$, 1.6, 1H), 7.59 (s, 1H), 7.39 (d, $J = 8.3$, 1H), 7.26-7.23 (m, 1H), 7.22-7.19 (dd, $J = 8.3$, 1.5, 1H), 7.06 (s, 1H), 6.57-6.54 (m, 1H), 3.67 (s, 2H), 3.61-3.51 (m, 4H), 2.61-2.47 (m, 4H).

10 Example 217: 4-(3,4-Dibromobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide.



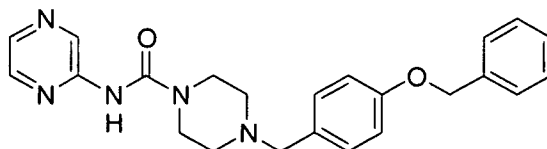
MS: 453.3. ^1H NMR (CDCl_3): 9.35 (d, $J = 1.5$, 1H), 8.24 (d, $J = 2.6$, 1H), 8.15-8.13 (m, 1H), 7.62 (d, $J = 2.0$, 1H), 7.57 (d, $J = 8.2$, 1H), 7.16-7.10 (m, 2H), 3.59-3.53 (m, 4H), 3.47 (s, 2H), 2.53-2.46 (m, 4H).

15 Example 218: 4-(1-Benzothiophen-2-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide.



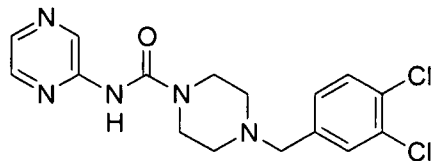
MS: 354.4. ^1H NMR (CDCl_3): 9.36 (d, $J = 1.5$, 1H), 8.23 (d, $J = 2.6$, 1H), 8.14-8.12 (m, 1H), 7.82-7.77 (m, 1H), 7.71-7.68 (m, 1H), 7.36-7.26 (m, 2H), 7.17-7.12 (m, 2H), 3.84 (br s, 2H), 3.62-3.54 (m, 4H), 2.64-2.56 (m, 4H).

Example 219: 4-[4-(Benzyloxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide.



MS: 404.5. ^1H NMR (CDCl_3): 9.36 (d, $J = 1.5$, 1H), 8.23 (d, $J = 2.6$, 1H), 8.14-8.12 (m, 1H), 7.46-7.14 (m, 8H), 6.94 (d, $J = 8.7$, 1H), 5.06 (s, 2H), 3.58-3.51 (m, 4H), 3.48 (s, 2H), 2.52-2.43 (m, 4H).

Example 220: 4-(3,4-Dichlorobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide.

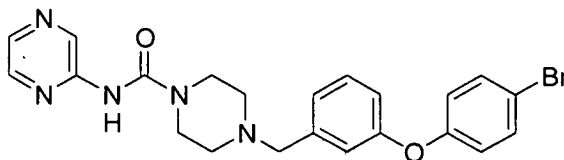


5

MS: 366.4. ^1H NMR (CDCl_3): 9.35 (d, $J = 1.5$, 1H), 8.24 (d, $J = 2.6$, 1H), 8.15-8.13 (m, 1H), 7.45 (d, $J = 2.0$, 1H), 7.40 (d, $J = 8.2$, 1H), 7.19-7.15 (m, 1H), 7.12 (s, 1H), 3.60-3.52 (m, 4H), 3.49 (s, 2H), 2.52-2.47 (m, 4H).

Example 221: 4-[3-(4-Bromophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-

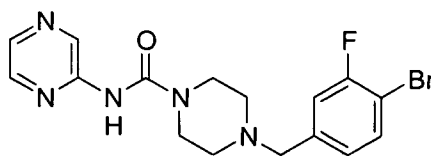
10 carboxamide.



15

MS: 469.5. ^1H NMR ($\text{d}_6\text{-DMSO}$): 9.49 (s, 1H), 9.01 (d, $J = 1.5$, 1H), 8.30-8.27 (m, 1H), 8.20 (d, $J = 2.6$, 1H), 7.58-7.53 (m, 2H), 7.39-7.35 (m, 1H), 7.13 (d, $J = 7.6$, 1H), 7.01-7.00 (m, 1H), 6.99-6.97 (m, 2H), 6.95-6.92 (m, 1H), 3.53-3.46 (m, 6H), 2.41-2.35 (m, 4H).

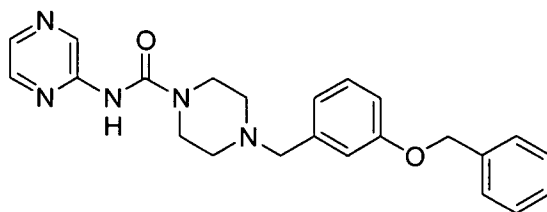
Example 222: 4-(4-Bromo-3-fluorobenzyl)-N-pyrazin-2-ylpiperazine-1-
carboxamide.



20

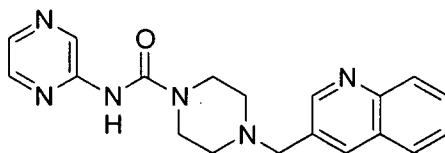
MS: 395.4. ^1H NMR ($\text{d}_6\text{-DMSO}$): 9.51 (s, 1H), 9.03 (d, $J = 1.5$, 1H), 8.30-8.28 (m, 1H), 8.21 (d, $J = 2.6$, 1H), 7.69-7.64 (m, 1H), 7.35-7.31 (m, 1H), 7.16-7.13 (m, 1H), 3.55-3.48 (m, 6H), 2.43-2.35 (m, 4H).

Example 223: 4-[3-(Benzyloxy)benzyl]-N-pyrazin-2-ylpiperazine-1-
carboxamide.



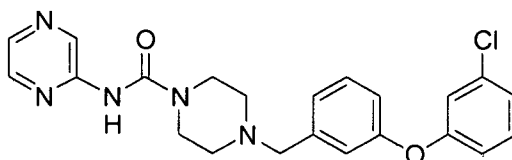
MS: 404.5. ^1H NMR ($\text{d}_6\text{-DMSO}$): 9.50 (s, 1H), 9.03 (d, $J = 1.5$, 1H), 8.31-8.26 (m, 1H), 8.20 (d, $J = 2.6$, 1H), 7.45 (d, $J = 7.0$, 2H), 7.39 (t, $J = 7.4$, 2H), 7.35-7.31 (m, 1H), 7.27-7.23 (m, 1H), 6.97 (s, 1H), 6.93-6.88 (m, 2H), 5.10 (s, 2H), 3.53-3.43 (m, 6H), 2.39-2.32 (m, 4H).

Example 224: N-Pyrazin-2-yl-4-(quinolin-3-ylmethyl)piperazine-1-carboxamide.



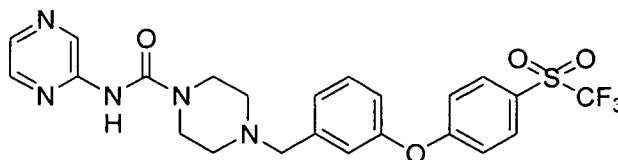
MS: 349.5. ^1H NMR ($\text{d}_6\text{-DMSO}$): 9.52 (s, 1H), 9.03 (d, $J = 1.5$, 1H), 8.89 (d, $J = 2.1$, 1H), 8.30-8.28 (m, 1H), 8.26-8.25 (m, 1H), 8.20 (d, $J = 2.6$, 1H), 8.04-7.98 (m, 2H), 7.77-7.72 (m, 1H), 7.63-7.60 (m, 1H), 3.74 (s, 2H), 3.55-3.50 (m, 4H), 2.49-2.43 (m, 4H).

Example 225: 4-[3-(3-Chlorophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide.



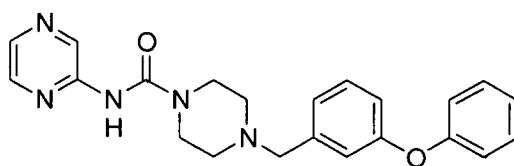
MS: 424.5. ^1H NMR (CDCl_3): 9.36 (d, $J = 1.5$, 1H), 8.24 (d, $J = 2.6$, 1H), 8.16-8.14 (m, 1H), 7.35-7.29 (m, 1H), 7.28-7.23 (m, 1H), 7.13-7.03 (m, 4H), 6.99-6.97 (m, 1H), 6.95-6.88 (m, 2H), 3.58-3.53 (m, 6H), 2.54-2.48 (m, 4H).

Example 226: N-Pyrazin-2-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}benzyl)-piperazine-1-carboxamide.



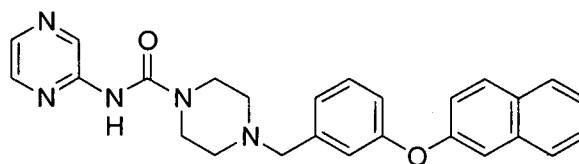
MS: 522.5. ^1H NMR (CDCl_3): 9.36 (d, $J = 1.5$, 1H), 8.24 (d, $J = 2.6$, 1H), 8.16-8.14 (m, 1H), 7.97 (d, $J = 8.9$, 2H), 7.45-7.39 (m, 1H), 7.28-7.25 (m, 1H), 7.16-7.12 (m, 3H), 7.08 (s, 1H), 7.04-7.01 (m, 1H), 3.61-3.54 (m, 6H), 2.57-2.49 (m, 4H).

5 Example 227: 4-(3-Phenoxy-benzyl)-piperazine-1-carboxylic acid pyrazin-2-ylamide.



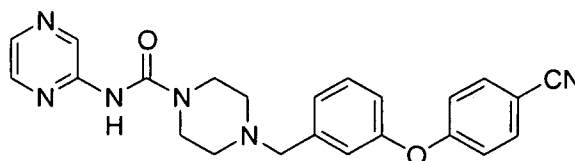
MS: 390.5. ^1H NMR (CDCl_3): 9.36 (d, $J = 1.8$, 1H), 8.24 (d, $J = 2.4$, 1H), 8.144-8.137 (m, 1H), 7.36-7.33 (m, 2H), 7.29 (t, $J = 7.8$, 1H), 7.12-7.10 (m, 2H), 7.06 (d, $J = 7.8$, 1H), 7.03-7.00 (m, 3H), 6.92-6.90 (m, 1H), 3.55 (t, $J = 4.8$, 4H), 3.53 (s, 2H), 2.51 (t, $J = 4.8$, 4H).

10 Example 228: 4-[3-(Naphthalen-2-yloxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide.



15 MS: 440.5. ^1H NMR (CDCl_3): 9.36 (d, $J = 1.8$, 1H), 8.24 (d, $J = 5.0$, 1H), 8.145-8.138 (dd, $J = 1.2$, 3.0, 1H), 7.84 (t, $J = 8.4$, 2H), 7.71 (d, $J = 7.2$, 1H), 7.48-7.45 (m, 1H), 7.43-7.40 (m, 1H), 7.33-7.31 (m, 2H), 7.27-7.25 (m, 1H), 7.11-7.07 (m, 3H), 6.99-6.97 (m, 1H), 3.55-3.53 (m, 6H), 2.51 (t, $J = 4.8$, 4H).

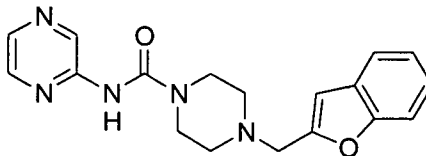
20 Example 229: 4-[3-(4-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide.



MS: 415.5. ^1H NMR (CDCl_3): 9.36 (d, $J = 1.8$, 1H), 8.25 (d, $J = 2.4$, 1H), 8.15-8.14 (m, 1H), 7.62-7.60 (m, 2H), 7.37 (t, $J = 7.8$, 1H), 7.19 (d, $J = 7.8$,

1H), 7.09-7.06 (m, 2H), 7.02-7.00 (m, 2H), 6.98-6.97 (dd, $J = 1.8, 7.2$, 1H), 3.56-3.55 (m, 6H), 2.52 (t, $J = 4.8$, 4H).

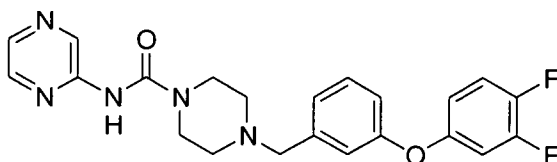
Example 230: 4-Benzofuran-2-ylmethyl-piperazine-1-carboxylic acid pyrazin-2-ylamide.



5

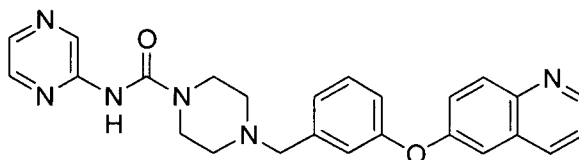
MS: 338.4. ^1H NMR (CDCl_3): 9.35 (s, 1H), 8.24 (d, $J = 3.0$, 1H), 8.15-8.14 (dd, $J = 1.8, 2.4$, 1H), 7.56-7.54 (m, 1H), 7.50-7.49 (m, 1H), 7.29-7.27 (m, 1H), 7.24-7.22 (m, 1H), 7.10 (s, 1H), 6.64 (s, 1H), 3.76 (s, 2H), 3.61 (t, $J = 4.8$, 4H), 2.63 (t, $J = 4.8$, 4H).

10 Example 231: 4-[3-(3,4-Difluorophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide.



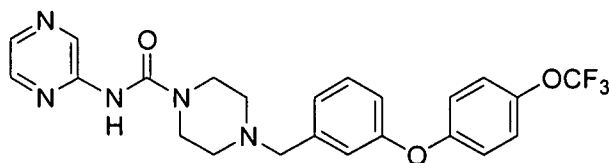
MS: 426.5. ^1H NMR ($\text{d}_4\text{-MeOH}$): 9.04-9.01 (m, 1H), 8.30-8.25 (m, 1H), 8.17-8.15 (m, 1H), 7.35 (t, $J = 7.9$, 1H), 7.29-7.21 (m, 1H), 7.17-7.14 (m, 1H), 15 7.07-7.04 (m, 1H), 6.96-6.89 (m, 2H), 6.81-6.76 (m, 1H), 3.62-3.54 (m, 6H), 2.55-2.46 (m, 4H).

Example 232: N-Pyrazin-2-yl-4-[3-(quinolin-6-yloxy)benzyl]piperazine-1-carboxamide.



