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(54) **4-(Benzil)-piperazin-1-karbonsav-fenilamid-származékok és rokon vegyületek mint a zsírsavamid-hidroláz (faah) modulátorai szorongás, fájdalom és más megbetegedések kezelésére**

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(54) **4-(BENZYL)-PIPERAZINE-1-CARBOXYLIC ACID PHENYLAMIDE DERIVATIVES AND RELATED COMPOUNDS AS MODULATORS OF FATTY ACID AMIDE HYDROLASE (FAAH) FOR THE TREATMENT OF ANXIETY, PAIN AND OTHER CONDITIONS**

4-(BENZYL)-PIPERAZIN-1-CARBONSÄURE PHENYLAMID-DERIVATE UND VERWANDTE VERBINDUNGEN ALS MODULATOREN DER FETTSÄUREAMIDHYDROLASE (FAAH) ZUR BEHANDLUNG VON ANGSTZUSTÄNDEN, SCHMERZ UND ANDEREN ERKRANKUNGEN

DÉRIVÉS D'PHÉNYLAMIDES DE 4-(BENZYL)-PIPÉRAZINE-1-ACIDE CARBOXYLIQUE ET COMPOSÉS SIMILAIRES EN TANT QUE MODULATEURS DE L'HYDROLASE DES AMIDES D'ACIDES GRAS (FAAH) POUR LE TRAITEMENT DE L'ANXIÉTÉ, DE LA DOULEUR ET D'AUTRES ÉTATS

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Description

Cross-Reference to Related Application

[0001] This application claims priority to United States Provisional Application No. 60/640,869, filed December 30, 2004.

Field of the Invention

[0002] The present invention relates to certain piperazinyl and piperidinyl urea compounds, pharmaceutical compositions containing them, and these compounds and pharmaceutical compositions for use in methods for treatment of disease states, disorders, and conditions mediated by fatty acid amide hydrolase (FAAH) activity.

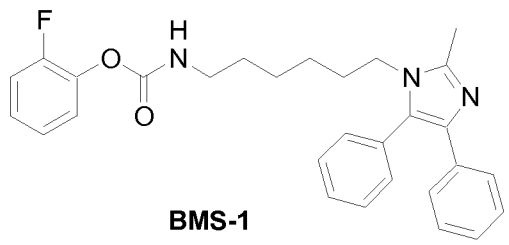
Background of the Invention

[0003] Medicinal benefits have been attributed to the cannabis plant for centuries. The primary bioactive constituent of cannabis is Δ^9-tetrahydro-cannabinol (THC). The discovery of THC eventually led to the identification of two endogenous cannabinoid receptors responsible for its pharmacological actions, namely CB_1 and CB_2 (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 "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).

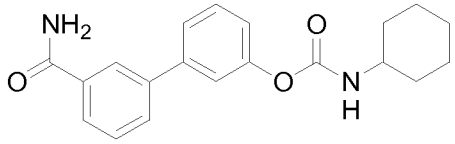
[0004] The catabolism of AEA is primarily attributable to the integral membrane bound protein fatty acid amide hydrolase (FAAH), which hydrolyzes AEA to arachidonic acid. FAAH was characterized in 1996 by Cravatt and co-workers (Cravatt, Nature 1996, 384, 83). It was subsequently determined that FAAH is additionally responsible for the catabolism of a large number of important lipid signaling fatty acid amides including: another major endocannabinoid, 2-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).

[0005] 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.

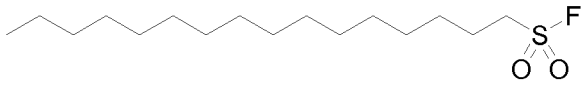
[0006] In particular, two carbamate-based inhibitors of FAAH were reported to have analgesic properties in animal models. In rats, BMS-1 (see WO 02/087569), which has the structure shown below, was reported to have an analgesic effect in the Chung spinal nerve ligation model of neuropathic pain, and 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).



BMS-1

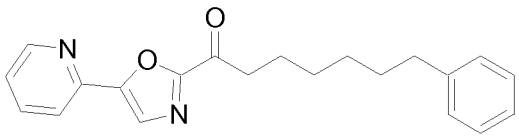


URB-597



AM-374

[0007] 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

[0008] 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, 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 available in some countries for these indications, namely, dronabinol (Marinol®) and nabilone.

[0009] 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 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 was reported to have been initiated in Germany in May 2002.

[0010] A number of individuals with multiple sclerosis have claimed a benefit from cannabis for both disease-related pain and spasticity, with support from small controlled trials (Svendsen, Br. Med. J. 2004, 329, 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 CB_1 and CB_2 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).

[0011] Reports of small-scale controlled trials have been conducted 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 control intraocular pressure (Robson, **2001**).

[0012] Inhibition of FAAH using a small-molecule inhibitor may be advantageous compared to treatment with a direct-acting CB_1 agonist. Administration of exogenous CB_1 agonists may produce a range of responses, including reduced nociception, catalepsy, hypothermia, and increased feeding 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 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 in tissue regions where synthesis and release of these signaling molecules is occurring in a given pathophysiological condition (Piomelli, **2003**).

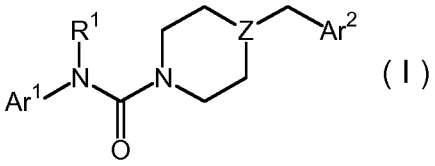
In addition to the effects of a FAAH inhibitor on AEA and other endocannabinoids, inhibitors of FAAH's catabolism of other lipid mediators may be used in treating other therapeutic indications. For example, PEA has demonstrated biological effects in animal models of inflammation, immunosuppression, analgesia, 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).

[0013] Certain piperazinyl or piperidinyl derivatives have been disclosed in the literature for different uses. For example, WO 01/36386 describes dipiperazine derivatives as a remedy for diabetes; JP 11139969 describes certain phenol derivatives as antioxidants and ACAT inhibitors; WO 96/21648 discloses various piperazine derivatives as antitumor agents; JP 48010160 describes certain piperazine derivatives as anti-inflammatory agents; WO 04/072025 discloses certain substituted N-arylheterocycles as obesity, diabetes, and drug abuse agents; DE 2123784 and U.S. Patent No. 3,813,395 disclose various piperazinylthieno-benzothiazepines as psychotropics and anesthetics; and WO 98/37077 and WO 99/42107 describe certain piperazine-based compounds as calcitonin mimetics for treatment of bone deficits. Additionally, WO 97/42230 describes a solid-phase synthesis of certain piperazine ureas. WO 97/23458 discloses certain piperidine derivatives as intermediates toward NMDA receptor ligands. In addition, various small-molecule FAAH modulators have been reported, e.g., in WO 04/033652, U.S. Patent No. 6,462,054, U.S. Patent No. 6,096,784, WO 99/26584, WO 97/49667, and WO 96/09817. However, there is still a need for other potent FAAH modulators with desirable pharmaceutical properties.

Summary of the Invention

[0014] Certain piperazinyl or piperidinyl derivatives have now been found to have FAAH-modulating activity.

[0015] In particular, in one general aspect the invention relates to compounds of the following Formula (I)



(I)

wherein:

- Z is -N- or >CH;
- R^1 is -H or-C_{1-4}alkyl;
- Ar^1 is 2-thiazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, or phenyl, each unsubstituted or substituted at a carbon ring member with one or two R^a moieties;
  where each R^a moiety is independently selected from the group consisting of -C_{1-4}alkyl, -C_{2-4}alkenyl, -OH, -OC_{1-4}alkyl, halo, -CF_3, -OCF_3, -SCF_3, -SH, -S(O)o-$_2C_{1-4}$alkyl, -OSO_2C_{1-4}alkyl, -CO_2C_{1-4}alkyl, -CO_2H, -COC_1-$_4$alkyl, -N(R^b)R^c, -$SO_2NR^bR^c$, -$NR^bSO_2R^c$, -C(=O)NR^bR^c, -NO_2, and -CN, wherein R^b and R^c are each independently -H or -C_1-$_4$alkyl; and
- Ar^2 is:

  phenyl fused at two adjacent ring carbon atoms to a group selected from the group consisting of-$(CH_2)_{3-5}$- having 0 or 1 double bonds, -$(CH_2)_2$-$_3$O-, -OCH_2CH_2O-, and -OCF_2O- to form a fused ring structure; or phenyl substituted on adjacent ring carbon atoms with -OCH_2O- (to form 4-benzo[1,3]dioxolyl); each phenyl moiety further unsubstituted or substituted with one, two, or three R^e substituents, wherein each R^e substituent is independently selected from the group consisting of -C_{1-4}alkyl, -C_{2-4}alkenyl, -OH, -OC_{1-4}alkyl, halo, -CF_3, -OCF_3, -SCF_3, -SH, -S(O)$_{0-2}C_{1-4}$alkyl, -OSO_2C_{1-4}alkyl, -CO_2C_{1-4}alkyl, -CO_2H, -COC_{1-4}alkyl, -N(R^b)R^c, -$SO_2NR^bR^c$, -$NR^bSO_2R^c$, -C(=O)NR^bR^c, -NO_2, and -CN, wherein R^b and R^c as previously defined;

or a pharmaceutically acceptable salt of said compound.

[0016] In preferred embodiments, the compound of Formula (I) is a compound specifically described or exemplified in the detailed description below.

[0017] In a further general aspect, the invention relates to pharmaceutical compositions each comprising: (a) an effective amount of an agent selected from compounds of Formula (I) and pharmaceutically acceptable salts thereof; and (b) a pharmaceutically acceptable excipient.

[0018] In another general aspect, the invention is directed to a compound of formula (I) for use in 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 a compound of Formula (I) wherein:

- Z is as defined above;
- R^1 is as defined above;
- Ar^1 is as previously defined; and
- Ar^2 is as previously defined;

or a pharmaceutically acceptable salt of said compound.

[0019] In certain preferred embodiments of the inventive compounds for use in the method, the disease, disorder, or medical condition is selected from: anxiety, pain, sleep disorders, eating disorders, inflammation, multiple sclerosis and other movement disorders, HIV wasting syndrome, closed head injury, stroke, 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.

[0020] Additional embodiments, features, and advantages of the invention will be apparent from the following detailed

description as well as the appended claims.

Detailed Description of Invention and Its Preferred Embodiments

[0021] The invention may be more fully appreciated by reference to the following description, including the following glossary of terms and the concluding examples. As used herein, the terms "including", "containing" and "comprising" are used herein in their open, non-limiting sense.

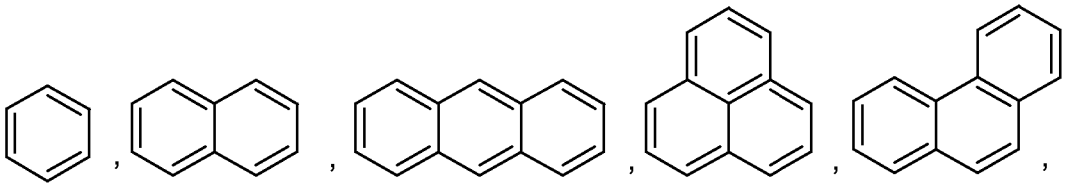
[0022] The term "alkyl" refers to a straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain. Exemplary alkyl groups include methyl (Me, which also may be structurally depicted by /), ethyl (Et), n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and the like.

[0023] The term "alkylene" refers to a divalent straight- or branched-chain alkyl group having from 1 to 12 carbon atoms in the chain. Exemplary alkylene groups include methylene, ethylene, propylene, and the like.

[0024] 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 the like.

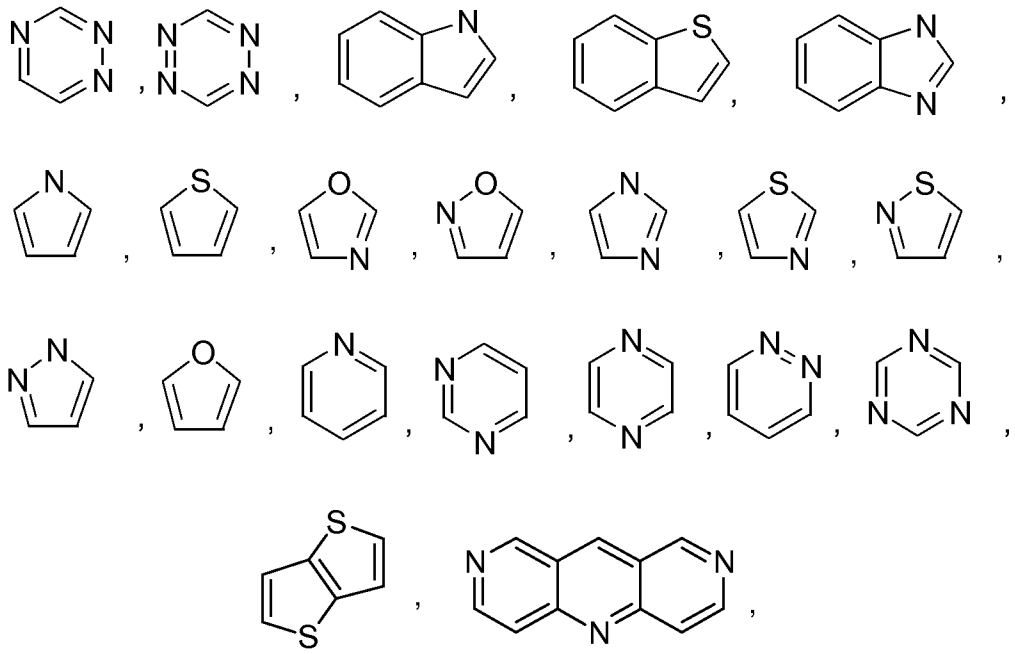
[0025] The term "alkynyl" refers to a straight- or branched-chain alkynyl group having from 2 to 12 carbon atoms in the chain. (The triple bond of the alkynyl group is formed by two sp hybridized carbon atoms.) Illustrative alkynyl groups include prop-2-ynyl, but-2-ynyl, but-3-ynyl, 2-methylbut-2-ynyl, hex-2-ynyl, and the like.

