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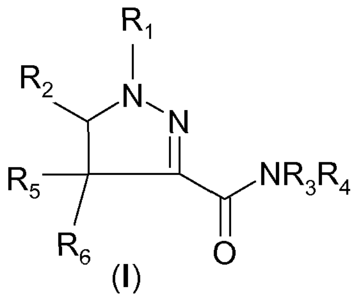
(54) Title: 5-ARYL-4,5-DIHYDRO-(1H)-PYRAZOLES AS CANNABINOID CB$_1$ RECEPTOR AGONISTS



(I)

(57) Abstract: This invention relates to 5-(hetero)aryl-4,5-dihydro-(1H)-pyrazole (pyrazoline) derivatives as cannabinoid CB$_1$ receptor agonists, to pharmaceutical compositions containing these compounds, to methods for their syntheses, methods for preparing novel intermediates useful for their syntheses, and methods for preparing compositions. The invention also relates to the uses of such compounds and compositions, particularly their use in administering them to patients to achieve a therapeutic effect in disorders in which CB$_1$ receptors are involved, or that can be treated via manipulation of those receptors. The compounds have the general Formula (I), wherein the symbols have the meanings given in the specification.

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5-ARYL-4,5-DIHYDRO-(1H)-PYRAZOLES AS CANNABINOID CB_1 RECEPTOR AGONISTS

INDEX

TECHNICAL FIELD

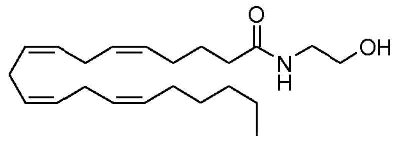
This invention relates to the fields of pharmaceutical and organic chemistry, and provides 5-(hetero)aryl-4,5-dihydro-(1H)-pyrazole (pyrazoline) derivatives, intermediates, formulations and methods.

BACKGROUND ART

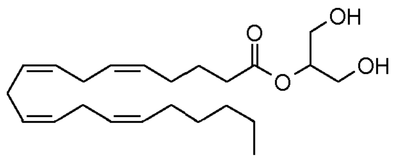
The endogenous cannabinoid receptor agonist, anandamide, is too unstable to be of practical value as a drug. The same is true for other endocannabinoids such as 2-arachidonoyl-glycerol and noladin ether. With the exception of Δ^9-tetrahydrocannabinol (Δ^9-THC, dronabinol, Marinol®) and Nabilone (Cesamet®) no other cannabinoid receptor agonists have been registered as drugs. In addition, Sativex® (an extract from the *Cannabis sativa* L. plant) has been recently approved as a prescription medicine (*Barnes, 2006*). Compounds like CP 55,940 and WIN 55,212-2 are not registered drugs, but have been, and still are, used as pharmacological tools.

It has been postulated that cannabinoid CB_1 receptors can occur in two different states: the active 'R*-state' to which agonists bind, and the inactive 'R-state' to which antagonists or inverse agonists—such as rimonabant—bind. Both states have considerably different three-dimensional geometries. Key interaction in the cannabinoid-CB_1 receptor model (based on Palczewski's X-ray structure of bovine rhodopsin) is a hydrogen bond between the carbonyl group of e.g. the CB_1 receptor inverse agonist rimonabant, and the LYS192 residue of the CB_1 receptor. This hydrogen bond has a stabilizing effect on the Lys192-Asp366 salt bridge of the intracellular end of the transmembrane helices 3 and 6. The existence of this specific salt bridge is induced by a pronounced kink at Pro 358 in transmembrane helix 6, present in the inactive R-state of the receptor, but not in the active R*-state which is stabilized by CB_1 receptor agonist binding *(Hurst, 2002; Shim, 2002; Reggio, 2003; Pertwee, 2005 and Lange, 2005).* Thus it is not possible to apply structural features of known CB_1 receptor antagonists or inverse agonists to design novel CB_1 receptor agonists in a straightforward manner.

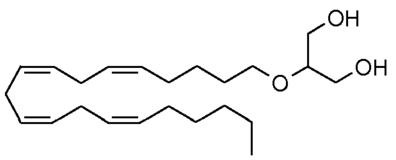
Ample evidence exists that cannabinoid receptor agonists have therapeutic possibilities as appetite stimulants, enti-emetics, analgesics, anti-glaucoma agents *(Croxford, 2003; Drysdale, 2003)*, tumor growth inhibitors *(Ligresti, 2003),* and agents for the treatment of neurodegenerative disorders, including multiple sclerosis and Alzheimer's disease *(Smith, 2004; Croxford, 2004).*



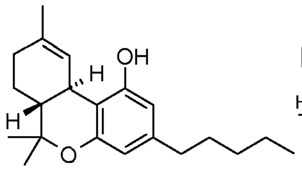
Anandamide



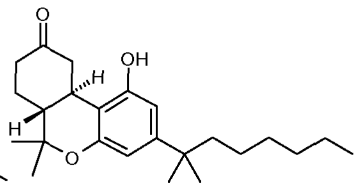
2-Arachidonoyl-glycerol (2-AG)



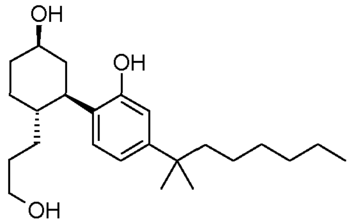
Noladin ether



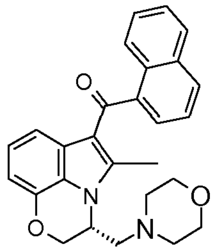
Δ^9-THC (dronabinol)



Nabilone



CP 55,940



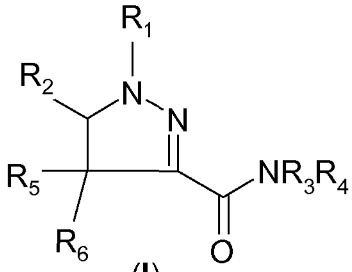
WIN 55,212-2

The objective of the present invention was to develop novel compounds with CB_1 receptor agonistic activity, structurally unrelated to known cannabinoid receptor agonists.

DISCLOSURE

Surprisingly, it was found that replacing the 1-aryl or 1-heteroaryl group in 4,5-dihydro-pyrazole CB_1 receptor antagonists described in WO 2005/074920, WO 2005/077911 or WO 2007/009689 by an optionally substituted alkyl moiety, resulted in novel compounds with a high affinity for CB_1 receptors. Many of these compounds were found to act as full or partial agonists at CB_1 receptors. Most compounds of the invention also showed affinity for CB_2 receptors.

The invention relates to compounds of the general formula (I):



(I)

or a tautomer, stereoisomer, N-oxide, isotopically-labelled analogue, or a pharmacologically acceptable salt of any of the foregoing, wherein:

- R_1 is chosen from a C_{3-10} linear alkyl group, a C_{4-10} branched alkyl group, a C_{4-10} alkenyl group, a C_{4-10} alkynyl group, a C_{3-10}-heteroalkyl group, a C_{5-8}-cycloalkyl-C_{1-5}-alkyl group, a C_{5-8}-heterocycloalkyl-C_{1-5}-alkyl group, which groups are optionally substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl, hydroxy, amino, cyano or fluoro, or

  R_1 is chosen from an aryl-C_{1-3}-alkyl group, a heteroaryl-C_{1-3}-alkyl group, an aryl-C_{1-3}-heteroalkyl group or a heteroaryl-C_{1-3}-heteroalkyl group, wherein the aryl or heteroaryl groups are unsubstituted, or substituted with 1-5 substituents Y, which can be the same or different, selected from C_{1-3}-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, *trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl* (C_{1-2})*-amino, mono- or* dialkyl (C_{1-2})-amido, (C_{1-3})-alkyl sulfonyl, dimethylsulfamido, C_{1-3}-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl, phenyl and acetyl, or

  R_1 is 2-cyano-ethyl,
- R_2 is an aryl group or a heteroaryl group, unsubstituted or substituted with 1-5 substituents Y, which can be the same or different, wherein Y has the abovementioned meaning,
- R_3 is chosen from a linear or branched C_{3-10} alkyl group, a C_{3-8} cycloalkyl group, C_{5-10} bicycloalkyl group, C_{6-10} tricycloalkyl group or C_{8-11} tetracycloalkyl group, which groups are unsubstituted, or substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl, hydroxy, amino, fluoro, or

  R_3 is a C_{3-8} cycloalkyl group substituted with an aryl group or a heteroaryl group, which is unsubstituted or substituted with 1-5 substituents Y, which can be the same or different, wherein Y has the meaning given above, or

  R_3 is a 2,2,2-trifluoroethyl, or a 2-fluoroethyl group, or

R_3 is chosen from a C_{5-8} heterocycloalkyl group, C_{6-10} bicycloheteroalkyl group, C_{7-10} tricycloheteroalkyl group, which groups are unsubstituted or substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl, hydroxy, amino or fluoro, or

R_3 is chosen from a C_{3-8} cycloalkyl-C_{1-3}–alkyl group, C_{5-10}-bicycloalkyl-C_{1-3}–alkyl group, C_{6-10}-tricycloalkyl-C_{1-3}–alkyl group, which groups are unsubstituted or substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl, hydroxy, amino or fluoro, or

R_3 is chosen from a branched or linear C_{3-8} heterocycloalkyl-C_{1-3}–alkyl group, C_{5-10} bicycloheteroalkyl-C_{1-3}–alkyl group, C_{6-10} tricycloheteroalkyl-C_{1-3}–alkyl group, which groups are unsubstituted or substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl, hydroxy, amino or fluoro, or

R_3 is an aryl group or a heteroaryl group, which groups are unsubstituted or substituted with 1-5 substituents Y, which can be the same or different, wherein Y has the abovementioned meaning, or

R_3 is an aryl-C_{1-5}–alkyl group, a heteroaryl-C_{1-5}–alkyl or a diaryl-C_{1-5}–alkyl group, wherein the aryl or heteroaryl groups are unsubstituted or substituted with 1-5 substituents Y, which can be the same or different, wherein Y has the abovementioned meaning, or

R_3 is chosen from a linear or branched C_{4-8} alkenyl or C_{4-8} alkynyl group, which groups are unsubstituted or substituted with 1-3 fluoro atoms, or,

R_3 is a branched or linear C_{2-10} heteroalkyl group, containing 1-2 heteroatoms selected from N, O or S,

- R_4 is a hydrogen atom or a C_{1-4} alkyl group,
- R_5 is a hydrogen atom or a C_{1-2} alkyl group, unsubstituted or substituted with 1-3 fluoro atoms,
- R_6 is a hydrogen atom or a C_{1-2} alkyl group, unsubstituted or substituted with 1-3 fluoro atoms.

The invention also relates, in some embodiments, to a compound of formula (I) wherein:

- R_1 is chosen from a C_{3-10} linear alkyl group, a C_{4-10} branched alkyl group, a C_{5-8}-cycloalkyl-C_{1-5}-alkyl group, which groups are optionally substituted with 1-3 substituents, which can be the same or different, chosen from methyl, ethyl, cyano or fluoro, or

  R_1 is chosen from an aryl-C_{1-3}-alkyl group, wherein the aryl group is unsubstituted, or substituted with 1-3 substituents Y, which can be the same or different, selected from C_{1-3}-alkyl or alkoxy, halogen, trifluoromethyl, trifluoro-methoxy, nitro, cyano and phenyl, or

  R_1 is 2-cyano-ethyl,

- R_2 is chosen from phenyl, thienyl, benzothienyl, or pyridyl, groups that are unsubstituted, or substituted with 1 or 2 substituents, which can be the same or different, chosen from halogen, methyl, CF_3, OCH_3 or OCF_3,
- R_3 is chosen from a linear or branched C_{3-10} alkyl group, a C_{3-8} cycloalkyl group, C_{5-10} bicycloalkyl group or C_{6-10} tricycloalkyl group, which groups are unsubstituted, or substituted with 1-3 substituents, which can be the same or different, chosen from methyl, ethyl, hydroxy, amino, fluoro or aryl, or

  R_3 is a C_{5-8} heterocycloalkyl group, unsubstituted or substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl, or fluoro, or

  R_3 is chosen from a C_{3-8} cycloalkyl-C_{1-3}–alkyl group, C_{5-10}-bicycloalkyl-C_{1-3}–alkyl group, C_{6-10}-tricycloalkyl-C_{1-3}–alkyl group, which groups are unsubstituted or substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl or fluoro, or

  R_3 is an aryl group or a heteroaryl group, which groups are unsubstituted or substituted with 1-5 substituents Y, which can be the same or different, chosen from C_{1-3}-alkyl or alkoxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, cyano or phenyl, or

  R_3 is an aryl-C_{1-5}–alkyl group, a heteroaryl-C_{1-5}–alkyl or a diaryl-C_{1-5}–alkyl group, wherein the aryl or heteroaryl groups are unsubstituted or substituted with 1-5 substituents, which can be the same or different, chosen from C_{1-3}-alkyl or alkoxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, cyano or phenyl, or

  R_3 is a branched or linear C_{2-10} heteroalkyl group, containing 1-2 heteroatoms selected from N, O or S,
- R_4, R_5 and R_6 have the meanings as given above.

Other embodiments provide one or more compounds of formula (I) wherein:

- R_1 is chosen from a C_{3-8} linear alkyl group, a C_{4-8} branched alkyl group, a C_{5-6}-cycloalkyl-C_{1-5}-alkyl group, which groups are optionally substituted with 1-3 substituents, chosen from cyano or fluoro, or

  R_1 is an aryl-C_{1-3}-alkyl group or

  R_1 is 2-cyano-ethyl,
- R_2 is chosen from phenyl, thienyl, benzothienyl, or pyridyl, groups that are unsubstituted, or substituted with halogen, methyl, CF_3, OCH_3 or OCF_3,
- R_3, R_4, R_5 and R_6 have the meanings as given above.

Further embodiments provide one or more compounds of formula (I) wherein:

- R_1 is chosen from 2-cyano-ethyl, n-propyl, n-butyl, 4,4,4-trifluorobutyl, isobutyl, n-pentyl, cyclohexylmethyl, or phenethyl,

- R_2 is chosen from 2-fluorophenyl, 3-(trifluoromethyl)phenyl, 3-chlorophenyl, 3-fluorophenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, benzothien-3-yl, pyrid-2-yl, thien-3-yl or phenyl,
- R_3 is chosen from 3-(trifluoromethyl)benzyl, 3-(trifluoromethyl)benzyl, 1-(4-fluorophenyl)-1-methyl-ethyl, 1-phenyl-1-methyl-ethyl, 1-phenyl-ethyl, 2-indanyl, 2-(4-fluorophenyl)-1,1-dimethyl-ethyl, 2-(trifluoromethyl)benzyl, 2,2-dimethylpropyl, 2,2-diphenylethyl, 2,2-diphenylpropyl, 2-methoxybenzyl, 2-phenyl-propyl, 2-phenyl-*trans*-cyclopropyl, 2-trifluoromethyl)phenyl, 3,4,5-trimethoxybenzyl, 3,4-dimethoxybenzyl, 3-fluorobenzyl, 3-methoxybenzyl, 4-chlorobenzyl, 4-methoxybenzyl, 5-methyl-thiazol-2-yl, adamant-1-yl, adamant-2-yl, adamantylmethyl, benzyl, cycloheptyl, cyclohexylmethyl, cyclooctyl, endo-bicyclo[2.2.1]hept-2-yl, exo-bicyclo[2.2.1]hept-2-yl, indan-2-yl, N,2,2,6,6-pentamethylpiperidin-4-yl, naphth-1-yl, naphthalen-1-yl-methyl, noradamant-1-yl, pyridin-3-ylmethyl, quinolin-3-yl, tert-butyl, (1-ethyl)propyl, (1R,2S,5R)-rel-6,6-dimethylbicyclo[3.1.1.]heptan-2-methyl, (3-dimethylamino)-2,2-dimethylpropyl, (furan-2-yl)methyl, (pyridin-3-yl)-methyl, 1-(4-fluorophenyl)-1-methyl-ethyl, 1-(adamant-1-yl)-ethyl, 1-phenyl-1-methyl-ethyl, 2-(4-fluorophenyl)ethyl, 2-(7-methyl-indol-3-yl)ethyl, 2-(indol-3-yl)ethyl, 2-(thien-2-yl)ethyl, 3-(trifluoromethyl)benzyl, 3,3-diphenylpropyl, 3,4-difluorobenzyl, 4-(trifluoromethyl)benzyl, endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl, naphthalen-1-yl-methyl, benzyl, cyclohexylmethyl, cyclopentyl, methyl-N-(Naphthalen-1-yl-methyl) or phenyl,
- R_4 is a hydrogen atom or a methyl group,
- R_5 is a hydrogen atom or a methyl group,
- R_6 is a hydrogen atom.

In another embodiment the invention relates to compounds of formula (I), or a tautomer, stereoisomer, N-oxide, isotopically-labelled analogue, or a pharmacologically acceptable salt of any of the foregoing, said compound being an optically active enantiomer.

The compounds of the invention of the general formula (I), as well as the pharmacologically acceptable salts thereof, have cannabinoid CB_1 receptor agonistic activity. They are useful in the treatment of disorders in which cannabinoid receptors are involved, or that can be treated via manipulation of those receptors. For instance in the treatment of multiple sclerosis, traumatic brain injury, pain including chronic pain, neuropathic pain, acute pain and inflammatory pain, osteoporosis, appetite disorders, epilepsy, Alzheimer's disease, Tourette's syndrome, cerebral ischaemia and gastrointestinal disorders.

Other embodiments of the invention include, but are not limited to:

pharmaceutical compositions for treating, for example, a disorder or condition that may be treated by activating cannabinoid CB_1 receptors, the compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier;

methods of treatment of a disorder or condition that may be treated by activating cannabinoid CB_1 receptors, the methods comprising administering to a mammal in need of such treatment a compound of formula (I) or a pharmaceutically acceptable salt thereof;

pharmaceutical compositions for treating, for example, a disorder or condition chosen multiple sclerosis, traumatic brain injury, pain including chronic pain, neuropathic pain, acute pain and inflammatory pain, osteoporosis, appetite disorders, epilepsy, Alzheimer's disease, Tourette's syndrome, cerebral ischaemia and gastrointestinal disorders;

methods of treatment of a disorder or condition chosen from the disorders listed herein, the methods comprising administering to a mammal in need of such treatment a compound of formula (I) or a pharmaceutically acceptable salt thereof;

pharmaceutical compositions for treatment of a disorder or condition chosen from the disorders listed herein, the compositions comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier;

methods of treatment of a disorder or condition that may be treated by activating cannabinoid CB_1 receptors, the methods comprising administering to a patient in need of such treatment a compound of formula (I) or a pharmaceutically acceptable salt thereof.

methods of antagonizing a cannabinoid CB_1 receptor, which comprises administering to a subject in need thereof, an effective amount of a compound of formula (I);

The invention also provides the use of a compound or salt according to formula (I) for the manufacture of a medicament.

The invention further relates to combination therapies wherein a compound of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed. Such other therapeutic agent(s) may be administered prior to, simultaneously with, or following the administration of the compounds of the invention.

The invention also provides compounds, pharmaceutical compositions, kits and methods for the treatment of a disorder or condition that may be treated by activating cannabinoid CB_1 receptors, the method comprising administering to a patient in need of such treatment a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention also provides methods of preparing the compounds of the invention and the intermediates used in those methods.

Isolation and purification of the compounds and intermediates described herein can be affected, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography, thick-layer chromatography, preparative low or high-pressure liquid chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be taken from the preparations and examples. However, other equivalent separation or isolation procedures could, of course, also be used.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers.

All compounds of the present invention do contain at least one chiral centre (at the 5-position of the 4,5-dihydropyrazole ring). Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers, and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention.

Cis and trans isomers of the compound of formula (I) or a pharmaceutically acceptable salt thereof are also within the scope of the invention, and this also applies to tautomers of the compounds of formula (I) or a pharmaceutically acceptable salt thereof.

Some of the crystalline forms for the compounds may exist as polymorphs, and as such are intended to be included in the present invention. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents, and such solvates are also intended to be encompassed within the scope of this invention.

Isotopically-labeled compound of formula (I) or pharmaceutically acceptable salts thereof, including compounds of formula (I) isotopically-labeled to be detectable by PET or SPECT, are also included within the scope of the invention, and same applies to compounds of formula (I) labeled with $[^{13}C]$-, $[^{14}C]$-, $[^{3}H]$-, $[^{18}F]$-, $[^{125}I]$- or other isotopically enriched atoms, suitable for receptor binding or metabolism studies.

The compounds of the invention may also be used as reagents or standards in the biochemical study of neurological function, dysfunction and disease.

DEFINITIONS

General terms used in the description of compounds herein disclosed bear their usual meanings. The term **alkyl** as used herein denotes a univalent saturated branched or straight hydrocarbon chain. Unless otherwise stated, such chains can contain from 1 to 18 carbon atoms. Representative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, isopentyl, neopentyl, *tert*-pentyl, hexyl, isohexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, and the like. When qualified as 'lower', the alkyl group will contain from 1 to 6 carbon atoms. The same carbon content applies to the parent term 'alkane', and to derivative terms such as 'alkoxy'. The carbon content of various hydrocarbon containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix C_x-C_y defines the number of carbon atoms present from the integer "x" to the integer "y" inclusive. '**Alkyl(C_{1-3})**' for example, means methyl, ethyl, n-propyl or isopropyl, and '**alkyl(C_{1-4})**' means 'methyl, ethyl, n-propyl, isopropyl, n-butyl, *sec*-butyl, isobutyl or *tert*-butyl'. The term **'alkenyl'** denotes straight or branched hydrocarbon radicals having one or more carbon-carbon double bonds, such as vinyl, allyl, butenyl, *etc.*, and for example comprises (C_{2-4}) alkenyl. In **'alkynyl'** groups the straight or branched hydrocarbon radicals have one or more carbon-carbon triple bonds, such as ethynyl, propargyl, 1-butynyl, 2-butynyl, *etc.*, and e.g. includes (C_{2-4}) alkynyl. Unless otherwise stated, álkenyl' and 'alkynyl chains can contain from 1 to 18 carbon atoms.

The term **'acyl'** comprises alkyl(C_{1-3}) carbonyl, arylcarbonyl or aryl-alkyl(C_{1-3})carbonyl. **'Aryl'** embraces mono- or polycyclic aromatic groups, including phenyl, naphthyl, 1,2,3,4-tetrahydro-naphtyl, indenyl, fluorenyl, anthracenyl, phenanthrenyl, naphthacenyl and azulenyl. **'Heteroaryl'** embraces mono- or polycyclic hetero-aromatic, including furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, imidazo[2,1-b][1,3]thiazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, indazolyl, indolyl, indolizinyl, isoindolyl, benzo[b]furanyl, 1,2,3,4-tetrahydroiso-quinolinyl, indanyl, indenyl, benzo[b]thienyl, 2,3-dihydro-1,4-benzodioxin-5-yl, benzimidazolyl, cinnolinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, benzothiazolyl, benzo[1,2,5]thia-diazolyl, purinyl, quinolinyl, isoquinolinyl, quinolizinyl, phtalazinyl, quinazolinyl, quinoxalinyl, 1,8-naphthyridinyl and pteridinyl.

'Halo' or **'Halogen'** means chloro, fluoro, bromo or iodo; '**hetero**' as in 'heteroalkyl, heteroaromatic' etc. means containing one or more N, O or S atoms. '**heteroalkyl**' includes alkyl groups with heteroatoms in any position, thus including N-bound O-bound or S-bound alkyl groups.

The term **"substituted"** means that the specified group or moiety bears one or more substituents. Where any group may carry multiple substituents, and a variety of possible substituents is provided, the substituents are independently selected, and need not to be the same. The term **"unsubstituted"** means that the specified group bears no substituents. With reference to substituents, the term **"independently"** means that when more than one of such substituents are possible, they may be the same or different from each other.

'C_{3-8}-cycloalkyl' means cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl; **'C_{5-8} heterocycloalkyl'** refers to heteroatom containing rings including but not limited to piperidinyl, morpholinyl, azepanyl, pyrrolidinyl, thiomorpholinyl, piperazinyl, tetrahydrofuryl, tetrahydropyranyl; **'C_{5-10} bicycloalkyl group'** refers to carbo-bicyclic ring systems including but not limited to bicyclo[2.2.1]heptanyl, bicyclo[3.3.0]octanyl or the bicyclo[3.1.1] heptanyl group; **'C_{6-10} tricycloalkyl group'** refers to carbo-tricyclic ring systems including but not limited to the 1-adamantyl, noradamantyl or the 2-adamantyl group. The abbreviation **'C_{8-11} tetracycloalkyl group'** refers to carbo-tetracyclic ring systems including but not limited to the cubyl, homocubyl or bishomocubyl group.

The terms **"oxy"**, **"thio"** and **"carbo"** as used herein as part of another group respectively refer to an oxygen atom, a sulphur atom and a carbonyl (C=O) group, serving as linker between two groups, such as for instance hydroxyl, oxyalkyl, thioalkyl, carboxyalkyl, etc. The term **"amino"** as used herein alone, or as part of another group, refers to a nitrogen atom that may be either terminal, or a linker between two other groups, wherein the group may be a primary, secondary or tertiary (two hydrogen atoms bonded to the nitrogen atom, one hydrogen atom bonded to the nitrogen atom and no hydrogen atoms bonded to the nitrogen atom, respectively) amine. The terms **"sulfinyl"** and **"sulfonyl"** as used herein as part of another group respectively refer to an –SO- or an – SO_2- group.

To provide a more concise description, the terms '**compound**' or '**compounds**' include tautomers, stereoisomers, N-oxides, isotopically-labelled analogues, or pharmacologically acceptable salts, also when not explicitly mentioned.

As used herein, the term "**leaving group**" (L) shall mean a charged or uncharged atom or group that departs during a substitution or displacement reaction. The term refers to groups readily displaceable by a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art (*Smith, 2001*). Examples include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides (Br, Cl, I), triflates, mesylates, tosylates, and the like.

N-oxides of the compounds mentioned above belong to the invention. Tertiary amines may or may not give rise to N-oxide metabolites. The extent to what N-oxidation takes place varies from trace amounts to a near quantitative conversion. N-oxides may be more active than their corresponding tertiary amines, or less active. Whilst N-oxides can easily be reduced to their corresponding tertiary amines by chemical means, in the human body this happens to varying degrees. Some N-oxides undergo nearly quantitative reductive conversion to the corresponding tertiary amines, in other cases conversion is a mere trace reaction, or even completely absent (*Bickel, 1969*).

'**Form**' is a term encompassing all solids: polymorphs, solvates, amorphous forms. '**Crystal form**' refers to various solid forms of the same compound, for example polymorphs, solvates and amorphous forms. '**Cocrystals**' are multicomponent crystals with a unique lattice: new chemical species produced with neutral compounds. '**Amorphous forms**' are non-crystalline materials with no long range order, and generally do not give a distinctive powder X-ray diffraction pattern. Crystal forms in general have been described by Byrn *(1995)* and Martin *(1995)*. '**Polymorphs**' are crystal structures in which a compound can crystallize in different crystal packing arrangements, all of which have the same elemental composition. Polymorphism is a frequently occurring phenomenon, affected by several crystallization conditions such as temperature, level of supersaturation, the presence of impurities, polarity of solvent, rate of cooling. Different polymorphs usually have different X-ray diffraction patterns, solid state NMR spectra, infrared or Raman spectra, melting points, density, hardness, crystal shape, optical and electrical properties, stability, and solubility. Recrystallization solvent, rate of crystallization, storage temperature, and other factors may cause one crystal form to dominate.