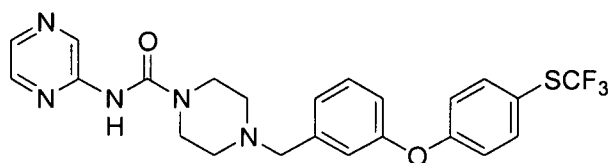
20 MS: 441.5. ^1H NMR ($\text{d}_4\text{-MeOH}$): 9.04-9.01 (m, 1H), 8.78-8.74 (m, 1H), 8.29-8.26 (m, 1H), 8.25-8.22 (m, 1H), 8.17-8.15 (m, 1H), 8.07-8.02 (m, 1H), 7.58-7.54 (m, 1H), 7.52-7.48 (m, 1H), 7.43-7.38 (m, 1H), 7.36-7.33 (m, 1H), 7.23-7.19 (m, 1H), 7.17-7.14 (m, 1H), 7.07-7.02 (m, 1H), 3.61-3.55 (m, 6H), 2.58-2.47 (m, 4H).

Example 233: N-Pyrazin-2-yl-4-{3-[4-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide.



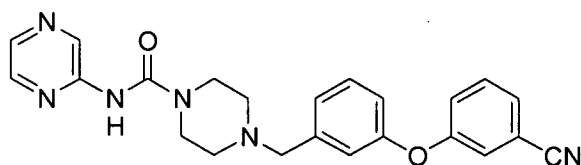
MS: 474.5. ¹H NMR (d₄-MeOH): 9.04-9.01 (m, 1H), 8.29-8.26 (m, 1H),
 5 8.17-8.15 (m, 1H), 7.39-7.32 (m, 1H), 7.29-7.25 (m, 2H), 7.18-7.14 (m, 1H),
 7.08-7.03 (m, 3H), 6.96-6.92 (m, 1H), 3.61-3.55 (m, 6H), 2.53-2.48 (m, 4H).

Example 234: N-Pyrazin-2-yl-4-{3-[(trifluoromethyl)sulfanyl]phenoxy}benzyl)-piperazine-1-carboxamide.



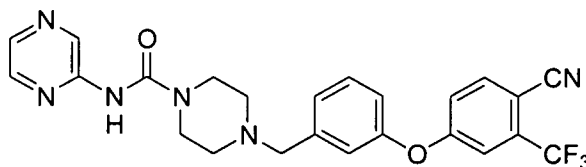
10 MS: 490.5. ¹H NMR (d₄-MeOH): 9.04-9.02 (m, 1H), 8.30-8.26 (m, 1H),
 8.18-8.15 (m, 1H), 7.69-7.63 (m, 2H), 7.43-7.37 (m, 1H), 7.25-7.19 (m, 1H),
 7.14-7.11 (m, 1H), 7.08-6.98 (m, 3H), 3.64-3.55 (m, 6H), 2.55-2.48 (m, 4H).

Example 235: 4-[3-(3-Cyanophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide.



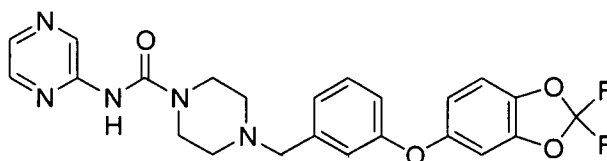
15 MS: 415.2. ¹H NMR (d₄-MeOH): 9.04-9.01 (m, 1H), 8.29-8.25 (m, 1H),
 8.16-8.14 (m, 1H), 7.55-7.49 (m, 1H), 7.47-7.43 (m, 1H), 7.42-7.36 (m, 1H),
 7.31-7.26 (m, 2H), 7.23-7.19 (m, 1H), 7.11-7.08 (m, 1H), 7.00-6.95 (m, 1H),
 3.62-3.55 (m, 6H), 2.56-2.47 (m, 4H).

20 Example 236: 4-{3-[4-Cyano-3-(trifluoromethyl)phenoxy]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide.



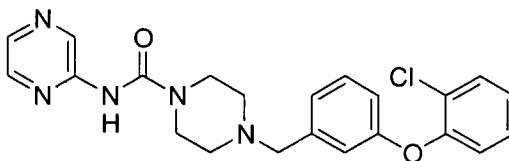
MS: 483.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 9.04-9.01 (m, 1H), 8.29-8.26 (m, 1H), 8.17-8.15 (m, 1H), 7.95-7.92 (m, 1H), 7.49-7.45 (m, 1H), 7.42-7.40 (m, 1H), 7.33-7.31 (m, 1H), 7.29-7.26 (m, 1H), 7.21-7.19 (m, 1H), 7.10-7.07 (m, 1H), 3.63-3.56 (m, 6H), 2.54-2.50 (m, 4H).

5 Example 237: 4-{3-[(2,2-Difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide.



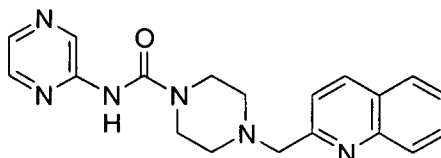
MS: 470.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 9.04-9.00 (m, 1H), 8.29-8.25 (m, 1H), 8.17-8.14 (m, 1H), 7.36-7.30 (m, 1H), 7.19-7.11 (m, 2H), 7.05-7.01 (m, 1H),
10 6.95-6.89 (m, 2H), 6.80-6.76 (m, 1H), 3.61-3.53 (m, 6H), 2.55-2.46 (m, 4H).

Example 238: 4-[3-(2-Chlorophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide.



MS: 424.2. ^1H NMR ($\text{d}_4\text{-MeOH}$): 9.03-9.00 (m, 1H), 8.29-8.23 (m, 1H),
15 8.17-8.13 (m, 1H), 7.52-7.47 (m, 1H), 7.34-7.27 (m, 2H), 7.19-7.13 (m, 1H), 7.11-7.07 (m, 1H), 7.06-7.01 (m, 1H), 6.97-6.93 (m, 1H), 6.86-6.80 (m, 1H), 3.60-3.51 (m, 6H), 2.54-2.43 (m, 4H).

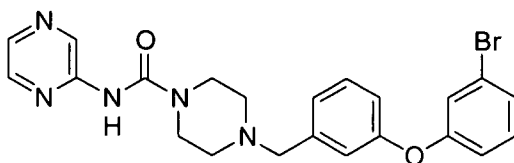
Example 239: N-Pyrazin-2-yl-4-(quinolin-2-ylmethyl)piperazine-1-carboxamide.



20 MS: 349.5. ^1H NMR (CDCl_3): 9.39 (d, $J = 1.5$, 1H), 8.26 (d, $J = 2.6$, 1H), 8.20-8.15 (m, 2H), 8.11 (d, $J = 8.4$, 1H), 7.84 (d, $J = 8.0$, 1H), 7.76-7.71 (m, 1H), 7.65 (d, $J = 8.4$, 1H), 7.58-7.54 (m, 1H), 7.10 (s, 1H), 3.92 (s, 2H), 3.65-3.60 (m, 4H), 2.69-2.61 (m, 4H).

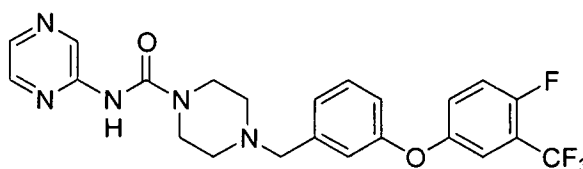
Example 240: 4-[3-(3-Bromophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide.

25



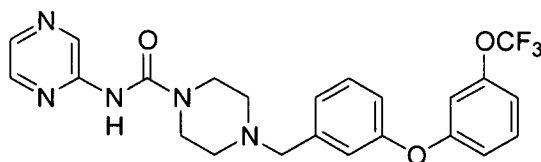
MS: 468.1. ¹H NMR (d₄-MeOH): 9.05 (d, *J* = 1.5, 1H), 8.30-8.28 (dd, *J* = 2.6, 1.6, 1H), 8.17 (d, *J* = 2.6, 1H), 7.38 (t, *J* = 7.9, 1H), 7.29-7.26 (m, 2H), 7.20-7.16 (m, 1H), 7.13-7.11 (m, 1H), 7.09-7.07 (m, 1H), 7.00-6.94 (m, 2H),
 5 3.66-3.52 (m, 6H), 2.55-2.49 (m, 4H).

Example 241: 4-{3-[4-Fluoro-3-(trifluoromethyl)phenoxy]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide.



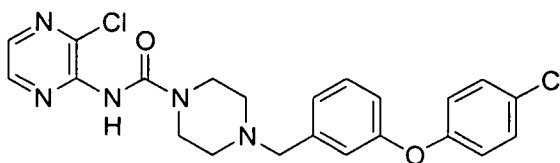
MS: 476.2. ¹H NMR (d₄-MeOH): 9.07-9.02 (m, 1H), 8.34-8.25 (m, 1H),
 10 8.20-8.16 (m, 1H), 7.45-7.32 (m, 2H), 7.32-7.25 (m, 2H), 7.23-7.18 (m, 1H), 7.11-7.08 (m, 1H), 6.99-6.94 (m, 1H), 3.64-3.56 (m, 6H), 2.59-2.44 (m, 4H).

Example 242: N-Pyrazin-2-yl-4-{3-[3-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide.



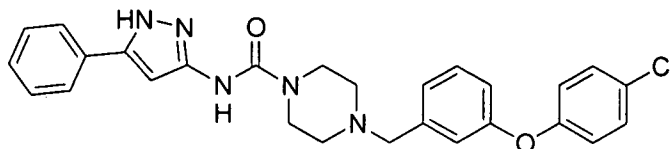
MS: 474.2. ¹H NMR (d₄-MeOH): 9.08-8.99 (m, 1H), 8.35-8.24 (m, 1H),
 15 8.19-8.16 (m, 1H), 7.48-7.33 (m, 2H), 7.23-7.18 (m, 1H), 7.12-7.09 (m, 1H), 7.05-6.96 (m, 3H), 6.89-6.84 (m, 1H), 3.66-3.53 (m, 6H), 2.58-2.43 (m, 4H).

Example 243: 4-[3-(4-Chlorophenoxy)benzyl]-N-(3-chloropyrazin-2-yl)piperazine-1-carboxamide.



MS: 458.1. ¹H NMR (CDCl₃): 8.26 (s, 1H), 8.00 (s, 1H), 7.32-7.27 (m, 3H), 7.11-7.06 (m, 1H), 7.03-6.87 (m, 5H), 3.64-3.48 (m, 6H), 2.56-2.46 (m, 4H).

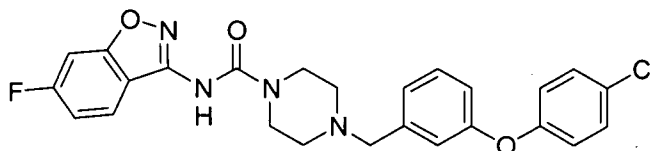
Example 244: 4-[3-(4-Chlorophenoxy)benzyl]-N-(5-phenyl-1H-pyrazol-3-yl)piperazine-1-carboxamide trifluoroacetate salt.



MS: 488.2. ¹H NMR (d₆-acetone): 7.96-7.78 (dd, *J* = 1.8, 8.4, 2H), 7.50 (t, *J* = 7.8, 1H), 7.45 (d, *J* = 7.2, 1H), 7.41-7.34 (m, 7H), 7.15-7.13 (m, 1H), 7.08-7.06 (m, 2H), 4.58 (s, 2H), 3.62 (br hump, 8H).

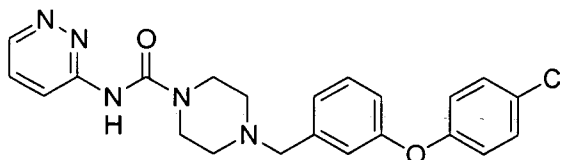
The compounds in Examples 245-246 were prepared using methods analogous to those described for Example 1.

Example 245: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-fluoro-benzo[d]isoxazol-3-yl)-amide.



MS: 481.1. ¹H NMR (d₆-acetone): 8.02-7.56 (m, 2H), 7.49 (t, *J* = 8.4, 1H), 7.43-7.34 (m, 4H), 7.31 (t, *J* = 1.8, 1H), 7.14-7.11 (m, 2H), 7.06-7.04 (m, 2H), 4.51 (s, 2H), 3.49 (br hump, 8H).

Example 246: 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyridazin-3-ylamide.



MS: 424.2. ¹H NMR (CDCl₃): 8.81 (s, 1H), 8.26 (s, 2H), 7.44-7.36 (m, 1H), 7.32-7.26 (m, 3H), 7.08 (d, *J* = 7.6, 1H), 7.02-6.99 (m, 1H), 6.96-6.92 (m, 2H), 6.91-6.88 (dd, *J* = 8.1, 2.4, 1H), 3.64-3.55 (m, 4H), 3.52 (s, 2H), 2.51-2.47 (m, 4H).

Biological Testing:

- Assay Method 1

25 A. Transfection of Cells with Human FAAH

A 10-cm tissue culture dish with a confluent monolayer of SK-N-MC cells was split 2 days (d) prior to transfection. Using sterile technique, the media was removed and the cells were detached from the dish by the addition of trypsin. One fifth of the cells were then placed onto a new 10-cm dish. Cells
5 were grown in a 37 °C incubator with 5% CO₂ in Minimal Essential Media Eagle with 10% Fetal Bovine Serum. After 2 d, cells were approximately 80% confluent. These cells were removed from the dish with trypsin and pelleted in a clinical centrifuge. The pellet was re-suspended in 400 µL complete media and transferred to an electroporation cuvette with a 0.4 cm gap between the
10 electrodes. Supercoiled human FAAH cDNA (1 µg) was added to the cells and mixed. The voltage for the electroporation was set at 0.25 kV, and the capacitance was set at 960 µF. After electroporation, the cells were diluted into complete media (10 mL) and plated onto four 10-cm dishes. Because of the variability in the efficiency of electroporation, four different concentrations
15 of cells were plated. The ratios used were 1:20, 1:10, and 1:5, with the remainder of the cells being added to the fourth dish. The cells were allowed to recover for 24 h before adding the selection media (complete media with 600 µg/mL G418). After 10 d, dishes were analyzed for surviving colonies of cells. Dishes with well-isolated colonies were used. Cells from individual
20 colonies were isolated and tested. The clones that showed the most FAAH activity, as measured by anandamide hydrolysis, were used for further study.