[0026] The term "aryl" refers to a monocyclic, or fused or spiro polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) having from 3 to 12 ring atoms per ring. (Carbon atoms in aryl groups are sp^2 hybridized.) Illustrative examples of aryl groups include the following moieties:



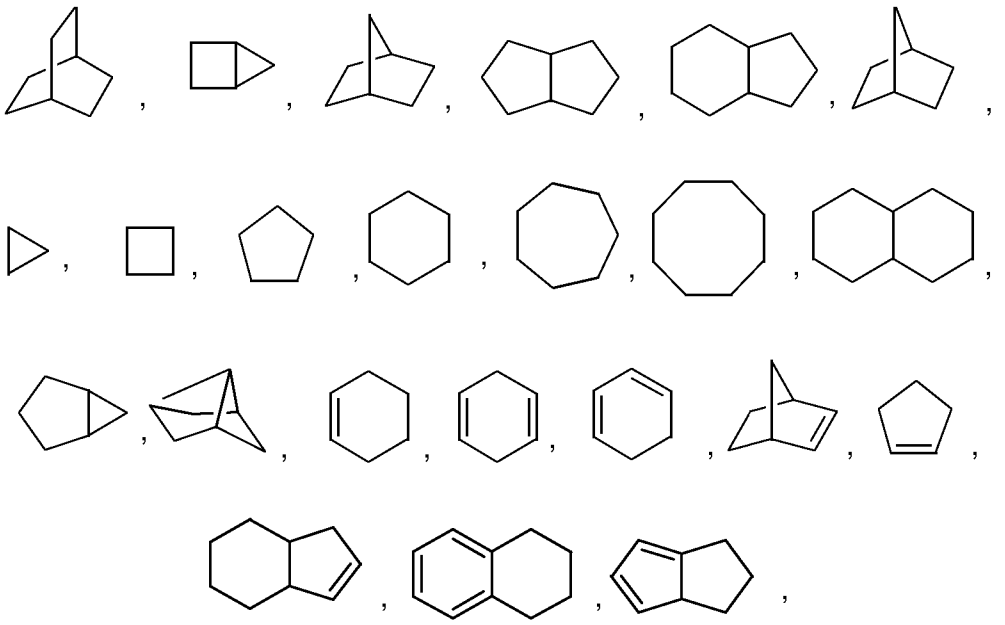
and the like.

[0027] The term "heteroaryl" refers to a monocyclic, or fused or spiro bicyclic or polycyclic, aromatic heterocycle (ring structure having ring atoms selected from carbon atoms as well as nitrogen, oxygen, and sulfur heteroatoms) having from 3 to 12 ring atoms per ring. Illustrative examples of heteroaryl groups include the following moieties:



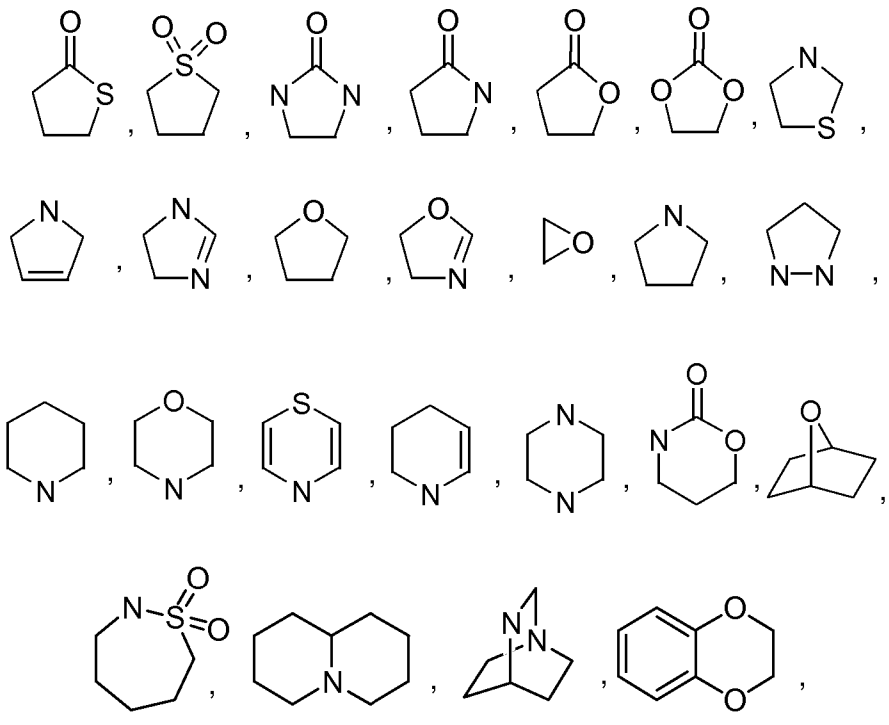
and the like.

[0028] The term "cycloalkyl" refers to a saturated or partially saturated, monocyclic or fused or spiro polycyclic, carbocycle having from 3 to 12 ring atoms per ring. Illustrative examples of cycloalkyl groups include the following moieties:



and the like.

[0029] A "heterocycloalkyl" refers to a monocyclic, or fused or spiro polycyclic, ring structure that is saturated or partially saturated and has from 3 to 12 ring atoms per ring selected from C atoms and N, O, and S heteroatoms. Illustrative examples of heterocycloalkyl groups include:



and the like.

[0030] The term "halogen" represents chlorine, fluorine, bromine or iodine. The term "halo" represents chloro, fluoro, bromo or iodo.

[0031] 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.

[0032] Formula (I) is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. In particular, compounds of 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 Formula (I) is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, and mixtures thereof.

[0033] Furthermore, certain structures depicted by Formula (I) may exist as geometric isomers (i.e., *cis* and *trans* isomers) or as tautomers. Additionally, Formula (I) is intended to represent hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

Formula (I) is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by Formula (I) except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Various isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H, ^{11}C, and ^{14}C are incorporated, are useful in drug or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may 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
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 available isotopically labeled reagent for a non-isotopically labeled reagent.

[0034] When referring to Formula (I), 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 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.

[0035] In preferred embodiments of compounds of Formula (I), the variable Z is -N-.

[0036] In other preferred embodiments, the variable R^1 is -H, methyl, ethyl, isopropyl, propyl, or t-butyl. More preferably, R^1 is -H. Alternatively, R^1 is methyl.

[0037] Preferably, Ar^1 is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, or 4-pyrimidinyl, each unsubstituted or substituted at a carbon ring atom with one or two R^a moieties as previously defined. Alternatively, Ar^1 is 2-thiazolyl. In an alternate embodiment, Ar^1 is phenyl unsubstituted or substituted at a carbon ring atom with one or two R^a moieties as previously defined. When Ar^1 is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, or phenyl, substituted with one or more R^a substituents, preferably each R^a is independently selected from methyl, ethyl, isopropyl, tert-butyl, vinyl, allyl, hydroxyl, methoxy, ethoxy, isopropoxy, fluoro, bromo, chloro, iodo, $-CF_3$, $-OCF_3$, methylsulfanyl, methylsulfoxy, methylsulfonyl, ethylsulfonyl, isopropylsulfonyl, methanesulfonyloxy, carbomethoxy, $-CO_2H$, acetyl, propionyl, amino, methylamino, dimethylamino, ethylmethylamino, $-SO_2NH_2$, $-SO_2NHCH_3$, $-NHSO_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-NO_2$, and -CN. More preferably, R^a is independently selected from the group consisting of fluoro, bromo, iodo, methoxy, methyl, carbomethoxy, and carboxy. In some preferred embodiments, Ar^1 is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-carbomethoxyphenyl, 3-carbomethoxyphenyl, 4-carbomethoxyphenyl, 2-carboxyphenyl, 3-carboxyphenyl, or unsubstituted phenyl.

[0038] Preferably, the substituent on variable Ar^2 designated as R^e is methyl, ethyl, isopropyl, tert-butyl, vinyl, allyl, hydroxyl, methoxy, ethoxy, isopropoxy, fluoro, bromo, chloro, iodo, $-CF_3$, $-OCF_3$, methylsulfanyl, methylsulfoxy, methylsulfonyl, ethylsulfonyl, isopropylsulfonyl, methanesulfonyloxy, carbomethoxy, $-CO_2H$, acetyl, propionyl, amino, methylamino, dimethylamino, ethylmethylamino, $-SO_2NH_2$, $-SO_2NHCH_3$, $-NHSO_2CH_3$, $-C(=O)NH_2$, $-C(=O)NHCH_3$, $-NO_2$, or -CN.

[0039] Preferably, Ar^2 is indanyl, indenyl, tetrahydronaphthyl, 2,3-dihydro-benzofuranyl, chromanyl, 2,3-dihydro-benzo[1,4]dioxinyl, and 2,2-difluoro-benzo[1,3]dioxolyl, wherein each phenyl moiety is unsubstituted or substituted with one, two, or three R^e substituents as previously defined.

[0040] In other more preferred embodiments, Ar^2 is unsubstituted 2,2-difluoro-benzo[1,3]dioxolyl or unsubstituted 4-benzo[1,3]dioxolyl.

[0041] Compounds of the present invention are defined in the claims. Of the following compounds, those falling within the scope of the claims are preferred compounds of the present invention, whereas those not falling within the scope of the claims are for reference only:

4-Naphthalen-2-ylmethyl-piperazine-1-carboxylic acid phenylamide;

4-Quinolin-2-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-Benzo[b]thiophen-2-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(1-Methyl-1H-indol-2-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-(4-Iodo-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(3-Benzyloxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(5-Bromo-2-hydroxy-3-methoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(4-Bromo-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(3-Phenoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(3-Bromo-4-fluoro-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-Indan-5-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-Benzo[b]thiophen-3-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-(4-Isopropyl-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(4-Ethyl-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(5-Bromo-2-hydroxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-(4-Methoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(3-Vinyl-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(2,3-Dihydro-benzofuran-5-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-(3-Methoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-Naphthalen-1-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-(2-Hydroxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(3-Methyl-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(1H-Indol-5-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-(3,4-Dimethoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-Pyridin-4-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-Pyridin-2-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-Pyridin-3-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-(4-Isopropoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-Biphenyl-4-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-Quinolin-4-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-Benzo[1,3]dioxol-4-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-(1-Methyl-1 H-indol-5-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-(6-Chloro-quinolin-2-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-(8-Chloro-quinolin-2-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-(2-Chloro-quinolin-3-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-Naphthalen-2-ylmethyl-piperazine-1-carboxylic acid (4-fluoro-phenyl)-amide;
4-Quinolin-2-ylmethyl-piperazine-1-carboxylic acid (4-fluoro-phenyl)-amide;
4-(1-Hydroxy-naphthalen-2-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-[3-(4-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-[3-(3,4-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-(3-p-Tolyloxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-[3-(4-tert-Butyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-[3-(3-Trifluoromethyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-[3-(4-Methoxy-phenoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-(6-Methoxy-naphthalen-2-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-Phenanthren-9-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-Pyren-1-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-(6-Chloro-quinolin-3-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-Biphenyl-3-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-(6-Bromo-pyridin-2-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-[3-(4-Chloro-benzenesulfonyl)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-(1H-Indol-6-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-(4-Phenoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(2-Chloro-8-methyl-quinolin-3-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-(1-Methyl-1H-indol-6-ylmethyl)-piperazine-1-carboxylic acid phenylamide;

4-(4-Benzyloxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-[3-(3,5-Dichloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-(9H-Fluoren-2-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-(9-Ethyl-9H-carbazol-3-ylmethyl)-piperazine-1-carboxylic acid phenylamide;
4-(4-Styryl-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(4-Chloro-3-trifluoromethyl-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-[2,5-Dimethyl-1-(3-trifluoromethyl-phenyl)-1H-pyrrol-3-ylmethyl]-piperazine-1-carboxylic acid phenylamide;
4-(2-Bromo-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid (3-fluoro-phenyl)-amide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid (4-fluoro-phenyl)-amide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid (3-methoxy-phenyl)-amide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid m-tolylamide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid (2-fluoro-phenyl)-amide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid (4-methoxy-phenyl)-amide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid (2-methoxy-phenyl)-amide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid (3-chloro-phenyl)-amide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid (2-chloro-phenyl)-amide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid p-tolylamide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid o-tolylamide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid (3-fluoro-phenyl)-amide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid (4-fluoro-phenyl)-amide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid (2-chloro-phenyl)-amide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid (3-chloro-phenyl)-amide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid (4-chloro-phenyl)-amide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid (2-methoxy-phenyl)-amide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid o-tolylamide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid p-tolylamide;
2-[(4-Quinolin-3-ylmethyl-piperazine-1-carbonyl)-amino]-benzoic acid methyl ester;
3-[(4-Quinolin-3-ylmethyl-piperazine-1-carbonyl)-amino]-benzoic acid methyl ester;
4-[(4-Quinolin-3-ylmethyl-piperazine-1-carbonyl)-amino]-benzoic acid methyl ester;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid (4-methoxy-phenyl)-amide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid m-tolylamide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid (3-methoxy-phenyl)-amide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid (2,4-difluoro-phenyl)-amide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid (2-fluoro-phenyl)-amide;
4-Benzyl-piperidine-1-carboxylic acid p-tolylamide;
4-Benzyl-piperidine-1-carboxylic acid m-tolylamide;
4-Benzyl-piperidine-1-carboxylic acid (2-chloro-phenyl)-amide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid pyridin-4-ylamide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid pyridin-2-ylamide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid pyridin-3-ylamide;
4-(4-Cyclohexyloxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(3-Propoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(3-Isobutoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(3-Ethoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(4-Propoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-(4-Isobutoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-[3-(2-Dimethylamino-ethoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-[3-(2-Piperidin-1-yl-ethoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-[3-(3-Dimethylamino-propoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-[3-(3-Piperidin-1-yl-propoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-(4-Ethoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-[3-(3-Chloro-phenoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-[3-(Naphthalen-2-yloxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-[3-(Phenanthren-9-yloxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-[3-(4-Phenylcarbamoyl-piperazin-1-ylmethyl)-phenoxy]-benzoic acid methyl ester;
4-[3-(4-Methanesulfonyl-phenoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;