To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "**about**". It is understood that whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including approximations due to the experimental and/or measurement conditions for such given value.

Throughout the description and the claims of this specification the word "**comprise**" and variations of the word, such as "comprising" and "comprises" is not intended to exclude other additives, components, integers or steps.

While it may be possible for the compounds of formula (I) to be administered as the raw chemical, it is preferable to present them as a '**pharmaceutical composition**'. According to a further aspect, the present invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, together with one or more pharmaceutically acceptable carriers thereof, and optionally one or more other therapeutic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The term "**composition**" as used herein encompasses a product comprising specified ingredients in predetermined amounts or proportions, as well as any product that results, directly or indirectly, from combining specified ingredients in specified amounts. In relation to pharmaceutical compositions, this term encompasses a product comprising one or more active ingredients, and an optional carrier comprising inert ingredients, as well as any product that results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. In general, pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. The pharmaceutical composition includes enough of the active object compound to produce the desired effect upon the progress or condition of diseases. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "**pharmaceutically acceptable**" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Within the context of this application, the term '**combination preparation**' comprises both true combinations, meaning a compound of formula (I) and other medicaments physically combined in one preparation such as a tablet or injection fluid, as well as '**kit-of-parts**', comprising a compound of formula (I) and another medicament in separate dosage forms, together with instructions for use, optionally with further means for facilitating compliance with the administration of the component compounds, e.g. label or drawings. With true combinations, the pharmacotherapy by definition is **simultaneous**. The contents of 'kit-of-parts', can be administered either simultaneously or at different time intervals. Therapy being either concomitant or **sequential** will be dependant on the characteristics of the other medicaments used, characteristics like onset and duration of action, plasma levels, clearance, etc., as well as on the disease, its stage, and characteristics of the individual patient.

The affinity of the compounds of the invention for cannabinoid CB_1 receptors was determined as described below. From the binding affinity measured for a given compound of formula (I), one can estimate a theoretical lowest effective **dose**. At a concentration of the compound equal to twice the measured K_i-value, nearly 100% of the cannabinoid CB_1 receptors likely will be occupied by the compound. Converting that concentration to mg of compound per kg of patient—assuming ideal bioavailability—results in a theoretical lowest effective dose. Pharmacokinetic, pharmacodynamic, and other considerations may alter the dose actually administered to a higher or lower value. The dose of the compound to be administered will depend on the relevant indication, the age, weight and sex of the patient and may be determined by a physician. The dosage will preferably be in the range of from 0.01 mg/kg to 10 mg/kg. The typical daily dose of the active ingredients varies within a wide range and will depend on various factors such as the relevant indication, the route of administration, the age, weight and sex of the patient and may be determined by a physician. In general, total daily dose administration to a patient in single or individual doses, may be in amounts, for example, from 0.001 to 10 mg/kg body weight daily, and more usually from 0.01 to 1,000 mg per day, of total active ingredients. Such dosages will be administered to a patient in need of treatment from one to three times each day, or as often as needed for efficacy, and for periods of at least two months, more typically for at least six months, or chronically.

The term **"therapeutically effective amount"** as used herein refers to an amount of a therapeutic agent to treat a condition treatable by administrating a composition of the invention. That amount is the amount sufficient to exhibit a detectable therapeutic or ameliorative response in a tissue system, animal or human. The effect may include, for example, treating the conditions listed herein. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the condition being treated, recommendations of the treating physician (researcher, veterinarian, medical doctor or other clinician), and the therapeutics, or combination of therapeutics, selected for administration. Thus, it is not useful to specify an exact effective amount in advance.

A "**pharmaceutical salt**' refers to an acid:base complex containing an active pharmaceutical ingredient (API) along with additional non-toxic molecular species in the same crystal structure. The term **"pharmaceutically acceptable salt"** refers to those salts that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, etc., and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well-known in the art. They can be prepared *in situ* when finally isolating and purifying the compounds of the invention, or separately by reacting them with pharmaceutically acceptable non-toxic bases or acids, including inorganic or organic bases and inorganic or organic acids (*Berge, 1977*). Common anions used in pharmaceutically acceptable salts include: chloride, bromide, sulfate, nitrate, phosphate, bicarbonate, mesylate, esylate, isothianate, tosylate, napsylate, besylate, acetate, propionate, maleate, benzoate, salicylate, fumarate, citrate, lactate, maleate, tartrate, pamoate, succinate, glycolate, hexanoate, octanoate, decanoate, stearate, oleate, aspartate and glutamate. Common cations used as counterions in pharmaceutically acceptable salts include: sodium, potassium, calcium, magnesium, lithium, zinc, aluminum, arginine, lysine, histidine, triethylamine, ethanolamine, triethanolamine, ethilenediamine, meglumine, procaine and benzathine.

The **'free base'** form may be regenerated by contacting the salt with a base or acid, and isolating the parent compound in the conventional matter. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

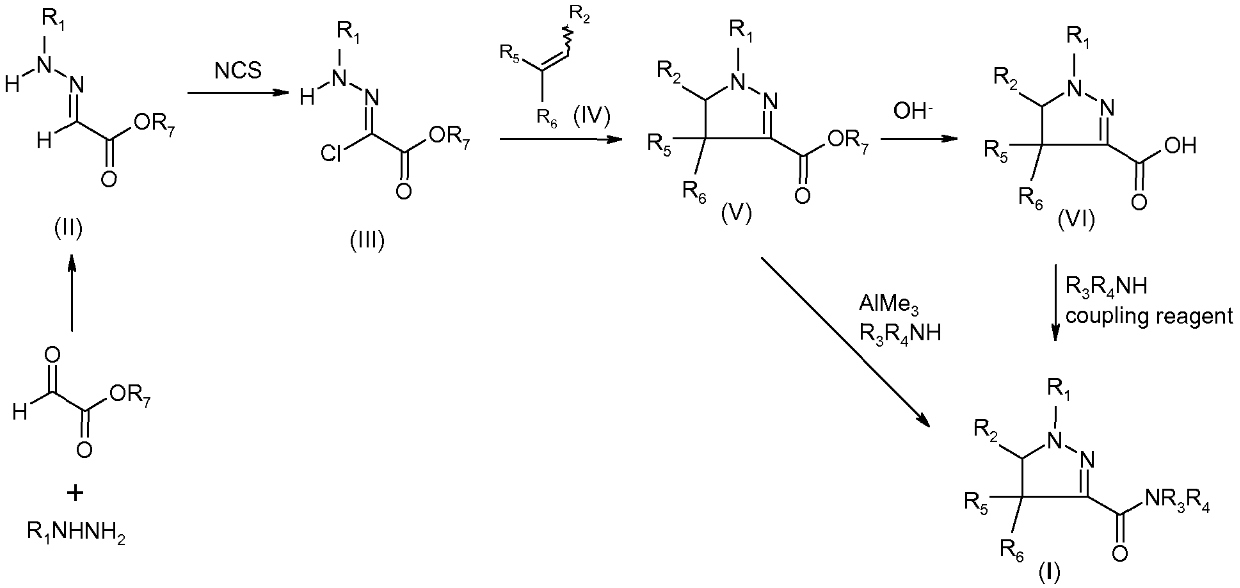
The term **"treatment"** as used herein refers to any treatment of a mammalian, for example human condition or disease, and includes: (1) inhibiting the disease or condition, i.e., arresting its development, (2) relieving the disease or condition, i.e., causing the condition to regress, or (3) stopping the symptoms of the disease. The term **'inhibit'** includes its generally accepted meaning which includes restraining, alleviating, ameliorating, and slowing, stopping or reversing progression, severity, or a resultant symptom. As used herein, the term **"medical therapy"** intendeds to include diagnostic and therapeutic regimens carried out *in vivo* or *ex vivo* on humans or other mammals. **'Mammals'** include animals of economic importance such as bovine, ovine, and porcine animals, especially those that produce meat, as well as domestic animals, sports animals, zoo animals, and humans, the latter being preferred. The term **"subject"** as used herein, refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

EXAMPLE 1: ANALYTICAL METHODS

^{1}H NMR spectra were recorded on a Varian UN400 instrument (400 MHz) using DMSO-d_6 or $CDCl_3$ as solvents with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ scale) downfield from tetramethylsilane. Coupling constants (J) are expressed in Hz. Flash chromatography was performed using silica gel 60 (0.040-0.063 mm, Merck). Column chromatography was performed using silica gel 60 (0.063-0.200 mm, Merck). Sepacore chromatographic separations were carried out using Supelco equipment, VersaFLASH^{TM} columns, VersaPak^{TM} silica cartridges, Büchi UV monitor C-630, Büchi Pump module C-605, Büchi fraction collector C-660 and Büchi pump manager C-615. Melting points were recorded on a Büchi B-545 melting point apparatus or determined by DSC (differential scanning calorimetry) methods. Optical rotations ($[\alpha]_D$) were measured on an Optical Activity polarimeter. Specific rotations are given as deg/dm, the concentration values are reported as g/100 mL of the specified solvent and were recorded at 23 °C, unless indicated otherwise.

EXAMPLE 2: GENERAL ASPECTS OF SYNTHESES

Pyrazoline derivatives can be obtained by published methods (*Bach, 1994).* The synthesis of compounds having formula (I) is outlined in Scheme 1. Additional information on activating and coupling methods of amines to carboxylic acids can be found in the literature (*Bodanszky, 1994; Akaji, 1994; Alberticio, 1997; Montalbetti, 2005).*



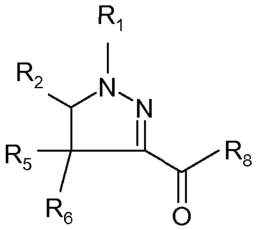
Scheme 1

A hydrazone derivative of general formula (II) wherein R_1 has the abovementioned meaning and R_7 is a C_{1-3} alkyl group, such as an ethyl group, can be obtained from a compound of general formula R_1NHNH_2 and ethylglyoxalate. A hydrazone derivative of general formula (II) can be reacted with a chlorinating agent such as tert-butyl hypochlorite or N-chlorosuccinimide (NCS) in an inert solvent to give a compound of general formula (III). A compound of general formula (III) wherein R_1 has the abovementioned meaning, and R_7 is a C_{1-3} alkyl group can be reacted with a compound of general formula (IV), wherein R_2, R_5 and R_6 have the abovementioned meaning, to give a compound of general formula (V) wherein R_1, R_2, R_5, R_6 and R_7 have the abovementioned meaning. A compound of general formula (V) can be reacted with a base such as aqueous potassium hydroxide or lithium hydroxide to give a carboxylic acid derivative of general formula (VI), or a sodium, potassium, lithium or cesium salt thereof, wherein R_1, R_2, R_5 and R_6 have the abovementioned meaning. A compound of general formula (VI) can be reacted with an amine of general formula R_3R_4NH, wherein R_3 and R_4 have the abovementioned meaning, in the presence of an activating or coupling reagent such as 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate (CIP), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) or O-benzotriazol-1-yl-N,N,N',N'-tetramethyl-uronium hexafluorophosphate (HBTU) in an inert organic solvent such as dichloromethane to give a compound of general formula (I) wherein R_1, R_2, R_3, R_4, R_5 and R_6 have the abovementioned meaning. Preferably, a base such as triethylamine or Hünigs base (DIPEA) may be added in such reactions.

Alternatively, an ester derivative having formula (V) can be reacted in a so-called Weinreb amidation reaction with an amine of general formula R_3R_4NH to give a compound of general formula (I). Such Weinreb amidation reactions can be promoted by the use of trimethylaluminum $Al(CH_3)_3$ (*For more information on aluminum-mediated conversion of esters to amides, see Levin, 1982*).

Another alternative is to chlorinate a carboxylic acid derivative having formula (VI) to the corresponding acid chloride (Va) wherein R_8 is a chloro atom using a chlorinating agent such as thionyl chloride ($SOCl_2$) or oxalyl chloride. The formed acid chloride derivative can subsequently be reacted with an amine of general formula R_3R_4NH to give a compound of general formula (I), wherein R_1, R_2, R_3, R_4, R_5 and R_6 have the abovementioned meaning.

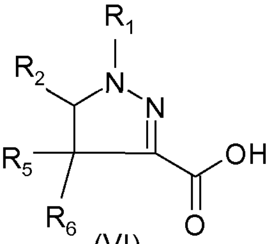
Compounds of formula (Va)



(Va)

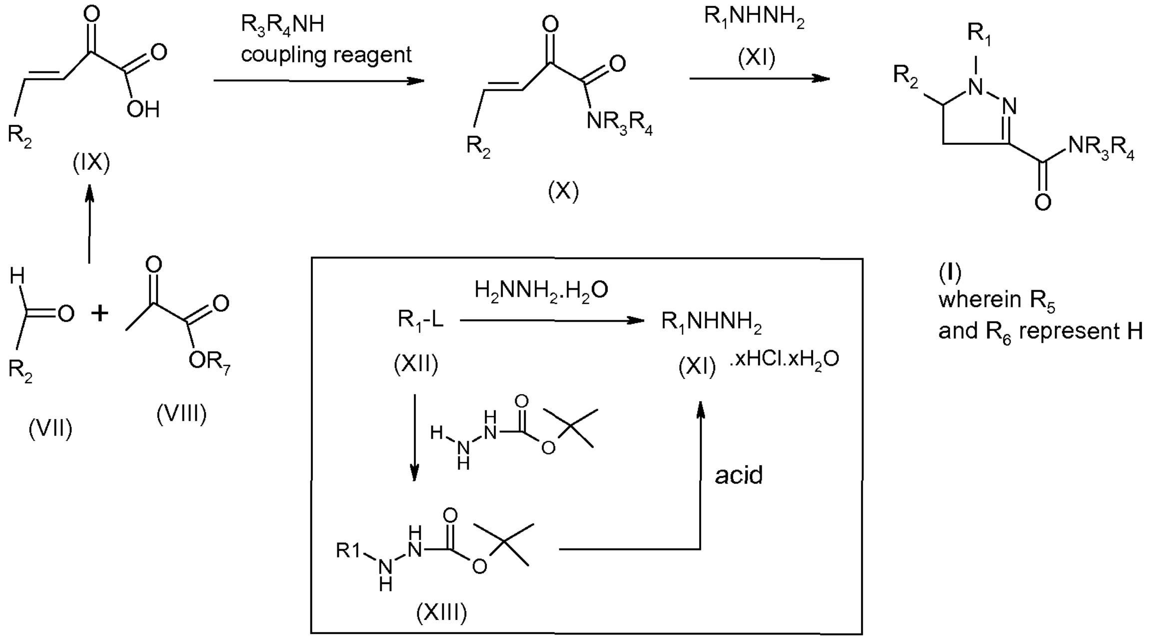
wherein R_1, R_2, R_5 and R_6 have the abovementioned meaning and R_8 is a group O-R_7 wherein R_7 is a C_{1-3} alkyl group or R_8 is a chloro atom, are new, with the proviso that when R_2 is phenyl, and R_1 is a benzyl group, R_7 is not an ethyl group. Such compounds are useful in the synthesis of compounds of the general formula (I).

New are also compounds of formula (VI) or their sodium, potassium, lithium or cesium salts:



(VI)

wherein R_1, R_2, R_5 and R_6 have the same meanings as given above, with the proviso that when R_2 is phenyl, R_1 is not a benzyl group. Such compounds are useful in the synthesis of compounds of the general formula (I).



Scheme 2

Alternatively, a compound of general formula (I) wherein R_5 and R_6 are hydrogen atoms, and R_1, R_2, R_3 and R_4 have the abovementioned meaning can be prepared according to the route described in Scheme 2. A compound of general formula (IX) wherein R_2 has the abovementioned meaning can be obtained from an aldehyde of general formula (VII) and a compound of general formula (VIII) in the presence of a base such as aqueous potassium hydroxide or sodium hydroxide in a solvent such as ethanol *(Annan, 1989).* The formed 2-oxo-buten-3-oic acid derivative (IX) can be reacted with a compound of general formula R_3R_4NH in an inert organic solvent such as dichloromethane in the presence of an activating or coupling reagent such as HBTU to give an amide derivative of general formula (X), wherein R_2, R_3 and R_4 have the abovementioned meaning. Preferably, a base such as triethylamine or Hünigs base (DIPEA) may be added in such a reaction. A compound of of general formula (X) can be reacted with a hydrazine derivative of general formula R_1NHNH_2 or its hydrate $R_1NHNH_2.H_2O$ or a salt thereof, wherein R_1 has the abovementioned meaning, to give a compound of general formula (I) wherein R_1, R_2, R_3 and R_4 have the abovementioned meaning, and R_5 and R_6 are hydrogen atoms. A hydrazine of general formula R_1NHNH_2 (XI) can be prepared from hydrazine or hydrazine hydrate or a salt thereof and a compound of general formula R_1-L (XII) wherein L is a 'leaving group' such as iodide, bromide or choride in an organic solvent such as ethanol, analogously to the method described (*Chem. Ber. 1965*). Alternatively, a hydrazine of general formula R_1NHNH_2 (XI) or its hydrate $R_1NHNH_2.H_2O$ or a salt thereof, wherein R_1 has the abovementioned meaning, can be prepared from a compound of general formula R_1-L (XII) in an organic solvent such as acetonitrile, in a reaction with a protected hydrazine derivative such as tert-butylcarbazate to give a compound of general formula (XIII) which compound of general formula (XIII) is subsequently reacted with an acid such as hydrochloric acid in an inert organic solvent such as 1,4-dioxane.

Compounds of the general formula (X) wherein R_2 has the same meaning as given hereinabove, R_3 is a hydrogen atom, and R_4 is chosen from a C_{6-10} bicycloalkyl group or a C_{7-10} tricycloalkyl group, which groups may be substituted with 1-5 substituents selected from methyl, ethyl, hydroxyl, amino or fluor or R_4 is chosen from a 2-phenyl-1,1-dimethyl-ethyl or 1-phenyl-1-methyl-ethyl group, wherein their phenyl groups may be substituted with 1-5 substituents Y, wherein Y has the abovementioned meaning, such compounds being useful in the synthesis of compounds of the general formula (I) are new.

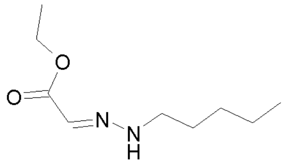
The selection of the particular synthetic procedures depends on factors known to those skilled in the art such as the compatibility of functional groups with the reagents used, the possibility to use protecting groups, catalysts, activating and coupling reagents and the ultimate structural features present in the final compound being prepared.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by mixing a compound of the present invention with a suitable acid, for instance an inorganic acid such as hydrochloric acid, or with an organic acid such as fumaric acid.

According to these procedures the compounds described below have been prepared. They are intended to further illustrate the invention in more detail, and therefore are not deemed to restrict the scope of the invention in any way. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is thus intended that the specification and examples be considered as exemplary only.

EXAMPLE 3: SYNTHESIS AND SPECTRAL DATA OF INTERMEDIATES

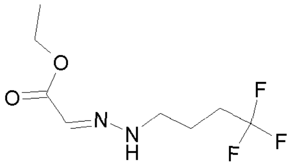
Intermediate II-1



Intermediate II-1

To a magnetically stirred solution of oxo-acetic acid ethyl ester (35.08 ml, 177 mmol; 50 % solution in toluene) in ethanol (450 ml) was added n-pentylhydrazine (21.7 g, 212 mmol) and the resulting solution was heated at 80 °C for 16 hours. The obtained mixture was allowed to attain room temperature and concentrated. The resulting residue was taken up in ethylacetate and water. The organic layer was separated and subsequently dried over $MgSO_4$, filtered and concentrated to give (pentylhydrazono)acetic acid ethyl ester (Intermediate II-1) (32 .2 gram, 93 % yield) as a purple colored oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.87-0.94 (m, 3H), 1.25-1.42 (m, 7H), 1.55-1.68 (m, 2H), 3.17-3.23 (m, 1H), 3.35-3.45 (m, 1H), 4.28 (q, J = 7, 2H), 6.51 (br s, 1H), 6.72 (s, 1H).

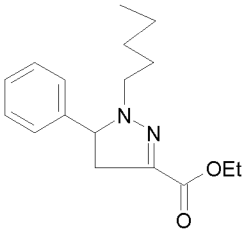
Intermediate II-2



Intermediate II-2

Intermediate (II-2) was obtained in 94 % yield analogously to the preparation of intermediate (II-1) from oxo-acetic acid ethyl ester and 4,4,4-trifluorobutylhydrazine.HCl.H_2O (Intermediate XI-3) in the presence of 1.2 molar equivalent of Hünig's base (DIPEA). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3H), 1.84-1.97 (m, 2H), 2.11-2.27 (m, 2H), 3.33-3.40 (m, 2H), 4.28 (q, J = 7.2 Hz, 2H), 6.50 (br s, 1H), 6.80 (s, 1H).

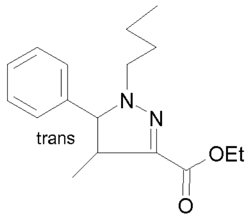
Intermediate V-1



Intermediate V-1

To a magnetically stirred solution of (pentylhydrazono)acetic acid ethyl ester (Intermediate II-1) (35.16 g, 179 mmol) in ethylacetate (450 ml) was added N-chlorosuccinimide (NCS) (26.34 g, 197 mmol) and the resulting mixture was heated at 60 °C for 1 hour in a nitrogen atmosphere. To the reaction mixture was added styrene (41.1 ml, 359 mmol) and potassium bicarbonate (89.8 g, 897 mmol) and water (8 ml). The resulting mixture was heated at 70 °C for 16 hours. The resulting mixture was allowed to attain room temperature, concentrated in vacuo and the resulting residue was chromatographically separated using Sepacore equipment (eluant: dichloromethane/methanol = 98/2 v/v) to give ethyl 1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxylate (Intermediate (V-1) (12.1 g, 22 % yield) as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.83 (t, J = 7, 3H), 1.13-1.28 (m, 4H), 1.35 (t, J = 7, 3H), 1.53-1.67 (m, 2H), 2.89 (dd, J = 16 and 13, 1H), 3.01-3.09 (m, 1H), 3.14-3.22 (m, 1H), 3.41 (dd, J = 16 and 12, 1H), 4.31 (double (diastereotopic) quartet, J ~ 7, 2H), 4.63 (dd, J = 13 and 12, 1H), 7.27-7.39 (m, 5H).

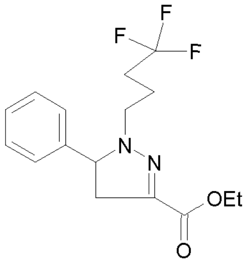
Intermediate V-2



Intermediate V-2

Intermediate (V-2) was obtained analogously to the preparation of intermediate (V-1) from (butylhydrazono)acetic acid ethyl ester via successive chlorination with N-chlorosuccinimide (NCS) and treatment with trans-beta-methylstyrene. Chromatographic purification using Sepacore equipment (eluant: petroleum eter (40-60)/ethylacetate = 9/1 v/v)) gave ethyl 1-(n-butyl)-trans-4-methyl-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxylate (Intermediate (V-2) in 14 % yield. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7, 3H), 1.18-1.43 (m, 8H), 1.49-1.66 (m, 2H), 3.03-3.26 (m, 3H), 4.09 (d, J = 12 Hz, 1H), 4.27-4.37 (m, 2H), 7.28-7.40 (m, 5H).

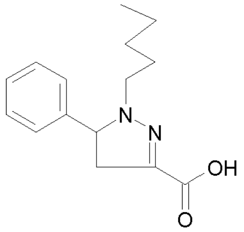
Intermediate V-3



Intermediate V-3

Intermediate (V-3) was obtained analogously to the preparation of intermediate (V-1) from (4,4,4-trifluorobutylhydrazono)acetic acid ethyl ester (Intermediate II-2) via successive reactions with N-chlorosuccinimide (NCS) and styrene to give crude intermediate (V-3). This crude material was chromatographically purified by using flash chromatography (eluant gradient: petroleum ether (40-60)/ethylacetate = 95/5 => petroleum ether (40-60)/ethylacetate = 93/7 (v/v)) to give ethyl 1-(4,4,4-trifluorobutyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxylate (Intermediate (V-3) (34 % yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J = 7 Hz, 3H), 1.75-2.22 (m, 4H), 2.93 (dd, J = 18 and 14 Hz, 1H), 3.06-3.21 (m, 2H), 3.41 (dd, J = 18 and 12 Hz, 1H), 4.33 (double (diastereotopic) quartet, J ~ 7, 2H), 4.55 (dd, J = 14 and 12 Hz, 1H), 7.31-7.42 (m, 5H).

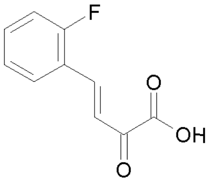
Intermediate VI-1



Intermediate VI-1

To a magnetically stirred solution of ethyl 1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxylate (Intermediate (V-1) (11.76 g, 38.74 mmol) in tetrahydrofuran (100 ml) and water (100 ml) was added lithium hydroxide (1.86 g, 77.5 mmol) and the resulting mixture was heated at 70 °C for 1 hour. The reaction mixture was allowed to attain room temperature and diethyl ether (200 ml) and concentrated hydrochloric acid (7 ml) were added. The organic layer was separated, washed three times with water and with brine and subsequently dried over Na_2SO_4, filtered and concentrated in vacuo to give 1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxylic acid (Intermediate (VI-1) (7.9 g, 74 % yield) as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84 (t, J = 7, 3H), 1.15-1.28 (m, 4H), 1.53-1.65 (m, 2H), 2.92 (dd, J = 17 and 13, 1H), 3.02-3.11 (m, 1H), 3.18-3.27 (m, 1H), 3.44 (dd, J = 17 and 13, 1H), 4.75 t, J = 13, 1H), 7.31-7.41 (m, 5H), 7.42-9.00 (br s, 1H).

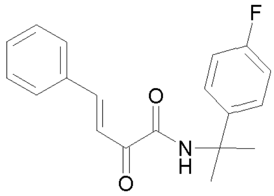
Intermediate IX-1



Intermediate IX-1

To a magnetically stirred solution of ethyl 2-fluorobenzaldehyde (11.7 ml, 110 mmol) and ethylglyoxalate (11.1 ml, 100 mmol) in ethanol (50 ml) was slowly added a solution of sodium hydroxide (4.4 g (110 mmol) in 50 ml water) in a nitrogen atmosphere while the temperature was kept between 0 °C and 10 °C. After stirring for another 45 minutes the reaction mixture was allowed to attain room temperature and stirred for 2 hours. The formed precipitate was collected by filtration and successively washed with ethanol and a 1N HCl solution (200 ml) and subsequently dried to give E-2-oxo-4-(2-fluorophenyl)-but-3-enoic acid (11.1 gram, 57 % yield). Melting point:100-102.5 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.13-7.27 (m, 2H), 7.45-7.53 (m, 1H) 7.66-7.74 (m, 2H), 8.26 (d, J = 16, 1H), invisible –OH proton.