B. FAAH Assay

T84 frozen cell pellets or transfected SK-N-MC cells (contents of 1 x 15 cm culture dishes) were homogenized in 50 mL of FAAH assay buffer (125 mM
25 Tris, 1mM EDTA, 0.2% Glycerol, 0.02% Triton X-100, 0.4 mM Hepes, pH 9). The assay mixture consisted of 50 µL of the cell homogenate, 10 µL of the test compound, and 40 µL of anandamide [1-³H-ethanolamine] (³H-AEA, Perkin-Elmer, 10.3 Ci/mmol), which was added last, for a final tracer concentration of 80 nM. The reaction mixture was incubated at rt for 1 h. During the incubation,
30 96-well Multiscreen filter plates (catalog number MAFCNOB50; Millipore, Bedford, MA, USA) were loaded with 25 µL of activated charcoal (Multiscreen column loader, catalog number MACL09625, Millipore) and washed once with

100 μ L of MeOH. Also during the incubation, 96-well DYNEX MicroLite plates (catalog number NL510410) were loaded with 100 μ L of MicroScint40 (catalog number 6013641, Packard Bioscience, Meriden, CT, USA). After the 1 h incubation, 60 μ L of the reaction mixture were transferred to the charcoal plates, which were then assembled on top of the DYNEX plates using Centrifuge Alignment Frames (catalog number MACF09604, Millipore). The unbound labeled ethanolamine was centrifuged through to the bottom plate (5 min at 2000 rpm), which was preloaded with the scintillant, as described above. The plates were sealed and left at rt for 1 h before counting on a Hewlett Packard TopCount.

- Assay Method 2

- A. Transfection of Cells with Rat FAAH

A 10-cm tissue culture dish with a confluent monolayer of SK-N-MC cells was split 2 days (d) prior to transfection. Using sterile technique, the media was removed and the cells were detached from the dish by the addition of trypsin. One fifth of the cells were then placed onto a new 10-cm dish. Cells were grown in a 37 °C incubator with 5% CO₂ in Minimal Essential Media Eagle with 10% Fetal Bovine Serum. After 2 d, cells were approximately 80% confluent. These cells were removed from the dish with trypsin and pelleted in a clinical centrifuge. The pellet was re-suspended in 400 μ L complete media and transferred to an electroporation cuvette with a 0.4 cm gap between the electrodes. Supercoiled rat FAAH cDNA (1 μ g) was added to the cells and mixed. The voltage for the electroporation was set at 0.25 kV, and the capacitance was set at 960 μ F. After electroporation, the cells were diluted into complete media (10 mL) and plated onto four 10-cm dishes. Because of the variability in the efficiency of electroporation, four different concentrations of cells were plated. The ratios used were 1:20, 1:10, and 1:5, with the remainder of the cells being added to the fourth dish. The cells were allowed to recover for 24 h before adding the selection media (complete media with 600 μ g/mL G418). After 10 d, dishes were analyzed for surviving colonies of cells. Dishes with well-isolated colonies were used. Cells from individual

colonies were isolated and tested. The clones that showed the most FAAH activity, as measured by anandamide hydrolysis, were used for further study.

B. FAAH Assay

T84 frozen cell pellets or transfected SK-N-MC cells (contents of 1 x 15
5 cm culture dishes) were homogenized in 50 mL of FAAH assay buffer (125 mM Tris, 1 mM EDTA, 0.2% Glycerol, 0.02% Triton X-100, 0.4 mM Hepes, pH 9). The assay mixture consisted of 50 μ L of the cell homogenate, 10 μ L of the test compound, and 40 μ L of anandamide [1 - ^{3} H-ethanolamine] (^{3} H-AEA, Perkin-Elmer, 10.3 Ci/mmol), which was added last, for a final tracer concentration of
10 80 nM. The reaction mixture was incubated at rt for 1 h. During the incubation, 96-well Multiscreen filter plates (catalog number MAFCNOB50; Millipore, Bedford, MA, USA) were loaded with 25 μ L of activated charcoal (Multiscreen column loader, catalog number MACL09625, Millipore) and washed once with 100 μ L of MeOH. Also during the incubation, 96-well DYNEX MicroLite plates
15 (catalog number NL510410) were loaded with 100 μ L of MicroScint40 (catalog number 6013641, Packard Bioscience, Meriden, CT, USA). After the 1 h incubation, 60 μ L of the reaction mixture were transferred to the charcoal plates, which were then assembled on top of the DYNEX plates using Centrifuge Alignment Frames (catalog number MACF09604, Millipore). The
20 unbound labeled ethanolamine was centrifuged through to the bottom plate (5 min at 2000 rpm), which was preloaded with the scintillant, as described above. The plates were sealed and left at rt for 1 h before counting on a Hewlett Packard TopCount.

Results for compounds tested in these assays are summarized in Table
25 1, as an average of results obtained. Compounds were tested in free base, hydrochloride salt, and/or trifluoroacetic acid salt forms. Where activity is shown as greater than (>) a particular value, the value is the solubility limit of the compound in the assay medium or the highest concentration tested in the assay.

Table 1

Ex.	Assay 1 IC₅₀ (μM)	Assay 2 IC₅₀ (μM)		Ex.	Assay 1 IC₅₀ (μM)	Assay 2 IC₅₀ (μM)
1	0.103	0.337		124	0.055	0.200
2	0.212	10.000		125	0.015	0.012
3	1.200	9.000		126	0.060	0.200
4	0.059	0.260		127	0.040	0.040
5	0.170	1.200		128	0.230	0.400
6	0.308	0.352		129	0.080	0.120
7	2.000	2.400		130	0.020	0.004
8	0.770	0.290		131	0.007	0.004
9	0.552	0.057		132	0.023	0.005
10	0.244	0.036		133	0.024	0.115
11	1.000	0.170		134	0.010	0.100
12	5.000	3.000		135	0.825	10.000
13	0.005	0.087		136	0.055	1.000
14	0.218	0.063		137	0.060	0.360
15	0.059	0.023		138	5.000	>10
16	0.039	0.005		139	0.860	>10
17	10.000	0.517		140	0.700	6.001
18	>10	8.999		141	0.050	0.870
19	1.500	0.055		142	2.000	10.000
20	0.935	0.250		143	>10	>10
21	0.043	0.007		144	0.350	3.000
22	0.108	0.077		145	0.016	0.430
23	10.000	5.000		146	3.000	10.000
24	10.000	4.000		147	10.000	>10
25	1.300	1.300		148	5.000	>10
26	5.000	1.000		149	10.000	10.000
27	0.077	0.047		150	0.400	1.200
28	0.095	0.017		151	3.000	6.001
29	0.016	0.023		152	0.330	5.000

30	0.0001	0.014		153	0.460	8.000
31	0.022	0.017		154	1.300	10.000
32	0.003	0.004		155	0.020	0.270
33	0.052	0.030		156	0.043	5.000
34	0.152	0.190		157	0.080	0.360
35	0.005	0.020		158	0.010	0.150
36	0.008	0.010		159	0.050	0.300
37	0.032	0.006		160	3.000	8.000
38	0.070	0.009		161	0.004	0.160
39	0.310	0.573		162	0.240	6.400
40	0.156	0.015		163	1.000	>10
41	0.048	0.141		164	0.141	7.000
42	0.311	0.018		165	8.000	6.001
43	0.983	0.006		166	0.013	0.007
44	0.643	0.046		167	0.340	0.080
45	1.500	0.410		168	1.200	0.480
46	0.615	0.025		169	0.610	0.600
47	1.145	0.066		170	1.200	1.800
48	0.627	0.049		171	0.200	0.035
49	2.000	0.360		172	0.050	0.010
50	0.042	0.018		173	0.225	0.200
51	0.028	0.029		174	0.100	0.030
52	0.074	0.322		175	10.000	1.000
53	0.210	0.030		176	2.000	0.450
54	0.370	0.050		177	5.000	1.700
55	7.746	0.764		178	>10	>10
56	1.500	0.550		179	1.600	1.200
57	0.068	0.167		180	>10	10.000
58	0.084	0.009		181	5.000	1.600
59	0.270	0.022		182	1.700	0.340
60	0.166	0.016		183	1.400	0.430
61	2.300	7.000		184	10.000	10.000

62	0.041	0.035		185	0.450	0.440
63	0.070	0.077		186	0.330	0.160
64	0.105	0.080		187	1.600	1.000
65	0.395	0.300		188	0.080	0.020
66	0.024	0.046		189	0.070	0.017
67	0.006	0.052		190	3.000	3.700
68	0.016	0.315		191	3.000	>10
69	0.044	2.000		192	4.000	>10
70	0.046	0.046		193	0.327	6.001
71	0.013	0.050		194	0.220	4.000
72	0.024	0.030		195	0.110	0.310
73	0.024	0.033		196	6.001	1.600
74	0.410	0.325		197	1.300	8.999
75	0.123	0.110		198	0.390	6.001
76	0.010	0.400		199	0.280	0.590
77	0.012	0.064		200	0.038	0.500
78	0.059	0.410		201	>10	>10
79	0.046	0.320		202	0.045	0.085
80	5.000	4.000		203	0.210	0.350
81	0.453	0.238		204	0.014	0.032
82	0.272	0.256		205	0.106	0.225
83	0.035	0.020		206	0.011	0.021
84	0.016	0.295		207	0.034	0.046
85	0.018	0.023		208	0.021	0.017
86	3.000	0.580		209	0.009	0.002
87	2.000	0.480		210	1.750	1.160
88	0.015	0.065		211	3.000	>10
89	0.645	0.544		212	0.500	8.000
90	0.195	0.815		213	0.100	0.320
91	0.030	0.021		214	0.015	0.090
92	0.027	0.262		215	0.001	0.030
93	0.102	0.225		216	>10	>10

94	0.380	0.630		217	0.150	0.250
95	2.800	10.000		218	0.170	0.700
96	0.200	1.100		219	0.230	10.000
97	0.270	5.000		220	0.320	0.430
98	0.022	0.300		221	0.003	0.050
99	0.016	0.260		222	0.700	0.600
100	>10	>10		223	0.180	10.000
101	6.299	10.000		224	4.000	>10
102	>10	>10		225	0.043	0.535
103	0.120	0.110		226	0.006	0.040
104	0.037	0.690		227	0.400	5.300
105	0.100	0.013		228	0.030	0.080
106	0.080	0.027		229	0.200	3.000
107	0.080	0.037		230	4.000	6.001
108	0.140	0.050		231	0.130	3.600
109	0.006	0.004		232	0.040	0.240
110	0.045	0.042		233	0.010	0.140
111	0.035	0.040		234	0.006	0.012
112	0.040	0.270		235	0.600	6.001
113	0.020	0.030		236	0.300	8.000
114	0.020	0.020		237	0.005	0.030
115	0.040	0.025		238	0.200	1.600
116	0.400	0.760		239	0.700	6.001
117	0.130	0.440		240	0.020	0.080
118	1.800	8.000		241	0.008	0.370
119	0.045	0.009		242	0.009	0.050
120	0.080	0.120		243	0.002	0.009
121	0.017	0.025		244	1.400	7.000
122	0.148	0.115		245	0.019	0.015
123	0.020	0.040		246	0.010	0.199

- Assay Method 3 – Rat Mild Thermal Injury Model (MTI)

Pathogen-free, male albino Sprague-Dawley rats were purchased from Harlan Industries (San Diego, CA) and maintained on a 12-h light/dark cycle (lights on at 9:00 AM and off at 9:00 PM) in a climate-controlled room. Food and water were available *ad libitum* up to the time of the testing.

5 Under isoflurane/oxygen anesthesia, a first-degree burn injury (erythema without blistering) was produced as follows: the plantar surface of the rat's left hind paw was placed on water-dampened 56 °C hotplate for 20 seconds and steady contact was maintained by applying an 84 g weight to the dorsum (after Nozaki-Taguchi & Yaksh, *Neurosci. Lett.* 1998, 254, 25-28).

10 Mild thermal injury results in mechanical allodynia in the left hind paw. Mechanical (tactile) allodynia was assessed by determining the median threshold at which the affected paw was withdrawn from graded stimuli (von Frey filaments ranging from 0.41 to 15.8 g) applied perpendicularly with sufficient force to bend slightly and held for 2-3 seconds against the proximal
15 half of the third and fourth toe surfaces through wire-mesh observation cages. Paw flinching during or immediately following the removal of the stimulus was considered a positive response. A paw withdrawal threshold (PWT) was determined by sequentially increasing and decreasing the stimulus strength and analyzing withdrawal data using an adaptation of the Dixon up-down
20 method, as described (Chaplan et al., *J. Neurosci.* 1994, 14, 55-63). Rats were included in the study only if their baseline PWT was 3.1623 g or lower (4.5 logarithmically).

Rats were tested for pre-injury thresholds prior to mild thermal injury and again for baseline thresholds after development of mechanical allodynia.

25 Immediately after baseline measurement, test compound or vehicle was administered orally and the measurement was repeated at 0.5 h after administration. The tactile thresholds (log value) were converted to percent of a maximum possible effect (%MPE): $\%MPE = [\text{Threshold}(t) - \text{Threshold}(\text{baseline})] * 100 / [\text{Threshold}(\text{pre}) - \text{Threshold}(\text{baseline})]$, where t =
30 post-treatment time. Data were expressed as mean $\pm$ standard error of the mean (S.E.M.). Statistical analysis was performed using two-way ANOVA with repeated measures with a significance level of $p < 0.05$.

Results for compounds tested in this assay are presented in Table 2, as an average of results obtained. Compounds were tested in free base, hydrochloride salt, and/or trifluoroacetic acid salt forms.

Table 2

Ex.	Dose p.o.	%MPE
36	20 mg/Kg	38 +/- 13
46	6 mg/Kg	0
58	20 mg/Kg	52 +/- 7
109	10 mg/Kg	0
245	10 mg/Kg	36 +/- 10
246	20 mg/Kg	32 +/- 3

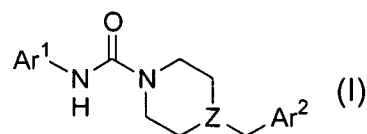
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While the invention has been illustrated by reference to exemplary and preferred embodiments, it will be understood that the invention is intended not to be limited to the foregoing detailed description, but to be defined by the appended claims as properly construed under principles of patent law.