4-[3-(3-Methoxy-phenoxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
4-[3-(Benzo[1,3]dioxol-5-yloxy)-benzyl]-piperazine-1-carboxylic acid phenylamide;
Methanesulfonic acid 3-(4-phenylcarbamoyl-piperazin-1-ylmethyl)-phenyl ester;
Benzenesulfonic acid 3-(4-phenylcarbamoyl-piperazin-1-ylmethyl)-phenyl ester;
4-Chloro-benzenesulfonic acid 3-(4-phenylcarbamoyl-piperazin-1-ylmethyl)-phenyl ester;
2-[(4-Quinolin-3-ylmethyl-piperazine-1-carbonyl)-amino]-benzoic acid (potassium salt);
3-[(4-Quinolin-3-ylmethyl-piperazine-1-carbonyl)-amino]-benzoic acid (potassium salt);
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid pyridin-3-ylamide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid pyridin-2-ylamide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid pyridin-4-ylamide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid pyrimidin-2-ylamide;
4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carboxylic acid pyridin-3-ylamide;
4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carboxylic acid pyridin-4-ylamide;
4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carboxylic acid pyrimidin-2-ylamide;
4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carboxylic acid pyridin-2-ylamide;
4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid pyridin-3-ylamide;
4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid pyridin-4-ylamide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid pyrimidin-4-ylamide;
4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid pyrimidin-4-ylamide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid pyrimidin-4-ylamide;
4-[(4-Quinolin-3-ylmethyl-piperazine-1-carbonyl)-amino]-benzoic acid;
4-Quinoxalin-2-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-(3,4-Dichloro-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-Quinolin-3-ylmethyl-piperazine-1-carboxylic acid thiazol-2-ylamide;
4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carboxylic acid thiazol-2-ylamide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid methyl-phenyl-amide;
4-(2-Methoxy-benzyl)-piperazine-1-carboxylic acid phenylamide;
4-Benzofuran-2-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid (4-nitro-phenyl)-amide;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid (4-trifluoromethyl-phenyl)-amide;
4-(5-Bromo-2-hydroxy-3-methoxy-benzyl)-piperazine-1-carboxylic acid phenylamide hydrochloride;
4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid phenylamide hydrochloride;
4-Quinolin-2-ylmethyl-piperazine-1-carboxylic acid phenylamide dihydrochloride;
4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carboxylic acid phenylamide;
4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carboxylic acid phenylamide hydrochloride; and
4-Benzo[1,3]dioxol-5-ylmethyl-piperazine-1-carboxylic acid (4-fluoro-phenyl)-amide.

[0042] The invention includes also pharmaceutically acceptable salts of the compounds represented by Formula (I), such as those described above and falling within the scope of the claims.

[0043] Pharmaceutically acceptable salts of the specific compounds exemplified herein and falling within the scope of the claims are especially preferred.

[0044] 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 not toxic,
biologically intolerable, or otherwise biologically undesirable. *See,* generally, *e.g.,* S.M. Berge, et al., "Pharmaceutical Salts", J. Pharm. Sci., 1977, 66:1-19, and Handbook of Pharmaceutical Salts, Propertions, Selection, and Use; Stahl, P.H., Wermuth, C.G., 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. Exemplary pharmaceutically acceptable salts include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogen-phosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, 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, 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, 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, naphthoic acid, or cinnamic acid, a sulfonic acid, such as laurylsulfonic acid, p-toluenesulfonic acid, methanesulfonic acid, or ethanesulfonic acid, or the like.

[0045] 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 any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide, or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such 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.

[0046] Also described herein are treatment methods employing 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 physiological conditions (e.g., a prodrug on being brought to physiological pH is converted to the compound of Formula (I)). A "pharmaceutically acceptable prodrug" is a prodrug that is not toxic, biologically intolerable, or otherwise biologically unsuitable 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.

[0047] Exemplary prodrugs include compounds having an amino acid 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-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone.

[0048] Additional types of prodrugs may be produced, for instance, by derivatizing free carboxyl groups of structures of Formula (I) as amides or alkyl esters. Exemplary amides include those derived from ammonia, primary C_{1-6}alkyl amines and secondary di(C_{1-6}alkyl) amines. Secondary amines include 5- or 6-membered heterocycloalkyl or heteroaryl ring moieties having from 1 to 3 heteroatoms where at least one is a nitrogen atom. Preferred amides are derived from ammonia, C_{1-3}alkyl primary amines, and di(C_{1-2}alkyl)amines. Exemplary esters described herein include C_{1-7}alkyl, C_{5-7}carbocyclyl, phenyl, and phenyl(C_{1-6}alkyl) 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 Adv. Drug Delivery Rev. 1996, 19, 115. 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 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 J. Med. Chem. 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including ether, amine and carboxylic acid functionalities.

[0049] Pharmaceutically active metabolites may also be used in methods described herein. 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, 224-331; 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).

[0050] The compounds of Formula (I) and their pharmaceutically acceptable salts(collectively, "agents") of the present invention are useful as FAAH inhibitors for use in the methods of the invention. The agents may be for use in the inventive methods for the treatment or prevention of medical conditions, diseases, or disorders mediated through inhibition or modulation of FAAH, such as those described herein. Agents according to the invention may therefore be used as an analgesic, neuroprotectant, sedative, appetite stimulant, or contraceptive.

[0051] Exemplary medical conditions, diseases, and disorders include anxiety, pain, sleep disorders, eating disorders, inflammation, multiple sclerosis and other movement disorders, HIV wasting syndrome, closed head injury, stroke, 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, or cerebral vasospasm.

[0052] Thus, the pharmaceutical agents may be used to treat subjects diagnosed with or suffering from a disorder or condition mediated through FAAH activity. 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 or prophylactic benefit through modulation of FAAH activity. Treating includes reversing, ameliorating, alleviating, inhibiting the progress of, lessening the severity 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.

[0053] Accordingly, the invention relates to the pharmaceutical agents described herein for use in methods of treating subjects diagnosed with or suffering from a disorder or condition mediated through FAAH activity, such as: anxiety, pain, sleep disorders, eating disorders, inflammation, or movement disorders (e.g., multiple sclerosis).

[0054] 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 and disorders, and may include various etiologies. Illustrative types of pain treatable with a FAAH-modulating agent according to the invention include cancer pain, post-operative 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, neurogenerative 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 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 example, anorexia or appetite loss associated with a disease such as cancer or HIV infection/AIDS.

[0055] In a pharmaceutical agent according to the invention for use in a treatment method according to the invention, an effective amount of a pharmaceutical agent according to the invention is administered to a subject suffering from or diagnosed as having such a disease, disorder or condition. An "effective amount" means an amount or dose sufficient to generally bring about the desired therapeutic or prophylactic benefit in patients in need of such treatment.

[0056] Effective amounts or doses of the agents of the present invention may be ascertained by routine methods such 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 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 physician. An exemplary dose is in the range of from about 0.001 to about 200 mg of agent per kg of subject's body weight per day, preferably about 0.05 to 100 mg/kg/day, or about 1 to 35 mg/kg/day, 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 0.05 to about 7 g/day, or about 0.2 to about 2.5 g/day.

[0057] Once improvement of the patient's conditions has occurred, the dose may be adjusted for preventative or 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 or prophylactic 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.

[0058] In addition, the agents of the invention may be used in combination with additional active compounds in the treatment of the above conditions. The additional compounds may be coadministered separately with an agent of Formula (I) or included with such an agent as an additional active ingredient in a pharmaceutical composition according to the invention. In an exemplary embodiment, additional active compounds 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 agent according to the invention), decrease one or more side effects, or decrease the required dose of the 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.

[0059] The agents of the invention are used, alone or in combination with one or more other active ingredients, to formulate pharmaceutical compositions of the invention. A pharmaceutical composition of the invention comprises: an

effective amount of a pharmaceutical agent in accordance with the invention; and a pharmaceutically acceptable excipient. A "pharmaceutically acceptable excipient" refers to a substance that is not toxic, biologically intolerable, or otherwise biologically unsuitable 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 pharmaceutical 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.

[0060] Delivery forms of the pharmaceutical compositions containing one or more dosage units of the pharmaceutical agents may be prepared using suitable pharmaceutical excipients and compounding techniques now or later known or available to those skilled in the art. The compositions may be administered by oral, parenteral, rectal, topical, or ocular routes or by inhalation.

[0061] 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.

[0062] For oral administration, the compounds 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 agents may be formulated to yield a dosage of, e.g., from about 0.05 to about 50 mg/kg daily, or from about 0.05 to about 20 mg/kg daily, or from about 0.1 to about 10 mg/kg daily.

[0063] Oral tablets may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavoring agents, coloring agents and preservatives 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, polyvinylpyrrolidone (PVP), sodium starch glycolate, microcrystalline cellulose, and alginic acid are suitable 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.

[0064] Capsules for oral administration include hard and soft gelatin capsules. To prepare hard gelatin capsules, active ingredient may be mixed with a solid, semisolid, 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 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.

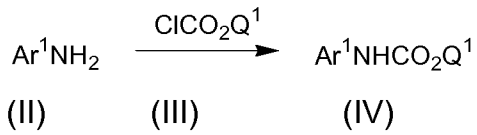
[0065] The agents of this invention may also be administered by non-oral routes. For example, the compositions may be formulated for rectal administration as a suppository. For parenteral use, including intravenous, intramuscular, intraperitoneal, or subcutaneous routes, the agents of the invention may 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 will 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 may range from about 1 to 1000 μg/kg/minute of agent, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days.

[0066] 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.

[0067] Agents may alternatively be administered in by inhalation, via the nasal or oral routes, e.g., in a spray formulation also containing a suitable carrier.

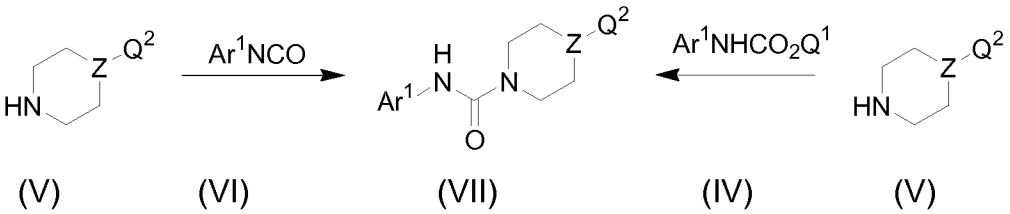
[0068] Exemplary agents for use in methods of the invention will now be described by reference to the illustrative synthetic schemes for their general preparation below and the specific examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may 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, 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:



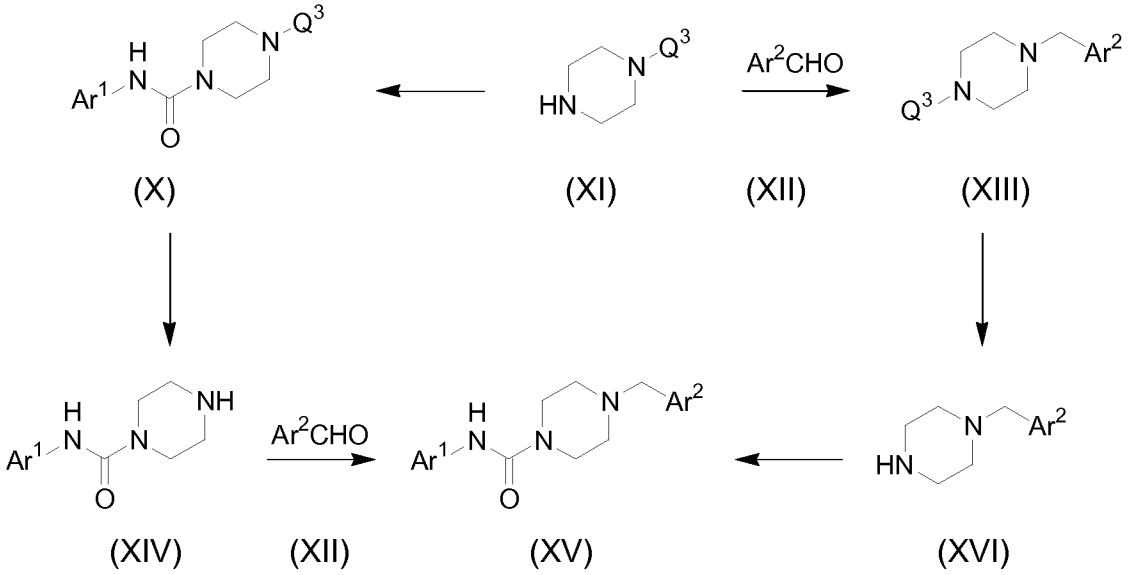
[0069] Referring to Scheme A, a compound of formula (IV) may be obtained by reacting a compound of formula (II) with a compound of formula (III), in which Q^1 represents an aryl group, under chloroformate condensation conditions. In a preferred embodiment, Q^1 is substituted or unsubstituted phenyl, and the reaction occurs in the presence of a base in a solvent at a temperature from 0 °C to 50 °C. In a particularly preferred embodiment, Q^1 is phenyl, and the reaction occurs in the presence of pyridine in dichloromethane at 0 °C followed by warming to room temperature.

SCHEME B:



[0070] Referring to Scheme B, a compound of formula (VII) is prepared from a compound of formula (V). The group Q^2 is either CH_2Ar^2 or a nitrogen protecting group Q^3 when Z is N. 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 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. In a preferred embodiment, the reaction takes place in a solvent at a temperature from room temperature to 120 °C. In a particularly preferred embodiment, Q^1 is phenyl, and the reaction is performed in DMSO in a microwave reactor at 100 °C.