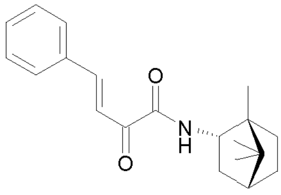
Intermediate X-1



Intermediate X-1

To a magnetically stirred solution of the commercially available E-2-oxo-4-phenyl-but-3-enoic acid (4.40 gram, 25 mmol) in dichloromethane (100 ml) was successively added 1-(4-fluorophenyl)-1-methyl-ethylamine (3.83 g, 25 mmol), N-ethyldiisopropylamine (DIPEA) (8.56 ml, 50 mmol) and O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) (9.48 gram, 25 mmol) and the resulting mixture was reacted at room temperature for 16 hours in a nitrogen atmosphere. The organic layer was washed twice with water and subsequently dried over $MgSO_4$, filtered and concentrated in vacuo to give crude E-2-oxo-4-phenyl-but-3-enoic acid [1-(4-fluorophenyl)-1-methyl-ethyl]amide (Intermediate X-I) as an oil. Further chromatographic purification using Sepacore equipment (eluant: petroleum ether/ethylacetate = 95/5 (v/v)) gave intermediate X-I as an oil which slowly solidified on standing (5.15 g, 65 % yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.77 (s, 6H), 7.00-7.05 (m, 2H), 7.35-7.45 (m, 5H), 7.52 (br s, 1H), 7.61-7.65 (m, 2H), 7.73 (d, J = 16, 1H), 7.92 (d, J = 16, 1H).

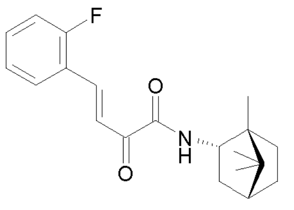
Intermediate X-2



Intermediate X-2

Intermediate X-2 (E-2-oxo-4-phenyl-but-3-enoic acid [endo-(1R,2S,4R)-1,7,7-trimethylbicyclo-[2.2.1]hept-2-ylamide]) was obtained from E-2-oxo-4-phenyl-but-3-enoic acid and endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamine (CAS 32511-34-5) analogously to the procedure described for intermediate X-1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84-1.00 (m, 10H), 1.21-1.29 (m, 1H), 1.38-1.48 (m, 1H), 1.53-1.62 (m, 1H) , 1.70-1.86 (m, 2H) , 2.33-2.44 (m, 1H), 4.22-4.30 (m, 1H), 7.20-7.26 (m, 1H), 7.39-7.46 (m, 3H), 7.65-7.70 (m, 2H), 7.78 (d, J = 16, 1H), 7.95 (d, J = 16, 1H).

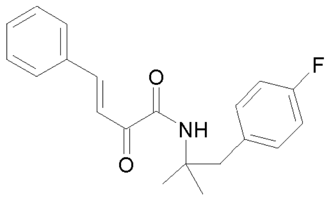
Intermediate X-3



Intermediate X-3

Intermediate X-3 (E-2-oxo-4-(2-fluorophenyl)-but-3-enoic acid [endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamide]) was obtained from E-2-oxo-4-(2-fluorophenyl)-but-3-enoic acid (Intermediate IX-1) and endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamine analogously to the procedure described for intermediate X-1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84-1.00 (m, 10H), 1.21-1.30 (m, 1H), 1.38-1.48 (m, 1H), 1.53-1.62 (m, 1H) , 1.70-1.87 (m, 2H), 2.34-2.44 (m, 1H), 4.21-4.30 (m, 1H), 7.10-7.25 (m, 3H), 7.38-7.45 (m, 1H), 7.70-7.75 (m, 1H), 7.85 (d, J = 16, 1H), 8.12 (d, J = 16, 1H).

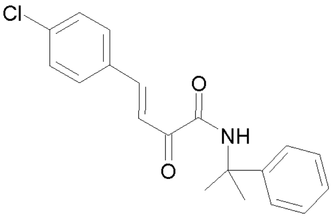
Intermediate X-4



Intermediate X-4

Intermediate X-4 (E-2-oxo-4-phenyl-but-3-enoic acid [2-(4-fluorophenyl)-2,2-dimethyl-ethyl]amide was obtained from E-2-oxo-4-phenyl-but-3-enoic acid and 2-(4-fluorophenyl)-2,2-dimethyl-ethylamine analogously to the procedure described for intermediate X-1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 6H), 3.08 (s, 2H), 6.91-6.99 (m, 3H), 7.06-7.11 (m, 2H), 7.38-7.47 (m, 3H), 7.65-7.70 (m, 2H), 7.82 (d, J = 16, 1H), 7.92 (d, J = 16, 1H).

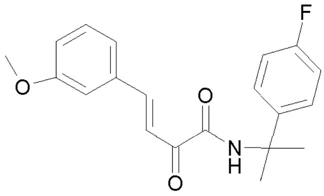
Intermediate X-5



Intermediate X-5

Intermediate X-5 (E-2-oxo-4-(4-chlorophenyl)-but-3-enoic acid [1-phenyl-1-methyl-ethyl]amide was obtained from E-2-oxo-4-(4-chlorophenyl)-but-3-enoic acid and 1-phenyl-1-methyl-ethylamine analogously to the procedure described for intermediate X-1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.79 (s, 6H), 7.23-7.28 (m, 1H), 7.32-7.43 (m, 6H), 7.51-7.57 (m, 3H), 7.71 (d, J = 16 Hz, 1H), 7.85 (d, J = 16 Hz, 1H).

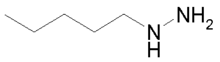
Intermediate X-6



Intermediate X-6

Intermediate X-6 (E-2-oxo-4-(3-methoxyphenyl)-but-3-enoic acid [1-(4-fluorophenyl)-1-methyl-ethyl]amide was obtained from E-2-oxo-4-(3-methoxyphenyl)-but-3-enoic acid and 1-(4-fluorophenyl)-1-methyl-ethylamine analogously to the procedure described for intermediate X-1. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.77 (s, 6H), 3.81 (s, 3H), 6.95-7.05 (m, 3H), 7.13-7.16 (m, 1H), 7.18-7.22 (m, 1H), 7.28-7.33 (m, 1H), 7.36-7.40 (m, 2H), 7.54 (br s, 1H), 7.71 (d, J = 16 Hz, 1H), 7.88 (d, J = 16 Hz, 1H).

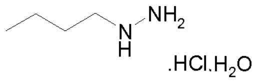
Intermediate XI-1



Intermediate XI-1

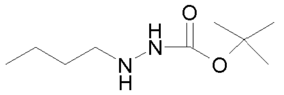
To a magnetically stirred solution of hydrazine hydrate (243 ml, 5 mol) was very slowly added a solution of 1-bromopentane (62 ml, 0.50 mol) in ethanol (50 ml) while keeping the temperature at 20 °C. The resulting mixture was reacted at room temperature for 2 hours. The mixture was extracted with diethyl ether. The diethyl ether extract was concentrated and BaO (5 gram) was added to the residue. Distillation in vacuo gave n-pentylhydrazine (Intermediate XI-1) at 30-40 mbar pressure at 72 °C-78 °C (30.36 gram, 48 % yield). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 7, 3H), 1.27-1.38 (m, 4H), 1.45-1.58 (m, 2H), 2.76 (t, J= 7, 2H), 2.85 (br s, 3H).

Intermediate XI-2



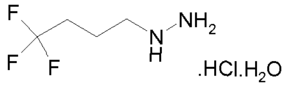
Intermediate XI-2

Step A: To a magnetically stirred solution of tert-butylcarbazate (47.5 gram, 359 mmol) in anhydrous acetonitrile (300 ml) was successively added DIPEA (Hünig's base) (37.6 ml, 216 mmol) and 1-bromobutane (19.3 ml, 180 mmol). The resulting mixture was reacted at 60 °C for 16 hours. The resulting mixture was allowed to attain room temperature and subsequently concentrated in vacuo and further purified by Sepacore chromatography (eluant: petroleum ether 40-60/ ethylacetate = 4/1 (v/v)) to give N'-butylhydrazine-carboxylic acid tert-butyl ester (intermediate XIII-1) (13.2 gram, 39 %) as a pale yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7, 3H), 1.30-1.49 (m, 13H), 2.81-2.87 (m, 2H), 4.00 (br s, 1H), 6.20 (br s, 1H).

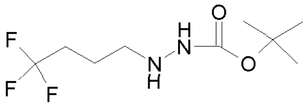

Intermediate XIII-1

Step B: To a magnetically stirred solution of N'-butylhydrazine-carboxylic acid tert-butyl ester (intermediate XIII-1) (13.17 gram, 70 mmol) in 1,4-dioxane (100 ml) was added excess (12 mol equivalents) hydrochloric acid (12 N) and the resulting mixture was reacted for 16 hours at room temperature. The resulting mixture was concentrated in vacuo and triturated with diethyl ether to give n-butylhydrazine.HCl.H_2O (Intermediate XI-2) (9.63 gram, 92 % yield). ^{1}H-NMR (400 MHz, DMSO-d_6/$CDCl_3$ = 4/1 (v/v)) δ 0.93 (t, J = 7, 3H), 1.32-1.43 (m, 2H), 1.56-1.65 (m, 2H), 2.92-2.98 (m, 2H), 7.20 (br s, ~ 6H).

Intermediate XI-3


Intermediate XI-3

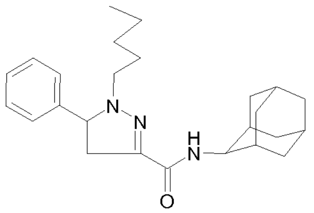
Step A: Intermediate (XI-3) was obtained analogously to the procedure described for intermediate (XI-2) from tert-butylcarbazate and 1-bromo-4,4,4-trifluorobutane via N'-(4,4,4-trifluorobutyl)hydrazine-carboxylic acid tert-butyl ester (intermediate XIII-2): Intermediate XIII-2: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 1.67-1.76 (m, 2H), 2.10-2.24 (m, 2H), 2.87-2.94 (m, 2H), 3.97 (br s, 1H), 6.05 (br s, 1H).


Intermediate XIII-2

Step B: N'-(4,4,4-trifluorobutyl)hydrazine-carboxylic acid tert-butyl ester (intermediate XIII-2) was converted with excess hydrochloric acid to intermediate (XI-3) (4,4,4-trifluorobutylhydrazine.HCl.H_2O) analogously as described for the preparation of intermediate XI-2 (part B). Intermediate (XI-3): ^{1}H-NMR (400 MHz, DMSO-d_6 δ 1.77 (quintet, J = 7.7 Hz, 2H), 2.28-2.43 (m, 2H), 2.94 (t, J = 7.4 Hz, 2H), 7.95 (br s, ~3H).

EXAMPLE 4: SYNTHESIS OF SPECIFIC COMPOUNDS

Compound 1



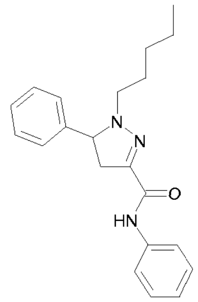
Compound 1

N-(Adamant-2-yl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

To a magnetically stirred solution of 1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxylic acid (Intermediate (VI-1) (0.70 g, 2.55 mmol) in dichloromethane (40 ml) was successively added 2-adamantanamine.HCl (480 mg, 2.55 mmol), N-ethyldiisopropylamine (DIPEA) (1.78 ml, 10.22 mmol) and 2-chloro-1,3-dimethylimidazolinium hexafluorophosphate (CIP) (853 mg, 3.07 mol) and the resulting mixture was reacted at room temperature for 16 hours in a nitrogen atmosphere. The reaction mixture was successively washed twice with water, twice with aqueous citric acid (0.5 M), twice with $NaHCO_3$ (5 % aqueous solution) and brine, and subsequently dried over Na_2SO_4, filtered and concentrated in vacuo to give crude N-(adamant-2-yl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (1.26 g) as an orange oil. Further chromatographic purification using Sepacore equipment (eluant: petroleum ether/diethyl ether = 85/15 (v/v)) gave compound 1 (750 mg, 67 % yield) as an oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7, 3H), 1.21-1.30 (m, 4H), 1.55-1.65 (m, 2H), 1.65-1.70 (m, 2H), 1.76 (br s, 2H), 1.75-1.92 (m, 8H), 1.97-2.01 (m, 2H), 2.82 (dd, J = 17 and 14, 1H), 2.92-2.97 (m, 2H), 3.42 (dd, J = 17 and 11, 1H), 4.09-4.14 (m, 1H), 4.40 (dd, J = 14 and 11, 1H), 6.99-7.07 (m, 1H), 7.28-7.38 (m, 5H).

Analogously were prepared the compounds 2-100.

Compound 2

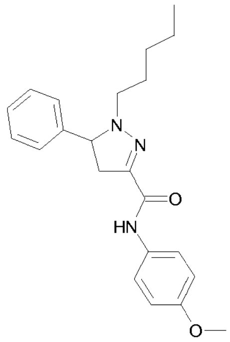


Compound 2

N-Phenyl-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.87 (t, *J*=7 Hz, 3 H), 1.17 - 1.34 (m, 4 H), 1.55 - 1.73 (m, 2 H), 2.85 - 3.08 (m, 3 H), 3.49 (dd, *J*=17 and 11.4 Hz, 1 H), 4.53 (dd, *J*=14 and 11.4 Hz, 1 H), 7.09 (t, *J*=7.5 Hz, 1 H), 7.28 - 7.42 (m, 7 H), 7.62 (d, *J*=7.5 Hz, 2 H), 8.43 (s, 1 H).

Compound 3

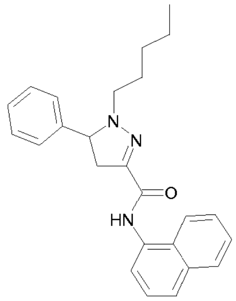


Compound 3

N-(4-Methoxyphenyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.86 (t, *J*=6.9 Hz, 3 H), 1.19 - 1.34 (m, 4 H) 1.57 - 1.69 (m, 2 H), 2.85 - 3.06 (m, 3 H), 3.48 (dd, *J*=17 and 11 Hz, 1 H), 3.80 (s, 3 H), 4.50 (dd, *J*=14 and 11.4 Hz, 1 H), 6.88 (d, *J*=9 Hz, 2 H), 7.28 – 7.40 (m, 5 H) 7.54 (d, *J*=9 Hz, 2 H), 8.35 (br s, 1 H).

Compound 4

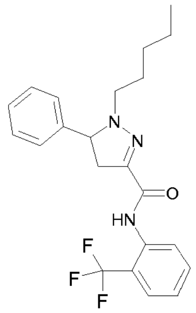


Compound 4

N-(Napht-1-yl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.86 (t, *J*=7 Hz, 3 H), 1.20 - 1.40 (m, 4 H), 1.66 – 1.77 (m, 2 H), 2.92 - 3.14 (m, 3 H), 3.55 (dd, *J*=17 and 11.4 Hz, 1 H), 4.59 (dd, *J*=14 and 11.4 Hz, 1 H), 7.30 - 7.44 (m, 5 H), 7.46 - 7.61 (m, 3 H), 7.67 (d, *J*=8.4 Hz, 1 H), 7.88 (d, *J*=7.5 Hz, 1 H), 7.95 (d, *J*=8.4 Hz, 1 H), 8.20 (d, *J*=7.5 Hz, 1 H), 9.05 (br s, 1 H).

Compound 5

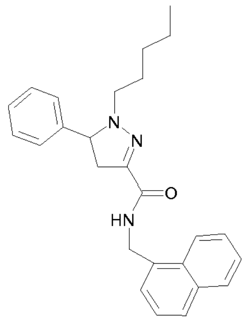


Compound 5

N-(2-Trifluoromethyl)phenyl-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.88 (t, J=7.2 Hz, 3 H), 1.18 - 1.38 (m, 4 H), 1.61 - 1.70 (m, 2 H), 2.86 - 3.11 (m, 3 H), 3.49 (dd, J=17 and 11.7 Hz, 1 H), 4.59 (dd, J=14 and 11.4 Hz, 1 H), 7.17 (t, J=7.7 Hz, 1 H), 7.29 - 7.42 (m, 5 H), 7.55 (t, J=7.8 Hz, 1 H), 7.61 (d, J=7.8 Hz, 1 H), 8.45 (d, J=8.4 Hz, 1 H), 9.05 (br s, 1 H).

Compound 6

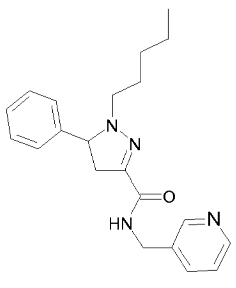


Compound 6

N-(Naphthalen-1-ylmethyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.79 (t, J=6.9 Hz, 3 H), 1.07 - 1.25 (m, 4 H), 1.44 - 1.58 (m, 2 H), 2.78 - 2.92 (m, 3 H), 3.46 (dd, J=17.3, and 11.3 Hz, 1 H), 4.41 (dd, J=14.3 and 11.3 Hz, 1 H), 5.00 (d, J=5.7 Hz, 2 H), 6.90 (br t, J=5.6 Hz, 1 H), 7.27 - 7.37 (m, 5 H), 7.42 - 7.60 (m, 4 H), 7.83 (d, J=7.8 Hz, 1 H), 7.88 (d, J=1.2 Hz, 1 H), 8.10 (d, J=8.1 Hz, 1 H).

Compound 7

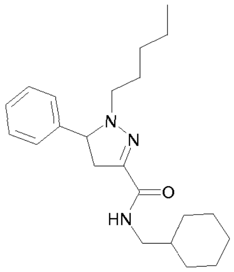


Compound 7

N-(Pyridin-3-ylmethyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.83 (t, *J*=6.9 Hz, 3 H), 1.14 - 1.30 (m, 4 H), 1.51 - 1.64 (m, 2 H), 2.81 - 2.99 (m, 3 H), 3.44 (dd, *J*=17.3 and 11.3 Hz, 1 H), 4.45 (dd, *J*=14.30 and 11.29 Hz, 1 H), 4.56 (d, *J*=6.3 Hz, 2 H), 7.00 (br t, *J*=5.9 Hz, 1 H), 7.26 - 7.39 (m, 6 H), 7.70 (br d, *J*=7.8 Hz, 1 H), 8.54 (dd, *J*=4.8 and 1.50 Hz, 1 H), 8.60 (d, 1 H).

Compound 8

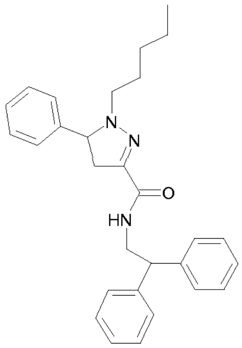


Compound 8

N-(Cyclohexylmethyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.85 (t, *J*=6.9 Hz, 3 H), 0.90 - 1.04 (m, 2 H), 1.12 - 1.33 (m, 7 H), 1.47 - 1.82 (m, 8 H), 2.76 - 2.98 (m, 3 H), 3.18 (dq, *J*=12.9 and 6.6 Hz, 2 H), 3.41 (dd, *J*=17.3 and 11 Hz, 1 H), 4.39 (dd, *J*=14.3 and 11 Hz, 1 H), 6.68 (br t, *J*=5.9 Hz, 1 H), 7.27 - 7.41 (m, 5 H).

Compound 9

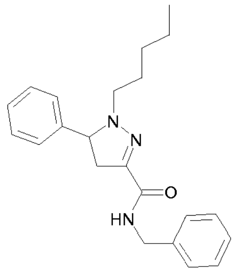


Compound 9

N-(2,2-diphenylethyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.83 (t, *J*=7.07 Hz, 3 H), 1.09 - 1.28 (m, 4 H), 1.43-1.58 m, 2 H), 2.73 - 2.91 (m, 3 H), 3.37 (dd, *J*=17.2 and 11.1 Hz, 1 H), 3.98 (dd, *J*=7.8 and 6.2 Hz, 2 H), 4.26 (t, *J*=7.8 Hz, 1 H), 4.36 (dd, *J*=14.3 and 11.3 Hz, 1 H), 6.62 (br t, *J*=5.9 Hz, 1 H), 7.18 - 7.37 (m, 15 H).

Compound 10

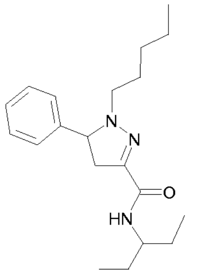


Compound 10

N-(Benzyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J*=6.9 Hz, 3 H), 1.13 - 1.29 (m, 4 H), 1.49 - 1.64 (m, 2 H), 2.81 - 2.96 (m, 3 H), 3.44 (dd, *J*=17.3 and 11.3 Hz, 1 H), 4.42 (dd, *J*=14.5 and 11.1 Hz, 1 H), 4.54 (d, *J*=6 Hz, 2 H), 6.94 (br t, *J*=5.7 Hz, 1 H), 7.26 - 7.40 (m, 10 H).

Compound 11

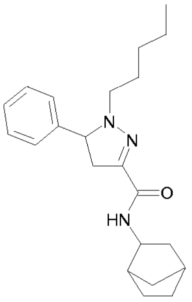


Compound 11

N-[(1-Ethyl)propyl]-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*=6.9 Hz, 3 H), 0.94 (t, J = 7, 6 H), 1.17 - 1.31 (m, 4 H), 1.39 - 1.52 (m, 2 H), 1.53 - 1.69 (m, 4 H), 2.78 - 2.98 (m, 3 H), 3.42 (dd, *J*=17.3 and 11 Hz, 1 H), 3.79 - 3.90 (m, 1 H), 4.40 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.35 (d, *J*=9.3 Hz, 1 H), 7.27 - 7.40 (m, 5 H).

Compound 12



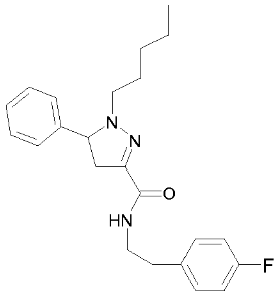
Compound 12

2-exo isomer

N-(Exo-bicyclo[2.2.1]hept-2-yl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J*=6.9 Hz, 3 H), 1.10 - 1.65 (m, 13 H), 1.83 (ddd, *J*=13.1 and 8 and 2.1 Hz, 1 H), 2.25-2.34 (m, 2 H), 2.76 - 2.97 (m, 3 H), 3.40-3.41 (2x dd, *J*=18.4 and 11.1 Hz, 1 H), 3.79 (br td, *J*=7.7 and 3.6 Hz, 1 H), 4.37-4.38 (2x dd, *J*=14.4 and 11.1 and 3.3 Hz, 1 H), 6.46 (br d, *J*=7.2 Hz, 1 H), 7.27 - 7.40 (m, 5 H).

Compound 13

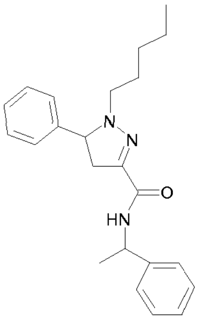


Compound 13

N-[2-(4-Fluorophenyl)ethyl]-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*=6.9 Hz, 3 H), 1.15 - 1.31 (m, 4 H), 1.51-1.65 (m, 2 H), 2.78 - 2.97 (m, 5 H), 3.41 (dd, *J*=17.1 and 11.1 Hz, 1 H), 3.52 - 3.60 (m, 2 H), 4.41 (dd, *J*=14.3 and 11.3 Hz, 1 H), 6.69 (br t, *J*=5.9 Hz, 1 H), 7.00 (br t, *J*=8.7 Hz, 2 H), 7.19 (dd, *J*=8.4 and 5.4 Hz, 2 H), 7.27 - 7.40 (m, 5 H).

Compound 14

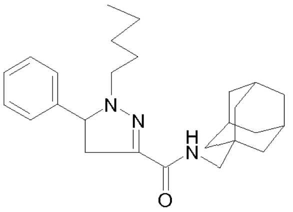


Compound 14

N-(1-Phenyl-ethyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (1:1 diastereomeric mixture)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J*=6.5 Hz, 3 H), 1.15 - 1.30 (m, 4 H), 1.48 - 1.67 (m, 5 H), 2.76 - 2.96 (m, 3 H), 3.39-3.40 (2 x dd, *J*=17.4 and 11.1, 1 H), 4.39-4.40 (2 x dd, *J*=14.3 and 11.1 Hz, 1 H), 5.14 – 5.25 (m, 1 H), 6.86 (br d, *J*=8.1 Hz, 1 H), 7.26 - 7.41 (m, 10 H).

Compound 15

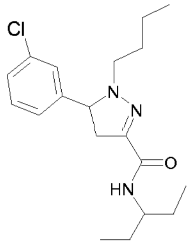


Compound 15

N-(Adamantylmethyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*=6.9 Hz, 3 H), 1.18 - 1.32 (m, 4 H), 1.49 - 1.78 (m, 14 H), 2.00 (br s, 3 H), 2.78 - 3.11 (m, 5 H), 3.42 (dd, *J*=17.1 and 11.1 Hz, 1 H), 4.40 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.69 (br t, *J*=6.3 Hz, 1 H), 7.26 - 7.40 (m, 5 H).

Compound 16

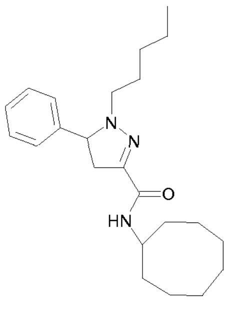


Compound 16

N-[(1-Ethyl)propyl]-1-(n-butyl)-5-(3-chlorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.4 Hz, 3 H), 0.94 (t, *J*=7.4 Hz, 6 H), 1.19 - 1.70 (m, 8 H), 2.79 (dd, *J*=17.3 and 14.3 Hz, 1 H), 2.89-2.95 (m, 2 H), 3.43 (dd, *J*=17.4 and 11.1 Hz, 1 H), 3.79 - 3.90 (m, 1 H), 4.36 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.33 (br d, *J*=9.3 Hz, 1 H), 7.23 - 7.36 (m, 3 H), 7.38 (br s, 1 H).

Compound 17

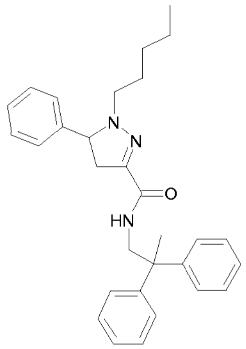


Compound 17

N-(Cyclooctyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*=6.92 Hz, 3 H), 1.16 - 1.31 (m, 4 H), 1.48 - 1.75 (m, 14 H), 1.82 - 1.94 (m, 2 H), 2.76 - 2.97 (m, 3 H), 3.40 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.00-4.10 (m, 1 H), 4.37 (dd, *J*=14.3 and 11 Hz, 1 H), 6.58 (br d, *J*=8.4 Hz, 1 H), 7.27 - 7.39 (m, 5 H).

Compound 18

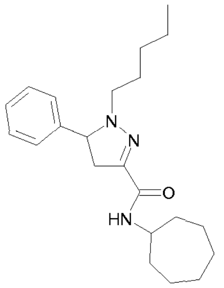


Compound 18

N-(2,2-diphenylpropyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*=7.1 Hz, 3 H), 1.10 - 1.28 (m, 4 H), 1.44 - 1.55 (m, 2 H), 1.71 (s, 3 H), 2.71 - 2.87 (m, 3 H), 3.37 (dd, *J*=17.1 and 11.1 Hz, 1 H), 4.02 (d, *J*=6.3 Hz, 2 H), 4.34 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.41 (br t, *J*=5.87 Hz, 1 H), 7.19 - 7.37 (m, 15 H).

Compound 19

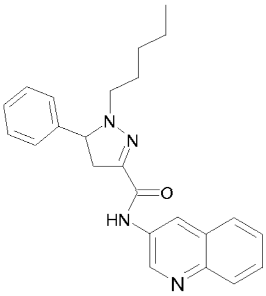


Compound 19

N-(Cycloheptyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*=6.9 Hz, 3 H), 1.15 - 1.31 (m, 4 H), 1.45 - 1.72 (m, 12 H), 1.91 - 2.03 (m, 2 H), 2.76 - 2.97 (m, 3 H), 3.40 (dd, *J*=17.1 and 11.1 Hz, 1 H), 3.95-4.08 (m, 1 H), 4.38 (dd, *J*=14.3 and 11 Hz, 1 H), 6.57 (br d, *J*=8.4 Hz, 1 H), 7.27 - 7.40 (m, 5 H).