10

What is claimed is:

1. A compound of Formula (I):



wherein:

- 5 Ar¹ is a benzo[d]isoxazol-3-yl, 6-fluorobenzo[d]isoxazol-3-yl, 3-phenyl-[1,2,4]thiadiazol-5-yl, 1H-tetrazol-5-yl, benzo[1,2,5]thiadiazol-4-yl, benzo[1,2,5]oxadiazol-4-yl, thiophen-2-yl, thiophen-3-yl, 6-chloro-pyridazin-3-yl, pyrazin-2-yl, isoxazol-3-yl, 1H-benzotriazol-5-yl, [1,5]naphthyridin-2-yl, quinolin-2-yl, benzothiazol-6-yl, quinolin-5-yl, 1H-pyrazol-3-yl, 5-methylpyrazin-2-yl, 3-chloropyrazin-2-yl, pyridazin-3-yl, 6-methoxypyridazin-3-yl, 5-methylisoxazol-3-yl, 1,5-dimethyl-1H-pyrazol-3-yl, 4-bromo-1-methyl-1H-pyrazol-3-yl, 2-ethyl-2H-pyrazol-3-yl, 5-methyl-1H-pyrazol-3-yl, or 5-phenyl-1H-pyrazol-3-yl group;

Z is -N- or >CH; and

15 Ar² is:

(i) phenyl unsubstituted or substituted with one or two R^a moieties;

where each R^a moiety is independently -C₁₋₄alkyl, -C≡C-R^d, -OC₁₋₄alkyl, halo, -CF₃, -OCF₃, -OCH₂CF₃, -SCF₃, -S(O)₀₋₂C₁₋₄alkyl, -SO₂CF₃, -OSO₂C₁₋₄alkyl, -(CH₂)₀₋₁CO₂C₁₋₄alkyl, -CO₂H, -COC₁₋₄alkyl, -N(R^b)R^c, -SO₂NR^bR^c, -NR^bSO₂R^c, -C(O)NR^bR^c, -NO₂, or -(CH₂)₀₋₁CN; or two adjacent R^a moieties taken together form -O(CH₂)₁₋₂O- or -OCF₂O-;

where R^b and R^c are each independently -H or -C₁₋₄alkyl; and

R^d is H, C₃₋₆cycloalkyl, or -CH₂NR^eR^f;

25 where R^e and R^f are each independently H or C₁₋₄alkyl;

(ii) phenyl substituted at the 3- or 4-position with -L-Ar³, unsubstituted or substituted with R^a, wherein:

L is a linker selected from the group consisting of -(CH₂)₁₋₃-, -CH=CH-, -O-, -OCH₂-, -CH₂O-, -NH-, >NC₁₋₄alkyl, -S-, -C≡C-, -C(=O)-, and a covalent bond; and

30

Ar³ is:

- (a) phenyl;
- (b) naphthyl; or
- (c) a monocyclic or bicyclic heteroaryl group; or

5 (iii) a 9- or 10-membered fused bicyclic heteroaryl group;

where when Ar¹ is 6-chloro-pyridazin-3-yl, isoxazol-3-yl, or 1H-pyrazol-3-yl,
then Ar² is not benzo[1,3]dioxol-5-yl or 2,2-difluoro-benzo[1,3]dioxol-5-yl;
or a pharmaceutically acceptable salt, pharmaceutically acceptable
prodrug, or pharmaceutically active metabolite of said compound.

10

2. A compound or pharmaceutically acceptable salt as defined in claim 1,
wherein Ar¹ is a benzo[d]isoxazol-3-yl, 6-fluorobenzo[d]isoxazol-3-yl,
benzo[1,2,5]thiadiazol-4-yl, benzo[1,2,5]oxadiazol-4-yl, 6-chloro-pyridazin-3-yl,
pyrazin-2-yl, isoxazol-3-yl, 1H-benzotriazol-5-yl, benzothiazol-6-yl, or 1H-
15 pyrazol-3-yl group.

3. A compound or pharmaceutically acceptable salt as defined in claim 1,
wherein Ar¹ is a benzo[d]isoxazol-3-yl group.

20 4. A compound or pharmaceutically acceptable salt as defined in claim 1,
wherein Ar¹ is a pyrazin-2-yl group.

5. A compound or pharmaceutically acceptable salt as defined in claim 1,
wherein Ar¹ is an isoxazol-3-yl group.

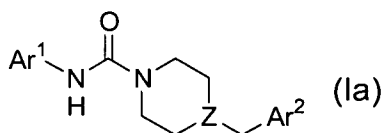
25

6. A compound or pharmaceutically acceptable salt as defined in claim 1,
wherein Ar¹ is a pyridazin-3-yl group.

7. A compound or pharmaceutically acceptable salt as defined in claim 1,
30 wherein Z is -N-.

8. A compound or pharmaceutically acceptable salt as defined in claim 1, wherein Z is >CH.
9. A compound or pharmaceutically acceptable salt as defined in claim 1,
5 wherein Ar² is phenyl, substituted with one or two R^a moieties.
10. A compound or pharmaceutically acceptable salt as defined in claim 9, wherein each R^a moiety is independently selected from the group consisting of: chloro, cyano, isobutyl, methylsulfanyl, methanesulfonyl, trifluoromethyl,
10 trifluoromethoxy, 2,2,2-trifluoroethoxy, fluoro, methyl, methoxy, tert-butyl, bromo, methoxycarbonyl, cyanomethyl, methoxycarbonylmethyl, trifluoromethanesulfonyl, trifluoromethanesulfanyl, and butyl; or two adjacent R^a moieties taken together form -OCH₂O- or -OCF₂O-.
11. A compound or pharmaceutically acceptable salt as defined in claim 1,
15 wherein Ar² is phenyl substituted at the 3- or 4-position with -L-Ar³, unsubstituted or substituted with one or two R^a moieties.
12. A compound or pharmaceutically acceptable salt as defined in claim 11,
20 wherein L is -CH₂CH₂-, -O-, -OCH₂-, or -C≡C-.
13. A compound or pharmaceutically acceptable salt as defined in claim 11, wherein Ar³ is phenyl.
14. A compound or pharmaceutically acceptable salt as defined in claim 13,
25 wherein each R^a moiety is independently selected from the group consisting of: chloro, cyano, isobutyl, methylsulfanyl, methanesulfonyl, trifluoromethyl, trifluoromethoxy, 2,2,2-trifluoroethoxy, fluoro, methyl, methoxy, tert-butyl, bromo, methoxycarbonyl, cyanomethyl, methoxycarbonylmethyl,
30 trifluoromethanesulfonyl, trifluoromethanesulfanyl, and butyl; or two adjacent R^a moieties taken together form -OCH₂O- or -OCF₂O-.

15. A compound or pharmaceutically acceptable salt as defined in claim 11, wherein Ar³ is naphthyl.
16. A compound or pharmaceutically acceptable salt as defined in claim 11,
5 wherein Ar³ is a monocyclic or bicyclic heteroaryl group.
17. A compound or pharmaceutically acceptable salt as defined in claim 16, wherein Ar³ is a thiophenyl, pyrimidinyl, pyridyl, pyrazinyl, or quinolinyl group.
- 10 18. A compound or pharmaceutically acceptable salt as defined in claim 1, wherein Ar² is a 9- or 10-membered fused bicyclic heteroaryl group.
19. A compound or pharmaceutically acceptable salt as defined in claim 18, wherein Ar² is a benzimidazolyl, indazolyl, benzothiophenyl, quinolinyl, indolyl,
15 or benzofuranyl group.
20. A compound of Formula (Ia):



wherein:

- 20 Ar¹ is a benzo[d]isoxazol-3-yl, 6-fluorobenzo[d]isoxazol-3-yl, 3-phenyl-
[1,2,4]thiadiazol-5-yl, 1H-tetrazol-5-yl, benzo[1,2,5]thiadiazol-4-yl,
benzo[1,2,5]oxadiazol-4-yl, thiophen-2-yl, thiophen-3-yl, 6-chloro-pyridazin-
3-yl, pyrazin-2-yl, isoxazol-3-yl, 1H-benzotriazol-5-yl, [1,5]naphthyridin-2-yl,
quinolin-2-yl, benzothiazol-6-yl, quinolin-5-yl, or 1H-pyrazol-3-yl group;
- 25 Z is -N- or >CH; and
Ar² is:
- (i) phenyl or 3-phenoxyphenyl substituted with one or two R^a moieties;
where each R^a moiety is independently -C₁₋₄alkyl, -OC₁₋₄alkyl, halo,
-CF₃, -OCF₃, -OCH₂CF₃, -SCF₃, -S(O)₀₋₂C₁₋₄alkyl, -OSO₂C₁₋₄alkyl,

-CO₂C₁₋₄alkyl, -CO₂H, -COC₁₋₄alkyl, -N(R^b)R^c, -SO₂NR^bR^c,
-NR^bSO₂R^c, -C(O)NR^bR^c, -NO₂, or -CN;

where R^b and R^c are each independently -H or -C₁₋₄alkyl; or

(ii) benzo[1,3]dioxol-5-yl, 2,2-difluoro-benzo[1,3]dioxol-5-yl, or naphthyl;

- 5 where when Ar¹ is 6-chloro-pyridazin-3-yl, isoxazol-3-yl, or 1H-pyrazol-3-yl,
then Ar² is not benzo[1,3]dioxol-5-yl or 2,2-difluoro-benzo[1,3]dioxol-5-yl;
or a pharmaceutically acceptable salt, pharmaceutically acceptable
prodrug, or pharmaceutically active metabolite of said compound.

- 10 21. A compound or pharmaceutically acceptable salt as defined in claim 20,
wherein Ar¹ is a benzo[d]isoxazol-3-yl, 6-fluorobenzo[d]isoxazol-3-yl,
benzo[1,2,5]thiadiazol-4-yl, benzo[1,2,5]oxadiazol-4-yl, 6-chloro-pyridazin-3-yl,
pyrazin-2-yl, isoxazol-3-yl, 1H-benzotriazol-5-yl, benzothiazol-6-yl, or 1H-
pyrazol-3-yl group.

15

22. A compound or pharmaceutically acceptable salt as defined in claim 20,
wherein Ar¹ is a benzo[d]isoxazol-3-yl group.

23. A compound or pharmaceutically acceptable salt as defined in claim 20,
20 wherein Ar¹ is a pyrazin-2-yl group.

24. A compound or pharmaceutically acceptable salt as defined in claim 20,
wherein Ar¹ is an isoxazol-3-yl group.

- 25 25. A compound or pharmaceutically acceptable salt as defined in claim 20,
wherein Ar¹ is a pyridazin-3-yl group.

26. A compound or pharmaceutically acceptable salt as defined in claim 20,
wherein Ar² is 3-phenoxyphenyl substituted with one or two R^a moieties
30 independently selected from the group consisting of fluoro, chloro, bromo,
-CF₃, -OCF₃, and -OCH₂CF₃.

27. A compound or pharmaceutically acceptable salt as defined in claim 20, wherein Ar² is naphthyl.

28. A compound or pharmaceutically acceptable salt selected from the
5 group consisting of:

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid
benzo[d]isoxazol-3-ylamide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid (3-
phenyl-[1,2,4]thiadiazol-5-yl)-amide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid (1H-
tetrazol-5-yl)-amide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid
benzo[1,2,5]thiadiazol-4-ylamide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid
benzo[1,2,5]oxadiazol-4-ylamide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid (3H-
benzotriazol-5-yl)-amide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid
thiophen-2-ylamide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid
thiophen-3-ylamide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-
amide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid pyrazin-2-ylamide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid isoxazol-3-ylamide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (3-phenyl-
[1,2,4]thiadiazol-5-yl)-amide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (1H-tetrazol-5-yl)-amide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (2H-pyrazol-3-yl)-amide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid benzo[1,2,5]oxadiazol-4-
ylamide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (1H-benzotriazol-5-yl)-amide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid [1,5]naphthyridin-2-ylamide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid quinolin-2-ylamide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid benzothiazol-6-ylamide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid quinolin-5-ylamide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-(4-Fluoro-benzyl)-piperidine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-(4-Fluoro-benzyl)-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;

4-(4-Fluoro-benzyl)-piperidine-1-carboxylic acid isoxazol-3-ylamide;

4-(3-Trifluoromethyl-benzyl)-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;

4-(3-Trifluoromethyl-benzyl)-piperidine-1-carboxylic acid isoxazol-3-ylamide;

4-(3-Trifluoromethyl-benzyl)-piperidine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Fluoro-3-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3-Trifluoromethoxy-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Trifluoromethoxy-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3-Bromo-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Bromo-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3,4-Difluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3,5-Difluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-{3-[4-(2,2,2-Trifluoro-ethoxy)-phenoxy]-benzyl}-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide;

4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide;

4-[3-(3,5-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide;

4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide;

4-(3-Trifluoromethoxy-benzyl)-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;

4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;

4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;

4-(4-Fluoro-3-phenoxy-benzyl)-piperazine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide;

4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide;

4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide;

4-(4-Fluoro-3-phenoxy-benzyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide;

4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-(3-Trifluoromethoxy-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide;
4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide;
4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide;
4-(4-Fluoro-3-phenoxy-benzyl)-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-tetrazol-5-yl)-amide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide; and
4-(3-Trifluoromethoxy-benzyl)-piperazine-1-carboxylic acid pyrazin-2-ylamide;
and pharmaceutically acceptable salts thereof.