SCHEME C:

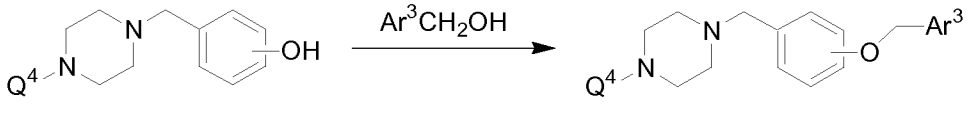


[0071] Referring to Scheme C, a compound of formula (XV) is prepared from a compound of formula (XI). A suitable protecting group Q^3 compatible with the transformations in Scheme C is selected. Preferably, Q^3 is *tert*-butyl-carbamoyl. A compound of formula (X) is obtained by reacting a compound of formula (XI) with either a compound of formula (VI) or with a compound of formula (IV) as described in Scheme B. An amine of formula (XIV) is obtained by deprotecting a

compound of formula (X) with a reagent under suitable Q^3 deprotection conditions. In a particularly preferred embodiment, a compound of formula (X), in which Q^3 is *tert*-butyl-carbamoyl, is reacted with ethereal hydrogen chloride in the presence or absence of methanol at room temperature. A compound of formula (XV) is obtained by reacting a compound of formula (XIV) with a compound of formula (XII) under reductive amination conditions in the presence of a reductant such as sodium triacetoxyborohydride, sodium cyanoborohydride, or phenylsilane in a solvent such as THF, DCE, DCM, methanol, ethanol, or diethyl ether at a temperature from 0 °C to 80 °C. The use of a promoter or catalyst with acidic character such as organometallic complexes or carboxylic acids may increase the rate of the reaction and/or reduce the formation of bypoducts. In a particularly
preferred embodiment, sodium triacetoxyborohydride in DCE is employed at room temperature.

[0072] Alternatively, a compound of formula (XIII) is obtained by reacting a compound of formula (XI) with a compound of formula (XII) under reductive amination conditions as outlined above. A compound of formula (XVI) is obtained by removing Q^3 from a compound of formula (XIII) under deprotection conditions as described above. A compound of formula (XV) is obtained by reacting a compound of formula (XVI) with either a compound of formula (IV) or with a compound of formula (VI) as described in Scheme B.

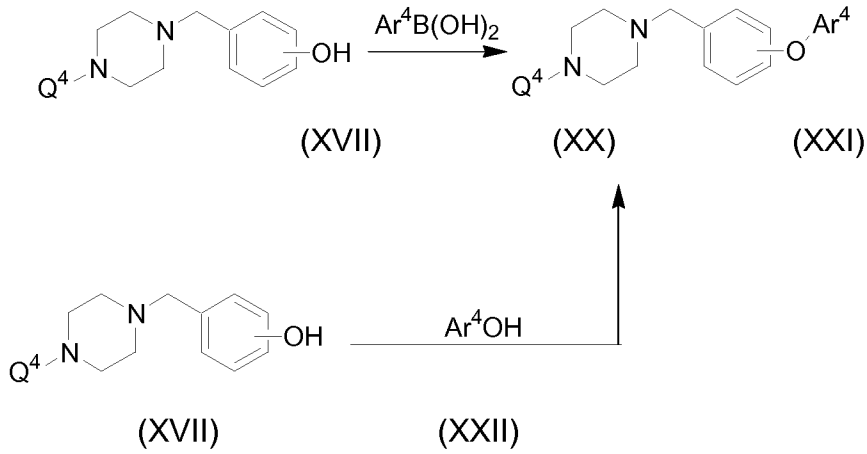
SCHEME D:



(XVII) (XVIII) (XIX)

[0073] Referring to Scheme D, a compound of formula (XIX) is prepared from a compound of formula (XVII), in which Q^4 is either $CONR^1Ar^1$ or the nitrogen protecting group Q^3. A compound of formula (XVII) is prepared in analogy with Scheme C. A compound of formula (XIX) is obtained by reacting a compound of formula (XVII) with a compound of formula (XVIII) under Mitsunobu conditions in the presence of a phosphine such as triphenylphosphine or polymer supported triphenyl phosphine, and an azodicarboxylate such as DBAD or DEAD, in an organic solvent such as DCM, THF, and the like.

SCHEME E:

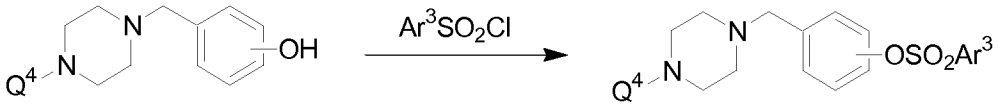


(XVII) (XX) (XXI)

(XVII) (XXII)

[0074] Referring to Scheme E, a compound of formula (XVII), where Q^4 is either $CONR^1Ar^1$ or the nitrogen protecting group Q^3, prepared in analogy with Scheme C, is converted to a compound of formula (XXI). A compound of formula (XXI), wherein Ar^4 is a moiety Ar^3 as defined in Formula (I) and is directly bound to the linking oxygen atom, is obtained by reacting a compound of formula (XVII) with a boronic acid (XX) in the presence of a drying agent such as powdered 4Å molecular sieves, a promoter such as copper(II) acetate, and a base such as pyridine or triethylamine in a solvent such as DCM or DCE. Alternatively, a compound of formula (XXI), in which Ar^4 contains an sp^3 hybridized carbon atom directly bound to the linking oxygen atom, is prepared by reacting a phenol (XVII) with a compound of formula (XXII) under Mitsunobu conditions as described in Scheme D.

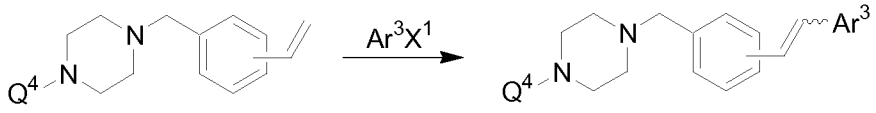
SCHEME F:



(XVII) (XXIII) (XXIV)

[0075] Referring to Scheme F, a compound of formula (XXIV), where Q^4 is defined as above, is obtained by reacting a compound of formula (XVII), where Ar^3 is a moiety as defined for Formula (I), with a compound of formula (XXIII), in the presence of a base such as pyridine or triethylamine in a solvent such as DCM at a temperature from 0 °C to room temperature.

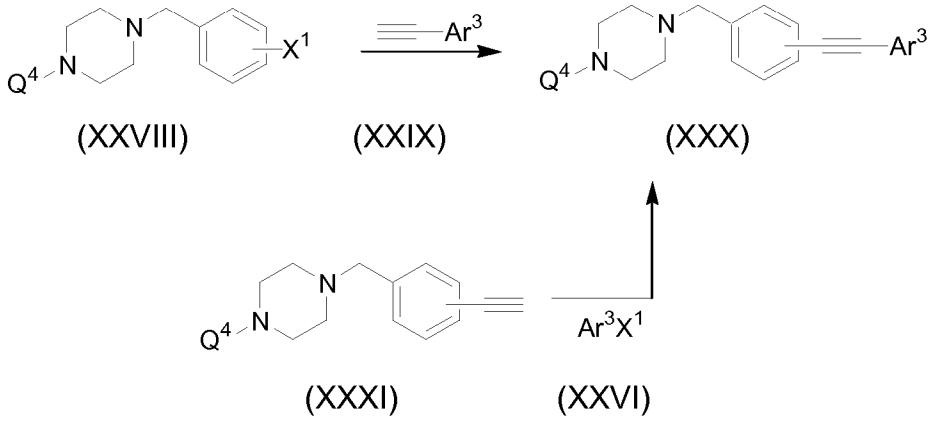
SCHEME G:



(XXV) (XXVI) (XXVII)

[0076] Referring to Scheme G, a compound of formula (XXV), , where Q^4 is defined as above and where Ar^3 is as defined for Formula (I), is obtained as described in Scheme C. Compound (XXV) is converted to a compound of formula (XXVII) by reaction with a compound of formula (XXVI), in which X^1 is iodo, bromo, chloro, or trifluoromethanesulfonate ester, under Heck conditions in the presence of a palladium source such as palladium(II) acetate, a phosphine ligand such as triphenylphosphine, an optional promoter such as tetrabutylammonium chloride, and a base such as aqueous potassium carbonate in a solvent such as DMF.

SCHEME H:



(XXVIII) (XXIX) (XXX)

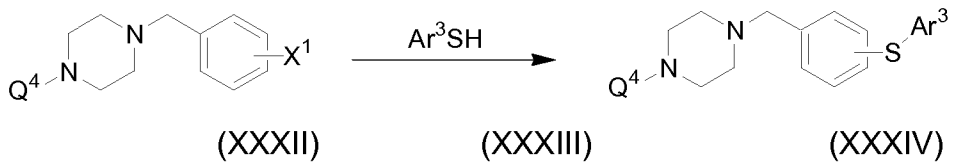
(XXXI) (XXVI)

[0077] Referring to Scheme H, a compound of formula (XXX), where Q^4 is defined as above, is prepared from a compound of formula (XXVIII) or (XXXI), each available from a preparation in analogy with Scheme C. Ar^3 and X^1 are defined as described above. A compound of formula (XXX) is prepared by reacting a compound of formula (XXVIII) with a compound of formula (XXIX) under Sonogashira conditions in the presence of a palladium-containing entity such as palladium on carbon, $Pd_2(dba)_3$, $Pd_2(dba)_3$•$CHCl_3$, $Pd(P^tBu_3)_2$, $Pd_2(dba)_3$•$CHCl_3$/ $Pd(P^tBu_3)_2$, $Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$, or $PdCl_2$ and a base such as triethylamine, DIEA, di-*iso*-propylamine, sodium carbonate, potassium carbonate, or cesium carbonate in a solvent such as THF, DME, dioxane, DCE, DCM, toluene, and acetonitrile at a temperature from 0 °C to 100 °C. The use of substoichiometric quantities of a copper salt such as CuI and phosphine ligands such as PPh_3 or $P(^tBu)_3$ may be necessary or desirable. Additionally, the use of water as a cosolvent may accelerate the reaction and prevent the formation of byproducts.

[0078] Alternatively, a compound of formula (XXX) is prepared by reacting a compound of formula (XXXI) with a

compound of formula (XXVI) using Sonogashira conditions.

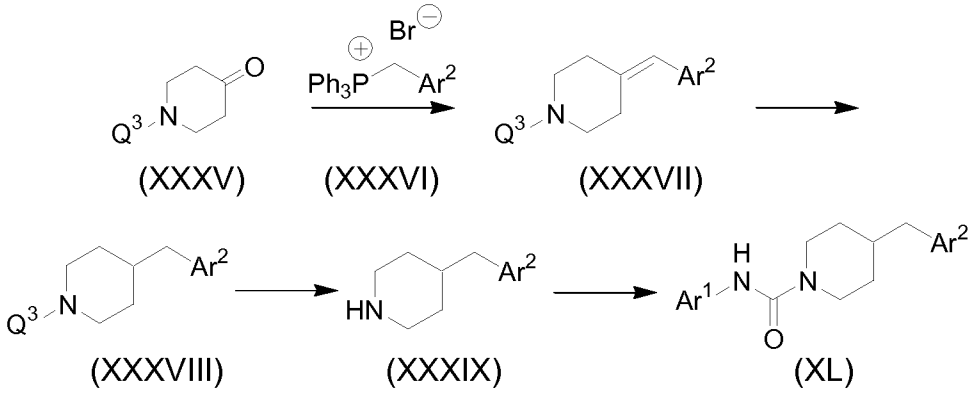
SCHEME I:



(XXXII) (XXXIII) (XXXIV)

[0079] As depicted above, a compound of formula (XXXII), where Q^4 is defined as above, prepared in analogy with Scheme C, is reacted with a compound of formula (XXXIII) in the presence of a base such as sodium hydride, and a palladium source such as tetrakis(triphenylphosphine)palladium(0), in a solvent such as *n*-butanol, at a temperature from room temperature to 116 °C.

SCHEME J:



(XXXV) (XXXVI) (XXXVII) (XXXVIII) (XXXIX) (XL)

Referring to Scheme J, a compound of formula (XL) is prepared from a compound of formula (XXXV), in which Q^3 is a nitrogen protecting group. A protecting group Q^3 compatible with the processes outlined in Scheme J is selected, e.g., benzyl. A compound of formula (XXXVI) may be obtained from a commercial source or may be prepared from a suitable bromide, alcohol, aldehyde, or other precursor following methods known in the art. A compound of formula (XXXVII) is prepared by treating a compound of formula (XXXVI) with a base such as sodium hydride in a solvent such as DMSO followed by treatment with a compound of formula (XXXV). A compound of formula (XXXVIII) is prepared by treating a compound of formula (XXXVII) with a catalyst such as platinum(II) oxide in solvent such as methanol in the presence of 10-100 psi hydrogen gas. A compound of formula (XXXIX) is prepared by reacting a compound of formula (XXXVIII) with a reagent capable of removing the protecting group Q^3. In a preferred embodiment, in which Q^3 is benzyl, suitable conditions include a catalyst such as palladium on carbon in a solvent such as ethanol in the presence of 20-100 psi hydrogen gas. A compound of formula (XL) is prepared by reacting a compound of formula (XXXIX) with either a compound of formula (IV) or a compound of formula (VI) as described in Scheme B.

[0080] The following specific examples are provided to further illustrate the invention and various preferred embodiments.

Examples

Chemistry:

[0081] In obtaining the characterization data described in the examples below, the following analytical protocols were followed as indicated.