Compound 20

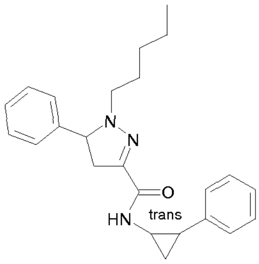


Compound 20

N-(Quinolin-3-yl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=6.92 Hz, 3 H), 1.18 - 1.36 (m, 4 H), 1.58 - 1.71 (m, 2 H), 2.91 - 3.14 (m, 3 H), 3.53 (dd, *J*=17.3 and 11.6 Hz, 1 H), 4.62 (dd, *J*=13.8 and 11.7 Hz, 1 H), 7.29 - 7.45 (m, 5 H), 7.53 (br t, *J*=6.9 Hz, 1 H), 7.62 (dt, *J*=7.7 and 1.50 Hz, 1 H), 7.81 (d, *J*=7.5 Hz, 1 H), 8.05 (d, *J*=8.4 Hz, 1 H), 8.69 (s, 1 H), 8.83 (d, *J*=2.4 Hz, 1 H), 8.86 (d, *J*=2.7 Hz, 1 H).

Compound 21

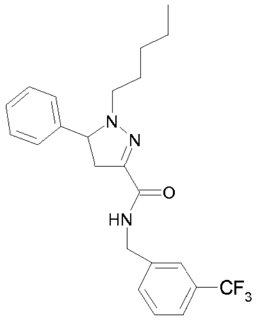


Compound 21

N-(2-phenyl-*trans*-cyclopropyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*=6.92 Hz, 3 H), 1.15 - 1.33 (m, 6 H), 1.52 - 1.68 (m, 2 H), 2.11-2.19 (m, 1 H), 2.76 - 2.98 (m, 4 H), 3.41 and 3.43 (2x dd, *J*=17.2 and 11.2 Hz, 1 H), 4.42 (dd, *J*=14.1 and 11.1 Hz, 1 H), 6.84 (br s, 1 H), 7.15 - 7.39 (m, 10 H).

Compound 22

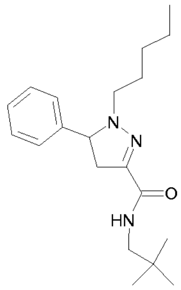


Compound 22

N-[3-(Trifluoromethyl)benzyl)]-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J*=6.92 Hz, 3 H), 1.15 - 1.30 (m, 4 H), 1.51 - 1.65 (m, 2 H), 2.81 – 2.99 (m, 3 H), 3.45 (dd, *J*=17.3 and 11.3 Hz, 1 H), 4.46 (dd, *J*=14.4 and 11.4 Hz, 1 H), 4.59 (s, 2 H), 7.28 - 7.39 (m, 5 H), 7.43 - 7.50 (m, 1 H), 7.52 - 7.60 (m, 3 H).

Compound 23

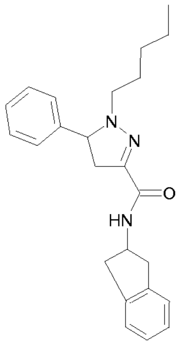


Compound 23

N-(2,2-Dimethylpropyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.85 (t, *J*=7.22 Hz, 3 H), 0.96 (s, 9 H), 1.16 - 1.32 (m, 4 H), 1.53 - 1.67 (m, 2 H), 2.77 - 2.97 (m, 3 H), 3.15 (dd, *J*=6.6 and 1.8 Hz, 2 H), 3.42 (dd, *J*=17.5 and 11.1 Hz, 1 H), 4.41 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.72 (br t, *J*=6.2 Hz, 1 H), 7.27 - 7.40 (m, 5 H).

Compound 24

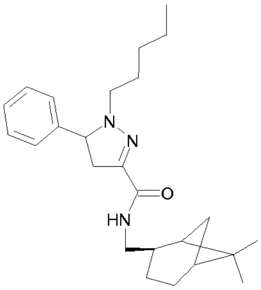


Compound 24

N-(2- Indanyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.82 (t, *J*=6.9 Hz, 3 H), 1.11 - 1.29 (m, 4 H), 1.47 - 1.64 (m, 2 H), 2.77 - 2.96 (m, 4 H), 3.32 - 3.47 (m, 3 H), 4.40 (dd, *J*=14.3 and 11.3 Hz, 1 H), 4.76-4.87 (m, 1 H), 6.80 (br d, *J*=7.8 Hz, 1 H), 7.14 - 7.40 (m, 10 H).

Compound 25

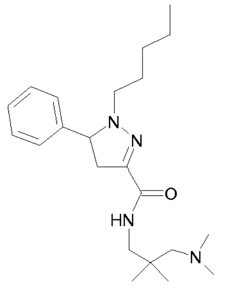


Compound 25

N-[(1R,2S,5R)-rel-6,6-dimethylbicyclo[3.1.1.]heptan-2-methyl]-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture) (from (-)-cis-myrtanylamine (CAS 38235-68-6))

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.80-0.90 (m, 3 H), 0.91 (d, *J*=9.6 Hz, 1 H), 1.07 (s, 3 H), 1.17 - 1.32 (m, 7 H), 1.47 - 1.67 (m, 3 H), 1.81 - 2.04 (m, 5 H), 2.27 - 2.42 (m, 2 H), 2.77 - 2.98 (m, 3 H), 3.27 - 3.49 (m, 3 H), 4.39 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.64 (br t, *J*=5.7 Hz, 1 H), 7.27 - 7.39 (m, 5 H).

Compound 26

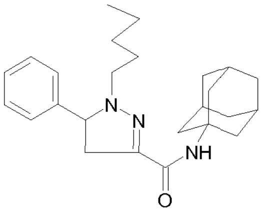


Compound 26

N-[(3-Dimethylamino)-2,2-dimethylpropyl]-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*=6.92 Hz, 3 H), 0.94 (s, 3H), 0.95 (s, 3H), 1.17 - 1.34 (m, 4 H), 1.58 - 1.70 (m, 2 H), 2.26 (s, 2 H), 2.33 (s, 6 H), 2.78 - 2.94 (m, 3 H), 3.24 (d, *J*=5.4 Hz, 2 H), 3.40 (dd, *J*=17.1 and 10.8 Hz, 1 H), 4.35 (dd, *J*=14.6 and 11 Hz, 1 H), 7.28 - 7.41 (m, 5 H), 8.58 (br s, 1 H).

Compound 27

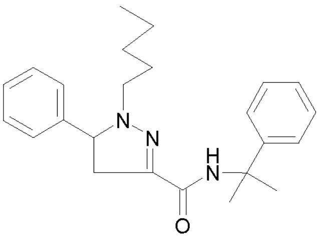


Compound 27

N-(Adamantyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J*=6.92 Hz, 3 H), 1.15 - 1.32 (m, 4 H) 1.49 - 1.64 (m, 2 H), 1.65 - 1.76 (m, 7 H), 2.08 (br s, 8 H), 2.78 (dd, *J*=17.1 and 14.4 Hz, 1 H), 2.89 (t, *J*=7.5 Hz, 2 H), 3.37 (dd, *J*=17.3 and 11 Hz, 1 H) 4.35 (dd, *J*=14.6 and 11 Hz, 1 H), 6.40 (br s, 1 H), 7.27 - 7.41 (m, 5 H).

Compound 28

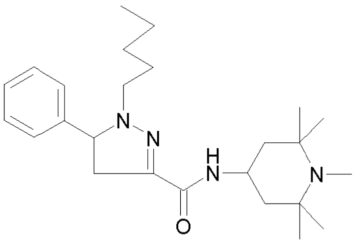


Compound 28

N-(1-Phenyl-1-methyl-ethyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.85 (t, *J*=6.9 Hz, 3 H), 1.16-1.33 (m, 4 H), 1.51-1.69 (m, 2 H), 1.75 (s, 3 H), 1.77 (s, 3 H), 2.78 (dd, *J*=17.3 and 14.6 Hz, 1 H), 2.92 (br t, *J*=7.1 Hz, 2 H), 3.35 (dd, *J*=17.3 and 11 Hz, 1 H), 4.38 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.97 (br s, 1 H), 7.19 - 7.24 (m, 1 H), 7.27 - 7.41 (m, 7 H), 7.45 (br d, *J*=7.2 Hz, 2 H).

Compound 29

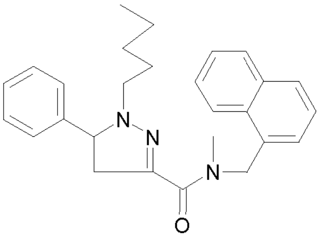


Compound 29

N-(N,2,2,6,6-pentamethylpiperidin-4-yl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.85 (t, *J*=7.1 Hz, 3 H), 1.10 (s, 6 H). 1.16 (s, 6 H). 1.19 - 1.30 (m, 4 H). 1.37 (br t, *J*=11.4 Hz, 2 H), 1.50 - 1.68 (m, 2 H), 1.86 (dd, *J*=12.3 and 3.3 Hz, 2 H), 2.26 (s, 3 H), 2.81 (dd, *J*=17.5 and 14.4 Hz, 1 H), 2.86 – 2.97 (m, 2 H), 3.40 (dd, *J*=17.1 and 11.1 Hz, 1 H), 4.14 - 4.30 (m, 1 H), 4.39 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.39 (br d, *J*=8.1 Hz, 1 H), 7.27 - 7.40 (m, 5 H).

Compound 30

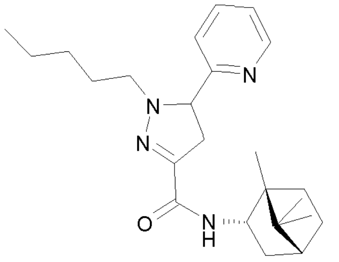


Compound 30

N-Methyl-N-(Naphthalen-1-yl-methyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) (broad signals due to restricted amide bond rotation) δ 0.56 - 1.78 (m, 9 H), 2.48 - 3.08 (m, 3 H), 3.10 (br s) and 3.26 (br s: Together integrates for 3 H), 3.40 - 3.59 (m, 1 H), 4.15 - 4.40 (m, 1 H), 5.18 (br s) and 5.50 (br d, *J*=16 Hz) and 5.64 (br d, *J*=16 Hz; Together integrates for 2 H), 7.26 - 7.58 (m, 9 H), 7.80 (br s, 1 H), 7.88 (br d, *J*=7 Hz, 1 H), 7.92 - 8.17 (m, 1 H),

Compound 31

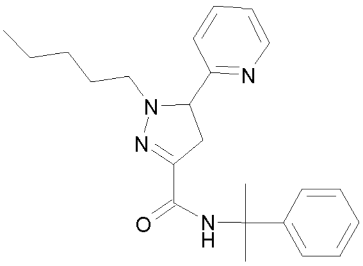


Compound 31

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-pentyl)-5-(pyrid-2-yl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 0.81 - 0.95 (m, 10 H), 0.97 (s, 3 H), 1.16 - 1.35 (m, 4 H), 1.35 - 1.66 (m, 5 H), 1.69 (t, *J*=4.4 Hz, 1 H), 1.74 - 1.87 (m, 1 H), 2.32 - 2.44 (m, 1 H), 2.91 - 3.11 (m, 3 H), 3.44 - 3.59 (m, 1 H), 4.24 - 4.35 (m, 1 H), 4.54 - 4.67 (m, 1 H), 6.69 (br d, *J*=8.4 Hz, 1 H), 7.20-7.27 (m, 1 H), 7.46 (dd, *J*=7.8 and 4.5 Hz, 1 H), 7.72 (br t, *J*=7.5 Hz, 1 H), 8.58 (br t, *J*=4 Hz, 1 H).

Compound 32

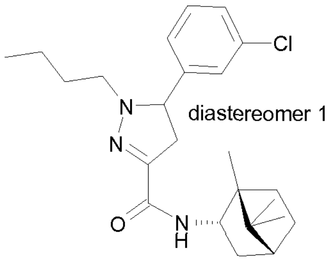


Compound 32

N-(1-Phenyl-1-methyl-ethyl)-1-(n-pentyl)-5-(pyrid-2-yl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 0.84 (t, *J*=6.9 Hz, 3 H), 1.17 - 1.31 (m, 4 H), 1.52 - 1.65 (m, 2 H), 1.73 (s, 3 H), 1.75 (s, 3 H), 2.88 - 3.10 (m, 3 H), 3.40 (dd, *J*=17.3 and 11.6 Hz, 1 H), 4.59 (dd, *J*=13.67 and 11.6 Hz, 1 H), 7.02 (br s, 1 H), 7.19 - 7.28 (m, 2 H), 7.33 (br t, *J*=7.7 Hz, 2 H), 7.40 - 7.48 (m, 3 H), 7.74 (dt, *J*=7.7 and 1.8 Hz, 1 H), 8.57 (br d, *J*=3.9 Hz, 1 H).

Compound 33



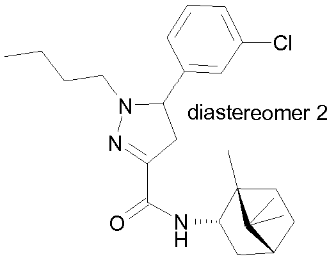
Compound 33

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-butyl)-5-(3-chlorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomer 1)

Compounds 33 and 34 were separated from the corresponding diastereomeric mixture by flash chromatography (silicagel). Eluant: petroleum ether (40-60)/diethyl ether = 4/1 v/v).

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.81 - 0.95 (m, 10 H), 0.97 (s, 3 H), 1.20 - 1.48 (m, 4 H), 1.52 - 1.63 (m, 3 H), 1.69 (t, *J*=4.5 Hz, 1 H), 1.74 - 1.86 (m, 1 H), 2.32 - 2.43 (m, 1 H), 2.78 (dd, *J*=17.4 and 14.1 Hz, 1 H), 2.95 (t, *J*=7.4 Hz, 2 H), 3.38-3.48 (m, 1 H) 4.25 - 4.34 (m, 1 H), 4.38 (dd, *J*=14.1 and 11.4 Hz, 1 H), 6.66 (br d, *J*=9.3 Hz, 1 H), 7.20 - 7.39 (m, 4 H).

Compound 34

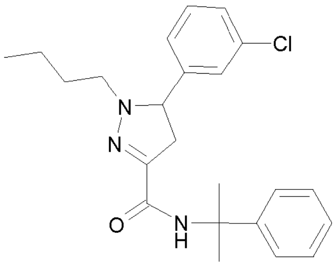


Compound 34

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-butyl)-5-(3-chlorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomer 2)

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.82 - 0.95 (m, 10 H), 0.97 (s, 3 H), 1.21 - 1.47 (m, 4 H) 1.51 - 1.65 (m, 3 H), 1.69 (t, *J*=4.3 Hz, 1 H), 1.75 - 1.86 (m, 1 H), 2.33 - 2.43 (m, 1 H), 2.79 (dd, *J*=17.3 and 14.3 Hz, 1 H), 2.94 (t, *J*=7.2 Hz, 2 H), 3.42 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.26 - 4.41 (m, 2 H), 6.65 (d, *J*=9 Hz, 1 H), 7.23 - 7.31 (m, 3 H), 7.39 (br s, 1 H).

Compound 35

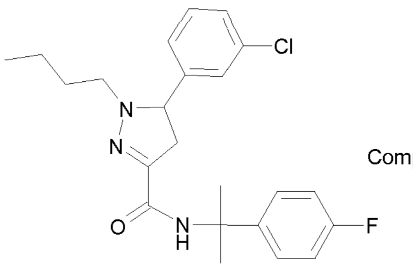


Compound 35

N-(1-Phenyl-1-methyl-ethyl)-1-(n-butyl)-5-(3-chlorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.4 Hz, 3 H), 1.21 - 1.43 (m, 2 H), 1.54 - 1.64 (m, 2 H), 1.75 (s, 3 H), 1.77 (s, 3 H), 2.74 (dd, *J*=17.4 and 14.1 Hz, 1 H), 2.93 (t, *J*=7.3 Hz, 2 H), 3.36 (dd, *J*=17.1 and 11.1 Hz, 1 H), 4.35 (dd, *J*=14.3 and 11.3 Hz, 1 H), 6.96 (br s, 1 H), 7.21 - 7.30 (m, 4 H), 7.31 - 7.38 (m, 3 H), 7.45 (br d, *J*=8.1 Hz, 2 H).

Compound 36

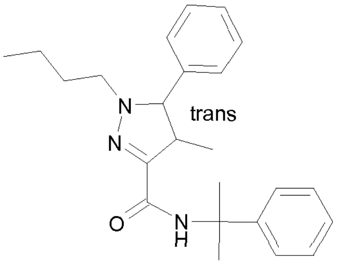


Compound 36

N-[1-(4-fluorophenyl)-1-methyl-ethyl]-1-(n-butyl)-5-(3-chlorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.87 (t, *J*=7.4 Hz, 3 H), 1.21 - 1.41 (m, 2 H), 1.54 - 1.64 (m, 2 H), 1.74 (s, 3 H), 1.75 (s, 3 H), 2.73 (dd, *J*=17.4 and 14.4 Hz, 1 H), 2.93 (t, *J*=7.4 Hz, 2 H), 3.35 (dd, *J*=17.3 and 11.3 Hz, 1 H), 4.35 (dd, *J*=14.1 and 11.1 Hz, 1 H), 6.93 (br s, 1 H), 7.01 (br t, *J*=8.7 Hz, 2 H), 7.21 - 7.31 (m, 3 H), 7.36 - 7.44 (m, 3 H).

Compound 37



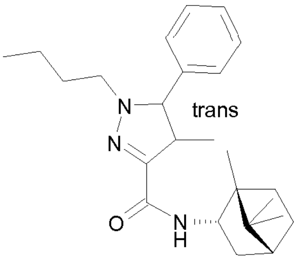
Compound 37

N-(1-Phenyl-1-methyl-ethyl)-1-(n-butyl)-*trans*-4-methyl-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

A Sepacore chromatographic purification was applied to purify the crude compound 37: Eluant: Dichloromethane.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=7.4 Hz, 3 H), 1.19 - 1.38 (m, 5 H), 1.51 - 1.61 (m, 2 H), 1.74 (s, 3 H), 1.77 (s, 3 H), 2.89 - 2.97 (m, 2 H), 3.14 (dq, *J*=13.4 and 6.7 Hz, 1 H), 3.84 (d, *J*=13.2 Hz, 1 H), 6.98 (br s, 1 H), 7.23 (br t, *J*=7.4 Hz, 1 H), 7.28 - 7.39 (m, 7 H), 7.45 (br d, *J*=7.2 Hz, 2 H).

Compound 38



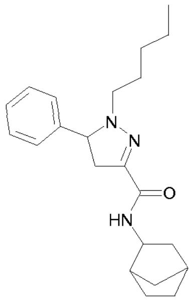
Compound 38

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-butyl)-*trans*-4-methyl-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

Two successive Sepacore chromatographic purifications were applied to isolate compound 38 from the crude reaction mixture: Separation A: Eluant: petroleum ether (40-60)/diethyl ether = 80/20. Separation B: Eluant: petroleum ether (40-60)/ethylacetate = 90/10.

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.81 - 0.94 (m, 10 H), 0.97 (s, 3 H) 1.21 - 1.47 (m, 6 H), 1.50 - 1.67 (m, 4 H), 1.69 (t, *J*=4.5 Hz, 1 H), 1.74 - 1.86 (m, 1 H), 2.32 - 2.44 (m, 1 H), 2.88 - 3.02 (m, 2 H), 3.13 - 3.25 (m, 1 H), 3.81 - 3.90 (m, 1 H), 4.22 - 4.36 (m, 1 H), 6.64 - 6.73 (m, 1 H), 7.29 - 7.41 (m, 5 H).

Compound 39



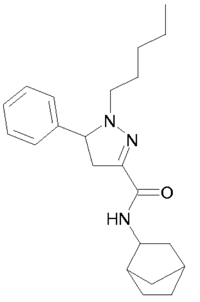
Compound 39

2-endo isomer

N-(Endo-bicyclo[2.2.1]hept-2-yl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.85 (t, *J*=7.1 Hz, 3 H), 1.16 - 1.38 (m, 7 H), 1.40-1.68 (m, 6 H), 2.06 - 2.17 (m, 1 H), 2.24 (br s , 1 H), 2.49 (br s, 1 H), 2.82 (dd, *J*=16.5 and 14.4 Hz, 1 H), 2.88 - 3.01 (m, 2 H), 3.41 (dd, *J*=17.1 and 11.1 Hz, 1 H), 4.13 - 4.24 (m, 1 H), 4.35 - 4.47 (m, 1 H), 6.60 - 6.73 (m, 1 H), 7.28 - 7.43 (m, 5 H).

Compounds 40-43



Compounds 40-43

stereoisomers 1-4

Compound 12 was separated by preparative chiral HPLC into 4 separate stereoisomers (compounds 40, 41, 42 and 43, respectively).

N-(Exo-bicyclo[2.2.1]hept-2-yl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (compound 40) (stereoisomer 1; first eluting diastereomer; retention time = 10.29 minutes; Diastereomeric excess = 97 %): [$\alpha^{25}{}_D$] = +147 °, c = 0.9, methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7 Hz, 3 H), 1.10 - 1.66 (m, 15 H), 1.83 (ddd, *J*=13, 8 and 2.1 Hz, 1 H), 2.25 - 2.33 (m, 2 H), 2.81 (dd, *J*=17.3 and 14.3 Hz, 1 H), 2.86 - 2.97 (m, 2 H), 3.40 (dd, *J*=17.4 and 11.1 Hz, 1 H), 3.79 (br td, *J*=7.6 and 3.4 Hz, 1 H), 4.37 (dd, *J*=14.30 and 11 Hz, 1 H), 6.45 (br d, *J*=7.5 Hz, 1 H), 7.27 - 7.40 (m, 5 H).

N-(Exo-bicyclo[2.2.1]hept-2-yl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (compound 41) (stereoisomer 2; second eluting diastereomer; retention time = 12.57 minutes; ; Diastereomeric excess > 99 %): [$\alpha^{25}{}_D$] = +158 °, c = 1.1, methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7 Hz, 3 H), 1.11 - 1.65 (m, 15 H), 1.83 (ddd, *J*=13, 8 and 2.1 Hz, 1 H), 2.26 - 2.33 (m, 2 H), 2.81 (dd, *J*=17.3 and 14.3 Hz, 1 H), 2.86 - 2.98 (m, 2 H), 3.40 (dd, *J*=17.4 and 11.1 Hz, 1 H), 3.79 (br td, *J*=7.6 and 3.4 Hz, 1 H), 4.38 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.45 (br d, *J*=7.2 Hz, 1 H), 7.27 - 7.38 (m, 5 H).

N-(Exo-bicyclo[2.2.1]hept-2-yl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (compound 42) (stereoisomer 3; third eluting diastereomer; retention time = 13.71 minutes; Diastereomeric excess > 99 %) : [$\alpha^{25}{}_D$] = -173 °, c = 1.0, methanol.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7 Hz, 3 H), 1.10 - 1.66 (m, 15 H), 1.83 (ddd, *J*=13, 8 and 2.1 Hz, 1 H), 2.24 - 2.34 (m, 2 H), 2.81 (dd, *J*=17.3 and 14.3 Hz, 1 H), 2.86 - 2.98 (m, 2 H), 3.40 (dd, *J*=17.4 and 11.1 Hz, 1 H), 3.79 (br td, *J*=7.6 and 3.4 Hz, 1 H), 4.38 (dd, *J*=14.2 and 11.1 Hz, 1 H), 6.45 (br d, *J*=7.5 Hz, 1 H), 7.27 - 7.37 (m, 5 H).

N-(Exo-bicyclo[2.2.1]hept-2-yl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (compound 43) (stereoisomer 4; fourth eluting diastereomer; retention time = 23.01 minutes; Diastereomeric excess > 99 %): [$\alpha^{25}{}_D$] = -162 °, c = 0.9, methanol.

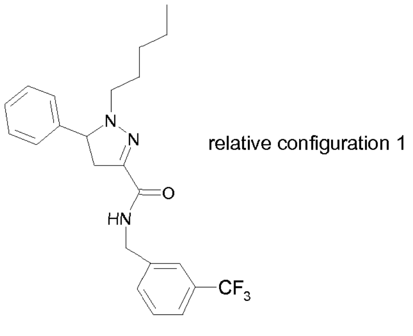
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7 Hz, 3 H), 1.10 - 1.66 (m, 15 H), 1.83 (ddd, *J*=12.9, 8.1 and 2.1 Hz, 1 H), 2.25 - 2.34 (m, 2 H), 2.81 (dd, *J*=17.2 and 14.4 Hz, 1 H), 2.85 - 2.98 (m, 2

H), 3.40 (dd, *J*=17.2 and 11.1 Hz, 1 H), 3.79 (br td, *J*=7.6 and 3.6 Hz, 1 H), 4.37 (dd, *J*=14.2 and 11.1 Hz, 1 H), 6.45 (br d, *J*=7.2 Hz, 1 H), 7.27 - 7.40 (m, 5 H).

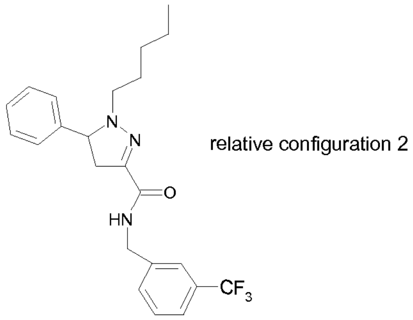
Preparative chiral HPLC method: First step: A 250 x 30 mm column was used. Stationary phase: CHIRALPAK® AD=H 5 µm. n-Heptane/isopropanol = 95/05 (v/v) was used as the mobile phase. Flow rate: 40 ml/minute. Temperature: 21.5 °C. Detection UV 325 nm. **Second step:** A 250 x 30 mm column was used. Stationary phase: CHIRALPAK® IA 5 µm. n-Heptane/ethylacetate = 85/15 (v/v) was used as the mobile phase. Flow rate: 40 ml/minute. Temperature: ambient. Detection UV 325 nm.

Analytical HPLC monitoring system: A 250 x 4.6 mm column was used. Stationary phase: CHIRALPAK® IA-H 5 µm. n-Heptane/ethylacetate = 80/20 (v/v) was used as the mobile phase. Flow rate: 1 ml/minute. Temperature: 25 °C. Detection: UV 300 nm.

Compound 44-45



Compound 44



Compound 45

Racemic compound 22 (1.88 gram) was separated by preparative chiral HPLC into 2 separate enantiomers (compounds 44 and 45, respectively).

(+)-N-[3-(Trifluoromethyl)benzyl)]-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (compound 44)

[$\alpha^{25}{}_{D}$] = 124 °, c = 1.0, methanol. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J*=6.92 Hz, 3 H), 1.15 - 1.30 (m, 4 H), 1.51 - 1.65 (m, 2 H), 2.81 – 2.99 (m, 3 H), 3.45 (dd, *J*=17.3 and 11.3 Hz, 1 H), 4.46 (dd, *J*=14.4 and 11.4 Hz, 1 H), 4.59 (s, 2 H), 7.28 - 7.39 (m, 5 H), 7.43 - 7.50 (m, 1 H), 7.52 - 7.60 (m, 3 H). Enantiomeric excess: > 98 %.