29. A compound or pharmaceutically acceptable salt selected from the group consisting of:

N-1,2-Benzisoxazol-3-yl-4-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]piperidine-1-carboxamide;
4-(3-o-Tolylethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
N-1,2-Benzisoxazol-3-yl-4-(3-{[2-(trifluoromethyl)-phenyl]-ethynyl}benzyl)-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-methoxyphenyl)-ethynyl]-benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-fluorophenyl)ethynyl]-benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-bromophenyl)-ethynyl]benzyl}-piperazine-1-carboxamide;

4-(3-Ethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[3-(dimethylamino)prop-1-yn-1-yl]benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(cyclohexylethynyl)benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(cyclopentylethynyl)benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-chlorophenyl)-ethynyl]benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(3-chlorophenyl)ethynyl]benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(4-chlorophenyl)ethynyl]benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(3,4-dichlorophenyl)ethynyl]-benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(cyclopropylethynyl)benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(thiophen-3-ylethynyl)benzyl]-piperazine-1-carboxamide;

4-{3-[(2-Chlorophenyl)ethynyl]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide;

4-{3-[(2-Chlorophenyl)ethynyl]benzyl}-N-pyridazin-3-ylpiperazine-1-carboxamide;

4-{3-[(2-Chlorophenyl)ethynyl]benzyl}-N-(5-methylpyrazin-2-yl)piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2,4-dichlorophenyl)-ethynyl]benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-(3-{[2-(trifluoromethoxy)phenyl]ethynyl}benzyl)-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(3,5-dichlorophenyl)ethynyl]benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2,5-dichlorophenyl)ethynyl]benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-cyanophenyl)ethynyl]benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(naphthalen-1-ylethynyl)benzyl]piperazine-1-carboxamide;

Methyl 2-[(3-{[4-(1,2-benzisoxazol-3-ylcarbamoyl)piperazin-1-yl]methyl}phenyl)ethynyl]benzoate;

N-1,2-Benzisoxazol-3-yl-4-{3-[(3-cyanophenyl)ethynyl]benzyl}piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(1,3-benzodioxol-5-ylethynyl)benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2,3-dichlorophenyl)ethynyl]benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-cyano-3-fluorophenyl)ethynyl]benzyl}piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-(3-{[2-(cyanomethyl)phenyl]ethynyl}benzyl)piperazine-1-carboxamide;

Methyl {2-[(3-{[4-(1,2-benzisoxazol-3-ylcarbamoyl)piperazin-1-yl]methyl}phenyl)ethynyl]phenyl}acetate;

4-[3-(2-o-Tolyl-ethyl)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(Pyrimidin-2-yloxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(pyridin-2-yloxy)benzyl]piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(pyrazin-2-yloxy)benzyl]piperazine-1-carboxamide;

4-[3-(2-Cyano-benzyloxy)-benzyl]-piperazine-1-carboxylic acid
benzo[d]isoxazol-3-ylamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(benzyloxy)benzyl]piperazine-1-carboxamide;
4-(1H-Benzimidazol-6-ylmethyl)-N-1,2-benzisoxazol-3-ylpiperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(1H-indazol-6-ylmethyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[4-(methylsulfonyl)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[4-(trifluoromethoxy)benzyl]piperazine-1-
carboxamide;
4-[3-(4-Chlorophenoxy)benzyl]-N-(6-methoxypyridazin-3-yl)piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[4-chloro-3-(trifluoromethoxy)benzyl]-piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[4-fluoro-3-(trifluoromethoxy)benzyl]-piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-chloro-4-(trifluoromethoxy)benzyl]-piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-fluoro-4-(trifluoromethoxy)benzyl]-piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}-piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3-phenoxybenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3,4-dichlorobenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[4-(benzyloxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(1-benzothiophen-2-ylmethyl)piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(quinolin-6-yloxy)benzyl]piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(4-bromo-3-fluorobenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(1,3-benzodioxol-5-ylmethyl)piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(quinolin-3-ylmethyl)piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-(1H-indol-5-ylmethyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(naphthalen-2-yloxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(4-bromobenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3,4-dibromobenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(2-chlorophenoxy)benzyl]piperazine-1-carboxamide;
4-Naphthalen-2-ylmethyl-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-Quinolin-2-ylmethyl-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-Benzofuran-2-ylmethyl-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(3-chlorophenoxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[4-cyano-3-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(3-cyanophenoxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}-benzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-[(2,2-difluoro-1,3-benzodioxol-5-yl)oxy]benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}-benzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{[3-(phenylethynyl)phenyl]methyl}piperazine-1-carboxamide;
N-Isioxazol-3-yl-4-{3-[4-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
4-[4-(Benzyloxy)benzyl]-N-isioxazol-3-ylpiperazine-1-carboxamide;
4-[3-(3-Chlorophenoxy)benzyl]-N-isioxazol-3-ylpiperazine-1-carboxamide;

N-Isoxazol-3-yl-4-(3-[4-(2,2,2-trifluoroethoxy)phenoxy]benzyl)piperazine-1-carboxamide;
4-(1-Benzofuran-2-ylmethyl)-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-[3-(3-Cyanophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-[3-(2-Chlorophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-{3-[(2,2-Difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-(1-Benzothiophen-2-ylmethyl)-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-(1,3-Benzodioxol-5-ylmethyl)-N-isoxazol-3-ylpiperazine-1-carboxamide;
N-Isoxazol-3-yl-4-(naphthalen-2-ylmethyl)piperazine-1-carboxamide;
4-[3-(4-Bromophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-Quinolin-2-ylmethyl-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-(4-Bromo-benzyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-(1H-Indol-6-ylmethyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-[3-(Naphthalen-2-yloxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-(4-Bromo-3-fluoro-benzyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-[3-(4-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-[3-(3,4-Difluorophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-(3,4-Dibromobenzyl)-N-isoxazol-3-ylpiperazine-1-carboxamide;
N-Isoxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfanyl]phenoxy}benzyl)-piperazine-1-carboxamide;
4-{3-[4-Fluoro-3-(trifluoromethyl)phenoxy]benzyl}-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-[3-(3-Bromophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
N-Isoxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}benzyl)-piperazine-1-carboxamide;
N-Isoxazol-3-yl-4-{3-[3-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
4-(3,4-Dichlorobenzyl)-N-isoxazol-3-ylpiperazine-1-carboxamide;

N-Isoxazol-3-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;

N-Isoxazol-3-yl-4-[3-(quinolin-6-yloxy)benzyl]piperazine-1-carboxamide;

4-{3-[4-Cyano-3-(trifluoromethyl)phenoxy]benzyl}-N-isoxazol-3-ylpiperazine-1-carboxamide;

4-[3-(4-Chlorophenoxy)benzyl]-N-(5-methylisoxazol-3-yl)piperazine-1-carboxamide;

4-(Quinolin-3-ylmethyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;

4-[3-(Naphthalen-2-yloxy)benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;

4-(3,4-Dibromobenzyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;

4-(4-Bromo-3-fluorobenzyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;

4-[3-(3,4-Difluorophenoxy)benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;

4-{3-[4-Cyano-3-(trifluoromethyl)phenoxy]benzyl}-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;

N-1H-Tetrazol-5-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;

N-1H-Tetrazol-5-yl-4-(3-{4-[(trifluoromethyl)sulfanyl]phenoxy}benzyl)-piperazine-1-carboxamide;

N-1H-Tetrazol-5-yl-4-{3-[3-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;

4-[3-(3,4-Dichlorophenoxy)benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;

4-(Quinolin-2-ylmethyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;

4-(Naphthalen-2-ylmethyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;

4-(4-Bromo-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;

4-(1H-Indol-6-ylmethyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;

4-(3-Benzyloxy-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;

4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;

4-(3-Phenoxy-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;

4-(3,4-Dichloro-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;

4-Benzo[b]thiophen-2-ylmethyl-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;

4-[3-(3-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;

4-{3-[4-Fluoro-3-(trifluoromethyl)phenoxy]benzyl}-N-2H-tetrazol-5-ylpiperazine-1-carboxamide;

N-2H-Tetrazol-5-yl-4-{3-[3-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;

4-[3-(4-Cyanophenoxy)benzyl]-N-2H-tetrazol-5-ylpiperazine-1-carboxamide;

N-2H-Tetrazol-5-yl-4-{3-[4-(2,2,2-trifluoroethoxy)phenoxy]benzyl}-piperazine-1-carboxamide;

4-{3-[(2,2-Difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}-N-2H-tetrazol-5-ylpiperazine-1-carboxamide;

4-[3-(2-Chlorophenoxy)benzyl]-N-2H-tetrazol-5-ylpiperazine-1-carboxamide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1,5-dimethyl-1H-pyrazol-3-yl)-amide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (4-bromo-1-methyl-1H-pyrazol-3-yl)-amide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide;

4-[3-(4-Chlorophenoxy)benzyl]-N-(5-methyl-1H-pyrazol-3-yl)piperazine-1-carboxamide;

4-(3,4-Dibromobenzyl)-N-pyridazin-3-ylpiperazine-1-carboxamide;

4-[(2,2-Difluoro-1,3-benzodioxol-5-yl)methyl]-N-pyridazin-3-ylpiperazine-1-carboxamide;

N-Pyridazin-3-yl-4-(quinolin-3-ylmethyl)piperazine-1-carboxamide;

N-Pyridazin-3-yl-4-(quinolin-2-ylmethyl)piperazine-1-carboxamide;

4-(3,4-Dichlorobenzyl)-N-pyridazin-3-ylpiperazine-1-carboxamide;

4-(Naphthalen-2-ylmethyl)-N-pyridazin-3-ylpiperazine-1-carboxamide;

4-(1H-Indol-5-ylmethyl)-N-pyridazin-3-ylpiperazine-1-carboxamide;

N-2,1,3-Benzothiadiazol-4-yl-4-{[3-(phenylethynyl)phenyl]methyl}-piperazine-1-carboxamide;

N-2,1,3-Benzoxadiazol-4-yl-4-{[3-(phenylethynyl)phenyl]methyl}-piperazine-1-carboxamide;

4-[3-(3-Chloro-4-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Chloro-3-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Chloro-3-fluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3-Chloro-4-fluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Fluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Butyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[(2,2-Difluoro-1,3-benzodioxol-5-yl)methyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;

4-(1,3-Benzodioxol-5-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;

4-(4-Bromobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;

4-(Naphthalen-2-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;

N-Pyrazin-2-yl-4-{3-[4-(2,2,2-trifluoroethoxy)phenoxy]benzyl}-piperazine-1-carboxamide;

N-Pyrazin-2-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;

4-(1H-Indol-5-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;

4-(3,4-Dibromobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;

4-(1-Benzothiophen-2-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;

4-[4-(Benzyloxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;

4-(3,4-Dichlorobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;

4-[3-(4-Bromophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;

4-(4-Bromo-3-fluorobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;

4-[3-(Benzyloxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;

N-Pyrazin-2-yl-4-(quinolin-3-ylmethyl)piperazine-1-carboxamide;

4-[3-(3-Chlorophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;

N-Pyrazin-2-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}benzyl)-piperazine-1-carboxamide;
4-(3-Phenoxy-benzyl)-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-[3-(Naphthalen-2-yloxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-[3-(4-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-Benzofuran-2-ylmethyl-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-[3-(3,4-Difluorophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
N-Pyrazin-2-yl-4-[3-(quinolin-6-yloxy)benzyl]piperazine-1-carboxamide;
N-Pyrazin-2-yl-4-{3-[4-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
N-Pyrazin-2-yl-4-(3-{4-[(trifluoromethyl)sulfanyl]phenoxy}benzyl)-piperazine-1-carboxamide;
4-[3-(3-Cyanophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-{3-[4-Cyano-3-(trifluoromethyl)phenoxy]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-{3-[(2,2-Difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-[3-(2-Chlorophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
N-Pyrazin-2-yl-4-(quinolin-2-ylmethyl)piperazine-1-carboxamide;
4-[3-(3-Bromophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-{3-[4-Fluoro-3-(trifluoromethyl)phenoxy]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide;
N-Pyrazin-2-yl-4-{3-[3-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
4-[3-(4-Chlorophenoxy)benzyl]-N-(3-chloropyrazin-2-yl)piperazine-1-carboxamide;
4-[3-(4-Chlorophenoxy)benzyl]-N-(5-phenyl-1H-pyrazol-3-yl)piperazine-1-carboxamide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-fluorobenzo[d]isoxazol-3-yl)-amide; and

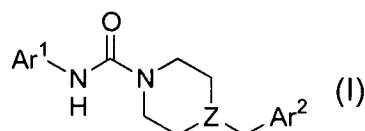
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyridazin-3-ylamide;

and pharmaceutically acceptable salts thereof.

30. A pharmaceutical composition for treating a disease, disorder, or medical condition mediated by FAAH activity, comprising:

5 (a) an effective amount of at least one active agent selected from the group consisting of:

compounds of Formula (I):



wherein:

10 Ar¹ is a benzo[d]isoxazol-3-yl, 6-fluorobenzo[d]isoxazol-3-yl, 3-phenyl-[1,2,4]thiadiazol-5-yl, 1H-tetrazol-5-yl, benzo[1,2,5]thiadiazol-4-yl, benzo[1,2,5]oxadiazol-4-yl, thiophen-2-yl, thiophen-3-yl, 6-chloro-pyridazin-3-yl, pyrazin-2-yl, isoxazol-3-yl, 1H-benzotriazol-5-yl, [1,5]naphthyridin-2-yl, quinolin-2-yl, benzothiazol-6-yl, quinolin-5-yl, 1H-pyrazol-3-yl, 5-
15 methylpyrazin-2-yl, 3-chloropyrazin-2-yl, pyridazin-3-yl, 6-methoxypyridazin-3-yl, 5-methylisoxazol-3-yl, 1,5-dimethyl-1H-pyrazol-3-yl, 4-bromo-1-methyl-1H-pyrazol-3-yl, 2-ethyl-2H-pyrazol-3-yl, 5-methyl-1H-pyrazol-3-yl, or 5-phenyl-1H-pyrazol-3-yl group;

Z is -N- or >CH; and

20 Ar² is:

(i) phenyl unsubstituted or substituted with one or two R^a moieties;

where each R^a moiety is independently -C₁₋₄alkyl, -C≡C-R^d, -OC₁₋₄alkyl, halo, -CF₃, -OCF₃, -OCH₂CF₃, -SCF₃, -S(O)₀₋₂C₁₋₄alkyl, -SO₂CF₃, -OSO₂C₁₋₄alkyl, -(CH₂)₀₋₁CO₂C₁₋₄alkyl, -CO₂H, -COC₁₋₄alkyl, -N(R^b)R^c,
25 -SO₂NR^bR^c, -NR^bSO₂R^c, -C(O)NR^bR^c, -NO₂, or -(CH₂)₀₋₁CN;
or two adjacent R^a moieties taken together form -O(CH₂)₁₋₂O- or -OCF₂O-;

where R^b and R^c are each independently -H or -C₁₋₄alkyl; and

R^d is H, C_{3-6} cycloalkyl, or $-CH_2NR^eR^f$;

where R^e and R^f are each independently H or C_{1-4} alkyl;

(ii) phenyl substituted at the 3- or 4-position with $-L-Ar^3$, unsubstituted or substituted with one or two R^a moieties, wherein:

5 L is a linker selected from the group consisting of $-(CH_2)_{1-3}-$, $-CH=CH-$, $-O-$, $-OCH_2-$, $-CH_2O-$, $-NH-$, $>NC_{1-4}$ alkyl, $-S-$, $-C\equiv C-$, $-C(=O)-$, and a covalent bond; and

Ar^3 is:

(a) phenyl;

10 (b) naphthyl; or

(c) a monocyclic or bicyclic heteroaryl group; or

(iii) a 9- or 10-membered fused bicyclic heteroaryl group;

where when Ar^1 is 6-chloro-pyridazin-3-yl, isoxazol-3-yl, or 1H-pyrazol-3-yl,

then Ar^2 is not benzo[1,3]dioxol-5-yl or 2,2-difluoro-benzo[1,3]dioxol-5-yl;

15 and pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites of said compounds of Formula (I); and
(b) a pharmaceutically acceptable excipient.