[0082] Preparative Reversed-Phase HPLC was performed under the following conditions: Instrument, Waters®; Column, Waters Xterra C-18, 5 μm, 19x50 mm; Flow rate, 30 mL/min; Detection, λ = 254 nm; Gradient, 5% to 100% acetonitrile/water (0.1% formic acid) over 8 min.

[0083] Analytical Reversed-Phase HPLC was performed under the following conditions: Instrument, Shimadzu; Column, Princeton SPHER HTS, 5 μm, 3x50 mm; Flow rate, 2.2 mL/min; Detection, Sedex 75 ELS coupled to Finnigan AQA electrospray mass spectrometer; Gradient, 0.1 to 100% acetonitrile/water (0.1 % trifluoroacetic acid) over 8 min.

[0084] Unless otherwise specified, column chromatography was performed on silica gel, eluting with 2 M NH_3 in MeOH/DCM.

[0085] Mass spectra were obtained on a Finnigan AQA using electrospray ionization (ESI) in either positive or negative modes as indicated.

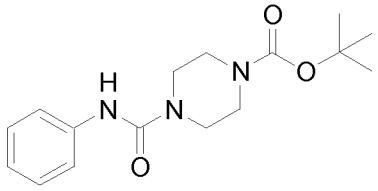
[0086] NMR spectra were obtained on either a Varian model VXR-300S (300 MHz) spectrometer. The format of the ^1H NMR data below is: chemical shift in ppm down field of the tetramethylsilane reference (multiplicity, coupling constant J in Hz, integration).

[0087] Where solutions are "concentrated", they are concentrated on a rotary evaporator under reduced pressure.

[0088] Examples 1 through 17 describe the synthesis of intermediates used to prepare certain compounds of the invention.

Example 1: 4-Phenylcarbamoyl-piperazine-1-carboxylic acid tert-butyl ester (intermediate)

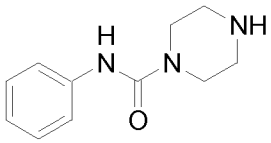
[0089]



[0090] A solution of piperazine-1-carboxylic acid tert-butyl ester (114 g) in DCM (500 mL) was cooled in an ice bath and treated with phenyl isocyanate (65 mL). After 1 hour (h), the bath was removed. After 15 h, the resulting mixture was filtered and the solid was washed with dichloromethane (DCM, 2x100 mL), giving the title compound as a white amorphous solid (95 g).

Example 2: Piperazine-1-carboxylic acid phenylamide (intermediate)

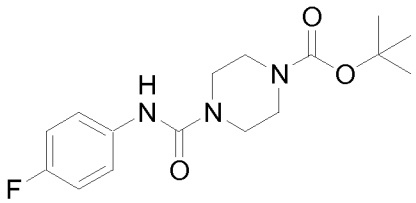
[0091]



[0092] A solution of 4-phenylcarbamoyl-piperazine-1-carboxylic acid tert-butyl ester (50 g) in MeOH (1 L) was treated with 2 M HCl in Et_2O (164 mL). After 48 h, the resulting suspension was diluted with Et_2O (1 L) and filtered. The solid was washed with Et_2O (3x100 mL) and dried *in vacuo*, giving a white powder (32 g). This powder was partitioned between DCM (400 mL) and 10% aq. KOH (400 mL). The aqueous phase was extracted with DCM (2x400 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated, giving the title compound as a white amorphous solid (26 g).

Example 3: 4-(4-Fluoro-phenylcarbamoyl)-piperazine-1-carboxylic acid tert-butyl ester (intermediate)

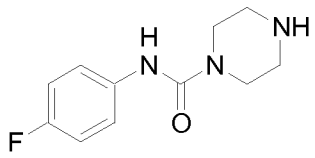
[0093]



[0094] The title compound was prepared in analogy with Example 1, using 4-fluorophenyl isocyanate.

Example 4: Piperazine-1-carboxylic acid (4-fluoro-phenyl)-amide (intermediate)

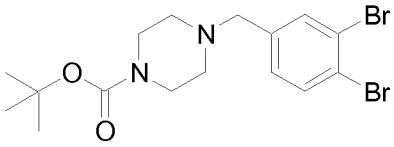
[0095]



[0096] The title compound was prepared in analogy with Example 2, using 4-(4-fluoro-phenylcarbamoyl)-piperazine-1-carboxylic acid tert-butyl ester.

Example 5: 4-(3,4-Dibromo-benzyl)-piperazine-1-carboxylic acid tert-butyl ester (intermediate)

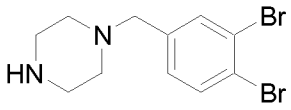
[0097]



[0098] A solution of piperazine-1-carboxylic acid tert-butyl ester (3.5 g) and 3,4-dibromobenzaldehyde (5.0 g) in DCM (80 mL) was treated with $NaB(OAc)_3H$ (5.6 g). After 16 h, the resulting mixture was treated with 10% aq. KOH (80 mL). The aqueous phase was extracted with DCM (1x80 mL). The organic extracts were combined and dried ($MgSO_4$). Most of the solvent was removed by concentration. Upon standing overnight, the resulting mixture produced crystals that were filtered and washed with DCM (1x5 mL), giving the title compound as a white crystalline solid (6.0 g).

Example 6: 1-(3,4-Dibromo-benzyl)-piperazine (intermediate)

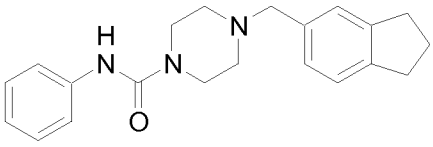
[0099]



[0100] A suspension of 4-(3,4-dibromo-benzyl)-piperazine-1-carboxylic acid tert-butyl ester (6.0 g) in MeOH (100 mL) was treated with 2 M HCl in Et_2O (28 mL). After 16 h, the resulting suspension was diluted with Et_2O (100 mL) and filtered. The solid was washed with Et_2O (2x20 mL) and dried *in vacuo,* giving a white solid (5.0 g). This solid was partitioned between 10% aq. KOH (50 mL) and DCM (3x50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to give the title compound as a colorless glassy oil.

Example 30: 4-indan-5-ylmethyl-piperazine-1-carboxylic acid phenylamide

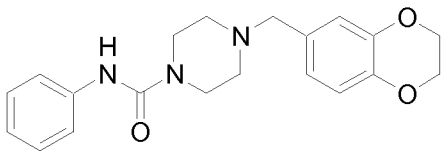
[0101]



[0102] The title compound was prepared from indan-5-carbaldehyde. ^1H NMR (400 MHz, $CDCl_3$): 7.35-7.00 (m, 8H), 6.30 (s, 1 H), 3.51-3.47 (m, 6H), 2.92-2.88 (m, 4H), 2.50-2.47 (m, 4H), 2.12-2.04 (m, 2H).

Example 35: 4-(2,3-Dihydro-benzo[1,4]dioxin-6-ylmethyl)-piperazine-1-carboxylic acid phenylamide

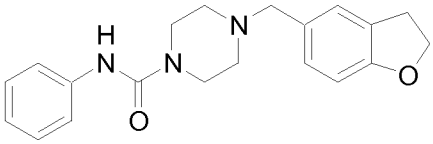
[0103]



[0104] The title compound was prepared from 2,3-dihydro-benzo[1,4]dioxine-6-carbaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): 7.36-7.25 (m, 4H), 7.05-7.00 (m, 1 H), 6.85-6.76 (m, 3H), 6.33 (br s, 1 H), 4.26 (s, 4H), 3.51-3.46 (m, 4H), 3.42 (s, 2H), 2.49-2.45 (m, 4H).

Example 38: 4-(2,3-Dihydro-benzofuran-5-ylmethyl)-piperazine-1-carboxlic acid phenylamide

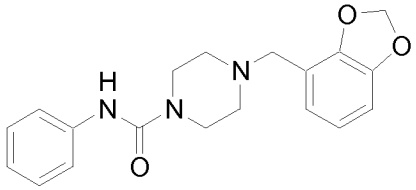
[0105]



[0106] The title compound was prepared from 2,3-dihydro-benzofuran-5-carbaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): 7.36-7.28 (m, 4H), 7.17 (s, 1 H), 7.06-7.01 (m, 1 H), 6.73 (d, J = 8.1 Hz, 1 H), 6.30 (s, 1 H), 4.60-4.55 (m, 2H), 3.51-3.46 (m, 6H), 3.23-3.19 (m, 2H), 2.49-2.47 (m, 4H).

Example 51: 4-Benzo[1,3]dioxol-4-ylmethyl-piperazine-1-carboxylic acid phenylamide

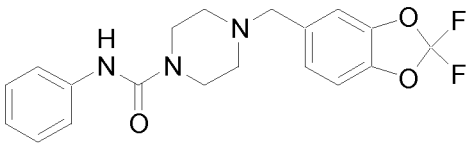
[0107]



[0108] The title compound was prepared from benzo[1,3]dioxole-4-carbaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): 7.36-7.25 (m, 4H), 7.06-7.00 (m, 1 H), 6.85-6.75 (m, 3H), 6.30 (s, 1 H), 3.57 (s, 2H), 3.54-3.49 (m, 4H), 2.56-2.50 (m, 4H).

Example 52: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid phenylamide

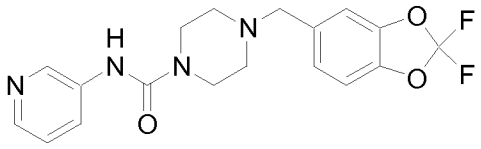
[0109]



[0110] The title compound was prepared from 2,2-difluoro-benzo[1,3]dioxole-5-carbaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): 7.37-7.25 (m, 4H), 7.12 (s, 1 H), 7.06-6.98 (m, 3H), 6.32 (s, 1 H), 3.54-3.46 (m, 6H), 2.50-2.45 (m, 4H).

Example 150: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid pyridin-3-ylamide

[0111]



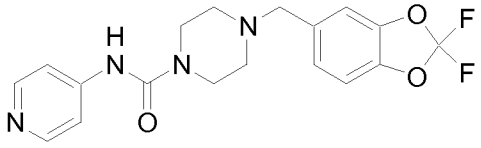
[0112] Step 1; 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester. The title compound was prepared from 2,2-difluoro-benzo[1,3]dioxole-5-carbaldehyde in analogy with Example 5.

[0113] Step 2; 1-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmetyl)-piperazine. The title compound was prepared from 4-(2,2-difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid tert-butyl ester in analogy with Example 6.

[0114] Step 3. The title compound was prepared from pyridin-3-yl-carbamic acid phenyl ester and 1-(2,2-difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine in analogy with Example 142. ^{1}H NMR (400 MHz, $CDCl_3$): 8.46 (d, J = 2.5 Hz, 1 H), 8.23-8.21 (m, 1 H), 7.99-7.96 (m, 1 H), 7.22-7.19 (m, 2H), 7.11 (s, 1 H), 6.99-6.98 (m, 2H), 3.54-3.52 (m, 4H), 3.49 (s, 2H), 2.46-2.44 (m, 4H).

Example 151: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid pyridin-4-ylamide

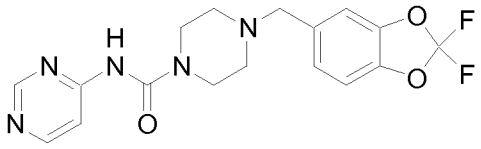
[0115]



[0116] The title compound was prepared from pyridin-4-yl-carbamic acid phenyl ester and 1-(2,2-difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine in analogy with Example 142. ^{1}H NMR (400 MHz, $CDCl_3$): 8.36-8.34 (d, J = 6.8 Hz, 2H), 7.41-7.39 (d, J = 5.8 Hz, 2H), 7.10 (s, 1 H), 6.99 (s, 2H), 3.55-3.53 (m, 4H), 3.49 (s, 2H), 2.47-2.44 (m, 4H).

Example 153: 4-(2,2-Difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine-1-carboxylic acid pyrimidin-4-ylamide

[0117]



[0118] The title compound was prepared from pyrimidin-4-yl-carbamic acid phenyl ester and 1-(2,2-difluoro-benzo[1,3]dioxol-5-ylmethyl)-piperazine in analogy with Example 142. ^{1}H NMR (400 MHz, $CDCl_3$): 8.76 (s, 1 H), 8.54 (d, J = 6.1 Hz, 1 H), 7.97 (d, J = 5.3 Hz, 1 H), 7.65-7.39 (m, 2H), 7.19-7.01 (m, 2H), 4.03-3.55 (m, 6H), 2.91-2.49 (m, 4H).

Biological Methods

Assay Method 1

[0119] T84 frozen pellets (contents of 1-4 x 15 cm culture dishes) were homogenized in 300 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 was prepared from 50 μL of the cell homogenate, 10 μL of the test compound, and 40 μL of anandamide [1-^{3}H-ethanolamine] (^{3}H-AEA; Perkin-Elmer, 10.3 C_i/mmol), which was added last, for a final tracer concentration of 200 nM. The reaction mixture was incubated at rt for 1 hour (h). During the incubation, 96-well Multiscreen filter plates (catalog number MAFCNOB50; Millipore, Bedford, Massachussetts, USA) were loaded with 25 μL of activated charcoal (Multiscreen column loader, catalog number MACL09625, Millipore) and washed once with 100 μL of MeOH. Also during the incubation, 96-well

DYNEX MicroLite plates (catalog number NL510410) were loaded with 100 μL of MicroScint40 (catalog number 6013641, Packard Bioscience, Meriden, Connecticut, USA). After the 1 h incubation, 60 μL 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. Results for compounds tested in this assay are presented in Table 1.