(-)-N-[3-(Trifluoromethyl)benzyl)]-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (compound 45)

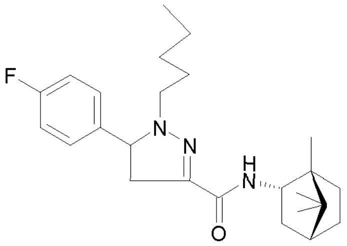
[$\alpha^{25}{}_{D}$] = -132 °, c = 0.8, methanol. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J*=6.92 Hz, 3 H), 1.15 - 1.30 (m, 4 H), 1.51 - 1.65 (m, 2 H), 2.81 – 2.99 (m, 3 H), 3.45 (dd, *J*=17.3 and 11.3 Hz, 1 H), 4.46 (dd, *J*=14.4 and 11.4 Hz, 1 H), 4.59 (s, 2 H), 7.28 - 7.39 (m, 5 H), 7.43 - 7.50 (m, 1 H), 7.52 - 7.60 (m, 3 H). Enantiomeric excess: > 98 %.

Preparative chiral HPLC method: A 250 x 76 mm column was used. Stationary phase: CHIRALPAK® IA 20 µm. n-Heptane/dichloromethane = 75/25 (v/v) was used as the mobile phase. Flow rate: 270 ml/minute. Temperature: 25 °C. Detection UV 300 nm

Analytical HPLC monitoring system: A 250 x 4.6 mm column was used. Stationary phase: CHIRALPAK® IA-H 5 µm. n-Heptane/dichloromethane = 75/25 (v/v) was used as the mobile phase. Flow rate: 1 ml/minute. Temperature: 25 °C. Detection: Diode array detection (DAD) 254 and 300 nm.

Enantiomeric excess: > 98 %

Compound 46

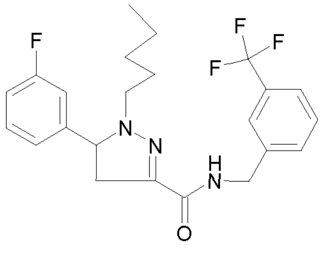


Compound 46

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-pentyl)-5-(4-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.81 - 0.94 (m, 10 H), 0.97 (s, 3 H), 1.07 - 1.47 (m, 7 H), 1.52 - 1.65 (m, 2 H), 1.69 (t, *J*=4.4 Hz, 1 H), 1.75 - 1.86 (m, 1 H), 2.33 - 2.43 (m, 1 H), 2.73 - 2.84 (m, 1 H), 2.88 - 2.96 (m, 2 H), 3.35-3.51 (m, 1 H), 4.26 - 4.44 (m, 2 H), 6.67 (br d, *J*=6 Hz, 1 H), 7.04 (t, *J*=8.4 Hz, 2 H), 7.31 - 7.39 (m, 2 H).

Compound 47

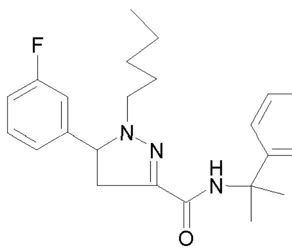


Compound 47

N-[3-(trifluoromethyl)benzyl]-1-(n-pentyl)-5-(3-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.81 - 0.91 (m, 3 H), 1.16 - 1.35 (m, 4 H), 1.52 - 1.65 (m, 2 H), 2.84 (dd, *J*=17.4 and 14.1 Hz, 1 H), 2.87-2.99 m, 2 H), 3.46 (dd, *J*=17.4 and 11.4 Hz, 1 H), 4.45 (dd, *J*=14.1 and 11.4 Hz, 1 H), 4.60 (d, *J*=6.3 Hz, 2 H), 7.01 (dt, *J*=8.1 and 2.1 Hz, 2 H), 7.07 - 7.16 (m, 2 H), 7.33 (dt, *J*=7.9 and 5.8 Hz, 1 H), 7.43 - 7.50 (m, 1 H), 7.51 - 7.61 (m, 3 H).

Compound 48

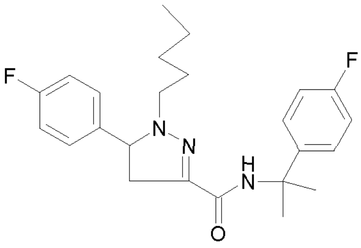


Compound 48

N-[1-(4-fluorophenyl)-1-methyl-ethyl]-1-(n-pentyl)-5-(3-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 - 0.90 (m, 3 H), 1.22 - 1.34 (m, 4 H), 1.54 - 1.67 (m, 2 H), 1.73 (s, 3 H), 1.74 (s, 3 H), 2.73 (dd, *J*=17.4 and 14.1 Hz, 1 H), 2.93 (t, *J*=7.4 Hz, 2 H), 3.35 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.38 (dd, *J*=14.3 and 11.3 Hz, 1 H), 6.94 (br s, 1 H), 6.96 - 7.05 (m, 3 H), 7.07 - 7.14 (m, 2 H), 7.28 - 7.35 (m, 1 H), 7.37 - 7.44 (m, 2 H).

Compound 49

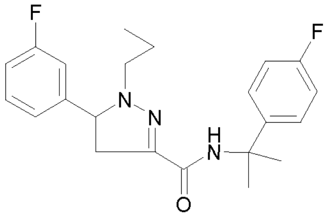


Compound 49

N-[1-(4-fluorophenyl)-1-methyl-ethyl]-1-(n-pentyl)-5-(4-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 - 0.90 (m, 3 H), 1.20 - 1.31 (m, 4 H), 1.53 - 1.67 (m, 2 H), 1.73 (s, 3 H), 1.74 (s, 3 H), 2.73 (dd, *J*=17.4 and 14.4 Hz, 1 H), 2.91 (t, *J*=7.4 Hz, 2 H), 3.33 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.36 (dd, *J*=14.1 and 11.1 Hz, 1 H), 6.95 (br s, 1 H), 6.97 - 7.08 (m, 4 H), 7.33 (dd, *J*=8.7 and 5.4 Hz, 2 H), 7.41 (dd, *J*=8.9 and 5.3 Hz, 2 H).

Compound 50

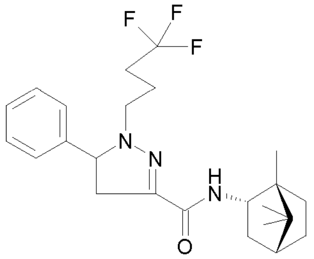


Compound 50

N-[1-(4-fluorophenyl)-1-methyl-ethyl]-1-(n-propyl)-5-(3-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.89 (t, *J*=7.4 Hz, 3 H), 1.55 - 1.71 (m, 2 H), 1.73 (s, 3 H), 1.74 (s, 3 H), 2.73 (dd, *J*=17.3 and 14.3 Hz, 1 H), 2.83 - 2.97 (m, 2 H), 3.36 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.38 (dd, *J*=14.3 and 11.3 Hz, 1 H), 6.94 (brs, 1 H), 6.96 - 7.05 (m, 3 H), 7.07 - 7.15 (m, 2 H), 7.28 - 7.35 (m, 1 H), 7.40 (dd, *J*=8.7 and 5.4 Hz, 2 H).

Compound 51



Compound 51

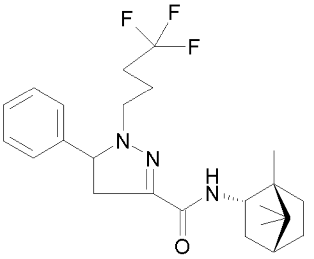
diastereomer 1

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(4,4,4-trifluorobutyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomer 1).

Compounds 51 and 52 were obtained from the corresponding diasteromeric mixture via a flash chromatographic purification (silicagel). Eluant: petroleum ether (40-60)/ethylacetate = 90/10 (v/v). Compound 52: second (slowest) eluting diastereomer: Compound 51: first (fastest) eluting diastereomer.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 - 0.95 (m, 7 H), 0.98 (s, 3 H), 1.22 - 2.11 (m, 8 H), 2.13-2.27 (m, 1 H), 2.34 - 2.45 (m, 1 H), 2.81 - 2.96 (m, 2 H), 2.99-3.08 (m, 1 H), 3.44 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.26 - 4.40 (m, 2 H), 6.65 (br d, *J*=9 Hz, 1 H), 7.30 - 7.42 (m, 5 H). [$\alpha^{25}{}_{D}$] = 102 °, c = 1, methanol.

Compound 52



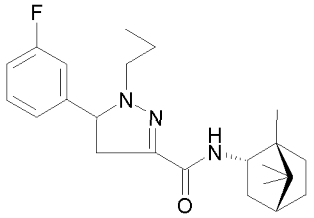
Compound 52

diastereomer 2

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(4,4,4-trifluorobutyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomer 2).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.83 - 0.94 (m, 7 H), 0.97 (s, 3 H), 1.20 - 1.32 (m, 1 H), 1.38 - 1.49 (m, 1 H), 1.54 - 1.63 (m, 1 H), 1.70 (t, *J*=4.4 Hz, 1 H), 1.75 - 1.88 (m, 2 H), 1.89 - 2.08 (m, 2 H), 2.13-2.29 (m, 1 H), 2.32 - 2.44 (m, 1 H), 2.81 - 2.95 (m, 2 H), 2.97-3.07 (m, 1 H), 3.42 (dd, *J*=17.4 and 10.8 Hz, 1 H), 4.26 - 4.38 (m, 2 H), 6.65 (br d, *J*=9.3 Hz, 1 H), 7.29 - 7.41 (m, 5 H). [α^{25}_D] = -102 °, c = 1, methanol.

Compound 53



Compound 53

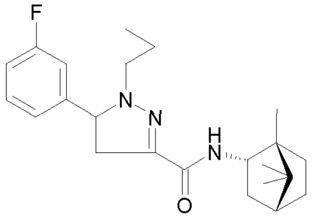
diastereomer 1

N-[*endo*-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-propyl-5-(3-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomer 1).

Compounds 53 and 54 were obtained from the corresponding diasteromeric mixture via a flash chromatographic purification (silicagel). Eluant gradient: petroleum ether (40-60)/ethylacetate = 95/5 => petroleum ether (40-60)/ethylacetate = 90/10 (v/v). Compound 53: second (slowest) eluting diastereomer: Compound 54: first (fastest) eluting diastereomer.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.83 - 0.94 (m, 10 H), 0.97 (s, 3 H), 1.21 - 1.30 (m, 1 H), 1.36 - 1.47 (m, 1 H), 1.54 - 1.73 (m, 4 H), 1.74 - 1.86 (m, 1 H), 2.31 - 2.43 (m, 1 H), 2.80 (dd, *J*=17.3 and 14.3 Hz, 1 H), 2.85 - 2.99 (m, 2 H), 3.43 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.25-4.35 (m, 1 H), 4.38 (dd, *J*=14.1 and 11.1 Hz, 1 H) 6.66 (br d, *J*=9 Hz, 1 H) 7.00 (br t, *J*=8.3 Hz, 1 H), 7.09 - 7.18 (m, 2 H), 7.28 - 7.37 (m, 1 H). [α^{25}_D] = -122 °, c = 1, methanol.

Compound 54



Compound 54

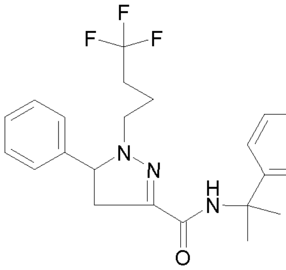
diastereomer 2

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-propyl-5-(3-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomer 2).

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 - 0.93 (m, 10 H), 0.97 (s, 3 H), 1.21 - 1.31 (m, 1 H), 1.37 - 1.47 (m, 1 H), 1.54 - 1.67 (m, 3 H), 1.69 (t, *J*=4.4 Hz, 1 H), 1.74-1.86 (m, 1 H), 2.31-2.43 (m, 1

H), 2.79 (dd, J=17.4 and 14.1 Hz, 1 H), 2.85 - 2.99 (m, 2 H), 3.44 (dd, J=17.1 and 11.1 Hz, 1 H), 4.30 (br tt, J=9.1 and 2.4 Hz, 1 H), 4.40 (dd, J=14.0 and 11.3 Hz, 1 H), 6.66 (br d, J=9 Hz, 1 H), 7.00 (dt, J=8.3 and 1.9 Hz, 1 H), 7.08 - 7.15 (m, 2 H), 7.31 (dd, J=7.8 and 6 Hz, 1 H). [$\alpha^{25}{}_D$] = 145 °, c = 1, methanol.

Compound 55

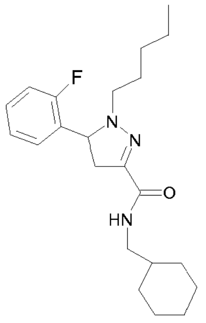


Compound 55

N-[1-(4-fluorophenyl)-1-methyl-ethyl]-1-(4,4,4-trifluorobutyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 3 H), 1.75 (s, 3 H), 1.78-1.88 (m, 1 H), 1.89 - 2.06 (m, 2 H), 2.14 - 2.26 (m, 1 H), 2.80 (dd, J=17.4 and 14.4 Hz, 1 H), 2.85 - 2.93 (m, 1 H), 2.98 - 3.06 (m, 1 H), 3.35 (dd, J=17.4 and 10.8 Hz, 1 H), 4.32 (dd, J=14.6 and 11 Hz, 1 H), 6.93 (br s, 1 H), 7.02 (t, J=8.7 Hz, 2 H), 7.29 - 7.38 (m, 5 H), 7.38 - 7.44 (m, 2 H).

Compound 56

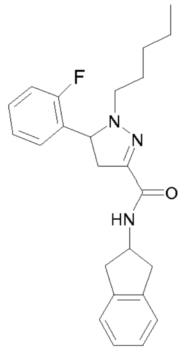


Compound 56

N-Cyclohexylmethyl-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.86 (t, J = 7, 3 H), 0.91 - 1.03 (m, 2 H), 1.10 - 1.34 (m, 7 H), 1.47 - 1.70 (m, 4 H), 1.70 - 1.81 (m, 4 H), 2.80 (dd, J=17.1 and 13.8 Hz, 1 H), 2.88 - 3.01 (m, 2 H), 3.12 - 3.25 (m, 2 H), 3.48 (dd, J=17.1 and 11.4 Hz, 1 H), 4.73 (dd, J=13.8 and 11.4 Hz, 1 H), 6.67 (br t, J ~ 6.5 Hz, 1 H), 7.05 (dd, J=10.1 and 8.6 Hz, 1 H), 7.15 (t, J=7.5 Hz, 1 H), 7.24 - 7.31 (m, 1 H), 7.48 (dt, J=7.5 and ~ 2 Hz, 1 H).

Compound 57

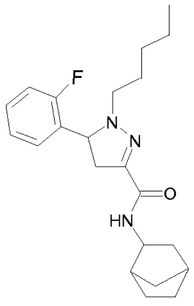


Compound 57

N-(Indan-2-yl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.81 - 0.86 (m, 3 H), 1.13-1.31 (m, 4 H) 1.51 - 1.64 (m, 2 H), 2.81 (dd, *J*=17.4 and 13.8 Hz, 1 H), 2.86 - 2.97 (m, 4 H), 3.32-3.41 (m, 2 H), 3.49 (dd, *J*=17.1 and 11.4 Hz, 1 H), 4.74 (dd, *J*=13.7 and 11.6 Hz, 1 H), 4.78-4.87 (m, 1 H), 6.78 (br d, *J*=8.1 Hz, 1 H), 7.01-7.08 (m, 1 H) 7.12 - 7.17 (m, 1 H), 7.17 - 7.22 (m, 2 H), 7.22 - 7.31 (m, 3 H), 7.42-7.49 (m, 1 H).

Compound 58



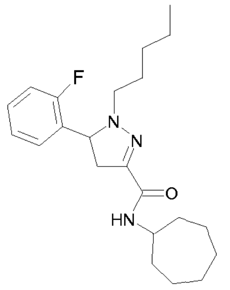
Compound 58

2-endo isomer

N-(Endo-bicyclo[2.2.1]hept-2-yl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.81 - 0.89 (m, 4 H), 1.20 - 1.38 (m, 6 H), 1.43 - 1.52 (m, 2 H), 1.53 - 1.70 (m, 4 H), 2.06-2.17 (m, 1 H), 2.24 (br t, *J*=4.5 Hz, 1 H), 2.49 (br t, *J*=4.3 Hz, 1 H), 2.79 (dd, *J*=17.3 and 13.7 Hz, 1 H), 2.89 - 3.03 (m, 2 H), 3.48 (dd, *J*=17.4 and 11.4 Hz, 1 H), 4.13 - 4.23 (m, 1 H), 4.70 - 4.78 (m, 1 H), 6.63 - 6.69 (m, 1 H), 7.02-7.08 (m, 1 H), 7.13 - 7.18 (m, 1 H), 7.24 - 7.31 (m, 1 H), 7.45 - 7.52 (m, 1 H).

Compound 59

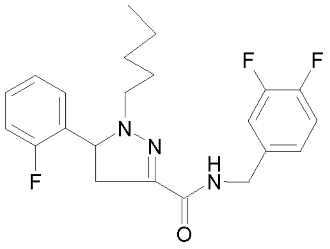


Compound 59

N-(Cycloheptyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=7 Hz, 3 H), 1.20 - 1.32 (m, 4 H), 1.46 - 1.71 (m, 11 H), 1.92 - 2.03 (m, 2 H), 2.74 - 2.84 (m, 2 H), 2.90 - 2.98 (m, 2 H), 3.47 (dd, *J*=17.1 and 11.4 Hz, 1 H), 3.96 - 4.07 (m, 1 H), 4.72 (dd, *J*=13.8 and 11.1 Hz, 1 H), 6.56 (br d, *J*=8.4 Hz, 1 H), 7.01-7.08 (m, 1 H), 7.12 - 7.18 (m, 1 H), 7.24 - 7.31 (m, 1 H), 7.46-7.51 (m, 1 H).

Compound 60

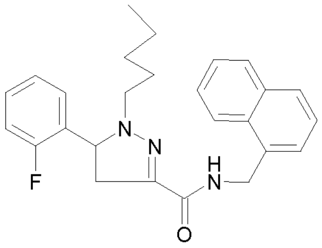


Compound 60

N-[3,4-difluorobenzyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*=6.9 Hz, 3 H), 1.17 - 1.33 (m, 4 H), 1.54 - 1.70 (m, 2 H), 2.84 (dd, *J*=17.3 and 13.7 Hz, 1 H), 2.88 - 3.02 (m, 2 H), 3.50 (dd, *J*=17.3 and 11.6 Hz, 1 H), 4.43-4.54 (m, 2 H), 4.79 (dd, *J*=13.8 and 11.7 Hz, 1 H), 6.96 (br t, *J*=6.3 Hz, 1 H), 7.02 - 7.20 (m, 5 H), 7.25 - 7.32 (m, 1 H), 7.47 (dt, *J*=7.5 and 1.8 Hz, 1 H).

Compound 61

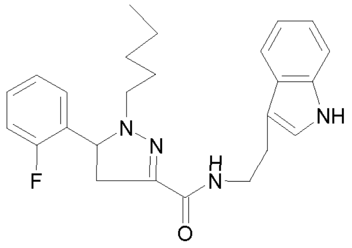


Compound 61

N-[Naphthalen-1-ylmethyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.80 (t, *J*=6.9 Hz, 3 H), 1.21 (m, 4 H), 1.49 - 1.61 (m, 2 H), 2.79 - 2.97 (m, 3 H), 3.53 (dd, *J*=17.1 and 11.4 Hz, 1 H), 4.71-4.80 (m, 1 H), 4.95-5.06 (m, 2 H), 6.84-6.90 (m, 1 H)m 7.02-7.08 (m, 1 H), 7.15 (t, *J*=7.5 Hz, 1 H), 7.24 - 7.31 (m, 1 H), 7.42 - 7.61 (m, 5 H), 7.83 (d, *J*=8.1 Hz, 1 H), 7.90 (d, *J*=8.1 Hz, 1 H), 8.10 (d, *J*=8.1 Hz, 1 H).

Compound 62

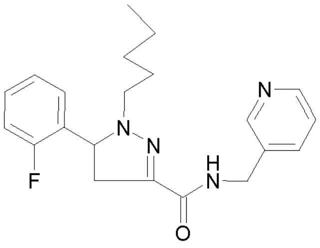


Compound 62

N-[2-(Indol-3-yl)ethyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.86 (t, *J*=6.9 Hz, 3 H), 1.17 - 1.32 (m, 4 H), 1.52-1.64 (m, 2 H), 2.81 (dd, *J*=17.3 and 13.7 Hz, 1 H), 2.86 - 2.98 (m, 2 H), 3.04 (t, *J*=6.9 Hz, 2 H), 3.48 (dd, *J*=17.1 and 11.4 Hz, 1 H), 3.68 (q, *J*=6.6 Hz, 2 H), 4.68-4.78 (m, 1 H), 6.77 (br t, *J*=6.2 Hz, 1 H), 7.01 - 7.10 (m, 2 H), 7.14 (q, *J*=7.1 Hz, 2 H), 7.21 (t, *J*=7.5 Hz, 1 H), 7.24 - 7.31 (m, 1 H), 7.38 (d, *J*=8.1 Hz, 1 H), 7.43-7.49 (m, 1 H), 7.65 (d, *J*=7.8 Hz, 1 H), 8.06 (br s, 1 H).

Compound 63

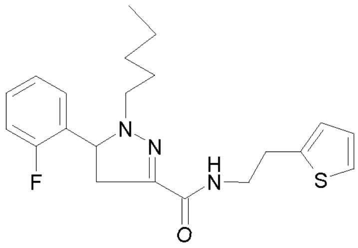


Compound 63

N-[(Pyridin-3-yl)methyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.81 - 0.89 (m, 3 H), 1.15 - 1.33 (m, 4 H), 1.53 - 1.69 (m, 2 H), 2.84 (dd, *J*=17.3 and 13.7 Hz, 1 H), 2.89 - 3.02 (m, 2 H), 3.50 (dd, *J*=17.3 and 11.6 Hz, 1 H), 4.51-4.60 (m, 2 H) 4.79 (dd, *J*=13.8 and 11.4 Hz, 1 H), 6.98 (br t, *J*=6.5 Hz, 1 H), 7.03-7.09 (m, 1 H), 7.16 (t, *J*=7 Hz, 1 H), 7.24 - 7.34 (m, 2 H), 7.46 (dt, *J*=7.5 and 2 Hz, 1 H), 7.69 (br d, *J*=7.8 Hz, 1 H), 8.54 (br d, *J*=4.8 Hz, 1 H), 8.58-8.62 (m, 1 H).

Compound 64

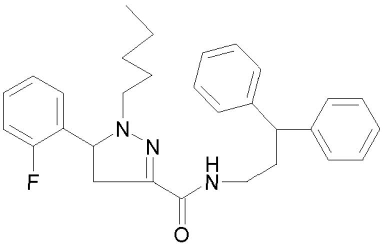


Compound 64

N-[2-(Thien-2-yl)ethyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.84 - 0.90 (m, 3 H), 1.18 - 1.34 (m, 4 H), 1.56 - 1.67 (m, 2 H), 2.80 (dd, *J*=17.1 and 13.8 Hz, 1 H), 2.86 - 3.01 (m, 2 H), 3.10 (t, *J*=6.9 Hz, 2 H), 3.48 (dd, *J*=17.1 and 11.4 Hz, 1 H), 3.62 (q, *J*=6.6 Hz, 2 H), 4.75 (dd, *J*=13.8 and 11.4 Hz, 1 H), 6.79 (br t, *J*=6.3 Hz, 1 H), 6.88 (dd, *J*=3.2 and 1 Hz, 1 H), 6.96 (dd, *J*=5.1 and 3.3 Hz, 1 H), 7.02 - 7.09 (m, 1 H), 7.13 - 7.19 (m, 2 H), 7.24 - 7.31 (m, 1 H), 7.44 - 7.50 (m, 1 H).

Compound 65

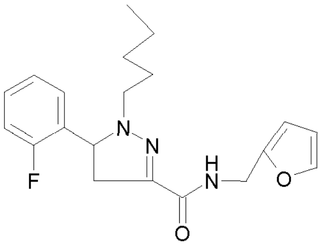


Compound 65

N-[3,3-diphenylpropyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.87 (t, *J*=6.9 Hz, 3 H), 1.20 - 1.34 (m, 4 H), 1.55-1.69 (m, 2 H), 2.31 - 2.39 (m, 2 H), 2.77 (dd, *J*=17.4 and 13.8 Hz, 1 H), 2.85 - 2.99 (m, 2 H), 3.31 (q, *J*=8 Hz, 2 H), 3.45 (dd, *J*=17.1 and 11.4 Hz, 1 H), 4.00 (t, *J*=7.8 Hz, 1 H), 4.72 (dd, *J*=14 and 11.23 Hz, 1 H), 6.59 (br t, *J*=6.6 Hz, 1 H), 7.01-7.09 (m, 1 H), 7.13 - 7.20 (m, 3 H), 7.24 - 7.31 (m, 9 H), 7.47 (dt, *J*=7.5 and 2 Hz, 1 H).

Compound 66

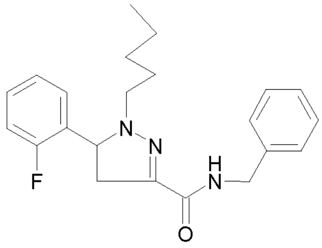


Compound 66

N-[(Furan-2-yl)methyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 - 0.90 (m, 3 H), 1.17 - 1.35 (m, 4 H), 1.54 - 1.69 (m, 2 H), 2.82 (dd, *J*=17.3 and 13.7 Hz, 1 H), 2.87 - 3.01 (m, 2 H), 3.49 (dd, *J*=17.3 and 11.6 Hz, 1 H), 4.48-4.60 (m, 2 H), 4.76 (dd, *J*=13.7 and 11.6 Hz, 1 H), 6.26-6.37 (m, 2 H), 6.90 (br t, *J*=6 Hz, 1 H), 7.02 - 7.09 (m, 1 H), 7.12-7.18 (m, 1 H), 7.24 - 7.32 (m, 1 H), 7.36 - 7.40 (m, 1 H), 7.46 (dt, *J*=8.2 and 2 Hz, 1 H).

Compound 67

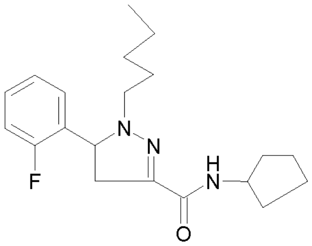


Compound 67

N-Benzyl-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J*=6.9 Hz, 3 H), 1.17 - 1.32 (m, 4 H), 1.54 - 1.66 (m, 2 H), 2.84 (dd, *J*=17.1 and 13.8 Hz, 1 H), 2.86 - 3.00 (m, 2 H), 3.51 (dd, *J*=17.4 and 11.4 Hz, 1 H), 4.50-4.58 (m, 2 H), 4.76 (dd, *J*=13.8 and 11.4 Hz, 1 H), 6.92 (br t, *J*=6 Hz, 1 H), 7.02-7.09 (m, 1 H), 7.16 (dt, *J*=7.5 and 1.2 Hz, 1 H), 7.25 - 7.32 (m, 3 H), 7.33 - 7.39 (m, 3 H), 7.47 (dt, *J*=7.1 and 1.3 Hz, 1 H).

