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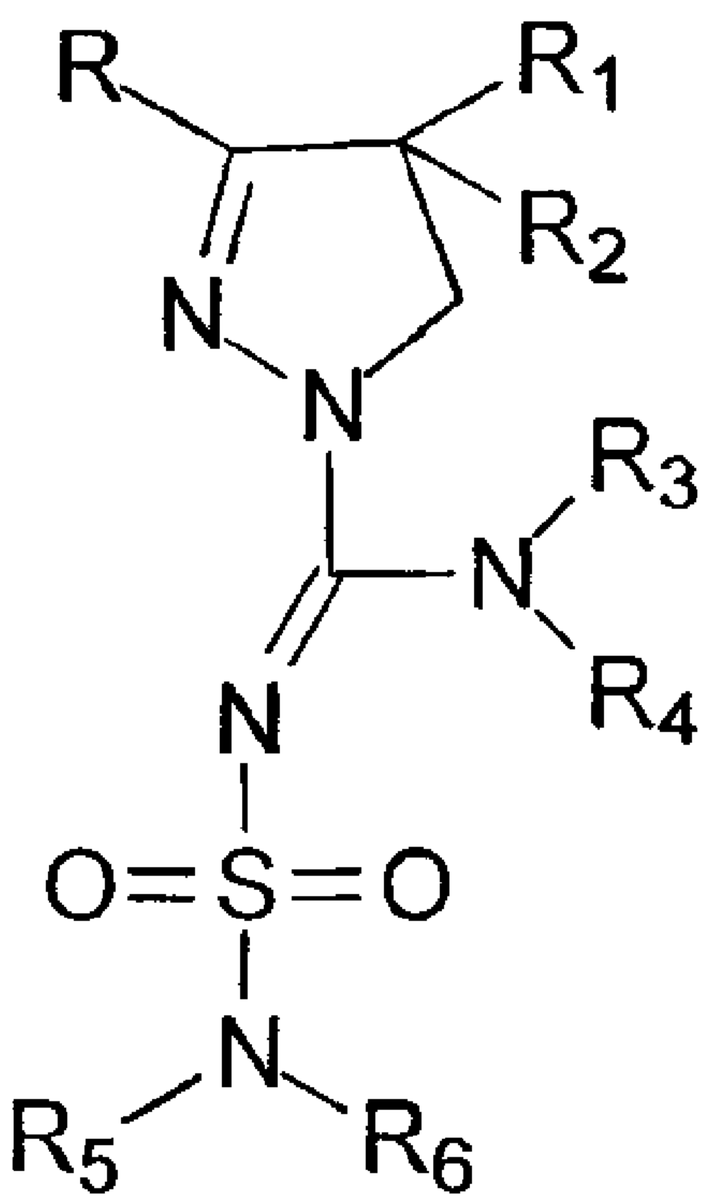
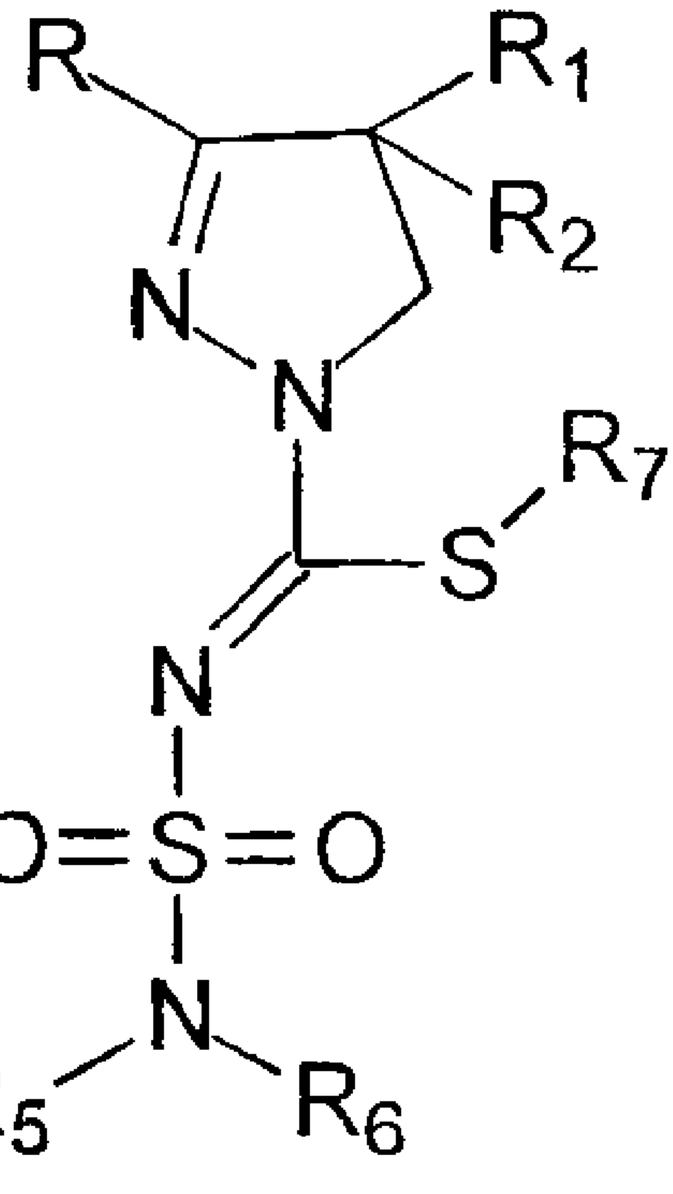
(54) Titre : DERIVES 4,5-DIHYDRO-1H-PYRAZOLE PRESENTANT UNE PUISSANTE ACTIVITE ANTAGONISTE DU RECEPTEUR CB_1