Table 1

Ex.	IC50 (nM)
30	180
35	460
38	620
51	6000
52	87

Assay Method 2

A. Transfection of Cells with Human FAAH

[0120] 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% CO_2 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 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 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 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

[0121] 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 Tris, 1 mM 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-^{3}H-ethanolamine] (^{3}H-AEA, Perkin-Elmer, 10.3 C_i/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, 96-well Multiscreen filter plates (catalog number MAFCNOB50; Millipore, Bedford, Massachussetts, USA) were loaded with 25 μL of activated charcoal (Multiscreen column loader, catalog number MACL09625, Millipore) and washed once with 100 μL of MeOH. Also during the incubation, 96-well DYNEX MicroLite plates (catalog number NL510410) were loaded with 100 μL of MicroScint40 (catalog number 6013641, Packard Bioscience, Meriden, Connecticut, USA). After the 1 h incubation, 60 μL 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. Results for compounds tested in this assay are presented in Table 2.

Table 2

Ex.	IC_{50} (nM)
52	100
150	130
151	1700
153	1000

Assay Method 3

A. Transfection of Cells with Rat FAAH

[0122] 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% CO_2 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 electrodes. Supercoiled rat 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 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 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

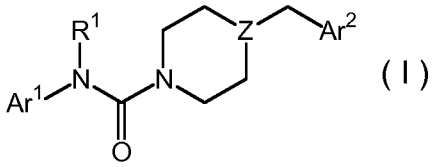
[0123] T84 frozen cell pellets or transfected SK-N-MC cells (contents of 1 x 15 cm culture dishes) were homogenized in 50 mL of FAAH assay buffer (125 mM Tris, 1 mM EDTA, 0.2% Glycerol, 0.02% Triton X-100, 0.4 mM Hepes, pH 9). The assay mixture consisted of 50 μL of the cell homogenate, 10 μL of the test compound, and 40 μL of anandamide [1-^{3}H-ethanolamine] (^{3}H-AEA, Perkin-Elmer, 10.3 C_i/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, 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 μL of MeOH. Also during the incubation, 96-well DYNEX MicroLite plates (catalog number NL510410) were loaded with 100 μL of MicroScint40 (catalog number 6013641, Packard Bioscience, Meriden, CT, USA). After the 1 h incubation, 60 μL 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. Results for compounds tested in this assay are presented in Table 3.

Table 3

Ex.	IC_{50} (nM)
52	290
150	290
151	2000
153	6000

Claims

1. A compound of Formula (I):



(I)

wherein:

- Z is -N- or >CH;
- R^1 is -H or -C_{1-4}alkyl;
- Ar^1 is 2-thiazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, or phenyl, each unsubstituted or substituted at a carbon ring member with one or two R^a moieties;
  where each R^a moiety is independently selected from the group consisting of -C_{1-4}alkyl, -C_{2-4}alkenyl, -OH, -OC_{1-4}alkyl, halo, -CF_3, -OCF_3, -SCF_3, -SH, -$S(O)_{0-2}C_{1-4}$alkyl, -OSO_2C_{1-4}alkyl, -CO_2C_{1-4}alkyl, -CO_2H, -COC_{1-4}alkyl, -$N(R^b)R^c$, -$SO_2NR^bR^c$, -$NR^bSO_2R^c$, -$C(=O)NR^bR^c$, -NO_2, and -CN, wherein R^b and R^c are each independently -H or -C_{1-4}alkyl; and
- Ar^2 is:

  phenyl fused at two adjacent ring carbon atoms to a group selected from the group consisting of -$(CH_2)_{3-5}$- having 0 or 1 double bonds, -$(CH_2)_{2-3}O$-, -OCH_2CH_2O-, and -OCF_2O- to form a fused ring structure; or phenyl substituted on adjacent ring carbon atoms with -OCH_2O- to form 4-benzo[1,3]dioxolyl; each phenyl moiety further unsubstituted or substituted with one, two, or three R^e substituents, wherein each R^e substituent is independently selected from the group consisting of -C_{1-4}alkyl, -C_{2-4}alkenyl, -OH, -OC_{1-4}alkyl, halo, -CF_3, -OCF_3, -SCF_3, -SH, -$S(O)_{0-2}C_{1-4}$alkyl, -OSO_2C_{1-4}alkyl, -CO_2C_{1-4}alkyl, -CO_2H, -COC_{1-4}alkyl, -$N(R^b)R^c$, -$SO_2NR^bR^c$, -$NR^bSO_2R^c$, -$C(=O)NR^bR^c$, -NO_2, and -CN, wherein R^b and R^c as previously defined;

or a pharmaceutically acceptable salt of such compound.

2. A compound as defined in claim 1, wherein:

- Z is -N- or >CH;
- R^1 is -H or-C_{1-4}alkyl;
- Ar^1 is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, or phenyl, each unsubstituted or substituted at a carbon ring member with one or two R^a moieties;
  where each R^a moiety is independently selected from the group consisting of -C_{1-4}alkyl, -C_{2-4}alkenyl, -OH, -OC_{1-4}alkyl, halo, -CF_3,-OCF_3, -SCF_3, -SH, -$S(O)_{0-2}C_{1-4}$alkyl, -OSO_2C_{1-4}alkyl, -CO_2C_{1-4}alkyl, -CO_2H, -COC_{1-4}alkyl, -$N(R^b)R^c$, -$SO_2NR^bR^c$, -$NR^bSO_2R^c$, -$C(=O)NR^bR^c$, -NO_2, and -CN, wherein R^b and R^c are each independently -H or -C_{1-4}alkyl; and
- Ar^2 is:

  phenyl fused at two adjacent ring carbon atoms to a group selected from the group consisting of-$(CH_2)_{3-5}$- having 0 or 1 double bonds, -OCH_2CH_2O-, and -OCF_2O- to form a fused ring structure; or phenyl substituted on adjacent ring carbon atoms with -OCH_2O- to form 4-benzo[1,3]dioxolyl; each phenyl moiety further unsubstituted or substituted with one, two, or three R^e substituents, wherein each R^e substituent is independently selected from the group consisting of -C_{1-4}alkyl, -C_{2-4}alkenyl, -OH, -OC_{1-4}alkyl, halo,-CF_3, -OCF_3, -SCF_3, -SH, -$S(O)_{0-2}C_{1-4}$alkyl, -OSO_2C_{1-4}alkyl, -CO_2C_{1-4}alkyl, -CO_2H, -COC_{1-4}alkyl, -$N(R^b)R^c$, -$SO_2NR^bR^c$, -$NR^bSO_2R^c$, -$C(=O)NR^bR^c$, -NO_2, and -CN, wherein R^b and R^c are as previously defined;

or a pharmaceutically acceptable salt of such compound.

3. A compound as defined in claim 2, wherein Z is -N-.

4. A compound as defined in claim 3, wherein R^1 is -H.

5. A compound as defined in claim 3, wherein Ar^2 is 2,3-dihydro-benzofuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, or 2,2-difluoro-benzo[1,3]dioxolyl, each unsubstituted or substituted with one, two, or three R^e substituents as previously defined.

6. A compound as defined in claim 5, wherein Ar^2 is unsubstituted 2,2-difluoro-benzo[1,3]dioxolyl.

7. A compound as defined in claim 4, wherein Ar^1 is 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, or 4-pyrimidinyl, each unsubstituted or substituted at a carbon ring atom with one or two R^a moieties as previously defined.

8. A compound as defined in claim 4, wherein Ar^1 is phenyl unsubstituted or substituted at a carbon ring atom with one or two R^a moieties as previously defined.

9. A compound as defined in claim 4, wherein Ar^1 is 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2-carbomethoxyphenyl, 3-carbomethoxyphenyl, 4-carbomethoxyphenyl, 2-carboxyphenyl, 3-carboxyphenyl, or unsubstituted phenyl.

10. A compound as defined in claim 9, wherein Ar^2 is unsubstituted 4-benzo[1,3]dioxolyl.

11. A compound of Formula (I) according to claim 1;
or a pharmaceutically acceptable salt of such compound for use in treating a disease, disorder or medical condition mediated by FAAH activity.

12. A compound according to claim 11, wherein the disease, disorder, or medical condition is selected from the group consisting of: anxiety, pain, sleep disorders, eating disorders, inflammation, movement disorders, HIV wasting syndrome, closed head injury, stroke, 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.

13. A compound according to claim 11, wherein the disease, disorder, or medical condition is selected from the group consisting of: anxiety, pain, inflammation, sleep disorders, eating disorders, and movement disorders.

14. A pharmaceutical composition for treating a disease, disorder, or medical condition mediated by FAAH activity, comprising:

    (a) an effective amount of an agent selected from the group consisting of compounds of Formula (I) according to claim 1 and pharmaceutically acceptable salts thereof; and
    (b) a pharmaceutically acceptable excipient.

15. A compound or a pharmaceutical composition for use according to claim 11 or 14, wherein Z is -N-.

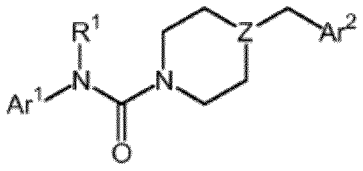
16. A compound or a pharmaceutical composition for use according to claim 15, wherein R^1 is -H.

17. A compound or a pharmaceutical composition for use according to claim 15, wherein Ar^2 is 2,3-dihydro-benzofuranyl, 2,3-dihydro-benzo[1,4]dioxinyl, or 2,2-difluoro-benzo[1,3]dioxolyl, each unsubstituted or substituted with one, two, or three R^e substituents as previously defined.

18. A compound or a pharmaceutical composition for use according to claim 17, wherein Ar^2 is unsubstituted 2,2-difluoro-benzo[1,3]dioxolyl.

Patentansprüche

1. Verbindung der Formel (I):



(I)

wobei:

- Z für -N- oder >CH steht,
- R^1 für -H oder -C_{1-4}-Alkyl steht,
- Ar^1 für 2-Thiazolyl, 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 2-Pyrimidinyl, 4-Pyrimidinyl, 5-Pyrimidinyl oder Phenyl, jeweils unsubstituiert oder an einem Kohlenstoffringglied durch eine oder zwei R^a-Gruppierungen substituiert, steht,
  wobei die R^a-Gruppierungen jeweils unabhängig voneinander aus der aus -C_{1-4}-Alkyl, -C_{2-4}-Alkenyl, -OH, -O-C_{1-4}-Alkyl, Halogen, -CF_3, -OCF_3, -SCF_3, -SH, -S (0) $_{0-2}$-C_{1-4}-Alkyl, -OSO_2-C_{1-4}-Alkyl, -CO_2-C_{1-4}-Alkyl, -CO_2H, -CO-C_{1-4}-Alkyl, -N(R^b)R^c, -$NR^bSO_2R^c$, -$SO_2NR^bR^c$, -C(=O)NR^bR^c, -NO_2 und -CN bestehenden Gruppe ausgewählt sind, wobei R^b und R^c jeweils unabhängig voneinander für -H oder -C_{1-4}-Alkyl stehen, und
- Ar^2 für :

  Phenyl, welches unter Bildung einer kondensierten Ringstruktur an zwei benachbarten Ringkohlenstoffatomen mit einer aus der aus - $(CH_2)_{3-5}$- mit 0 oder 1 Doppelbindung, - $(CH_2)_{2-3}$-O-, -OCH_2CH_2O- und -OCF_2O- bestehenden Gruppe ausgewählten Gruppe kondensiert ist, oder Phenyl, welches an benachbarten Ringkohlenstoffatomen unter Bildung von 4-Benzo[1,3]dioxolyl mit -OCH_2O-substituiert ist, steht, wobei die Phenylgruppierungen jeweils weiterhin unsubstituiert oder durch einen, zwei oder drei R^e-Substituenten substituiert sind, wobei die R^e-Substituenten jeweils unabhängig voneinander aus der aus -C_{1-4}-Alkyl, -C_{2-4}-Alkenyl, -OH, -O-C_{1-4}-Alkyl, Halogen, -CF_3, - OCF_3, -SCF_3, -SH, -$S(O)_{0-2}$-C_{1-4}-Alkyl, -OSO_2-C_{1-4}-Alkyl, -CO_2-C_{1-4}-Alkyl, -CO_2H, -CO-C_{1-4}-Alkyl, - N(R^b)R^c, -SO_2-NR^bR^c, -$NR^bSO_2R^c$, -C(=O)NR^bR^c, -NO_2 und -CN bestehenden Gruppe ausgewählt sind, wobei R^b und R^c wie oben definiert sind,

oder ein pharmazeutisch unbedenkliches Salz einer solchen Verbindung.

2. Verbindung nach Anspruch 1, wobei:

- Z für -N- oder >CH steht,
- R^1 für -H oder -C_{1-4}-Alkyl steht,
- Ar^1 für 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 2-Pyrimidinyl, 4-Pyrimidinyl, 5-Pyrimidinyl oder Phenyl, jeweils unsubstituiert oder an einem Kohlenstoffringglied durch eine oder zwei R^a-Gruppierungen substituiert, steht,
  wobei die R^a-Gruppierungen jeweils unabhängig voneinander aus der aus -C_{1-4}-Alkyl, -C_{2-4}-Alkenyl, -OH, -O-C_{1-4}-Alkyl, Halogen, -CF_3, -OCF_3, -SCF_3, -SH, -$S(O)_{0-2}$-C_{1-4}-Alkyl, -OSO_2-C_{1-4}-Alkyl, -CO_2-C_{1-4}-Alkyl, -CO_2H, -CO-C_{1-4}-Alkyl, -N(R^b)R^c, -$SO_2NR^bR^c$, -$NR^bSO_2R^c$, -C(=O)NR^bR^c, -NO_2 und -CN bestehenden Gruppe ausgewählt sind, wobei R^b und R^c jeweils unabhängig voneinander für -H oder -C1-4-Alkyl stehen, und
- Ar^2 für :

  Phenyl, welches unter Bildung einer kondensierten Ringstruktur an zwei benachbarten Ringkohlenstoffatomen mit einer aus der aus -$(CH_2)_{3-5}$- mit 0 oder 1 Doppelbindung, - OCH_2CH_2O- und -OCF_2O- bestehenden Gruppe ausgewählten Gruppe kondensiert ist, oder Phenyl, welches an benachbarten Ringkohlenstoffatomen unter Bildung von 4-Benzo[1,3]dioxolyl mit -OCH_2O- substituiert ist, steht, wobei die Phenylgruppierungen jeweils weiterhin unsubstituiert oder durch einen, zwei oder drei R^e-Substituenten substituiert sind, wobei die R^e-Substituenten jeweils unabhängig voneinander aus der aus -C_{1-4}-Alkyl, -C_{2-4}-Alkenyl, -OH, -O-C_{1-4}-Alkyl, Halogen, -CF_3, -OCF_3, -SCF_3, -SH, -$S(O)_{0-2}$-C_{1-4}-Alkyl, -OSO_2-C_{1-4}-Alkyl, -CO_2-C_{1-4}-Alkyl, -CO_2H, -CO-C_{1-4}-Alkyl, -N(R^b)R^c, -SO_2-NR^bR^c, -$NR^bSO_2R^c$, -C(=O)NR^bR^c, -NO_2 und -CN bestehenden Gruppe ausgewählt sind, wobei R^b und R^c wie oben definiert sind,

oder ein pharmazeutisch unbedenkliches Salz einer solchen Verbindung.