31. A pharmaceutical composition according to claim 30, wherein said
20 active agent is selected from the group consisting of:

N-1,2-Benzisoxazol-3-yl-4-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]piperidine-1-carboxamide;

4-(3-o-Tolylethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

N-1,2-Benzisoxazol-3-yl-4-(3-[(2-(trifluoromethyl)-phenyl)-ethynyl]benzyl)-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-methoxyphenyl)-ethynyl]-benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-fluorophenyl)ethynyl]-benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-bromophenyl)-ethynyl]benzyl}-piperazine-1-carboxamide;

4-(3-Ethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[3-(dimethylamino)prop-1-yn-1-yl]benzyl}-
piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(cyclohexylethynyl)benzyl]-piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(cyclopentylethynyl)benzyl]-piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[(2-chlorophenyl)-ethynyl]benzyl}-piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[(3-chlorophenyl)ethynyl]benzyl}-piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[(4-chlorophenyl)ethynyl]benzyl}-piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[(3,4-dichlorophenyl)ethynyl]-benzyl}-piperazine-
1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(cyclopropylethynyl)benzyl]-piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(thiophen-3-ylethynyl)benzyl]-piperazine-1-
carboxamide;
4-{3-[(2-Chlorophenyl)ethynyl]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-{3-[(2-Chlorophenyl)ethynyl]benzyl}-N-pyridazin-3-ylpiperazine-1-
carboxamide;
4-{3-[(2-Chlorophenyl)ethynyl]benzyl}-N-(5-methylpyrazin-2-yl)piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[(2,4-dichlorophenyl)-ethynyl]benzyl}-piperazine-
1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[[2-(trifluoromethoxy)phenyl]-ethynyl]benzyl}-
piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[(3,5-dichlorophenyl)ethynyl]benzyl}-piperazine-1-
carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[(2,5-dichlorophenyl)ethynyl]benzyl}-piperazine-1-
carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-cyanophenyl)ethynyl]benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(naphthalen-1-ylethynyl)benzyl]piperazine-1-carboxamide;

Methyl 2-[(3-{[4-(1,2-benzisoxazol-3-ylcarbamoyl)piperazin-1-yl]methyl}phenyl)ethynyl]benzoate;

N-1,2-Benzisoxazol-3-yl-4-{3-[(3-cyanophenyl)ethynyl]benzyl}piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(1,3-benzodioxol-5-ylethynyl)benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2,3-dichlorophenyl)ethynyl]benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-cyano-3-fluorophenyl)ethynyl]benzyl}piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[[2-(cyanomethyl)phenyl]ethynyl]benzyl}piperazine-1-carboxamide;

Methyl {2-[(3-{[4-(1,2-benzisoxazol-3-ylcarbamoyl)piperazin-1-yl]methyl}phenyl)ethynyl]phenyl}acetate;

4-[3-(2-o-Tolyl-ethyl)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(Pyrimidin-2-yloxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(pyridin-2-yloxy)benzyl]piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(pyrazin-2-yloxy)benzyl]piperazine-1-carboxamide;

4-[3-(2-Cyano-benzyloxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(benzyloxy)benzyl]piperazine-1-carboxamide;

4-(1H-Benzimidazol-6-ylmethyl)-N-1,2-benzisoxazol-3-ylpiperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-(1H-indazol-6-ylmethyl)piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[4-(methylsulfonyl)benzyl]piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[4-(trifluoromethoxy)benzyl]piperazine-1-carboxamide;
4-[3-(4-Chlorophenoxy)benzyl]-N-(6-methoxypyridazin-3-yl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[4-chloro-3-(trifluoromethoxy)benzyl]-piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[4-fluoro-3-(trifluoromethoxy)benzyl]-piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-chloro-4-(trifluoromethoxy)benzyl]-piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-fluoro-4-(trifluoromethoxy)benzyl]-piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}-piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3-phenoxybenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3,4-dichlorobenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[4-(benzyloxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(1-benzothiophen-2-ylmethyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(quinolin-6-yloxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(4-bromo-3-fluorobenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(1,3-benzodioxol-5-ylmethyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(quinolin-3-ylmethyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(1H-indol-5-ylmethyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(naphthalen-2-yloxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(4-bromobenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3,4-dibromobenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(2-chlorophenoxy)benzyl]piperazine-1-carboxamide;

4-Naphthalen-2-ylmethyl-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-Quinolin-2-ylmethyl-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-Benzofuran-2-ylmethyl-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(3-chlorophenoxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[4-cyano-3-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(3-cyanophenoxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}-benzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[(2,2-difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}-benzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{[3-(phenylethynyl)phenyl]methyl}piperazine-1-carboxamide;
N-Isoxazol-3-yl-4-{3-[4-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
4-[4-(Benzyloxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-[3-(3-Chlorophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
N-Isoxazol-3-yl-4-{3-[4-(2,2,2-trifluoroethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
4-(1-Benzofuran-2-ylmethyl)-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-[3-(3-Cyanophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-[3-(2-Chlorophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-{3-[(2,2-Difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}-N-isoxazol-3-ylpiperazine-1-carboxamide;

4-(1-Benzothiophen-2-ylmethyl)-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-(1,3-Benzodioxol-5-ylmethyl)-N-isoxazol-3-ylpiperazine-1-carboxamide;
N-Isloxazol-3-yl-4-(naphthalen-2-ylmethyl)piperazine-1-carboxamide;
4-[3-(4-Bromophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-Quinolin-2-ylmethyl-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-(4-Bromo-benzyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-(1H-Indol-6-ylmethyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-[3-(Naphthalen-2-yloxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-(4-Bromo-3-fluoro-benzyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-[3-(4-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-[3-(3,4-Difluorophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-(3,4-Dibromobenzyl)-N-isoxazol-3-ylpiperazine-1-carboxamide;
N-Isloxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfanyl]phenoxy}benzyl)-piperazine-1-carboxamide;
4-{3-[4-Fluoro-3-(trifluoromethyl)phenoxy]benzyl}-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-[3-(3-Bromophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
N-Isloxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}benzyl)-piperazine-1-carboxamide;
N-Isloxazol-3-yl-4-{3-[3-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
4-(3,4-Dichlorobenzyl)-N-isoxazol-3-ylpiperazine-1-carboxamide;
N-Isloxazol-3-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;
N-Isloxazol-3-yl-4-[3-(quinolin-6-yloxy)benzyl]piperazine-1-carboxamide;
4-{3-[4-Cyano-3-(trifluoromethyl)phenoxy]benzyl}-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-[3-(4-Chlorophenoxy)benzyl]-N-(5-methylisoxazol-3-yl)piperazine-1-carboxamide;

4-(Quinolin-3-ylmethyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-[3-(Naphthalen-2-yloxy)benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-(3,4-Dibromobenzyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-(4-Bromo-3-fluorobenzyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-[3-(3,4-Difluorophenoxy)benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-{3-[4-Cyano-3-(trifluoromethyl)phenoxy]benzyl}-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
N-1H-Tetrazol-5-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;
N-1H-Tetrazol-5-yl-4-(3-{4-[(trifluoromethyl)sulfanyl]phenoxy}benzyl)-piperazine-1-carboxamide;
N-1H-Tetrazol-5-yl-4-{3-[3-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
4-[3-(3,4-Dichlorophenoxy)benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-(Quinolin-2-ylmethyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-(Naphthalen-2-ylmethyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-(4-Bromo-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-(1H-Indol-6-ylmethyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-(3-Benzyloxy-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-(3-Phenoxy-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-(3,4-Dichloro-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-Benzo[b]thiophen-2-ylmethyl-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-[3-(3-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-{3-[4-Fluoro-3-(trifluoromethyl)phenoxy]benzyl}-N-2H-tetrazol-5-ylpiperazine-1-carboxamide;
N-2H-Tetrazol-5-yl-4-{3-[3-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;
4-[3-(4-Cyanophenoxy)benzyl]-N-2H-tetrazol-5-ylpiperazine-1-carboxamide;

N-2H-Tetrazol-5-yl-4-{3-[4-(2,2,2-trifluoroethoxy)phenoxy]benzyl}-piperazine-1-carboxamide;

4-{3-[(2,2-Difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}-N-2H-tetrazol-5-ylpiperazine-1-carboxamide;

4-[3-(2-Chlorophenoxy)benzyl]-N-2H-tetrazol-5-ylpiperazine-1-carboxamide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1,5-dimethyl-1H-pyrazol-3-yl)-amide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (4-bromo-1-methyl-1H-pyrazol-3-yl)-amide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide;

4-[3-(4-Chlorophenoxy)benzyl]-N-(5-methyl-1H-pyrazol-3-yl)piperazine-1-carboxamide;

4-(3,4-Dibromobenzyl)-N-pyridazin-3-ylpiperazine-1-carboxamide;

4-[(2,2-Difluoro-1,3-benzodioxol-5-yl)methyl]-N-pyridazin-3-ylpiperazine-1-carboxamide;

N-Pyridazin-3-yl-4-(quinolin-3-ylmethyl)piperazine-1-carboxamide;

N-Pyridazin-3-yl-4-(quinolin-2-ylmethyl)piperazine-1-carboxamide;

4-(3,4-Dichlorobenzyl)-N-pyridazin-3-ylpiperazine-1-carboxamide;

4-(Naphthalen-2-ylmethyl)-N-pyridazin-3-ylpiperazine-1-carboxamide;

4-(1H-Indol-5-ylmethyl)-N-pyridazin-3-ylpiperazine-1-carboxamide;

N-2,1,3-Benzothiadiazol-4-yl-4-{[3-(phenylethynyl)phenyl]methyl}-piperazine-1-carboxamide;

N-2,1,3-Benzoxadiazol-4-yl-4-{[3-(phenylethynyl)phenyl]methyl}-piperazine-1-carboxamide;

4-[3-(3-Chloro-4-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Chloro-3-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Chloro-3-fluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3-Chloro-4-fluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Fluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Butyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[(2,2-Difluoro-1,3-benzodioxol-5-yl)methyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(1,3-Benzodioxol-5-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(4-Bromobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(Naphthalen-2-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
N-Pyrazin-2-yl-4-{3-[4-(2,2,2-trifluoroethoxy)phenoxy]benzyl}-piperazine-1-carboxamide;
N-Pyrazin-2-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;
4-(1H-Indol-5-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(3,4-Dibromobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(1-Benzothiophen-2-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-[4-(Benzyloxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(3,4-Dichlorobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-[3-(4-Bromophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(4-Bromo-3-fluorobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-[3-(Benzyloxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
N-Pyrazin-2-yl-4-(quinolin-3-ylmethyl)piperazine-1-carboxamide;
4-[3-(3-Chlorophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
N-Pyrazin-2-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}benzyl)-piperazine-1-carboxamide;
4-(3-Phenoxy-benzyl)-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-[3-(Naphthalen-2-yloxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-[3-(4-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide;

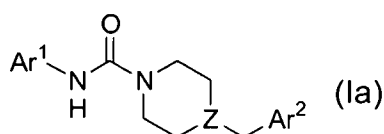
4-Benzofuran-2-ylmethyl-piperazine-1-carboxylic acid pyrazin-2-ylamide;
 4-[3-(3,4-Difluorophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
 N-Pyrazin-2-yl-4-[3-(quinolin-6-yloxy)benzyl]piperazine-1-carboxamide;
 N-Pyrazin-2-yl-4-{3-[4-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
 N-Pyrazin-2-yl-4-(3-{4-[(trifluoromethyl)sulfanyl]phenoxy}benzyl)-piperazine-1-carboxamide;
 4-[3-(3-Cyanophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
 4-{3-[4-Cyano-3-(trifluoromethyl)phenoxy]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide;
 4-{3-[(2,2-Difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide;
 4-[3-(2-Chlorophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
 N-Pyrazin-2-yl-4-(quinolin-2-ylmethyl)piperazine-1-carboxamide;
 4-[3-(3-Bromophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
 4-{3-[4-Fluoro-3-(trifluoromethyl)phenoxy]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide;
 N-Pyrazin-2-yl-4-{3-[3-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
 4-[3-(4-Chlorophenoxy)benzyl]-N-(3-chloropyrazin-2-yl)piperazine-1-carboxamide;
 4-[3-(4-Chlorophenoxy)benzyl]-N-(5-phenyl-1H-pyrazol-3-yl)piperazine-1-carboxamide;
 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-fluorobenzo[d]isoxazol-3-yl)-amide; and
 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyridazin-3-ylamide;
 and pharmaceutically acceptable salts thereof.

32. A pharmaceutical composition according to claim 30, further comprising:
 an analgesic selected from the group consisting of opioids and non-steroidal
 5 anti-inflammatory drugs.

33. A pharmaceutical composition according to claim 30, further comprising:
an additional active ingredient selected from the group consisting of aspirin,
acetaminophen, opioids, ibuprofen, naproxen, COX-2 inhibitors, gabapentin,
5 pregabalin, and tramadol.

34. A pharmaceutical composition for treating a disease, disorder, or
medical condition mediated by FAAH activity, comprising:

(a) an effective amount of at least one active agent selected from the
10 group consisting of:
compounds of Formula (Ia):



wherein:

Ar¹ is a benzo[d]isoxazol-3-yl, 6-fluorobenzo[d]isoxazol-3-yl, 3-phenyl-
15 [1,2,4]thiadiazol-5-yl, 1H-tetrazol-5-yl, benzo[1,2,5]thiadiazol-4-yl,
benzo[1,2,5]oxadiazol-4-yl, thiophen-2-yl, thiophen-3-yl, 6-chloro-pyridazin-
3-yl, pyrazin-2-yl, isoxazol-3-yl, 1H-benzotriazol-5-yl, [1,5]naphthyridin-2-yl,
quinolin-2-yl, benzothiazol-6-yl, quinolin-5-yl, or 1H-pyrazol-3-yl group;

Z is -N- or >CH; and

20 Ar² is:

- (i) phenyl or 3-phenoxyphenyl substituted with one or two R^a moieties;
where each R^a moiety is independently -C₁₋₄alkyl, -OC₁₋₄alkyl, halo,
-CF₃, -OCF₃, -OCH₂CF₃, -SCF₃, -S(O)₀₋₂C₁₋₄alkyl, -OSO₂C₁₋₄alkyl,
-CO₂C₁₋₄alkyl, -CO₂H, -COC₁₋₄alkyl, -N(R^b)R^c, -SO₂NR^bR^c,
25 -NR^bSO₂R^c, -C(O)NR^bR^c, -NO₂, or -CN;
where R^b and R^c are each independently -H or -C₁₋₄alkyl; or

- (ii) benzo[1,3]dioxol-5-yl, 2,2-difluoro-benzo[1,3]dioxol-5-yl, or naphthyl;

where when Ar¹ is 6-chloro-pyridazin-3-yl, isoxazol-3-yl, or 1H-pyrazol-3-yl,
then Ar² is not benzo[1,3]dioxol-5-yl or 2,2-difluoro-benzo[1,3]dioxol-5-yl;

and pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites of said compounds of Formula (Ia); and

(b) a pharmaceutically acceptable excipient.