Compound 68

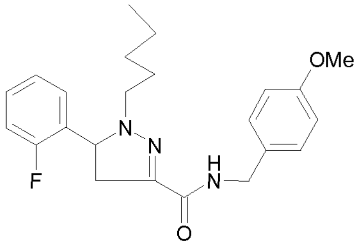


Compound 68

N-Cyclopentyl-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=6.9 Hz, 3 H), 1.18 - 1.35 (m, 4 H), 1.41 - 1.53 (m, 2 H), 1.55 - 1.80 (m, 6 H), 1.97 - 2.10 (m, 2 H), 2.79 (dd, *J*=17.4 and 13.8 Hz, 1 H), 2.87 - 3.01 (m, 2 H), 3.48 (dd, *J*=17.4 and 11.4 Hz, 1 H), 4.27 (sextet, *J*=7.1 Hz, 1 H), 4.72 (dd, *J*=14 and 11.3 Hz, 1 H), 6.54 (br d, *J*=7.8 Hz, 1 H), 7.05 (dd, *J*=11 and 7.7 Hz, 1 H), 7.15 (t, *J*=7.4 Hz, 1 H), 7.24 - 7.32 (m, 1 H), 7.48 (dt, *J*=7.4 and 1.6 Hz, 1 H).

Compound 69

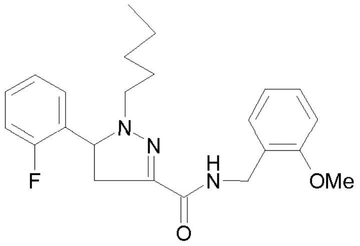


Compound 69

N-(4-Methoxybenzyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.84 (t, *J*=6.9 Hz, 3 H), 1.17-1.32 (m, 4 H), 1.54 - 1.67 (m, 2 H), 2.82 (dd, *J*=17.4 and 13.8 Hz, 1 H), 2.87 - 2.99 (m, 2 H), 3.50 (dd, *J*=17.1 and 11.4 Hz, 1 H), 3.81 (s, 3 H), 4.46-4.49 (m, 2 H), 4.75 (dd, *J*=14.1 and 11.4 Hz, 1 H), 6.82 - 6.91 (m, 3 H), 7.05 (dd, *J*=11 and 7.7 Hz, 1 H), 7.15 (t, *J*=7.5 Hz, 1 H), 7.24 - 7.31 (m, 3 H), 7.47 (dt, *J*=7.5 and 1.8 Hz, 1 H).

Compound 70

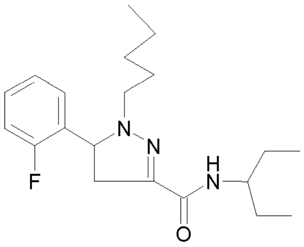


Compound 70

N-(2-Methoxybenzyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.86 (t, *J*=6.9 Hz, 3 H), 1.18 - 1.33 (m, 4 H), 1.56 - 1.67 (m, 2 H), 2.80 (dd, *J*=17.1 and 13.8 Hz, 1 H), 2.86 - 2.99 (m, 2 H), 3.49 (dd, *J*=17.1 and 11.4 Hz, 1 H), 3.88 (s, 3 H), 4.52-4.56 (m, 2 H), 4.73 (dd, *J*=14 and 11.3 Hz, 1 H), 6.87 - 6.96 (m, 2 H), 7.05 (dd, *J*=9.8 and 8.9 Hz, 1 H), 7.08 - 7.18 (m, 2 H), 7.23 - 7.34 (m, 3 H), 7.47 (dt, *J*=7.6 and 2 Hz, 1 H).

Compound 71

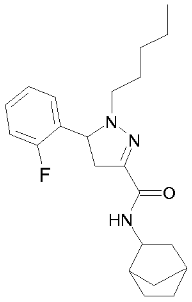


Compound 71

N-[(1-ethyl)propyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 - 0.89 (m, 3 H), 0.90-0.98 (m, 6 H), 1.19 - 1.34 (m, 4 H), 1.39 - 1.53 (m, 2 H), 1.54 - 1.70 (m, 4 H), 2.81 (dd, *J*=17.1 and 13.8 Hz, 1 H), 2.89 - 3.03 (m, 2 H), 3.49 (dd, *J*=17.3 and 11.23 Hz, 1 H), 3.79 - 3.91 (m, 1 H), 4.75 (dd, *J*=13.8 and 11.4 Hz, 1 H), 6.38 (br d, *J*=9.3 Hz, 1 H), 7.01 - 7.09 (m, 1 H), 7.16 (t, *J*=7.5 Hz, 1 H), 7.24 - 7.32 (m, 1 H), 7.49 (dt, *J*=7.5 and 1.8 Hz, 1 H).

Compound 72



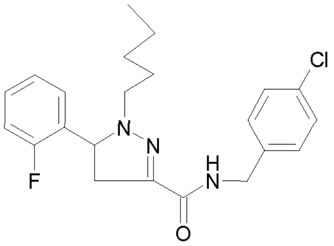
Compound 72

2-exo isomer

N-(Exo-bicyclo[2.2.1]hept-2-yl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=6.9 Hz, 3 H), 1.11 - 1.19 (m, 1 H), 1.19 - 1.33 (m, 7 H), 1.38 - 1.69 (m, 5 H), 1.79 - 1.87 (m, 1 H), 2.26 - 2.33 (m, 2 H), 2.79 (dd, *J*=17.4 and 13.8 Hz, 1 H), 2.88 - 3.01 (m, 2 H), 3.47 (dd, *J*=17.4 and 11.4 Hz, 1 H), 3.79 (dt, *J*=7.7 and 3.4 Hz, 1 H), 4.68-4.77 (m, 1 H), 6.48 (br d, *J*=7.5 Hz, 1 H), 7.05 (dd, *J*=9.8 and 8.6 Hz, 1 H), 7.12 - 7.18 (m, 1 H), 7.24 - 7.31 (m, 1 H), 7.44 - 7.51 (m, 1 H).

Compound 73

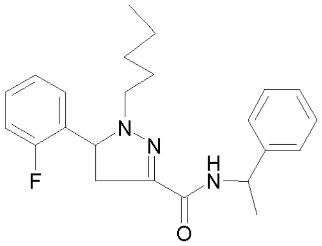


Compound 73

N-(4-chlorobenzyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84 (t, *J*=6.9 Hz, 3 H), 1.16 - 1.32 (m, 4 H), 1.52 - 1.67 (m, 2 H), 2.83 (dd, *J*=17.3 and 13.7 Hz, 1 H), 2.88 - 3.01 (m, 2 H), 3.50 (dd, *J*=17.4 and 11.4 Hz, 1 H), 4.46-4.55 (m, 2 H), 4.78 (dd, *J*=13.8 and 11.4 Hz, 1 H), 6.95 (br t, *J*=6.3 Hz, 1 H), 7.02-7.09 (m, 1 H), 7.12 - 7.19 (m, 1 H), 7.24 - 7.34 (m, 5 H), 7.46 (tt, *J*=7.5 and 2 Hz, 1 H).

Compound 74

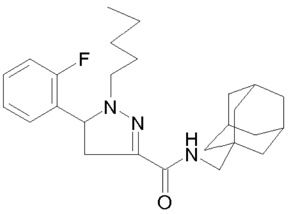


Compound 74

N-(1-Phenyl-ethyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (1: 1 diasteromeric mixture)

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.80-0.90 (m, 3 H), 1.17 - 1.33 (m, 4 H), 1.53 - 1.70 (m, 5 H), 2.73 - 2.87 (m, 1 H), 2.88 - 3.02 (m, 2 H), 3.42-3.54 (m, 1 H), 4.69 - 4.80 (m, 1 H), 5.20 (quintet, *J*=7.3 Hz, 1 H), 6.85 (br d, *J*=8.4 Hz, 1 H), 7.01 - 7.08 (m, 1 H), 7.11 - 7.19 (m, 1 H), 7.23 - 7.31 (m, 2 H), 7.32 - 7.41 (m, 4 H), 7.43 - 7.51 (m, 1 H).

Compound 75

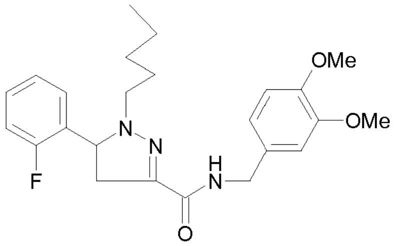


Compound 75

N-(Adamantylmethyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.84 - 0.89 (m, 3 H), 1.21 - 1.35 (m, 4 H), 1.51 - 1.57 (m, 6 H), 1.57 - 1.77 (m, 6 H), 2.00 (br s, 3 H), 2.81 (dd, *J*=17.4 and 13.8 Hz, 1 H), 2.90 - 3.10 (m, 4 H), 3.49 (dd, *J*=17.1 and 11.4 Hz, 1 H), 4.75 (dd, *J*=14 and 11.23 Hz, 1 H), 6.69 (t, *J*=6.8 Hz, 1 H), 7.02 - 7.08 (m, 1 H), 7.16 (br t, *J* ~ 8, 1 H), 7.24 - 7.31 (m, 1 H), 7.49 (dt, *J*=7.4 and 2 Hz, 1 H).

Compound 76

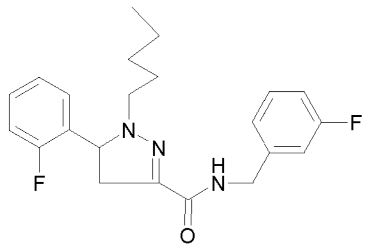


Compound 76

N-(3,4-Dimethoxybenzyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.84 (t, *J*=6.9 Hz, 3 H), 1.15 - 1.32 (m, 4 H), 1.54-1.66 (m, 2 H), 2.83 (dd, *J*=17.1 and 13.8 Hz, 1 H), 2.86 - 3.00 (m, 2 H), 3.51 (dd, *J*=17.3 and 11.6 Hz, 1 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 4.43-4.52 (m, 2 H), 4.76 (dd, *J*=14 and 11.6 Hz, 1 H), 6.82 - 6.92 (m, 4 H), 7.03-7.09 (m, 1 H), 7.16 (t, *J*=7.2 Hz, 1 H), 7.25 - 7.32 (m, 1 H), 7.47 (dt, *J*=7.5 and 2 Hz, 1 H).

Compound 77

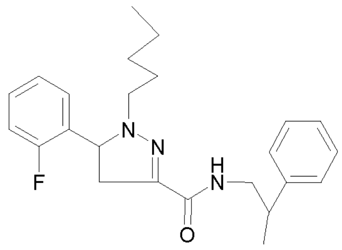


Compound 77

N-(3-Fluorobenzyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.82 - 0.88 (m, 3 H), 1.17 - 1.33 (m, 4 H), 1.53 - 1.71 (m, 2 H), 2.84 (dd, *J*=17.3 and 13.7 Hz, 1 H), 2.90 - 3.03 (m, 2 H), 3.51 (dd, *J*=17.3 and 11.6 Hz, 1 H), 4.48-4.58 (m, 2 H), 4.79 (dd, *J*=13.8 and 11.4 Hz, 1 H), 6.93-7.02 (m, 2 H), 7.02 - 7.13 (m, 3 H), 7.16 (t, *J*=7.5 Hz, 1 H), 7.25 - 7.35 (m, 2 H), 7.47 (dt, *J*=7.5 and 2 Hz, 1 H).

Compound 78

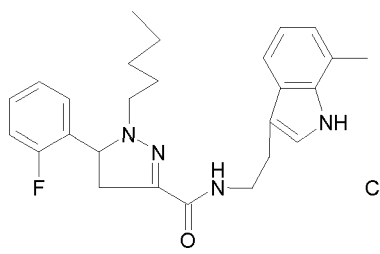


Compound 78

N-(2-Phenyl-propyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (1: 1 diasteromeric mixture)

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.86 (t, *J*=7 Hz, 3 H), 1.17 - 1.30 (m, 4 H), 1.32 (d, *J*=6.9 Hz, 3 H), 1.52 - 1.63 (m, 2 H), 2.72 - 3.06 (m, 4 H), 3.34 - 3.51 (m, 2 H), 3.58 - 3.67 (m, 1 H), 4.65-4.76 (m, 1 H), 6.57 (br t, *J*=6.3 Hz, 1 H), 7.04 (dd, *J*=9.8 and 8.9 Hz, 1 H), 7.11 - 7.17 (m, 1 H), 7.21 - 7.30 (m, 4 H), 7.30 - 7.36 (m, 2 H), 7.42 - 7.49 (m, 1 H).

Compound 79

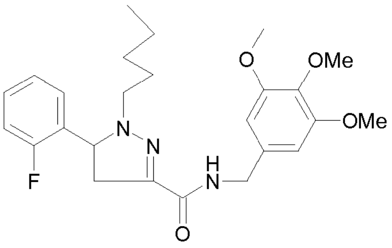


Compound 79

N-[2-(7-methyl-indol-3-yl)ethyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.86 (t, *J*=6.9 Hz, 3 H), 1.18 - 1.31 (m, 4 H), 1.53 - 1.65 (m, 2 H), 2.49 (s, 3 H), 2.80 (dd, *J*=17.1 and 13.8 Hz, 1 H), 2.83 - 2.97 (m, 2 H), 3.03 (t, *J*=7.1 Hz, 2 H), 3.48 (dd, *J*=17.1 and 11.4 Hz, 1 H), 3.68 (q, *J*=6.9 Hz, 2 H), 4.72 (dd, *J*=13.8 and 11.4 Hz, 1 H), 6.78 (t, *J*=6.2 Hz, 1 H), 6.99 - 7.09 (m, 4 H), 7.15 (t, *J*=7.5 Hz, 1 H), 7.24 - 7.31 (m, 1 H), 7.46 (dt, *J*=7.5 and 2 Hz, 1 H), 7.50 (d, *J*=7.8 Hz, 1 H), 8.10 (br s, 1 H).

Compound 80

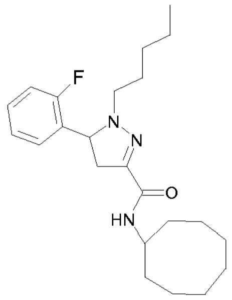


Compound 80

N-(3,4,5-Trimethoxybenzyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.84 (t, *J*=6.9 Hz, 3 H), 1.18 - 1.31 (m, 4 H), 1.55 - 1.66 (m, 2 H), 2.84 (dd, *J*=17.3 and 13.7 Hz, 1 H), 2.89 - 3.01 (m, 2 H), 3.52 (dd, *J*=17.3 and 11.6 Hz, 1 H), 3.84 (s, 3 H), 3.87 (s, 6 H), 4.42-4.52 (m, 2 H), 4.78 (dd, *J*=13.8 and 11.4 Hz, 1 H), 6.57 (s, 2 H), 6.91 (br t, *J*=6.2 Hz, 1 H), 7.06 (dd, *J*=9.6 and 8.7 Hz, 1 H), 7.16 (t, *J*=7.5 Hz, 1 H), 7.25 - 7.32 (m, 1 H), 7.44-7.50 (m, 1 H).

Compound 81

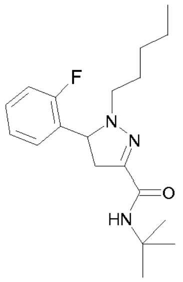


Compound 81

N-(Cyclooctyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.86 (t, *J*=6.92 Hz, 3 H), 1.18 - 1.34 (m, 4 H), 1.50 - 1.75 (m, 14 H), 1.82 - 1.95 (m, 2 H), 2.79 (dd, *J*=17.4 and 13.8 Hz, 1 H), 2.87-3.02 (m, 2 H), 3.47 (dd, *J*=17.3 and 11.3 Hz, 1 H), 4.01 - 4.11 (m, 1 H), 4.72 (dd, *J*=14 and 11.3 Hz, 1 H), 6.57 (br d, *J*=8.4 Hz, 1 H), 7.01-7.09 (m, 1 H), 7.12 - 7.18 (m, 1 H), 7.24 - 7.31 (m, 1 H), 7.45 - 7.51 (m, 1 H).

Compound 82

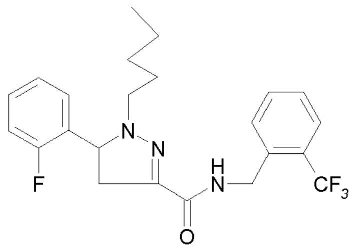


Compound 82

N-(tert-Butyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.86 (t, *J*=7.2 Hz, 3 H), 1.20 - 1.33 (m, 4 H), 1.42 (s, 9 H), 1.56 - 1.68 (m, 2 H), 2.77 (dd, *J*=17.1 and 13.8 Hz, 1 H), 2.92 (br t, *J*=7.1 Hz, 2 H), 3.45 (dd, *J*=17.3 and 11.3 Hz, 1 H), 4.70 (dd, *J*=14 and 11.3 Hz, 1 H), 6.50 (br s, 1 H), 7.01-7.08 (m, 1 H), 7.12-7.18 (m, 1 H), 7.24-7.31 (m, 1 H), 7.48 (dt, *J*=7.5 and 1.8 Hz, 1 H).

Compound 83

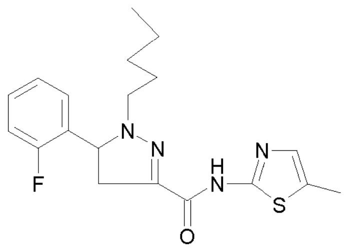


Compound 83

N-(2-(Trifluoromethyl)benzyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.85 (t, *J*=6.9 Hz, 3 H), 1.17 - 1.33 (m, 4 H), 1.54 - 1.70 (m, 2 H), 2.83 (dd, *J*=17.1 and 13.8 Hz, 1 H), 2.88 - 3.02 (m, 2 H), 3.50 (dd, *J*=17.3 and 11.6 Hz, 1 H), 4.67-4.82 (m, 3 H), 6.99 (br t, *J*=6.6 Hz, 1 H), 7.02-7.09 (m, 1 H), 7.15 (t, *J*=8.1 Hz, 1 H), 7.25 - 7.31 (m, 1 H), 7.38 (t, *J*=7.7 Hz, 1 H), 7.46 (dt, *J*=7.5 and 1.8 Hz, 1 H), 7.54 (t, *J*=7.7 Hz, 1 H), 7.60 - 7.68 (m, 2 H).

Compound 84

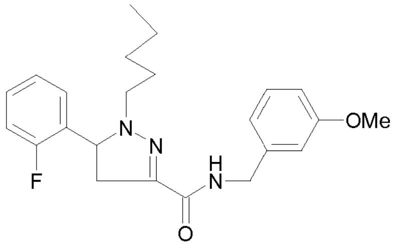


Compound 84

N-(5-Methyl-thiazol-2-yl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.85 - 0.89 (m, 3 H), 1.19 - 1.34 (m, 4 H), 1.59 - 1.69 (m, 2 H), 2.40 (s, 3 H), 2.93 (dd, *J*=17 and 13.1 Hz, 1 H), 2.97 - 3.14 (m, 2 H), 3.56 (dd, *J*=17.1 and 12.3 Hz, 1 H), 4.96 (t, *J*=12.6 Hz, 1 H), 7.05 - 7.12 (m, 2 H), 7.18 (t, *J*=7.4 Hz, 1 H), 7.28 - 7.34 (m, 1 H), 7.43 (dt, *J*=7.5 and 1.8 Hz, 1 H), 10.02 (br s, 1 H).

Compound 85

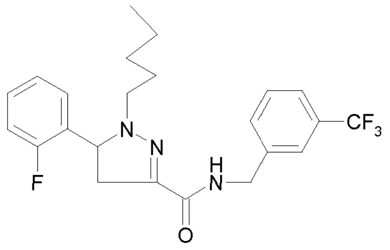


Compound 85

N-(3-Methoxybenzyl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.84 (t, *J*=6.9 Hz, 3 H), 1.17 - 1.32 (m, 4 H), 1.54 - 1.68 (m, 2 H), 2.83 (dd, *J*=17.1 and 13.8 Hz, 1 H), 2.88 - 3.00 (m, 2 H), 3.51 (dd, *J*=17.3 and 11.6 Hz, 1 H), 3.81 (s, 3 H), 4.48-4.57 (m, 2 H), 4.76 (dd, *J*=13.8 and 11.4 Hz, 1 H), 6.81-6.85 (m, 1 H), 6.87 - 6.95 (m, 3 H), 7.02-7.09 (m, 1 H), 7.16 (t, *J*=6.9 Hz, 1 H), 7.24 - 7.31 (m, 2 H), 7.47 (dt, *J*=7.5 and 1.8 Hz, 1 H).

Compound 86

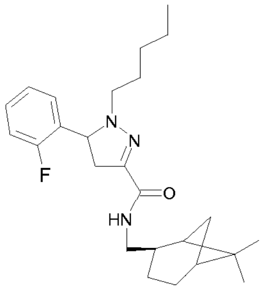


Compound 86

N-[3-(Trifluoromethyl)benzyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.80 - 0.88 (m, 3 H), 1.16 - 1.33 (m, 4 H), 1.53 - 1.69 (m, 2 H), 2.85 (dd, *J*=17.3 and 13.7 Hz, 1 H), 2.90 - 3.03 (m, 2 H), 3.51 (dd, *J*=17.1 and 11.7 Hz, 1 H), 4.56-4.64 (m, 2 H), 4.81 (dd, *J*=13.8 and 11.7 Hz, 1 H), 7.02 - 7.10 (m, 2 H), 7.16 (t, *J*=7.5 Hz, 1 H), 7.25 - 7.33 (m, 1 H), 7.43 - 7.50 (m, 2 H), 7.52 - 7.57 (m, 2 H), 7.58 (br s, 1 H).

Compound 87

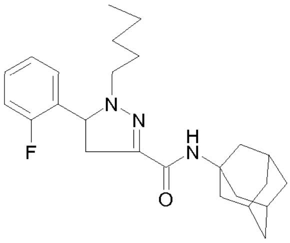


Compound 87

N-[(1R,2S,5R)-rel-6,6-dimethylbicyclo[3.1.1.]heptan-2-methyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (mixture of diastereoisomers) (from (-)-cis-myrtanylamine (CAS 38235-68-6))

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.84 - 0.93 (m, 4 H), 1.06 (s, 3 H), 1.21 (d, *J*=2.4 Hz, 3 H), 1.22 - 1.34 (m, 4 H), 1.48 - 1.69 (m, 3 H), 1.82 - 2.03 (m, 5 H), 2.22-2.32 (m, 1 H), 2.34 - 2.42 (m, 1 H), 2.75-2.85 (m, 1 H), 2.88 - 3.01 (m, 2 H), 3.28 - 3.41 (m, 2 H), 3.43-3.53 (m, 1 H), 4.74 (dd, *J*=13.8 and 11.4 Hz, 1 H), 6.64 (br t, *J*=6.3 Hz, 1 H), 7.02-7.08 (m, 1 H), 7.15 (t, *J*=7.5 Hz, 1 H), 7.24 - 7.31 (m, 1 H), 7.45-7.51 (m, 1 H).

Compound 88

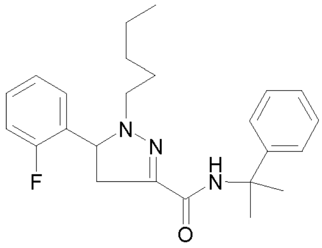


Compound 88

N-(Adamant-1-yl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=7.1 Hz, 3 H), 1.18 - 1.35 (m, 4 H), 1.52 - 1.75 (m, 8 H), 2.05 - 2.13 (m, 9 H), 2.75 (dd, *J*=17.3 and 14 Hz, 1 H), 2.92 (t, *J*=7.4 Hz, 2 H), 3.44 (dd, *J*=17.3 and 11.3 Hz, 1 H), 4.69 (dd, *J*=14 and 11.3 Hz, 1 H), 6.39 (br s, 1 H), 7.01-7.08 (m, 1 H), 7.15 (t, *J*=7.4 Hz, 1 H), 7.23 - 7.31 (m, 1 H), 7.45-7.51 (m, 1 H).

Compound 89

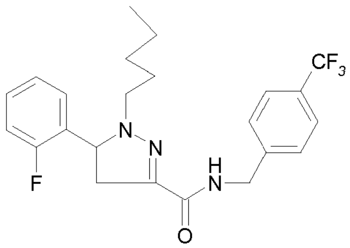


Compound 89

N-[1-phenyl-1-methyl-ethyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J*=6.9 Hz, 3 H), 1.19-1.35 (m, 4 H), 1.55 - 1.70 (m, 2 H), 1.76 (s, 3 H), 1.77 (s, 3 H), 2.76 (dd, *J*=17.5 and 13.8 Hz, 1 H), 2.91 - 2.99 (m, 2 H), 3.42 (dd, *J*=17.3 and 11.3 Hz, 1 H), 4.72 (dd, *J*=14 and 11.3 Hz, 1 H), 6.96 (br s, 1 H), 7.01-7.07 (m, 1 H), 7.15 (t, *J*=7.4 Hz, 1 H), 7.20 - 7.30 (m, 2 H), 7.34 (t, *J*=7.7 Hz, 2 H), 7.42 - 7.52 (m, 3 H).

Compound 90

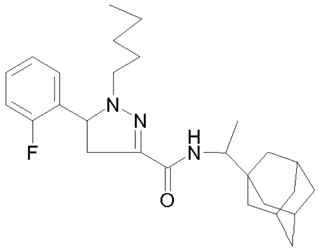


Compound 90

N-[4-(Trifluoromethyl)benzyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*=6.9 Hz, 3 H), 1.15 - 1.34 (m, 4 H), 1.53 - 1.69 (m, 2 H), 2.85 (dd, *J*=17.3 and 13.7 Hz, 1 H), 2.90 - 3.03 (m, 2 H), 3.51 (dd, *J*=17.3 and 11.6 Hz, 1 H), 4.54-4.64 (m, 2 H), 4.79 (dd, *J*=13.8 and 11.4 Hz, 1 H), 6.98 - 7.10 (m, 2 H), 7.16 (t, *J*=7.5 Hz, 1 H), 7.24 - 7.33 (m, 1 H), 7.43 - 7.50 (m, 3 H), 7.60 (d, *J*=8.1 Hz, 2 H).

Compound 91

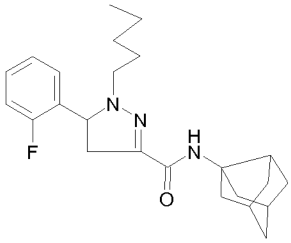


Compound 91

N-[1-(Adamant-1-yl)-ethyl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.83 - 0.90 (m, 3 H), 1.06 - 1.13 (m, 3 H), 1.20 - 1.36 (m, 4 H), 1.49 - 1.77 (m, 14 H), 1.98 - 2.04 (m, 3 H), 2.81 (dd, *J*=17.3 and 14 Hz, 1 H), 2.89 - 3.03 (m, 2 H), 3.49 (dd, *J*=17.1 and 11.1 Hz, 1 H), 3.72 - 3.82 (m, 1 H), 4.68 - 4.79 (m, 1 H), 6.51 (br d, *J*=10.2 Hz, 1 H), 7.01-7.09 (m, 1 H), 7.12 - 7.19 (m, 1 H), 7.24 - 7.31 (m, 1 H), 7.46 - 7.55 (m, 1 H).