3. Verbindung nach Anspruch 2, wobei Z für -N- steht.

4. Verbindung nach Anspruch 3, wobei R^1 für -H steht.

5. Verbindung nach Anspruch 3, wobei Ar^2 für 2,3-Dihydrobenzofuranyl, 2,3-Dihydrobenzo[1,4]dioxinyl oder 2,2-Difluorbenzo[1,3]dioxolyl steht, jeweils unsubstituiert oder substituiert durch einen, zwei oder drei wie oben definierte R^e-Substituenten.

6. Verbindung nach Anspruch 5, wobei Ar^2 für unsubstituiertes 2,2-Difluorbenzo[1,3]dioxolyl steht.

7. Verbindung nach Anspruch 4, wobei Ar^1 für 2-Pyridyl, 3-Pyridyl, 4-Pyridyl, 2-Pyrimidinyl oder 4-Pyrimidinyl steht, jeweils unsubstituiert oder an einem Kohlenstoffringatom durch eine oder zwei wie oben definierte R^a-Gruppierungen substituiert.

8. Verbindung nach Anspruch 4, wobei Ar^1 für Phenyl steht, unsubstituiert oder an einem Kohlenstoffringatom durch eine oder zwei wie oben definierte R^a-Gruppierungen substituiert.

9. Verbindung nach Anspruch 4, wobei Ar^1 für 2-Fluorphenyl, 3-Fluorphenyl, 4-Fluorphenyl, 2,4-Difluorphenyl, 2-Chlorphenyl, 3-Chlorphenyl, 4-Chlorphenyl, 2-Methylphenyl, 3-Methylphenyl, 4-Methylphenyl, 2-Methoxyphenyl, 3-Methoxyphenyl, 4-Methoxyphenyl, 2-Carbomethoxyphenyl, 3-Carbomethoxyphenyl, 4-Carbomethoxyphenyl, 2-Carboxyphenyl, 3-Carboxyphenyl oder unsubstituiertes Phenyl steht.

10. Verbindung nach Anspruch 9, wobei Ar^2 für unsubstituiertes 4-Benzo[1,3]dioxolyl steht.

11. Verbindung der Formel (I) nach Anspruch 1 oder ein pharmazeutisch unbedenkliches Salz einer solchen Verbindung zur Verwendung bei der Behandlung einer durch FAAH-Aktivität vermittelten Krankheit, einer durch FAAH-Aktivität vermittelten Erkrankung oder eines durch FAAH-Aktivität vermittelten medizinischen Leidens.

12. Verbindung nach Anspruch 11, wobei die Krankheit, die Erkrankung bzw. das medizinische Leiden ausgewählt ist aus der Gruppe bestehend aus: Angst, Schmerzen, Schlafstörungen, Essstörungen, Entzündung, Bewegungsstörungen, HIV-Wasting-Syndrom, geschlossener Kopfverletzung, Schlaganfall, Alzheimer-Krankheit, Epilepsie, Tourette-Syndrom, Niemann-Pick-Krankheit, Parkinson-Krankheit, Chorea Huntington, optischer Neuritis, Autoimmunuveitis, Drogenentzug, Übelkeit, Erbrechen, sexualer Dysfunktion, posttraumatischer Belastungsstörung, zerebralem Gefäßspasmus, Glaukom, Reizdarmsyndrom, entzündlicher Darmerkrankung, Immunsuppression, gastroösophagealer Rückflusskrankheit, paralytischem Ileus, sekretorischer Diarrhö, Magengeschwür, rheumatoider Arthritis, unbeabsichtigter Schwangerschaft, Bluthochdruck, Krebs, Hepatitis, allergischer Atemwegserkrankung, Autoimmundiabetes, therapierefraktärem Pruritus und Nervenentzündung.

13. Verbindung nach Anspruch 11, wobei die Krankheit, die Erkrankung bzw. das medizinische Leiden ausgewählt ist aus der Gruppe bestehend aus: Angst, Schmerzen, Entzündung, Schlafstörungen, Essstörungen und Bewegungsstörungen.

14. Pharmazeutische Zusammensetzung zur Behandlung einer durch FAAH-Aktivität vermittelten Krankheit, einer durch FAAH-Aktivität vermittelten Erkrankung oder eines durch FAAH-Aktivität vermittelten medizinischen Leidens, umfassend:

    (a)eine wirksame Menge eines aus der aus Verbindungen der Formel (I) nach Anspruch 1 und pharmazeutisch unbedenklichen Salzen davon bestehenden Gruppe ausgewählten Mittels und
    (b) einen pharmazeutisch unbedenklichen Exzipienten.

15. Verbindung oder pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 11 oder 14, wobei Z für -N- steht.

16. Verbindung oder pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 15, wobei R^1 für -H steht.

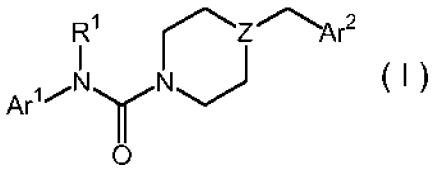
17. Verbindung oder pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 15, wobei Ar^2 für 2,3-Dihydrobenzofuranyl, 2,3-Dihydrobenzo[1,4]-dioxinyl oder 2,2-Difluorbenzo[1,3]dioxolyl, jeweils unsubstituiert oder substituiert durch einen, zwei oder drei wie oben definierte R^e-Substituenten, steht.

18. Verbindung oder pharmazeutische Zusammensetzung zur Verwendung nach Anspruch 17, wobei Ar^2 für unsubs-

tituiertes 2,2-Difluorbenzo[1,3]dioxolyl steht.

Revendications

1. Composé de formule (I) :



(I)

dans lequel :

- Z est -N-ou >CH ;
- R^1 est-H ou - (alkyle en C_{1-4}) ;
- Ar^1 est 2-thiazolyle, 2-pyridyle, 3-pyridyle, 4-pyridyle, 2-pyrimidinyle, 4-pyrimidinyle, 5-pyrimidinyle, ou phényle, chacun non substitué ou substitué au niveau d'un chaînon de carbone cyclique par un ou deux fragments R^a ; où chaque fragment R^a est indépendamment choisi dans le groupe constitué de - (alkyle en C_{1-4}), -(alcényle en C_{2-4}), -OH, -O(alkyle en C_{1-4}), halogéno, $-CF_3$, $-OCF_3$, $-SCF_3$, -SH, $-S(O)_{0-2}$(alkyle en C_{1-4}), $-OSO_2$(alkyle en C_{1-4}), $-CO_2$(alkyle en C_{1-4}), $-CO_2H$, -CO(alkyle en C_{1-4}), $-N(R^b)R^c$, $-SO_2NR^bR^c$, $-NR^bSO_2R^c$, $-C(=O)NR^bR^c$, $-NO_2$ et -CN, où R^b et R^c sont chacun indépendamment -H ou - (alkyle en C_{1-4}) ; et
- Ar^2 est :

  phényle condensé au niveau de deux atomes de carbone cycliques adjacents à un groupe choisi dans le groupe constitué de- $(CH_2)_{3-5}$- ayant 0 ou 1 double liaison, $-(CH_2)_{2-3}O$-, $-OCH_2CH_2O$-, et $-OCF_2O$- pour former une structure cyclique condensée ; ou phényle substitué sur des atomes de carbone cycliques adjacents par $-OCH_2O$-pour former 4-benzo[1,3]dioxolyle ; chaque fragment phényle étant en outre non substitué ou substitué par un, deux, ou trois substituants R^e, chaque substituant R^e étant indépendamment choisi dans le groupe constitué de - (alkyle en C_{1-4}), -(alcényle en C_{2-4}), -OH, -O(alkyle en C_{1-4}), halogéno, $-CF_3$, $-OCF_3$, $-SCF_3$, -SH, $-S(O)_{0-2}$ (alkyle en C_{1-4}), $-OSO_2$(alkyle en C_{1-4}), $-CO_2$(alkyle en C_{1-4}), $-CO_2H$, -CO(alkyle en C_{1-4}), $-N(R^b)R^c$, $-SO_2NR^bR^c$, $-NR^bSO_2R^c$, $-C(=O)NR^bR^c$, $-NO_2$, et -CN, où R^b et R^c sont tels que précédemment définis ;

ou sel pharmaceutiquement acceptable d'un tel composé.

2. Composé tel que défini dans la revendication 1, dans lequel :

- Z est -N- ou >CH ;
- R^1 est -H ou- (alkyle en C_{1-4}) ;
- Ar^1 est 2-pyridyle, 3-pyridyle, 4-pyridyle, 2-pyrimidinyle, 4-pyrimidinyle, 5-pyrimidinyle, ou phényle, chacun non substitué ou substitué au niveau d'un chaînon de carbone cyclique par un ou deux fragments R^a ; où chaque fragment R^a est indépendamment choisi dans le groupe constitué de - (alkyle en C_{1-4}), -(alcényle en C_{2-4}), -OH, -O(alkyle en C_{1-4}), halogéno, $-CF_3$, $-OCF_3$, $-SCF_3$, -SH, -S $(O)_{0-2}$ (alkyle en C_{1-4}), $-OSO_2$(alkyle en C_{1-4}), $-CO_2$(alkyle en C_{1-4}), $-CO_2H$, -CO(alkyle en C_{1-4}), $-N(R^b)R^c$, $-SO_2NR^bR^c$, $-NR^bSO_2R^c$, $-C(=O)NR^bR^c$, $-NO_2$ et -CN, où R^b et R^c sont chacun indépendamment -H ou - (alkyle en C_{1-4}) ; et
- Ar^2 est :

  phényle condensé au niveau de deux atomes de carbone cycliques adjacents à un groupe choisi dans le groupe constitué de- $(CH_2)_{3-5}$- ayant 0 ou 1 double liaison, - $(CH_2)_{2-3}O$-, $-OCH_2CH_2O$-, et $-OCF_2O$- pour former une structure cyclique condensée ; ou phényle substitué sur des atomes de carbone cycliques adjacents par $-OCH_2O$-pour former 4-benzo[1,3]dioxolyle ; chaque fragment phényle étant en outre non substitué ou substitué par un, deux, ou trois substituants R^e, chaque substituant R^e étant indépendamment choisi dans le groupe constitué de - (alkyle en C_{1-4}) , -(alcényle en C_{2-4}), -OH, -O(alkyle en C_{1-4}), halogéno, $-CF_3$, $-OCF_3$, $-SCF_3$, -SH, -S $(O)_{0-2}$ (alkyle en C_{1-4}), $-OSO_2$(alkyle en C_{1-4}), $-CO_2$(alkyle en C_{1-4}), $-CO_2H$, -CO(alkyle en C_{1-4}), $-N(R^b)R^c$, $-SO_2NR^bR^c$, $-NR^bSO_2R^c$, $-C(=O)NR^bR^c$, $-NO_2$, et -CN, où R^b et R^c sont tels

que précédemment définis ;

ou sel pharmaceutiquement acceptable d'un tel composé.

3. Composé tel que défini dans la revendication 2, dans lequel Z est -N-.

4. Composé tel que défini dans la revendication 3, dans lequel R^1 est -H.

5. Composé tel que défini dans la revendication 3, dans lequel Ar^2 est 2,3-dihydro-benzofuranyle, 2,3-dihydro-benzo[1,4]dioxinyle ou 2,2-difluoro-benzo[1,3]dioxolyle, chacun non substitué ou substitué par un, deux, ou trois substituants R^e tels que précédemment définis.

6. Composé tel que défini dans la revendication 5, dans lequel Ar^2 est 2,2-difluoro-benzo[1,3]dioxolyle non substitué.

7. Composé tel que défini dans la revendication 4, dans lequel Ar^1 est 2-pyridyle, 3-pyridyle, 4-pyridyle, 2-pyrimidinyle, ou 4-pyrimidinyle, chacun non substitué ou substitué au niveau d'un atome de carbone cyclique par un ou deux fragments R^a tels que précédemment définis.

8. Composé tel que défini dans la revendication 4, dans lequel Ar^1 est phényle non substitué ou substitué au niveau d'un atome de carbone cyclique par un ou deux fragments R^a tels que précédemment définis.

9. Composé tel que défini dans la revendication 4, dans lequel Ar^1 est 2-fluorophényle, 3-fluorophényle, 4-fluorophényle, 2,4-difluorophényle, 2-chlorophényle, 3-chlorophényle, 4-chlorophényle, 2-méthylphényle, 3-méthylphényle, 4-méthylphényle, 2-méthoxyphényle, 3-méthoxyphényle, 4-méthoxyphényle, 2-carbométhoxyphényle, 3-carbométhoxyphényle, 4-carbométhoxyphényle, 2-carboxyphényle, 3-carboxyphényle, ou phényle non substitué.