5

35. A pharmaceutical composition according to claim 34, wherein said active agent is selected from the group consisting of:

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid (3-phenyl-[1,2,4]thiadiazol-5-yl)-amide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid (1H-tetrazol-5-yl)-amide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid benzo[1,2,5]oxadiazol-4-ylamide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid (3H-benzotriazol-5-yl)-amide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid thiophen-2-ylamide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid thiophen-3-ylamide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid pyrazin-2-ylamide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid isoxazol-3-ylamide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (3-phenyl-[1,2,4]thiadiazol-5-yl)-amide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (1H-tetrazol-5-yl)-amide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (2H-pyrazol-3-yl)-amide;

4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid benzo[1,2,5]oxadiazol-4-ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (1H-benzotriazol-5-yl)-amide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid [1,5]naphthyridin-2-ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid quinolin-2-ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid benzothiazol-6-ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid quinolin-5-ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-(4-Fluoro-benzyl)-piperidine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-(4-Fluoro-benzyl)-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;
4-(4-Fluoro-benzyl)-piperidine-1-carboxylic acid isoxazol-3-ylamide;
4-(3-Trifluoromethyl-benzyl)-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;
4-(3-Trifluoromethyl-benzyl)-piperidine-1-carboxylic acid isoxazol-3-ylamide;
4-(3-Trifluoromethyl-benzyl)-piperidine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Fluoro-3-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(3-Trifluoromethoxy-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Trifluoromethoxy-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(3-Bromo-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Bromo-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(3,4-Difluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3,5-Difluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid
benzo[d]isoxazol-3-ylamide;
4-{3-[4-(2,2,2-Trifluoro-ethoxy)-phenoxy]-benzyl}-piperazine-1-carboxylic acid
benzo[d]isoxazol-3-ylamide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-
3-ylamide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid
benzo[1,2,5]thiadiazol-4-ylamide;
4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid
benzo[1,2,5]thiadiazol-4-ylamide;
4-[3-(3,5-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid
benzo[1,2,5]thiadiazol-4-ylamide;
4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid
benzo[1,2,5]thiadiazol-4-ylamide;
4-(3-Trifluoromethoxy-benzyl)-piperazine-1-carboxylic acid
benzo[1,2,5]thiadiazol-4-ylamide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-chloro-
pyridazin-3-yl)-amide;
4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-chloro-
pyridazin-3-yl)-amide;
4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-chloro-
pyridazin-3-yl)-amide;
4-(4-Fluoro-3-phenoxy-benzyl)-piperazine-1-carboxylic acid (6-chloro-pyridazin-
3-yl)-amide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-
ylamide;
4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-
ylamide;
4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-
3-ylamide;
4-(4-Fluoro-3-phenoxy-benzyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide;

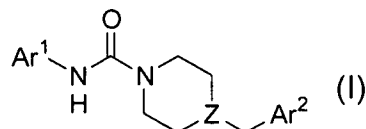
4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-(3-Trifluoromethoxy-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide;
4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide;
4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide;
4-(4-Fluoro-3-phenoxy-benzyl)-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-tetrazol-5-yl)-amide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide; and
4-(3-Trifluoromethoxy-benzyl)-piperazine-1-carboxylic acid pyrazin-2-ylamide;
and pharmaceutically acceptable salts thereof.

36. A pharmaceutical composition according to claim 34, further comprising:
an analgesic selected from the group consisting of opioids and non-steroidal
5 anti-inflammatory drugs.

37. A pharmaceutical composition according to claim 34, further comprising:
an additional active ingredient selected from the group consisting of aspirin,

acetaminophen, opioids, ibuprofen, naproxen, COX-2 inhibitors, gabapentin, pregabalin, and tramadol.

38. A method of treating a subject suffering from or diagnosed with a
 5 disease, disorder, or medical condition mediated by FAAH activity, comprising administering to the subject in need of such treatment an effective amount of at least one active selected from compounds of Formula (I):



wherein:

- 10 Ar¹ is a benzo[d]isoxazol-3-yl, 6-fluorobenzo[d]isoxazol-3-yl, 3-phenyl-[1,2,4]thiadiazol-5-yl, 1H-tetrazol-5-yl, benzo[1,2,5]thiadiazol-4-yl, benzo[1,2,5]oxadiazol-4-yl, thiophen-2-yl, thiophen-3-yl, 6-chloro-pyridazin-3-yl, pyrazin-2-yl, isoxazol-3-yl, 1H-benzotriazol-5-yl, [1,5]naphthyridin-2-yl, quinolin-2-yl, benzothiazol-6-yl, quinolin-5-yl, 1H-pyrazol-3-yl, 5-
 15 methylpyrazin-2-yl, 3-chloropyrazin-2-yl, pyridazin-3-yl, 6-methoxypyridazin-3-yl, 5-methylisoxazol-3-yl, 1,5-dimethyl-1H-pyrazol-3-yl, 4-bromo-1-methyl-1H-pyrazol-3-yl, 2-ethyl-2H-pyrazol-3-yl, 5-methyl-1H-pyrazol-3-yl, or 5-phenyl-1H-pyrazol-3-yl group;

Z is -N- or >CH; and

- 20 Ar² is:

(i) phenyl unsubstituted or substituted with one or two R^a moieties;

where each R^a moiety is independently -C₁₋₄alkyl, -C≡C-R^d, -OC₁₋₄alkyl, halo, -CF₃, -OCF₃, -OCH₂CF₃, -SCF₃, -S(O)₀₋₂C₁₋₄alkyl, -SO₂CF₃, -OSO₂C₁₋₄alkyl, -(CH₂)₀₋₁CO₂C₁₋₄alkyl, -CO₂H, -COC₁₋₄alkyl, -N(R^b)R^c,
 25 -SO₂NR^bR^c, -NR^bSO₂R^c, -C(O)NR^bR^c, -NO₂, or -(CH₂)₀₋₁CN;
 or two adjacent R^a moieties taken together form -O(CH₂)₁₋₂O- or -OCF₂O-;

where R^b and R^c are each independently -H or -C₁₋₄alkyl; and
 R^d is H, C₃₋₆cycloalkyl, or -CH₂NR^eR^f;

- 30 where R^e and R^f are each independently H or C₁₋₄alkyl;

(ii) phenyl substituted at the 3- or 4-position with $-L-Ar^3$, unsubstituted or substituted with one or two R^a moieties, wherein:

L is a linker selected from the group consisting of $-(CH_2)_{1-3}-$, $-CH=CH-$, $-O-$, $-OCH_2-$, $-CH_2O-$, $-NH-$, $>NC_{1-4}alkyl$, $-S-$, $-C\equiv C-$, $-C(=O)-$, and a covalent bond; and

Ar^3 is:

- (a) phenyl;
- (b) naphthyl; or
- (c) a monocyclic or bicyclic heteroaryl group; or

(iii) a 9- or 10-membered fused bicyclic heteroaryl group; where when Ar^1 is 6-chloro-pyridazin-3-yl, isoxazol-3-yl, or 1H-pyrazol-3-yl, then Ar^2 is not benzo[1,3]dioxol-5-yl or 2,2-difluoro-benzo[1,3]dioxol-5-yl; and pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites of said compounds of Formula (I).

39. A method according to claim 38, wherein said active agent is selected from the group consisting of:

N-1,2-Benzisoxazol-3-yl-4-[(2,2-difluoro-1,3-benzodioxol-5-yl)methyl]piperidine-1-carboxamide;

4-(3-o-Tolyethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

N-1,2-Benzisoxazol-3-yl-4-(3-[(2-(trifluoromethyl)-phenyl)-ethynyl]benzyl)-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-methoxyphenyl)-ethynyl]-benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-fluorophenyl)ethynyl]-benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[(2-bromophenyl)-ethynyl]benzyl}-piperazine-1-carboxamide;

4-(3-Ethynyl-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

N-1,2-Benzisoxazol-3-yl-4-{3-[3-(dimethylamino)prop-1-yn-1-yl]benzyl}-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(cyclohexylethynyl)benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(cyclopentylethynyl)benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-[(2-chlorophenyl)-ethynyl]benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-[(3-chlorophenyl)ethynyl]benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-[(4-chlorophenyl)ethynyl]benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-[(3,4-dichlorophenyl)ethynyl]-benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(cyclopropylethynyl)benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(thiophen-3-ylethynyl)benzyl]-piperazine-1-carboxamide;

4-{3-[(2-Chlorophenyl)ethynyl]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide;

4-{3-[(2-Chlorophenyl)ethynyl]benzyl}-N-pyridazin-3-ylpiperazine-1-carboxamide;

4-{3-[(2-Chlorophenyl)ethynyl]benzyl}-N-(5-methylpyrazin-2-yl)piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-[(2,4-dichlorophenyl)-ethynyl]benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-{[2-(trifluoromethoxy)phenyl]-ethynyl}benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-[(3,5-dichlorophenyl)ethynyl]benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-[(2,5-dichlorophenyl)ethynyl]benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-[(2-cyanophenyl)ethynyl]benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(naphthalen-1-ylethynyl)benzyl]piperazine-1-carboxamide;

Methyl 2-[(3-[[4-(1,2-benzisoxazol-3-ylcarbamoyl)piperazin-1-yl]methyl]phenyl)ethynyl]benzoate;

N-1,2-Benzisoxazol-3-yl-4-[3-[(3-cyanophenyl)ethynyl]benzyl]piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(1,3-benzodioxol-5-ylethynyl)benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-[(2,3-dichlorophenyl)ethynyl]benzyl]-piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-[(2-cyano-3-fluorophenyl)ethynyl]benzyl]piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-[(2-(cyanomethyl)phenyl)ethynyl]benzyl]piperazine-1-carboxamide;

Methyl 2-[(3-[[4-(1,2-benzisoxazol-3-ylcarbamoyl)piperazin-1-yl]methyl]phenyl)ethynyl]phenyl}acetate;

4-[3-(2-o-Tolyl-ethyl)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(Pyrimidin-2-yloxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(pyridin-2-yloxy)benzyl]piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(pyrazin-2-yloxy)benzyl]piperazine-1-carboxamide;

4-[3-(2-Cyano-benzyloxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

N-1,2-Benzisoxazol-3-yl-4-[3-(benzyloxy)benzyl]piperazine-1-carboxamide;

4-(1H-Benzimidazol-6-ylmethyl)-N-1,2-benzisoxazol-3-ylpiperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-(1H-indazol-6-ylmethyl)piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[4-(methylsulfonyl)benzyl]piperazine-1-carboxamide;

N-1,2-Benzisoxazol-3-yl-4-[4-(trifluoromethoxy)benzyl]piperazine-1-carboxamide;

4-[3-(4-Chlorophenoxy)benzyl]-N-(6-methoxypyridazin-3-yl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[4-chloro-3-(trifluoromethoxy)benzyl]-piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[4-fluoro-3-(trifluoromethoxy)benzyl]-piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-chloro-4-(trifluoromethoxy)benzyl]-piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-fluoro-4-(trifluoromethoxy)benzyl]-piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}-piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3-phenoxybenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3,4-dichlorobenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[4-(benzyloxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(1-benzothiophen-2-ylmethyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(quinolin-6-yloxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(4-bromo-3-fluorobenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(1,3-benzodioxol-5-ylmethyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(quinolin-3-ylmethyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(1H-indol-5-ylmethyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(naphthalen-2-yloxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(4-bromobenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3,4-dibromobenzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(2-chlorophenoxy)benzyl]piperazine-1-carboxamide;
4-Naphthalen-2-ylmethyl-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-Quinolin-2-ylmethyl-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-Benzofuran-2-ylmethyl-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(3-chlorophenoxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[4-cyano-3-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-[3-(3-cyanophenoxy)benzyl]piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfanyl]phenoxy}-benzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{3-[(2,2-difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}-benzyl)piperazine-1-carboxamide;
N-1,2-Benzisoxazol-3-yl-4-{[3-(phenylethynyl)phenyl]methyl}piperazine-1-carboxamide;
N-Isioxazol-3-yl-4-{3-[4-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
4-[4-(Benzyloxy)benzyl]-N-isioxazol-3-ylpiperazine-1-carboxamide;
4-[3-(3-Chlorophenoxy)benzyl]-N-isioxazol-3-ylpiperazine-1-carboxamide;
N-Isioxazol-3-yl-4-{3-[4-(2,2,2-trifluoroethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
4-(1-Benzofuran-2-ylmethyl)-N-isioxazol-3-ylpiperazine-1-carboxamide;
4-[3-(3-Cyanophenoxy)benzyl]-N-isioxazol-3-ylpiperazine-1-carboxamide;
4-[3-(2-Chlorophenoxy)benzyl]-N-isioxazol-3-ylpiperazine-1-carboxamide;
4-{3-[(2,2-Difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}-N-isioxazol-3-ylpiperazine-1-carboxamide;
4-(1-Benzothiophen-2-ylmethyl)-N-isioxazol-3-ylpiperazine-1-carboxamide;
4-(1,3-Benzodioxol-5-ylmethyl)-N-isioxazol-3-ylpiperazine-1-carboxamide;

N-Isoxazol-3-yl-4-(naphthalen-2-ylmethyl)piperazine-1-carboxamide;
4-[3-(4-Bromophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-Quinolin-2-ylmethyl-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-(4-Bromo-benzyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-(1H-Indol-6-ylmethyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-[3-(Naphthalen-2-yloxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-(4-Bromo-3-fluoro-benzyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-[3-(4-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide;
4-[3-(3,4-Difluorophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-(3,4-Dibromobenzyl)-N-isoxazol-3-ylpiperazine-1-carboxamide;
N-Isoxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfanyl]phenoxy}benzyl)-piperazine-1-carboxamide;
4-{3-[4-Fluoro-3-(trifluoromethyl)phenoxy]benzyl}-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-[3-(3-Bromophenoxy)benzyl]-N-isoxazol-3-ylpiperazine-1-carboxamide;
N-Isoxazol-3-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}benzyl)-piperazine-1-carboxamide;
N-Isoxazol-3-yl-4-{3-[3-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
4-(3,4-Dichlorobenzyl)-N-isoxazol-3-ylpiperazine-1-carboxamide;
N-Isoxazol-3-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;
N-Isoxazol-3-yl-4-[3-(quinolin-6-yloxy)benzyl]piperazine-1-carboxamide;
4-{3-[4-Cyano-3-(trifluoromethyl)phenoxy]benzyl}-N-isoxazol-3-ylpiperazine-1-carboxamide;
4-[3-(4-Chlorophenoxy)benzyl]-N-(5-methylisoxazol-3-yl)piperazine-1-carboxamide;
4-(Quinolin-3-ylmethyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-[3-(Naphthalen-2-yloxy)benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;