Compound 92

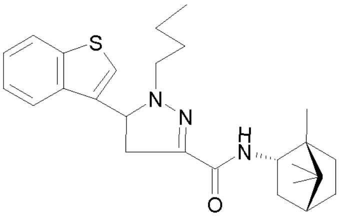


Compound 92

N-(Noradamant-1-yl)-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.83 - 0.90 (m, 3 H), 1.17 - 1.35 (m, 4 H), 1.51 - 1.71 (m, 6 H), 1.91 - 1.98 (m, 2 H), 2.01 - 2.10 (m, 2 H), 2.10 - 2.19 (m, 2 H), 2.29 (br s, 2 H), 2.50 (br t, *J*=6.8 Hz, 1 H), 2.79 (dd, *J*=17.4 and 13.8 Hz, 1 H), 2.93 (t, *J*=7.2 Hz, 2 H), 3.46 (dd, *J*=17.3 and 11.3 Hz, 1 H), 4.72 (dd, *J*=14 and 11.3 Hz, 1 H), 6.79 (br s, 1 H), 7.05 (ddd, *J*=10.2, 8.1 and 1.2 Hz, 1 H), 7.15 (br t, *J*=6.9 Hz, 1 H), 7.24 - 7.32 (m, 1 H), 7.48 (dt, *J*=7.5 and 2.1 Hz, 1 H).

Compound 93



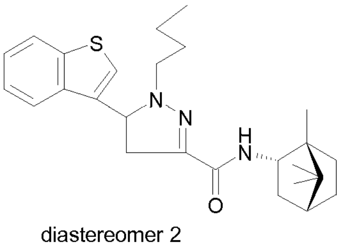
diastereomer 1

Compound 93

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-butyl)-5-(benzothien-3-yl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomer 1)

Compounds 93 and 94 were obtained from the corresponding diasteromeric mixture via a Sepacore column (40x150 mm) chromatographic purification. Eluant gradient: petroleum ether (40-60)/diethyl ether = 90/10 => petroleum ether (40-60)/diethyl ether = 80/20 (v/v)). Compound 93: first (fastest) eluting diastereomer: Compound 94: second (slowest) eluting diastereomer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 – 1.02, (m, 13 H), 1.20 - 1.49 (m, 4 H), 1.59 - 1.67 (m, 3 H), 1.70 (t, J=4.5 Hz, 1 H), 1.75 - 1.87 (m, 1 H), 2.38 (m, 1 H), 2.91 - 3.11 (m, 3 H), 3.51 (dd, J=17.4 and 11.4 Hz, 1 H), 4.38-4.48 (m, 1 H), 4.80 (dd, J=14.4 and 11.4 Hz, 1 H), 6.71 (br d, J=9.3 Hz, 1 H), 7.37 (dd, J=6.2 and 3.2 Hz, 2 H), 7.40 (s, 1 H), 7.75 - 7.81 (m, 1 H), 7.86 - 7.91 (m, 1 H).

Compound 94

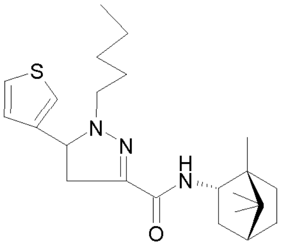


Compound 94

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-butyl)-5-(benzothien-3-yl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomer 2)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 – 1.03 (m, 13 H), 1.20 - 1.51 (m, 4 H). 1.62 - 1.68 (m, 3 H), 1.70 (t, J=4.4 Hz, 1 H), 1.76 - 1.88 (m, 1 H), 2.34 - 2.47 (m, 1 H), 2.90 - 3.11 (m, 3 H), 3.50 (dd, J=17.3 and 11.3 Hz, 1 H), 4.27-4.37 (m, 1 H), 4.78 (dd, J=14.4 and 11.4 Hz, 1 H), 6.71 (br d, J=9 Hz, 1 H), 7.35 - 7.45 (m, 3 H), 7.77 - 7.83 (m, 1 H), 7.86 - 7.92 (m, 1 H).

Compound 95



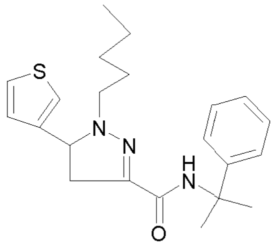
Compound 95

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-pentyl)-5-(thien-3-yl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.83 - 0.93 (m, 10 H), 0.97 (s, 3 H), 1.20 - 1.34 (m, 5 H), 1.36 - 1.46 (m, 1 H), 1.54 - 1.65 (m, 3 H), 1.69 (t, J=4.5 Hz, 1 H), 1.73-1.86 (m, 1 H), 2.32 - 2.42 (m, 1

H), 2.80 - 2.90 (m, 1 H), 2.90 - 3.04 (m, 2 H), 3.31 - 3.41 (m, 1 H), 4.26 - 4.34 (m, 1 H), 4.46 - 4.56 (m, 1 H), 6.66 (br d, *J*=9 Hz, 1 H), 7.08 - 7.13 (m, 1 H), 7.18-7.22 (m, 1 H), 7.31 - 7.35 (m, 1 H).

Compound 96

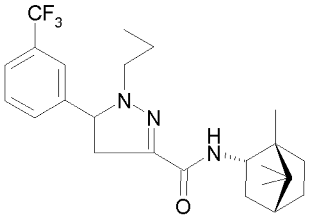


Compound 96

N-(1-phenyl-1-methyl-ethyl)-1-(n-pentyl)-5-(thien-3-yl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.83 - 0.90 (m, 3 H), 1.20 - 1.33 (m, 4 H), 1.53 - 1.68 (m, 2 H), 1.76 (s, 3 H), 1.77 (s, 3 H), 2.80 (dd, *J*=17.1 and 14.1 Hz, 1 H), 2.87 - 3.01 (m, 2 H), 3.29 (dd, *J*=17.1 and 10.8 Hz, 1 H), 4.49 (dd, *J*=14.1 and 10.8 Hz, 1 H), 6.96 (br s, 1 H), 7.08 - 7.12 (m, 1 H), 7.18 - 7.21 (m, 1 H), 7.23 (br t, *J*=7.2 Hz, 1 H), 7.30 - 7.38 (m, 3 H), 7.45 (br d, *J*=7.2 Hz, 2 H).

Compound 97



Compound 97

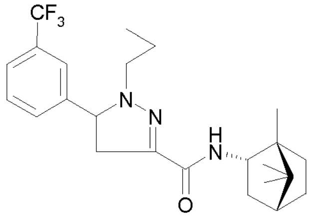
diastereomer 1

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-propyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomer 1)

Compounds 97 and 98 were obtained from the corresponding diasteromeric mixture via a Sepacore column (40x150 mm) chromatographic purification. Eluant gradient: petroleum ether (40-60)/diethyl ether = 90/10 => petroleum ether (40-60)/diethyl ether = 60/40 (v/v)). Compound 97: second (slowest) eluting diastereomer: Compound 98: first (fastest) eluting diastereomer.

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.84 - 0.93 (m, 10 H), 0.97 (s, 3 H), 1.21 - 1.30 (m, 1 H), 1.38 - 1.47 (m, 1 H), 1.56 - 1.68 (m, 3 H), 1.70 (t, *J*=4.4 Hz, 1 H), 1.76 - 1.86 (m, 1 H), 2.33-2.43 (m, 1 H), 2.80 (dd, *J*=17.4 and 14.4 Hz, 1 H), 2.82 - 2.98 (m, 2 H), 3.46 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.26 - 4.34 (m, 1 H), 4.45 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.67 (br d, *J*=9.1 Hz, 1 H), 7.46-7.51 (m, 1 H), 7.55 - 7.61 (m, 2 H), 7.67 (br s, 1 H).

Compound 98



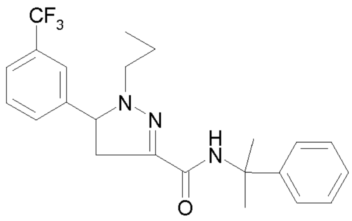
Compound 98

diastereomer 2

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-propyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomer 2)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.82 - 0.94 (m, 10 H), 0.97 (s, 3 H), 1.20-1.35 (m, 1 H), 1.38 - 1.48 (m, 1 H), 1.54 - 1.67 (m, 3 H), 1.69 (t, *J*=4.4 Hz, 1 H), 1.75 - 1.86 (m, 1 H), 2.33 - 2.42 (m, 1 H), 2.79 (dd, *J*=17.3 and 14.3 Hz, 1 H), 2.85 - 3.00 (m, 2 H), 3.48 (dd, *J*=17.4 and 11.4 Hz, 1 H), 4.25-4.35 (m, 1 H), 4.47 (dd, *J*=14.1 and 11.1 Hz, 1 H), 6.68 (br d, *J*=9.1 Hz, 1 H), 7.46 - 7.51 (m, 1 H), 7.55 - 7.60 (m, 2 H), 7.65 (br s, 1 H).

Compound 99

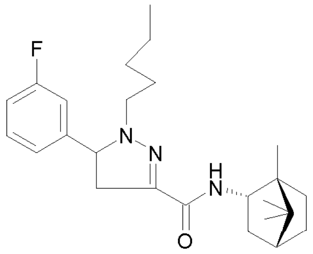


Compound 99

N-(1-phenyl-1-methyl-ethyl)-1-(n-propyl)-5-(3-(trifluoromethyl)phenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.4 Hz, 3 H), 1.55 - 1.71 (m, 2 H), 1.76 (s, 3 H), 1.77 (s, 3 H), 2.75 (dd, *J*=17.4 and 14.4 Hz, 1 H), 2.80 - 2.98 (m, 2 H), 3.41 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.44 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.97 (br s, 1 H), 7.21 - 7.27 (m, 1 H), 7.35 (br t, *J*=7.7 Hz, 2 H), 7.43 - 7.52 (m, 3 H), 7.55 - 7.60 (m, 2 H), 7.65 (br s, 1 H).

Compound 100

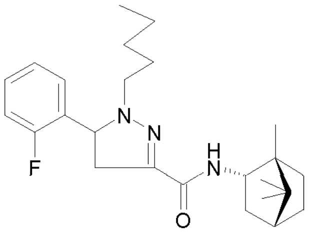


Compound 100

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-pentyl)-5-(3-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (1:1 diastereomeric mixture)

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.81 - 0.94 (m, 10 H), 0.97 (s, 3 H), 1.20-1.35 (m, 5 H), 1.37-1.47 (m, 1 H), 1.54 - 1.65 (m, 3 H), 1.67 - 1.72 (m, 1 H), 1.75 - 1.87 (m, 1 H), 2.32 - 2.42 (m, 1 H), 2.73-2.84 (m, 1 H), 2.91-2.99 (m, 2 H), 3.38 - 3.49 (m, 1 H), 4.26-4.45 (m, 2 H), 6.66 (br d, *J*=6.6 Hz, 1 H), 7.00 (dt, *J*=8.4 and 2.4 Hz, 1 H), 7.08 - 7.17 (m, 2 H), 7.28-7.35 (m, 1 H).

Compound 101

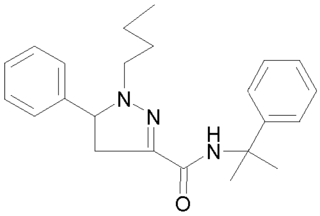


Compound 101

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-pentyl)-5-(2-fluorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

To a magnetically stirred solution of E-2-oxo-4-(2-fluorophenyl)-but-3-enoic acid [endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamide] (Intermediate X-3) (1.5 g, 4.83 mmol) in ethanol (50 ml) was successively added acetic acid (660 ml, 11.58 mmol) and n-pentylhydrazine (Intermediate XI-1) (1.45 ml, 9.65 mmol) and the resulting mixture was reacted in a nitrogen atmosphere at 60 °C for 8 hours in an oil bath. The reaction mixture was allowed to attain room temperature and concentrated in vacuo. The residue was dissolved in dichloromethane, washed with water and subsequently dried over MgSO$_4$, filtered and concentrated in vacuo. Further chromatographic purification using Sepacore equipment (eluant: petroleum ether/ethylacetate = 95/5 (v/v)) gave compound 101 (940 mg, 46 % yield) as an oil. ^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.83-0.94 (m, 10H), 1.20-1.85 (m, 14H), 2.32-2.42 (m, 1H), 2.74-2.85 (m, 1H), 2.91-3.02 (m, 2H), 3.43-3.54 (m, 1H), 4.26-4.36 (m, 1H), 4.69-4.80 (m, 1H), 6.63-6.70 (m, 1H), 7.02-7.09 (m, 1H), 7.12-7.19 (m, 1H), 7.25-7.31 (m, 1H), 7.46-7.54 (m, 1H).

Compound 102

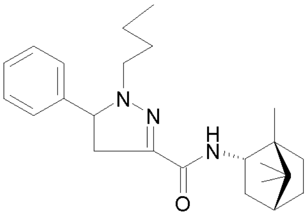


Compound 102

N-(1-phenyl-1-methyl-ethyl)-1-(n-butyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

Compound 102 was obtained from E-2-oxo-4-phenyl-but-3-enoic acid [1-phenyl-1-methyl-ethyl]amide and n-butylhydrazine analogously to the procedure described for compound 101. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7, 3H), 1.20-1.39 (m, 2H), 1.53-1.63 (m, 2H), 1.76 (s, 3H), 1.77 (s, 3H), 2.77 (dd, J = 17 and 14, 1H), 2.90-2.96 (m, 2H), 3.35 (dd, J = 17 and 11, 1H), 4.37 (dd, J = 14 and 11, 1H), 6.97 (br s, 1H), 7.21-7.48 (m, 10H).

Compound 103

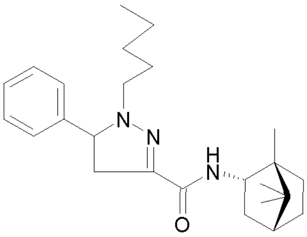


Compound 103

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-butyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

Compound 103 was obtained from E-2-oxo-4-phenyl-but-3-enoic acid [endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamide] (Intermediate X-2) and n-butylhydrazine analogously to the procedure described for compound 101. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.83-0.95 (m, 10H), 0.97 (s, 3H), 1.21-1.86 (m, 9H), 2.32-2.42 (m, 1H), 2.77-2.88 (m, 1H), 2.91-2.99 (m, 2H), 3.35-3.46 (m, 1H), 4.26-4.46 (m, 2H), 6.66 (br d, J ~8, 1H), 7.28-7.40 (m, 5H).

Compound 104

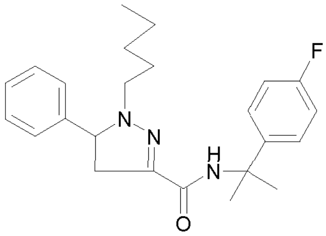


Compound 104

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

Compound 104 was obtained from E-2-oxo-4-phenyl-but-3-enoic acid [endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylamide] (Intermediate X-2) and n-pentylhydrazine (Intermediate XI-1) analogously to the procedure described for compound 101. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.83-0.94 (m, 10H), 0.97 (s, 3H), 1.20-1.47 (m, 5H), 1.54-1.65 (m, 3H), 1.69 (t, J ~6, 1H), 1.75-1.85 (m, 1H), 2.32-2.42 (m, 1H), 2.82 (dd, J = 17 and 14, 1H), 2.92-2.98 (m, 2H), 3.41 (dd, J = 17 and 11, 1H), 4.26-4.35 (m, 1H), 4.41 (dd, J = 14 and 11, 1H), 6.67 (br d, J ~ 8, 1H), 7.28-7.39 (m, 5H).

Compound 105

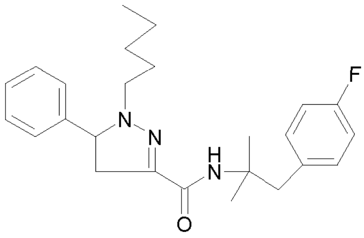


Compound 105

N-(1-(4-fluorophenyl)-1-methyl-ethyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

Compound 6 was obtained from E-2-oxo-4-phenyl-but-3-enoic acid [1-(4-fluorophenyl)-1-methyl-ethyl]amide and n-pentylhydrazine (Intermediate XI-1) analogously to the method described for compound 101. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7, 3H), 1.20-1.31 (m, 4H), 1.54-1.67 (m, 2H), 1.74 (s, 3H), 1.75 (s, 3H), 2.77 (dd, J = 17 and 14, 1H), 2.90-2.97 (m, 2H), 3.35 (dd, J = 17 and 11, 1H), 4.38 (dd, J = 14 and 11, 1H), 6.94 (br s, 1H), 6.98-7.04 (m, 2H), 7.27-7.43 (m, 7H).

Compound 106



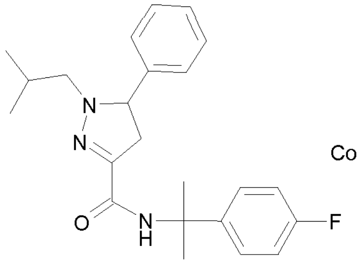
Compound 106

N-(2-(4-fluorophenyl)-1,1-dimethyl-ethyl)-1-(n-pentyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

Compound 106 was obtained from E-2-oxo-4-phenyl-but-3-enoic acid [2-(4-fluorophenyl)-2,2-dimethyl-ethyl]amide (Intermediate X-4) and n-pentylhydrazine (Intermediate XI-1) analogously to the procedure described for compound 101. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7, 3H), 1.16-1.27 (m, 4H), 1.36 (s, 3H), 1.39 (s, 3H), 1.50-1.62 (m, 2H), 2.77-2.94 (m, 4H), 3.04 (d, J = 13, 1H), 3.10 (d, J = 13, 1H), 3.41 (dd, J = 18 and 12, 1H), 4.39 (dd, J = 14 and 11, 1H), 6.38 (br s, 1H), 6.94-7.01 (m, 2H), 7.10-7.16 (m, 2H), 7.28-7.38 (m, 5H).

Furthermore, the compounds 107-118 were obtained analogously to the method described for compound 101.

Compound 107

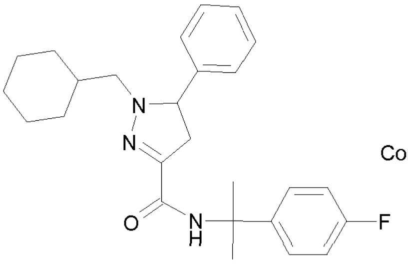


Compound 107

N-[1-(4-fluorophenyl)-1-methyl-ethyl]-1-isobutyl-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.85 (d, *J*=6.6 Hz, 3 H), 0.88 (d, *J*=6.6 Hz, 3 H), 1.73 (s, 3 H), 1.75 (s, 3 H), 1.96 - 2.07 (m, 1 H), 2.54 (dd, *J*=12.6 and 9 Hz, 1 H), 2.77 (dd, *J*=17.4 and 14.1 Hz, 1 H), 2.84 (dd, *J*=12.6 and 5.1 Hz, 1 H), 3.34 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.34 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.93 (br s, 1 H), 7.01 (t, *J*=8.9 Hz, 2 H), 7.27 - 7.37 (m, 5 H), 7.38 - 7.44 (m, 2 H).

Compound 108

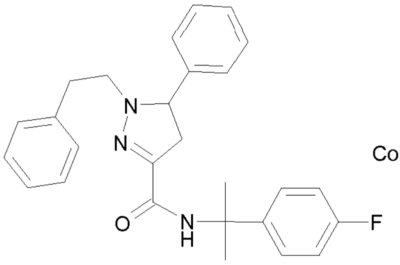


Compound 108

N-[1-(4-fluorophenyl)-1-methyl-ethyl]-1-cyclohexylmethyl-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.67 - 0.90 (m, 2 H), 1.05 - 1.29 (m, 4 H), 1.51 - 1.72 (m, 4 H), 1.74 (s, 3 H), 1.75 (s, 3 H), 1.82 - 1.90 (m, 1 H), 2.61 (dd, *J*=12.8 and 8.9 Hz, 1 H), 2.76 (dd, *J*=17.3 and 14.3 Hz, 1 H), 2.83 (dd, *J*=12.6 and 5.1 Hz, 1 H), 3.33 (dd, *J*=17.3 and 11 Hz, 1 H), 4.33 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.93 (br s, 1 H), 7.01 (t, *J*=8.7 Hz, 2 H), 7.27 - 7.37 (m, 5 H), 7.39-7.43 (m, 2 H).

Compound 109

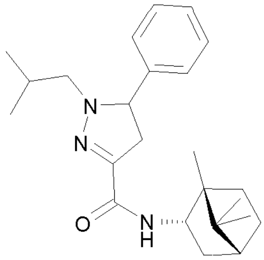


Compound 109

N-[1-(4-fluorophenyl)-1-methyl-ethyl]-1-phenethyl-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.74 (s, 3 H), 1.75 (s, 3 H), 2.77 (dd, *J*=17.4 and 14.4 Hz, 1 H), 2.84 - 2.93 (m, 1 H), 2.95 - 3.03 (m, 1 H), 3.13 - 3.29 (m, 2 H), 3.33 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.43 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.91 (br s, 1 H), 7.02 (t, *J*=8.7 Hz, 2 H), 7.14 (d, *J*=6.9 Hz, 2 H), 7.16 - 7.35 (m, 8 H), 7.38 - 7.44 (m, 2 H).

Compound 110

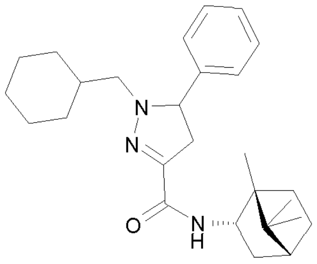


Compound 110

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-isobutyl-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.81 - 0.95 (m, 13 H), 0.96 (s, 3 H), 1.22 - 1.30 (m, 1 H), 1.37 - 1.47 (m, 1 H), 1.55 - 1.67 (m, 1 H), 1.69 (t, *J*=4.5 Hz, 1 H), 1.75 - 1.85 (m, 1 H), 1.96 - 2.08 (m, 1 H), 2.32 - 2.43 (m, 1 H), 2.52 - 2.60 (m, 1 H), 2.78 - 2.88 (m, 2 H), 3.36 - 3.46 (m, 1 H), 4.26 - 4.41 (m, 2 H), 6.67 (br d, *J* ~ 8 Hz, 1 H), 7.27 - 7.40 (m, 5 H).

Compound 111

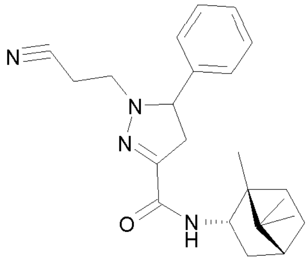


Compound 111

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-cyclohexylmethyl-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.70 - 0.95 (m, 9 H), 0.98 (s, 3 H), 1.04 - 1.32 (m, 5 H), 1.37 - 1.48 (m, 1 H), 1.55 - 1.90 (m, 8 H), 2.32 - 2.43 (m, 1 H), 2.60 - 2.70 (m, 1 H), 2.77 - 2.89 (m, 2 H), 3.35 - 3.46 (m, 1 H), 4.26 - 4.42 (m, 2 H), 6.65 (br d, *J* ~ 9 Hz, 1 H), 7.27 - 7.39 (m, 5 H).

Compound 112

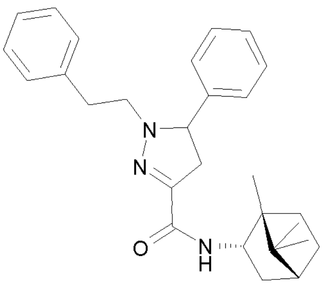


Compound 112

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(2-cyano-ethyl)-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.82 - 0.95 (m, 7 H), 0.97 (s, 3 H), 1.22 - 1.32 (m, 1 H), 1.38 - 1.49 (m, 1 H), 1.54 - 1.65 (m, 1 H), 1.70 (t, *J*=4.7 Hz, 1 H), 1.75 - 1.88 (m, 1 H), 2.34 - 2.44 (m, 1 H), 2.61 - 2.77 (m, 2 H), 2.88 (dd, *J*=17.6 and 14.3 Hz, 1 H), 3.20 (t, *J*=6.8 Hz, 2 H), 3.46 (dd, *J*=17.4 and 10.8 Hz, 1 H), 4.26 - 4.35 (m, 1 H), 4.39 (dd, *J*=14.4 and 10.8 Hz, 1 H), 6.67 (br d, *J*=9 Hz, 1 H), 7.31 - 7.44 (m, 5 H).

Compound 113

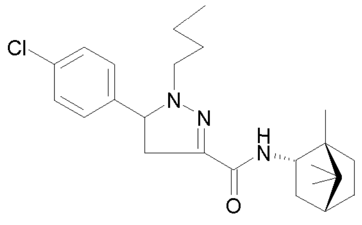


Compound 113

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-phenethyl-5-phenyl-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomeric mixture)

^{1}H-NMR (400 MHz, DMSO-d_6) δ 0.85-0.96 (m, 7 H), 0.98 (s, 3 H), 1.20 - 1.32 (m, 1 H), 1.39 - 1.48 (m, 1 H), 1.55-1.65 (m, 1 H) 1.70 (t, *J*=4.5 Hz, 1 H), 1.76 - 1.88 (m, 1 H) 2.33 - 2.43 (m, 1 H), 2.77 - 2.93 (m, 2 H), 2.95 - 3.04 (m, 1 H), 3.16 - 3.30 (m, 2 H), 3.42 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.26 - 4.35 (m, 1 H), 4.45 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.65 (br d, *J*=9.3 Hz, 1 H), 7.10 - 7.40 (m, 10 H).

Compound 114



Compound 114

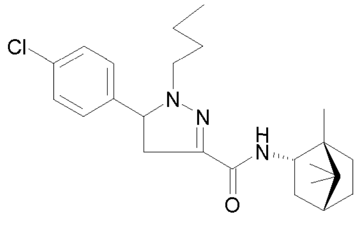
diastereomer 1

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-butyl)-5-(4-chlorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomer 1)

Compounds 114 and 115 were obtained from the corresponding diasteromeric mixture via a flash chromatographic purification. Eluant: petroleum ether (40-60)/diethyl ether = 75/25. Compound 115: first (fastest) eluting diastereomer): Compound 114: second (slowest) eluting diastereomer.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.81 - 0.93 (m, 10 H), 0.97 (s, 3 H), 1.08 - 1.65 (m, 7 H), 1.69 (t, *J*=4.5 Hz, 1 H), 1.74 - 1.85 (m, 1 H), 2.33 - 2.42 (m, 1 H), 2.78 (dd, *J*=17.1 and 14.4 Hz, 1 H), 2.92 (t, *J*=7.4 Hz, 2 H), 3.40 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.26 - 4.34 (m, 1 H), 4.36 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.65 (br d, *J*=9.3 Hz, 1 H), 7.33 (s, 4 H).

Compound 115



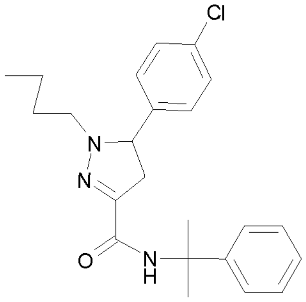
Compound 115

diastereomer 2

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-butyl)-5-(4-chlorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (diastereomer 2)

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.82 - 0.93 (m, 10 H), 0.97 (s, 3 H), 1.18 - 1.63 (m, 7 H), 1.69 (t, *J*=4.5 Hz, 1 H), 1.75 - 1.85 (m, 1 H), 2.32 - 2.42 (m, 1 H), 2.77 (dd, *J*=17.3 and 14.3 Hz, 1 H), 2.93 (t, *J*=7.4 Hz, 2 H), 3.37-3.46 (m, 1 H), 4.26 - 4.34 (m, 1 H), 4.38 (dd, *J*=14.1 and 11.1 Hz, 1 H), 6.66 (br d, *J*=9.3 Hz, 1 H), 7.29-7.35 (m, 4 H).