10. Composé tel que défini dans la revendication 9, dans lequel Ar^2 est 4-benzo[1,3]dioxolyle non substitué.

11. Composé de formule (I) selon la revendication 1 ; ou sel pharmaceutiquement acceptable d'un tel composé pour utilisation dans le traitement d'une maladie, un trouble ou une affection médicale médié par l'activité FAAH.

12. Composé selon la revendication 11, dans lequel la maladie, le trouble ou l'affection médicale est choisi dans le groupe constitué de : l'anxiété, la douleur, des troubles du sommeil, des troubles de l'alimentation, l'inflammation, des troubles du mouvement, le syndrome cachectique liée au VIH, une lésion fermée de la tête, un accident vasculaire cérébral, la maladie d'Alzheimer, l'épilepsie, le syndrome de Tourette, la maladie de Niemann-Pick, la maladie de Parkinson, la chorée de Huntington, la névrite optique, l'uvéite auto-immune, le syndrome de sevrage de drogue, la nausée, le vomissement, un trouble sexuel, un trouble de stress post-traumatique, un vasospasme cérébral, le glaucome, le syndrome du côlon irritable, un syndrome abdominal inflammatoire, une immunosuppression, une maladie de reflux gastro-oesophagien, l'iléus paralytique, une diarrhée sécrétoire, un ulcère de l'estomac, la polyarthrite rhumatoïde, une grossesse non désirée, l'hypertension, un cancer, une hépatite, une maladie allergique des voies respiratoires, le diabète auto-immun, un prurit réfractaire et une neuro-inflammation.

13. Composé selon la revendication 11, dans lequel la maladie, le trouble, ou l'affection médicale est choisi dans le groupe constitué de : l'anxiété, la douleur, l'inflammation, des troubles du sommeil, des troubles de l'alimentation et des troubles du mouvement.

14. Composition pharmaceutique pour traiter une maladie, un trouble ou une affection médicale médié par l'activité FAAH, comprenant :

(a) une quantité efficace d'un agent choisi dans le groupe constitué de composés de formule (I) selon la revendication 1 et des sels pharmaceutiquement acceptables de ceux-ci ; et
(b) un excipient pharmaceutiquement acceptable.

15. Composé ou composition pharmaceutique pour utilisation selon la revendication 11 ou 14, dans lesquels Z est -N-.

16. Composé ou une composition pharmaceutique pour utilisation selon la revendication 15, dans lesquels R^1 est -H.

17. Composé ou composition pharmaceutique pour utilisation selon la revendication 15, dans lesquels Ar^2 est 2,3-

dihydro-benzofuranyle, 2,3-dihydro-benzo[1,4]dioxinyle, ou 2,2-difluoro-benzo[1,3]dioxolyle, chacun non substitué ou substitué par un, deux ou trois substituants R^e tels que précédemment définis.

18. Composé ou composition pharmaceutique pour utilisation selon la revendication 17, dans lesquels Ar^2 est 2,2-difluoro-benzo[1,3]dioxolyle non substitué.

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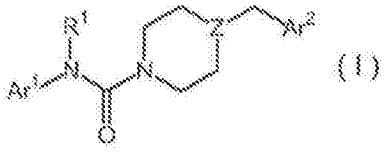
Szabadalmi igénypontok

1. Egy (I) képletű vegyület:



(I)

- ahol a képletben

• Z jelentése -N- vagy >CH;

• R^1 jelentése -H vagy -C_{1-4}alkil;

• Ar^1 jelentése 2-tiazolil, 2-piridil, 3-piridil, 4-piridil, 2-pirimidinil, 4-pirimidinil, 5-pirimidinil vagy fenil, amelyek mindegyike helyettesítetlen vagy az egyik szén-gyűrűtagon egy vagy kettő R^a csoporttal helyettesített;

ahol mindegyik R^a csoport jelentése egymástól függetlenül -C_{1-4}alkil, -C_{2-4}alkenil, -OH, -OC_{1-4}alkil, halogén, -CF_3, -OCF_3, -SCF_3, -SH, -$S(O)_{0-2}C_{1-4}$alkil, -OSO_2C_{1-4}alkil, -CO_2C_{1-4}alkil, -CO_2H, -COC_{1-4}alkil, -$N(R^b)R^c$, -$SO_2NR^bR^c$, -$NR^bSO_2R^c$, -$C(=O)NR^bR^c$, -NO_2 és -CN alkotta csoportból megválasztott, mimellett R^b és R^c jelentése egymástól függetlenül -H vagy -C_{1-4}alkil; és

• Ar^2 jelentése

fenil, amely két szomszédos gyűrűbeli szénatomon 0 vagy 1 kettőskötést tartalmazó -$(CH_2)_{3-5}$-, -$(CH_2)_{2-3}O$-, -OCH_2CH_2O- és -OCF_2O- alkotta csoportból megválasztott csoporttal van kondenzálva kondenzált gyűrűstruktúrát képezve; vagy fenil, amely szomszédos gyűrűbeli szénatomokon -OCH_2O- csoporttal szubsztituált 4-benzo[1,3]dioxolil-csoportot képez; ahol mindegyik fenil csoport továbbá helyettesítetlen vagy egy, kettő vagy három R^e szubsztituenssel helyettesített lehet, mimellett mindegyik R^e szubsztituens jelentése egymástól függetlenül -C_{1-4}alkil, -C_{2-4}alkenil, -OH, -OC_{1-4}alkil, halogén, -CF_3, -OCF_3, -SCF_3, -SH, -$S(O)_{0-2}C_{1-4}$alkil, -OSO_2C_{1-4}alkil, -CO_2C_{1-4}alkil, -CO_2H, -COC_{1-4}alkil, -$N(R^b)R^c$, -$SO_2NR^bR^c$, -$NR^bSO_2R^c$, -$C(=O)NR^bR^c$, -NO_2 és -CN alkotta csoportból megválasztott, ahol R^b és R^c jelentése az előzőekben definiált -

vagy egy ilyen vegyület egy gyógyászatilag elfogadható sója.

2. Az 1. igénypont szerinti vegyület, ahol

• Z jelentése -N- vagy >CH;

• R^1 jelentése -H vagy -C_{1-4}alkil;

• Ar^1 jelentése 2-piridil, 3-piridil, 4-piridil, 2-pirimidinil, 4-pirimidinil, 5-pirimidinil vagy fenil, amelyek mindegyike helyettesítetlen vagy az egyik szén-gyűrűtagon egy vagy kettő R^a csoporttal helyettesített;

ahol mindegyik R^a csoport jelentése egymástól függetlenül -C_{1-4}alkil, -C_{2-4}alkenil, -OH, -OC_{1-4}alkil, halogén, -CF_3, -OCF_3, -SCF_3, -SH, -$S(O)_{0-2}C_{1-4}$alkil, -OSO_2C_{1-4}alkil, -CO_2C_{1-4}alkil, -CO_2H,

$-COC_{1-4}$alkil, $-N(R^b)R^c$, $-SO_2NR^bR^c$, $-NR^bSO_2R^c$, $-C(=O)NR^bR^c$, $-NO_2$ és –CN alkotta csoportból megválasztott, mimellett R^b és R^c jelentése egymástól függetlenül -H vagy $-C_{1-4}$alkil; és

• Ar^2 jelentése

fenil, amely két szomszédos gyűrűbeli szénatomon 0 vagy 1 kettőskötést tartalmazó $-(CH_2)_{3-5}$-, $-(CH_2)_{2-3}O$-, $-OCH_2CH_2O$- és $-OCF_2O$- alkotta csoportból megválasztott csoporttal van kondenzálva kondenzált gyűrűstrukturát képezve; vagy fenil, amely szomszédos gyűrűbeli szénatomokon $-OCH_2O$- csoporttal szubsztituált 4-benzo[1,3]dioxolil-csoportot képez; ahol mindegyik fenil csoport továbbá helyettesítetlen vagy egy, kettő vagy három R^e szubsztituenssel helyettesített lehet, mimellett mindegyik R^e szubsztituens jelentése egymástól függetlenül megválasztva $-C_{1-4}$alkil, $-C_{2-4}$alkenil, -OH, $-OC_{1-4}$alkil, halogén, $-CF_3$, $-OCF_3$, $-SCF_3$, -SH, $-S(O)_{0-2}C_{1-4}$alkil, $-OSO_2C_{1-4}$alkil, $-CO_2C_{1-4}$alkil, $-CO_2H$, $-COC_{1-4}$alkil, $-N(R^b)R^c$, $-SO_2NR^bR^c$, $-NR^bSO_2R^c$, $-C(=O)NR^bR^c$, $-NO_2$ és –CN alkotta csoportból megválasztott, ahol R^b és R^c jelentése az előzőekben definiált -

vagy egy ilyen vegyület egy gyógyászatilag elfogadható sója.

3. A 2. igénypont szerinti vegyület, ahol Z jelentése -N-.

4. A 3. igénypont szerinti vegyület, ahol R^1 jelentése -H.

5. A 3. igénypont szerinti vegyület, ahol Ar^2 jelentése 2,3-dihidro-benzofuranil, 2,3-dihidro-benzo[1,4]-dioxinil vagy 2,2-difluor-benzo[1,3]dioxolil, amelyek mindegyike helyettesítetlen vagy egy, kettő vagy három, az előzőekben definiált R^e szubsztituenssel helyettesített.

6. Az 5. igénypont szerinti vegyület, ahol Ar^2 jelentése helyettesítetlen 2,2-difluor-benzo[1,3]dioxolil.

7. A 4. igénypont szerinti vegyület, ahol Ar^1 jelentése 2-piridil, 3-piridil, 4-piridil, 2-pirimidinil vagy 4-pirimidinil, amelyek mindegyike helyettesítetlen vagy az egyik szén-gyűrűtagon egy vagy kettő, az előzőekben definiált R^a csoporttal helyettesített.

8. A 4. igénypont szerinti vegyület, ahol Ar^1 jelentése fenil, amely helyettesítetlen vagy az egyik szén-gyűrűtagon egy vagy kettő, az előzőekben definiált R^a csoporttal helyettesített.

9. A 4. igénypont szerinti vegyület, ahol Ar^1 jelentése 2-fluorfenil, 3-fluorfenil, 4-fluorfenil, 2,4-difluorfenil, 2-klórfenil, 3-klórfenil, 4-klórfenil, 2-metilfenil, 3-metilfenil, 4-metilfenil, 2-metoxifenil, 3-metoxifenil, 4-metoxifenil, 2-metoxikarbonilfenil, 3-metoxikarbonilfenil, 4-metoxikarbonilfenil, 2-karboxifenil, 3-karboxifenil vagy helyettesítetlen fenil.

10. A 9. igénypont szerinti vegyület, ahol Ar^2 jelentése helyettesítetlen 4-benzo[1,3]dioxolil.

11. Egy, az 1. igénypont szerinti (I) képletű vegyület vagy egy ilyen vegyület egy gyógyászatilag elfogadható sója FAAH aktivitás által közvetített betegség, rendellenesség vagy kóros állapot kezelésében való alkalmazásra.

12. A 11. igénypont szerinti vegyület, ahol a betegség, rendellenesség vagy kóros állapot szorongás, fájdalom, alvási rendellenességek, táplálkozási rendellenességek, gyulladás, mozgászavarok, HIV okozta akut alultápláltság (HIV wasting syndrome), zárt fejsérülés, sztrók, Alzheimer-kór, epilepszia, Tourette-szindróma, Niemann-Pick-kór, Parkinson-kór, Huntington-kór, látóideggyulladás, autoimmun uveagyulladás, drogmegvonási tünetek, hányinger, hányás, szexuális diszfunkció, poszt-traumatikus stresszes rendellenesség, agyi érgörcs, zöldhályog, irritábilis bélszindróma, gyulladásos bélbetegség, immunszuppresszió, gyomor-nyelőcsövi

refluxbetegség, paralitikus bélelzáródás, szekréciós hasmenés, gyomorfekély, reumás ízületi gyulladás, nem kívánt terhesség, magas vérnyomás, rák, hepatitisz, allergiás légúti megbetegedés, autoimmun cukorbetegség, makacs viszketés és ideggyulladás alkotta csoportból van megválasztva.

13. A 11. igénypont szerinti vegyület, ahol a betegség, rendellenesség vagy kóros állapot szorongás, fájdalom, gyulladás, alvási rendellenességek, táplálkozási rendellenességek és mozgászavarok alkotta csoportból van megválasztva.

14. Gyógyászati készítmény FAAH aktivitás által közvetített betegség, rendellenesség vagy kóros állapot kezelésére, amely a következőket tartalmazza:

(a) hatásos mennyiségben egy, az 1. igénypont szerinti (I) általános képletű vegyületek és gyógyászatilag elfogadható sóik alkotta csoportból megválasztott hatóanyag; és

(b) egy gyógyászatilag elfogadható segédanyag.

15. Egy, a 11 – 14. igénypontok bármelyike szerinti alkalmazásra szolgáló vegyület vagy gyógyászati készítmény, ahol Z jelentése -N-.

16. Egy, a 15. igénypont szerinti alkalmazásra szolgáló vegyület vagy gyógyászati készítmény, ahol R^1 jelentése -H.

17. Egy, a 15. igénypont szerinti alkalmazásra szolgáló vegyület vagy gyógyászati készítmény, ahol Ar^2 jelentése 2,3-dihidro-benzofuranil, 2,3-dihidro-benzo[1,4]dioxinil vagy 2,2-difluor-benzo[1,3]dioxolil, amelyek mindegyike helyettesítetlen vagy egy, kettő vagy három, az előzőekben definiált R^6 szubsztituenssel helyettesített.

18. Egy, a 17. igénypont szerinti alkalmazásra szolgáló vegyület vagy gyógyászati készítmény, ahol Ar^2 jelentése helyettesítetlen 2,2-difluor-benzo[1,3]dioxolil.