4-(3,4-Dibromobenzyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-(4-Bromo-3-fluorobenzyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-[3-(3,4-Difluorophenoxy)benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-{3-[4-Cyano-3-(trifluoromethyl)phenoxy]benzyl}-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
N-1H-Tetrazol-5-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;
N-1H-Tetrazol-5-yl-4-(3-{4-[(trifluoromethyl)sulfanyl]phenoxy}benzyl)-piperazine-1-carboxamide;
N-1H-Tetrazol-5-yl-4-{3-[3-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
4-[3-(3,4-Dichlorophenoxy)benzyl]-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-(Quinolin-2-ylmethyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-(Naphthalen-2-ylmethyl)-N-1H-tetrazol-5-ylpiperazine-1-carboxamide;
4-(4-Bromo-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-(1H-Indol-6-ylmethyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-(3-Benzyloxy-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-(3-Phenoxy-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-(3,4-Dichloro-benzyl)-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-Benzo[b]thiophen-2-ylmethyl-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-[3-(3-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid (2H-tetrazol-5-yl)-amide;
4-{3-[4-Fluoro-3-(trifluoromethyl)phenoxy]benzyl}-N-2H-tetrazol-5-ylpiperazine-1-carboxamide;
N-2H-Tetrazol-5-yl-4-{3-[3-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;
4-[3-(4-Cyanophenoxy)benzyl]-N-2H-tetrazol-5-ylpiperazine-1-carboxamide;
N-2H-Tetrazol-5-yl-4-{3-[4-(2,2,2-trifluoroethoxy)phenoxy]benzyl}-piperazine-1-carboxamide;

4-{3-[(2,2-Difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}-N-2H-tetrazol-5-ylpiperazine-1-carboxamide;
4-[3-(2-Chlorophenoxy)benzyl]-N-2H-tetrazol-5-ylpiperazine-1-carboxamide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1,5-dimethyl-1H-pyrazol-3-yl)-amide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (4-bromo-1-methyl-1H-pyrazol-3-yl)-amide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (2-ethyl-2H-pyrazol-3-yl)-amide;
4-[3-(4-Chlorophenoxy)benzyl]-N-(5-methyl-1H-pyrazol-3-yl)piperazine-1-carboxamide;
4-(3,4-Dibromobenzyl)-N-pyridazin-3-ylpiperazine-1-carboxamide;
4-[(2,2-Difluoro-1,3-benzodioxol-5-yl)methyl]-N-pyridazin-3-ylpiperazine-1-carboxamide;
N-Pyridazin-3-yl-4-(quinolin-3-ylmethyl)piperazine-1-carboxamide;
N-Pyridazin-3-yl-4-(quinolin-2-ylmethyl)piperazine-1-carboxamide;
4-(3,4-Dichlorobenzyl)-N-pyridazin-3-ylpiperazine-1-carboxamide;
4-(Naphthalen-2-ylmethyl)-N-pyridazin-3-ylpiperazine-1-carboxamide;
4-(1H-Indol-5-ylmethyl)-N-pyridazin-3-ylpiperazine-1-carboxamide;
N-2,1,3-Benzothiadiazol-4-yl-4-[[3-(phenylethynyl)phenyl]methyl]-piperazine-1-carboxamide;
N-2,1,3-Benzoxadiazol-4-yl-4-[[3-(phenylethynyl)phenyl]methyl]-piperazine-1-carboxamide;
4-[3-(3-Chloro-4-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Chloro-3-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Chloro-3-fluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(3-Chloro-4-fluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Fluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[3-(4-Butyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-[(2,2-Difluoro-1,3-benzodioxol-5-yl)methyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(1,3-Benzodioxol-5-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(4-Bromobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(Naphthalen-2-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
N-Pyrazin-2-yl-4-{3-[4-(2,2,2-trifluoroethoxy)phenoxy]benzyl}-piperazine-1-carboxamide;
N-Pyrazin-2-yl-4-{3-[4-(trifluoromethyl)phenoxy]benzyl}piperazine-1-carboxamide;
4-(1H-Indol-5-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(3,4-Dibromobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(1-Benzothiophen-2-ylmethyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-[4-(Benzyloxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(3,4-Dichlorobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-[3-(4-Bromophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-(4-Bromo-3-fluorobenzyl)-N-pyrazin-2-ylpiperazine-1-carboxamide;
4-[3-(Benzyloxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
N-Pyrazin-2-yl-4-(quinolin-3-ylmethyl)piperazine-1-carboxamide;
4-[3-(3-Chlorophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
N-Pyrazin-2-yl-4-(3-{4-[(trifluoromethyl)sulfonyl]phenoxy}benzyl)-piperazine-1-carboxamide;
4-(3-Phenoxy-benzyl)-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-[3-(Naphthalen-2-yloxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-[3-(4-Cyano-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-Benzofuran-2-ylmethyl-piperazine-1-carboxylic acid pyrazin-2-ylamide;
4-[3-(3,4-Difluorophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;

N-Pyrazin-2-yl-4-[3-(quinolin-6-yloxy)benzyl]piperazine-1-carboxamide;
 N-Pyrazin-2-yl-4-{3-[4-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
 N-Pyrazin-2-yl-4-(3-{4-[(trifluoromethyl)sulfanyl]phenoxy}benzyl)-piperazine-1-carboxamide;
 4-[3-(3-Cyanophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
 4-{3-[4-Cyano-3-(trifluoromethyl)phenoxy]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide;
 4-{3-[(2,2-Difluoro-1,3-benzodioxol-5-yl)oxy]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide;
 4-[3-(2-Chlorophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
 N-Pyrazin-2-yl-4-(quinolin-2-ylmethyl)piperazine-1-carboxamide;
 4-[3-(3-Bromophenoxy)benzyl]-N-pyrazin-2-ylpiperazine-1-carboxamide;
 4-{3-[4-Fluoro-3-(trifluoromethyl)phenoxy]benzyl}-N-pyrazin-2-ylpiperazine-1-carboxamide;
 N-Pyrazin-2-yl-4-{3-[3-(trifluoromethoxy)phenoxy]benzyl}piperazine-1-carboxamide;
 4-[3-(4-Chlorophenoxy)benzyl]-N-(3-chloropyrazin-2-yl)piperazine-1-carboxamide;
 4-[3-(4-Chlorophenoxy)benzyl]-N-(5-phenyl-1H-pyrazol-3-yl)piperazine-1-carboxamide;
 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-fluoro-benzo[d]isoxazol-3-yl)-amide; and
 4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyridazin-3-ylamide;
 and pharmaceutically acceptable salts thereof.

40. A method according to claim 38, wherein the disease, disorder, or medical condition is selected from the group consisting of: anxiety, depression, pain, sleep disorders, eating disorders, inflammation, movement disorders, HIV wasting syndrome, closed head injury, stroke, learning and memory disorders, Alzheimer's disease, epilepsy, Tourette's syndrome, Niemann-Pick disease,

Parkinson's disease, Huntington's chorea, optic neuritis, autoimmune uveitis, drug withdrawal, nausea, emesis, sexual dysfunction, post-traumatic stress disorder, cerebral vasospasm, glaucoma, irritable bowel syndrome, inflammatory bowel disease, immunosuppression, gastroesophageal reflux disease, paralytic ileus, secretory diarrhea, gastric ulcer, rheumatoid arthritis, unwanted pregnancy, hypertension, cancer, hepatitis, allergic airway disease, autoimmune diabetes, intractable pruritis, and neuroinflammation.

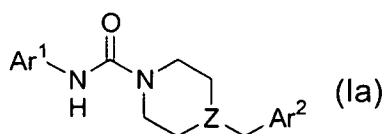
41. A method according to claim 38, wherein the disease, disorder, or medical condition is pain or inflammation.

42. A method according to claim 38, wherein the disease, disorder, or medical condition is anxiety, a sleep disorder, an eating disorder, or a movement disorder.

43. A method according to claim 38, wherein the disease, disorder, or medical condition is multiple sclerosis.

44. A method according to claim 38, wherein the disease, disorder, or medical condition is energy metabolism or bone homeostasis.

45. A method of treating a subject suffering from or diagnosed with a disease, disorder, or medical condition mediated by FAAH activity, comprising administering to the subject in need of such treatment an effective amount of at least one active selected from compounds of Formula (Ia):



wherein:

Ar¹ is a benzo[d]isoxazol-3-yl, 6-fluorobenzo[d]isoxazol-3-yl, 3-phenyl-
[1,2,4]thiadiazol-5-yl, 1H-tetrazol-5-yl, benzo[1,2,5]thiadiazol-4-yl,
benzo[1,2,5]oxadiazol-4-yl, thiophen-2-yl, thiophen-3-yl, 6-chloro-pyridazin-

3-yl, pyrazin-2-yl, isoxazol-3-yl, 1H-benzotriazol-5-yl, [1,5]naphthyridin-2-yl, quinolin-2-yl, benzothiazol-6-yl, quinolin-5-yl, or 1H-pyrazol-3-yl group;

Z is -N- or >CH; and

Ar² is:

5 (i) phenyl or 3-phenoxyphenyl substituted with one or two R^a moieties;

where each R^a moiety is independently -C₁₋₄alkyl, -OC₁₋₄alkyl, halo, -CF₃, -OCF₃, -OCH₂CF₃, -SCF₃, -S(O)₀₋₂C₁₋₄alkyl, -OSO₂C₁₋₄alkyl, -CO₂C₁₋₄alkyl, -CO₂H, -COC₁₋₄alkyl, -N(R^b)R^c, -SO₂NR^bR^c, -NR^bSO₂R^c, -C(O)NR^bR^c, -NO₂, or -CN;

10 where R^b and R^c are each independently -H or -C₁₋₄alkyl; or

(ii) benzo[1,3]dioxol-5-yl, 2,2-difluoro-benzo[1,3]dioxol-5-yl, or naphthyl;

where when Ar¹ is 6-chloro-pyridazin-3-yl, isoxazol-3-yl, or 1H-pyrazol-3-yl, then Ar² is not benzo[1,3]dioxol-5-yl or 2,2-difluoro-benzo[1,3]dioxol-5-yl; and

15 pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites of said compounds of Formula (Ia).

46. A method according to claim 45, wherein said active agent is selected from the group consisting of:

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid (3-phenyl-[1,2,4]thiadiazol-5-yl)-amide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid (1H-tetrazol-5-yl)-amide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid benzo[1,2,5]oxadiazol-4-ylamide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid (3H-benzotriazol-5-yl)-amide;

4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid
thiophen-2-ylamide;
4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid
thiophen-3-ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-
amide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid pyrazin-2-ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid isoxazol-3-ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (3-phenyl-
[1,2,4]thiadiazol-5-yl)-amide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (1H-tetrazol-5-yl)-amide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (2H-pyrazol-3-yl)-amide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid benzo[1,2,5]oxadiazol-4-
ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid (1H-benzotriazol-5-yl)-
amide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid [1,5]naphthyridin-2-
ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid quinolin-2-ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid benzothiazol-6-ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid quinolin-5-ylamide;
4-Naphthalen-2-ylmethyl-piperidine-1-carboxylic acid benzo[d]isoxazol-3-
ylamide;
4-(4-Fluoro-benzyl)-piperidine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;
4-(4-Fluoro-benzyl)-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;
4-(4-Fluoro-benzyl)-piperidine-1-carboxylic acid isoxazol-3-ylamide;
4-(3-Trifluoromethyl-benzyl)-piperidine-1-carboxylic acid (6-chloro-pyridazin-3-
yl)-amide;
4-(3-Trifluoromethyl-benzyl)-piperidine-1-carboxylic acid isoxazol-3-ylamide;
4-(3-Trifluoromethyl-benzyl)-piperidine-1-carboxylic acid benzo[d]isoxazol-3-
ylamide;

4-[3-(4-Fluoro-3-trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3-Trifluoromethoxy-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Trifluoromethoxy-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3-Bromo-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Bromo-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3,4-Difluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3,5-Difluoro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-[4-(2,2,2-Trifluoro-ethoxy)-phenoxy]-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide;

4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide;

4-[3-(3,5-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide;

4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide;

4-(3-Trifluoromethoxy-benzyl)-piperazine-1-carboxylic acid benzo[1,2,5]thiadiazol-4-ylamide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;

4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;

4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;

4-(4-Fluoro-3-phenoxy-benzyl)-piperazine-1-carboxylic acid (6-chloro-pyridazin-3-yl)-amide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide;

4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide;

4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid isoxazol-3-ylamide;

4-(4-Fluoro-3-phenoxy-benzyl)-piperazine-1-carboxylic acid isoxazol-3-ylamide;

4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-(3-Trifluoromethoxy-benzyl)-piperazine-1-carboxylic acid benzo[d]isoxazol-3-ylamide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide;

4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide;

4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide;

4-(4-Fluoro-3-phenoxy-benzyl)-piperazine-1-carboxylic acid (1H-pyrazol-3-yl)-amide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid (1H-tetrazol-5-yl)-amide;

4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide;

4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide;

4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid pyrazin-2-ylamide; and
4-(3-Trifluoromethoxy-benzyl)-piperazine-1-carboxylic acid pyrazin-2-ylamide;
and pharmaceutically acceptable salts thereof.

47. A method according to claim 45, wherein the disease, disorder, or medical condition is selected from the group consisting of: anxiety, depression, pain, sleep disorders, eating disorders, inflammation, movement disorders, HIV wasting syndrome, closed head injury, stroke, learning and memory disorders, Alzheimer's disease, epilepsy, Tourette's syndrome, Niemann-Pick disease, Parkinson's disease, Huntington's chorea, optic neuritis, autoimmune uveitis, drug withdrawal, nausea, emesis, sexual dysfunction, post-traumatic stress disorder, cerebral vasospasm, glaucoma, irritable bowel syndrome, inflammatory bowel disease, immunosuppression, gastroesophageal reflux disease, paralytic ileus, secretory diarrhea, gastric ulcer, rheumatoid arthritis, unwanted pregnancy, hypertension, cancer, hepatitis, allergic airway disease, autoimmune diabetes, intractable pruritis, and neuroinflammation.

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48. A method according to claim 45, wherein the disease, disorder, or medical condition is pain or inflammation.

49. A method according to claim 45, wherein the disease, disorder, or medical condition is anxiety, a sleep disorder, an eating disorder, or a movement disorder.

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50. A method according to claim 45, wherein the disease, disorder, or medical condition is multiple sclerosis.

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51. A method according to claim 45, wherein the disease, disorder, or medical condition is energy metabolism or bone homeostasis.