Compound 116

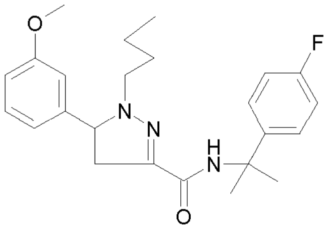


Compound 116

N-[1-phenyl-1-methyl-ethyl]-1-n-butyl-5-(4-chlorophenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.86 (t, *J*=7.4 Hz, 3 H), 1.20 - 1.38 (m, 2 H), 1.53 - 1.63 (m, 2 H), 1.76 (s, 3 H), 1.77 (s, 3 H), 2.72 (dd, *J*=17.3 and 14.3 Hz, 1 H), 2.90 (t, *J*=7.4 Hz, 2 H), 3.34 (dd, *J*=17.4 and 11.1 Hz, 1 H), 4.34 (dd, *J*=14.4 and 11.1 Hz, 1 H), 6.95 (br s, 1 H), 7.20 - 7.26 (m, 1 H), 7.28 - 7.37 (m, 6 H), 7.45 (d, *J*=7.8 Hz, 2 H).

Compound 117

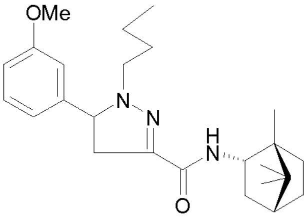


Compound 117

N-(1-(4-fluorophenyl)-1-methyl-ethyl)-1-(n-butyl)-5-(3-methoxyphenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide

^{1}H-NMR (400 MHz, CDCl$_3$) δ 0.85 - 0.89 (m, 3 H), 1.22 - 1.39 (m, 2 H), 1.55 - 1.66 (m, 2 H), 1.73 (s, 3 H), 1.74 (s, 3 H), 2.76 (dd, *J*=17.3 and 14.5 Hz, 1 H), 2.88-3.01 (m, 2 H), 3.33 (dd, *J*=17.3 and 11.1 Hz, 1 H), 3.80 (s, 3 H), 4.35 (dd, *J*=14.5 and 11.1 Hz, 1 H), 6.84 (ddd, *J*=8.12, 2.4 and 1.1 Hz, 1 H), 6.91 - 6.96 (m, 3 H), 6.97 - 7.05 (m, 2 H), 7.23 - 7.28 (m, 1 H), 7.38 - 7.44 (m, 2 H).

Compound 118



Compound 118

N-[endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl]-1-(n-butyl)-5-(3-methoxyphenyl)-4,5-dihydro-(1H)-pyrazole-3-carboxamide (1:1 diastereomeric mixture)
^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.84 - 0.94 (m, 10 H), 0.97 (s, 3 H), 1.22 - 1.47 (m, 4 H), 1.54 - 1.66 (m, 3 H), 1.69 (t, J=4.4 Hz, 1 H), 1.75 - 1.86 (m, 1 H), 2.32 - 2.43 (m, 1 H), 2.76-2.87 (m, 1 H), 2.89 - 3.03 (m, 2 H), 3.36-3.45 (m, 1 H), 3.81/3.82 (double s, 3 H), 4.26 - 4.43 (m, 2 H), 6.63-6.71 (m, 1 H), 6.81-6.87 (m, 1 H), 6.92 - 6.97 (m, 2 H), 7.23 - 7.30 (m, 1 H).

EXAMPLE 5: PHARMACOLOGICAL METHODS

In vitro affinity for cannabinoid-CB$_1$ receptors

The affinity of the compounds of the invention for cannabinoid CB$_1$ receptors can be determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB$_1$ receptor is stably transfected in conjunction with [^{3}H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [^{3}H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand is performed by filtration over glassfiber filters. Radioactivity on the filter is measured by liquid scintillation counting.

In vitro affinity for cannabinoid-CB$_2$ receptors

The affinity of the compounds of the invention for cannabinoid CB$_2$ receptors can be determined using membrane preparations of CHO cells in which the human cannabinoid CB$_2$ receptor is stably transfected in conjunction with [^{3}H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [^{3}H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand is performed by filtration over glassfiber filters. Radioactivity on the filter is measured by liquid scintillation counting.

In vitro cannabinoid-CB_1 receptor (ant)agonism

In vitro CB_1 receptor antagonism/agonism can be assessed with the human CB_1 receptor cloned in CHO cells. CHO cells are grown in a Dulbecco's Modified Eagle's medium (DMEM) culture medium, supplemented with 10% heat-inactivated fetal calf serum. Medium is aspirated and replaced by DMEM, without fetal calf serum, but containing [^{3}H]-arachidonic acid and incubated overnight in a cell culture stove (5% CO_2/95% air; 37 °C; water-saturated atmosphere). During this period [^{3}H]-arachidonic acid is incorporated in membrane phospholipids. On the test day, medium is aspirated and cells are washed three times using 0.5 ml DMEM, containing 0.2% bovine serum albumin (BSA). CB_1 agonist stimulation leads to activation of PLA_2 followed by release of [^{3}H]-arachidonic acid into the medium. This CB_1 agonist-induced release is concentration-dependently antagonized by CB_1 receptor antagonists, such as for example rimonabant.

In vitro cannabinoid-CB_2 receptor (ant)agonism

Functional activity at the cannabinoid CB_2 receptor was assessed using a forskolin-stimulated cAMP accumulation assay. The ability of compounds to stimulate and inhibit adenylate cyclase activity was assessed in Chinese ovarian hamster (CHO) K_1 cells expressing human CB2 (Euroscreen,Brussel) receptor. CHO cells were grown in a CHO-S-SFM-II culture medium, supplemented with 10 % heat- inactivated foetal calf serum, 2mM glutamine, 400μg/ml Hygromycine B and 500 μg/ml G418 at 37 °C in 93 % air / 5 % CO_2. For incubation with test compounds, confluent cultures grown in 24 well plates were used. Each condition or substance was routinely tested in quadruplicate. Cells were loaded with 1mCi [^{3}H]-adenine in 0.5 ml medium per well. After 2 hours, cultures were washed with 0.5 ml PBS containing 1mM IBMX and incubated for 20 minutes with 0.5 ml PBS containing 1mM IBMX and 3×10^{-7} M forskolin with or without the test compound. Antagonistic effects of test compounds were determined as inhibition of 0.1 μM JWH-133-decreased [^{3}H]cAMP formation. After aspiration the reaction was stopped with 1ml trichloroacetic acid (5% w/v). The [^{3}H]-ATP and [^{3}H]-cAMP formed in the cellular extract were assayed as follows: a volume of 0.8 ml of the extract was passed over Dowex (50WX-4200- 400 mesh) and aluminum oxide columns, eluted with water and 0.1M imidazole (pH=7.5). Eluates were mixed with 7 ml Ultima-Flo [AP] and the β-radioactivity was counted with a liquid scintillation counter. The conversion of [^{3}H]-ATP into [^{3}H]-cAMP was expressed as the ratio in percentage radioactivity in the cAMP fraction as compared to the combined radioactivity in both cAMP and ATP fractions, and basal activity was subtracted to correct for spontaneous activity. Reference compounds used to assess cannabinoid CB_2 receptor mediated adenylate cyclase activity were the full cannabinoid CB_2 receptor agonists

JWH-133 (Huffman, 1999[b]) and WIN 55,212-2 (Huffman, 1999[a]), and the inverse agonist or antagonist SR-144528 (Rinaldi-Carmona, 1998). Compounds were studied in a concentration range of 10^{-10} M to 10^{-6}M. pEC_{50} and the pA_2 were calculated according to Cheng-Prusoff equation (Cheng and Prusoff, 1973). Two independent experiments were performed in triplicate.

EXAMPLE 6: PHARMACOLOGICAL TEST RESULTS

Affinity for CB_1- and CB_2- receptors, and *in vitro* agonistic activity on CB_1- receptors

	receptor binding		Functional CB_1 assays
	Human CB_1	Human CB_2	Human CB_1
	affinity	affinity	agonism
Cmp	pK_i	pK_i	pEC_{50}
1	8.1	8.3	8.1
4	7.5	7.1	7.4
7	6.9	6.3	6.2
12	7.1	7.4	7.4
14	7.5	6.6	6.3
22	7.2	6.5	7.1
27	7.8	8.1	7.9
28	8.2	7.0	8.1
32	8.1	8.0	7.4
37	7.8	7.0	8.1
101	8.2	8.1	8.2
102	7.4	7.4	7.0
103	7.1	7.6	7.5
104	8.2	7.6	8.5
105	7.8	6.9	8.8
108	7.6	7.5	7.8
110	7.3	7.3	6.5

The compounds have a high affinity for cannabinoid-CB_1 and CB_2 receptors, and are agonists on CB_1 receptors. Surprising, because 1,3,5-trisubstituted pyrazoline derivatives described in e.g. WO 2005/074920, WO 2005/077911 and WO 2007/009689, as cannabinoid CB_1 receptor '*modulating*' agents, a definition embracing agonists, invariably were shown to be antagonists.

EXAMPLE 7: PHARMACEUTICAL PREPARATIONS

For clinical use, compounds of formula (I) are formulated into pharmaceutical compositions that are important and novel embodiments of the invention because they contain the compounds, more particularly specific compounds disclosed herein. Types of pharmaceutical compositions that may be used include, but are not limited to, tablets, chewable tablets, capsules (including microcapsules), solutions, parenteral solutions, ointments (creams and gels), suppositories, suspensions, and other types disclosed herein, or apparent to a person skilled in the art from the specification and general knowledge in the art. The active ingredeient for instance, may also be in the form of an inclusion complex in cyclodextrins, their ethers or their esters. The compositions are used for oral, intravenous, subcutaneous, tracheal, bronchial, intranasal, pulmonary, transdermal, buccal, rectal, parenteral or other ways to administer. The pharmaceutical formulation contains at least one compound of formula (I) in admixture with a pharmaceutically acceptable adjuvant, diluent and/or carrier. The total amount of active ingredients suitably is in the range of from about 0.1% (w/w) to about 95% (w/w) of the formulation, suitably from 0.5% to 50% (w/w) and preferably from 1% to 25% (w/w).

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxillary substances such as liquid or solid, powdered ingredients, such as the pharmaceutically customary liquid or solid fillers and extenders, solvents, emulsifiers, lubricants, flavorings, colorings and/or buffer substances. Frequently used auxillary substances include magnesium carbonate, titanium dioxide, lactose, saccharose, sorbitol, mannitol and other sugars or sugar alcohols, talc, lactoprotein, gelatin, starch, amylopectin, cellulose and its derivatives, animal and vegetable oils such as fish liver oil, sunflower, groundnut or sesame oil, polyethylene glycol and solvents such as, for example, sterile water and mono- or polyhydric alcohols such as glycerol, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture may then be processed into granules or pressed into tablets. A tablet is prepared using the ingredients below:

Ingredient	Quantity (mg/tablet)
COMPOUND No. 1	10
Cellulose, microcrystalline	200
Silicon dioxide, fumed	10
Stearic acid	10
Total	230

The components are blended and compressed to form tablets each weighing 230 mg.

The active ingredients may be separately premixed with the other non-active ingredients, before being mixed to form a formulation. The active ingredients may also be mixed with each other, before being mixed with the non-active ingredients to form a formulation.

Soft gelatin capsules may be prepared with capsules containing a mixture of the active ingredients of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatin capsules. Hard gelatin capsules may contain granules of the active ingredients. Hard gelatin capsules may also contain the active ingredients together with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared (i) in the form of suppositories that contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatin rectal capsule that contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatin rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations may be prepared in the form of syrups, elixirs, concentrated drops or suspensions, e.g. solutions or suspensions containing the active ingredients and the remainder consisting, for example, of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring agents, preservatives, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations may also be prepared in the form of a dry powder, reconstituted with a suitable solvent prior to use. Solutions for parenteral administration may be prepared as a solution of a formulation of the invention in a pharmaceutically acceptable solvent. These solutions may also contain stabilizing ingredients, preservatives and/or buffering ingredients. Solutions for parenteral administration may also be prepared as a dry preparation, reconstituted with a suitable solvent before use.

Also provided according to the present invention are formulations and 'kits of parts' comprising one or more containers filled with one or more of the ingredients of a pharmaceutical composition of the invention, for use in medical therapy. Associated with such container(s) can be various written materials such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals products, which notice reflects approval by the agency of manufacture, use, or sale for human or veterinary administration. The use of formulations of the invention in the manufacture of medicaments for use in the treatment of a condition in which activation of cannabinoid CB_1 receptors is required or desired, and methods of medical treatment or comprising the administration of a therapeutically effective total amount of at least one compound of formula (I), to a patient suffering from, or susceptible to, a condition in which activation of cannabinoid CB_1 receptors is required or desired.

By way of example and not of limitation, several pharmaceutical compositions are given, comprising preferred active compounds for systemic use or topical application. Other compounds of the invention or combinations thereof, may be used in place of (or in addition to) said compounds. The concentration of the active ingredient may be varied over a wide range as discussed herein. Amounts and types of ingredients that may be included are known in the art.

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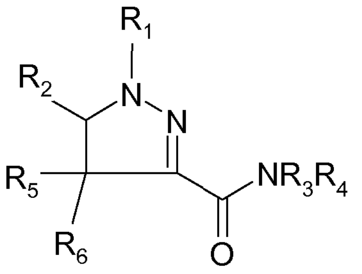
CLAIMS:

1. Compounds of the general formula (I)



(I)

or a tautomer, stereoisomer, N-oxide, isotopically-labelled analogue, or a pharmacologically acceptable salt of any of the foregoing, wherein:

- R_1 is chosen from a C_{3-10} linear alkyl group, a C_{4-10} branched alkyl group, a C_{4-10} alkenyl group, a C_{4-10} alkynyl group, a C_{3-10}-heteroalkyl group, a C_{5-8}-cycloalkyl-C_{1-5}-alkyl group, a C_{5-8}-heterocycloalkyl-C_{1-5}-alkyl group, which groups are optionally substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl, hydroxy, amino, cyano or fluoro, or
  R_1 is chosen from an aryl-C_{1-3}-alkyl group, a heteroaryl-C_{1-3}-alkyl group, an aryl-C_{1-3}-heteroalkyl group or a heteroaryl-C_{1-3}-heteroalkyl group, wherein the aryl or heteroaryl groups are unsubstituted, or substituted with 1-5 substituents Y, which can be the same or different, selected from C_{1-3}-alkyl or alkoxy, hydroxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, mono- or dialkyl (C_{1-2})-amino, mono- or dialkyl (C_{1-2})-amido, (C_{1-3})-alkyl sulfonyl, dimethylsulf-amido, C_{1-3}-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl, phenyl and acetyl, or
  R_1 is 2-cyano-ethyl,
- R_2 is an aryl group or a heteroaryl group, unsubstituted or substituted with 1-5 substituents Y, which can be the same or different, wherein Y has the abovementioned meaning,
- R_3 is chosen from a linear or branched C_{3-10} alkyl group, a C_{3-8} cycloalkyl group, C_{5-10} bicycloalkyl group, C_{6-10} tricycloalkyl group or C_{8-11} tetracycloalkyl group, which groups are unsubstituted, or substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl, hydroxy, amino, fluoro, or
  R_3 is a C_{3-8} cycloalkyl group substituted with an aryl group or a heteroaryl group, which is unsubstituted or substituted with 1-5 substituents Y, which can be the same or different, wherein Y has the meaning given above, or
  R_3 is a 2,2,2-trifluoroethyl, or a 2-fluoroethyl group, or

R_3 is chosen from a C_{5-8} heterocycloalkyl group, C_{6-10} bicycloheteroalkyl group, C_{7-10} tricycloheteroalkyl group, which groups are unsubstituted or substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl, hydroxy, amino or fluoro, or

R_3 is chosen from a C_{3-8} cycloalkyl-C_{1-3}–alkyl group, C_{5-10}-bicycloalkyl-C_{1-3}–alkyl group, C_{6-10}-tricycloalkyl-C_{1-3}–alkyl group, which groups are unsubstituted or substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl, hydroxy, amino or fluoro, or

R_3 is chosen from a branched or linear C_{3-8} heterocycloalkyl-C_{1-3}–alkyl group, C_{5-10} bicycloheteroalkyl-C_{1-3}–alkyl group, C_{6-10} tricycloheteroalkyl-C_{1-3}–alkyl group, which groups are unsubstituted or substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl, hydroxy, amino or fluoro, or

R_3 is an aryl group or a heteroaryl group, which groups are unsubstituted or substituted with 1-5 substituents Y, which can be the same or different, wherein Y has the *abovementioned meaning*, or

R_3 is an aryl-C_{1-5}–alkyl group, a heteroaryl-C_{1-5}–alkyl or a diaryl-C_{1-5}–alkyl group, wherein the aryl or heteroaryl groups are unsubstituted or substituted with 1-5 substituents Y, which can be the same or different, wherein Y has the abovementioned meaning, or

R_3 is chosen from a linear or branched C_{4-8} alkenyl or C_{4-8} alkynyl group, which groups are unsubstituted or substituted with 1-3 fluoro atoms, or,

R_3 is a branched or linear C_{2-10} heteroalkyl group, containing 1-2 heteroatoms selected from N, O or S,

- R_4 is a hydrogen atom or a C_{1-4} alkyl group,
- R_5 is a hydrogen atom or a C_{1-2} alkyl group, unsubstituted or substituted with 1-3 fluoro atoms,
- R_6 is a hydrogen atom or a C_{1-2} alkyl group, unsubstituted or substituted with 1-3 fluoro atoms.

2. A compound as claimed in claim 1, or a tautomer, stereoisomer, N-oxide, isotopically-labelled analogue, or a pharmacologically acceptable salt of any of the foregoing, wherein:

- R_1 is chosen from a C_{3-10} linear alkyl group, a C_{4-10} branched alkyl group, a C_{5-8}-cycloalkyl-C_{1-5}-alkyl group, which groups are optionally substituted with 1-3 substituents, which can be the same or different, chosen from methyl, ethyl, cyano or fluoro, or

  R_1 is chosen from an aryl-C_{1-3}-alkyl group, wherein the aryl group is unsubstituted, or substituted with 1-3 substituents Y, which can be the same or different, selected from C_{1-3}-alkyl or alkoxy, halogen, trifluoromethyl, trifluoro-methoxy, nitro, cyanoand phenyl, or

R_1 is 2-cyano-ethyl,

- R_2 is chosen from phenyl, thienyl, benzothienyl, or pyridyl, groups that are unsubstituted, or substituted with 1 or 2 substituents, which can be the same or different, chosen from halogen, methyl, CF_3, OCH_3 or OCF_3,
- R_3 is chosen from a linear or branched $C_{3\text{-}10}$ alkyl group, a $C_{3\text{-}8}$ cycloalkyl group, $C_{5\text{-}10}$ bicycloalkyl group or $C_{6\text{-}10}$ tricycloalkyl group, which groups are unsubstituted, or substituted with 1-3 substituents, which can be the same or different, chosen from methyl, ethyl, hydroxy, amino, fluoro or aryl, or

  R_3 is a $C_{5\text{-}8}$ heterocycloalkyl group, unsubstituted or substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl, or fluoro, or

  R_3 is chosen from a $C_{3\text{-}8}$ cycloalkyl-$C_{1\text{-}3}$–alkyl group, $C_{5\text{-}10}$-bicycloalkyl-$C_{1\text{-}3}$–alkyl group, $C_{6\text{-}10}$-tricycloalkyl-$C_{1\text{-}3}$–alkyl group, which groups are unsubstituted or substituted with 1-5 substituents, which can be the same or different, chosen from methyl, ethyl or fluoro, or

  R_3 is an aryl group or a heteroaryl group, which groups are unsubstituted or substituted with 1-5 substituents Y, which can be the same or different, chosen from $C_{1\text{-}3}$-alkyl or alkoxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, cyano or phenyl,

  R_3 is an aryl-$C_{1\text{-}5}$–alkyl group, a heteroaryl-$C_{1\text{-}5}$–alkyl or a diaryl-$C_{1\text{-}5}$–alkyl group, wherein the aryl or heteroaryl groups are unsubstituted or substituted with 1-5 substituents, which can be the same or different, chosen from $C_{1\text{-}3}$-alkyl or alkoxy, halogen, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, cyano or phenyl,

  R_3 is a branched or linear $C_{2\text{-}10}$ heteroalkyl group, containing 1-2 heteroatoms selected from N, O or S,
- R_4, R_5 and R_6 have the meanings as given in claim 1.

3. A compound as claimed in claim 2, or a tautomer, stereoisomer, N-oxide, isotopically-labelled analogue, or a pharmacologically acceptable salt of any of the foregoing, wherein:

- R_1 is chosen from a $C_{3\text{-}8}$ linear alkyl group, a $C_{4\text{-}8}$ branched alkyl group, a $C_{5\text{-}6}$-cycloalkyl-$C_{1\text{-}5}$-alkyl group, which groups are optionally substituted with 1-3 substituents, chosen from cyano or fluoro, or

  R_1 is an aryl-$C_{1\text{-}3}$-alkyl group or

  R_1 is 2-cyano-ethyl,
- R_2 is chosen from phenyl, thienyl, benzothienyl, or pyridyl, groups that are unsubstituted, or substituted with halogen, methyl, CF_3, OCH_3 or OCF_3,
- R_3, R_4, R_5 and R_6 have the meanings as given in claim 2.

4. A compound as claimed in claim 3, or a tautomer, stereoisomer, N-oxide, isotopically-labelled analogue, or a pharmacologically acceptable salt of any of the foregoing, wherein:

- R_1 is chosen from 2-cyano-ethyl, n-propyl, n-butyl, 4,4,4-trifluorobutyl, isobutyl, n-pentyl, cyclohexylmethyl, or phenethyl,
- R_2 is chosen from 2-fluorophenyl, 3-(trifluoromethyl)phenyl, 3-chlorophenyl, 3-fluorophenyl, 3-methoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, benzothien-3-yl, pyrid-2-yl, thien-3-yl or phenyl,
- R_3 *is chosen from* 3-(*trifluoromethyl*)*benzyl*, 3-(*trifluoromethyl*)*benzyl*, 1-(4-fluorophenyl)-1-methyl-ethyl, 1-phenyl-1-methyl-ethyl, 1-phenyl-ethyl, 2-indanyl, 2-(4-fluorophenyl)-1,1-dimethyl-ethyl, 2-(trifluoromethyl)benzyl, 2,2-dimethylpropyl, 2,2-diphenylethyl, 2,2-diphenylpropyl, 2-methoxybenzyl, 2-phenyl-propyl, 2-phenyl-*trans*-cyclopropyl, 2-trifluoromethyl)phenyl, 3,4,5-trimethoxybenzyl, 3,4-dimethoxybenzyl, 3-fluorobenzyl, 3-methoxybenzyl, 4-chlorobenzyl, 4-methoxybenzyl, 5-methyl-thiazol-2-yl, adamant-1-yl, adamant-2-yl, adamantylmethyl, benzyl, cycloheptyl, cyclohexylmethyl, cyclooctyl, endo-bicyclo[2.2.1]hept-2-yl, exo-bicyclo[2.2.1]hept-2-yl, indan-2-yl, N,2,2,6,6-pentamethylpiperidin-4-yl, naphth-1-yl, naphthalen-1-yl-methyl, noradamant-1-yl, pyridin-3-ylmethyl, quinolin-3-yl, tert-butyl, (1-ethyl)propyl, (1R,2S,5R)-rel-6,6-dimethylbicyclo[3.1.1.]heptan-2-methyl, (3-dimethylamino)-2,2-dimethylpropyl, (furan-2-yl)methyl, (pyridin-3-yl)-methyl, 1-(4-fluorophenyl)-1-methyl-ethyl, 1-(adamant-1-yl)-ethyl, 1-phenyl-1-methyl-ethyl, 2-(4-fluorophenyl)ethyl, 2-(7-methyl-indol-3-yl)ethyl, 2-(indol-3-yl)ethyl, 2-(thien-2-yl)ethyl, 3-(trifluoromethyl)benzyl, 3,3-diphenylpropyl, 3,4-difluorobenzyl, 4-(trifluoromethyl)benzyl, endo-(1R,2S,4R)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl, naphthalen-1-yl-methyl, benzyl, cyclohexylmethyl, cyclopentyl, methyl-N-(Naphthalen-1-yl-methyl) or phenyl,
- R_4 is a hydrogen atom or a methyl group,
- R_5 is a hydrogen atom or a methyl group,
- R_6 is a hydrogen atom.

5. A compound as claimed in claim 1 of formula (I), or a tautomer, stereoisomer, N-oxide, isotopically-labelled analogue, or a pharmacologically acceptable salt of any of the foregoing, said compound being an optically active enantiomer.

6. A medicament, comprising a compound according to any one of the claims 1-5, or a pharmacologically acceptable salt thereof.

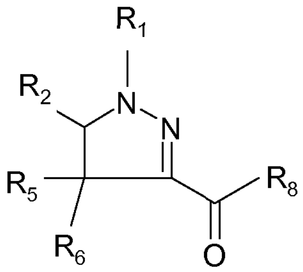
7. A pharmaceutical composition comprising, in addition to a pharmaceutically acceptable carrier and/or at least one pharmaceutically acceptable auxiliary substance, a pharmacologically active amount of at least one compound of one of the claims 1-5, or a pharmacologically acceptable salt thereof, as an active ingredient.

8. A pharmaceutical composition as claimed in claim 7, for the treatment of multiple sclerosis, traumatic brain injury, pain, appetite disorders, epilepsy, Alzheimer's disease, Tourette's syndrome, cerebral ischaemia or gastrointestinal disorders.

9. The pharmaceutical composition according to claim 7, further comprising: at least one additional therapeutic agent.

10. Use of a compound according to any of the claims 1 to 5 for the manufacture of a medicament for the treatment of a disorder or condition mediated by cannabinoid receptors, chosen from multiple sclerosis, traumatic brain injury, pain including chronic pain, neuropathic pain, acute pain and inflammatory pain, osteoporosis, appetite disorders, epilepsy, Alzheimer's disease, Tourette's syndrome, cerebral ischaemia and gastrointestinal disorders.

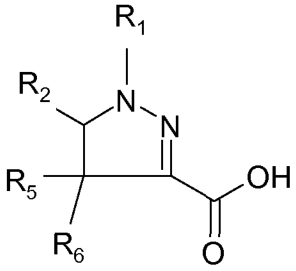
11. Compounds of the general formula (Va).



(Va)

wherein R_1, R_2, R_5 and R_6 have the same meanings as given in claim 1, and R_8 is a group O-R_7 wherein R_7 is a C_{1-3} alkyl group or R_8 is a chloro atom, with the proviso that when R_2 is phenyl, and R_1 is a benzyl group, R_7 is not an ethyl group, compounds that can be converted to compounds of formula (I) in one single step (I)

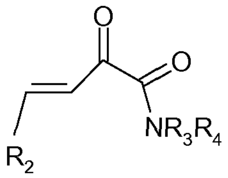
12. Compounds of the general formula (VI) or their sodium, potassium, lithium or cesium salts



(VI)

wherein R_1, R_2, R_5 and R_6 have the same meanings as given in claim 1, with the proviso that when R_2 is phenyl, R_1 is not a benzyl group, compounds that can be converted to compounds of formula (I) in one single step (I).

13. Compounds of the general formula (X)



(X)

wherein R_2 has the same meaning as given in claim 1, R_4 is a hydrogen atom and R_3 chosen from a C_{6-10} bicycloalkyl group or a C_{7-10} tricycloalkyl group, which groups may be substituted with 1-5 substituents selected from methyl, ethyl, hydroxyl, amino or fluor or R_4 chosen from a 2-phenyl-1,1-dimethyl-ethyl or 1-phenyl-1-methyl-ethyl group, wherein their phenyl groups may be substituted with 1-5 substituents Y, wherein Y has the meaning as given in claim 1, compounds that can be converted to compounds of formula (I) in one single step (I).