(54) Title: 4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING POTENT CB_1-ANTAGONISTIC ACTIVITY



(Ia)



(Ib)

(57) Abrégé/Abstract:
The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives which are potent cannabinoid (CB_1) receptor antagonists with utility for the treatment of diseases connected with disorders of the cannabinoid system. The compounds have the

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(57) Abrégé(suite)/Abstract(continued):
general formula (Ia) or (Ib) wherein the symbols have the meanings given in the specification. The invention also relates to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

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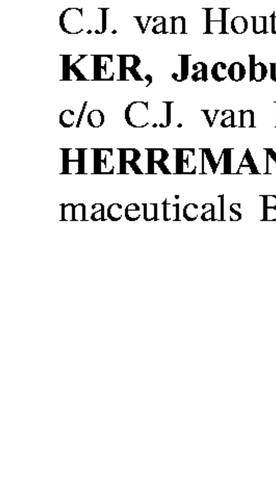
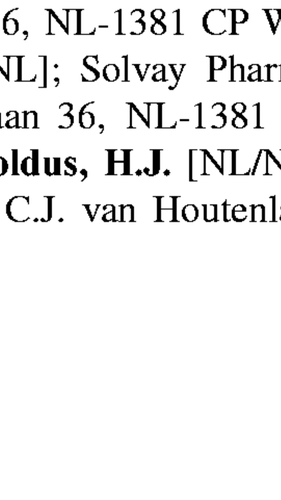
(54) Title: 4,5-DIHYDRO-1H-PYRAZOLE DERIVATIVES HAVING POTENT CB1-ANTAGONISTIC ACTIVITY



(Ia)



(Ib)

(57) Abstract: The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives which are potent cannabinoid (CB_1) receptor antagonists with utility for the treatment of diseases connected with disorders of the cannabinoid system. The compounds have the general formula (Ia) or (Ib) wherein the symbols have the meanings given in the specification. The invention also relates to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

4,5-Dihydro-1H-pyrazole derivatives having potent CB_1-antagonistic activity

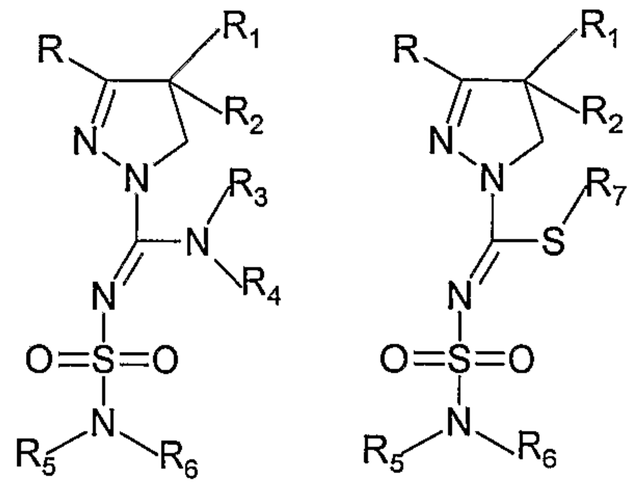
The present invention relates to a group of novel 4,5-dihydro-1H-pyrazole derivatives, to methods for the preparation of these compounds, and to pharmaceutical compositions containing one or more of these compounds as an active component.

The above mentioned 4,5-dihydro-1H-pyrazoles are potent cannabinoid (CB_1) receptor antagonists with utility for the treatment of disorders involving cannabinoid neurotransmission.

Cannabinoids are present in the Indian hemp *Cannabis sativa* and have been used as medicinal agents for centuries (Mechoulam, R. and Feigenbaum, J.J. *Prog. Med. Chem.* **1987**, *24*, 159). However, only within the past ten years the research in the cannabinoid area has revealed pivotal information on cannabinoid receptors and their (endogenous) agonists and antagonists. The discovery and the subsequent cloning of two different subtypes of cannabinoid receptors (CB_1 and CB_2) stimulated the search for novel cannabinoid receptor antagonists (Munro, S. *et al.*, *Nature* **1993**, *365*, 61. Matsuda, L.A. and Bonner, T.I. *Cannabinoid Receptors,* Pertwee, R.G. Ed. **1995**, 117, Academic Press, London). In addition, pharmaceutical companies became interested in the development of cannabinoid drugs for the treatment of diseases connected with disorders of the cannabinoid system (Consroe, P. *Neurobiology of Disease* **1998**, *5*, 534. Pop, E. *Curr. Opin. In CPNS Investigational Drugs* **1999**, *1*, 587. Greenberg, D.A. *Drug News Perspect.* **1999**, *12*, 458. Pertwee, R.G., *Progress in Neurobiology* **2001**, *63,* 569). Hitherto, several CB_1 receptor antagonists are known. Sanofi disclosed their diarylpyrazole congeners as selective CB_1 receptor antagonists. A representative example is SR-141716A (Dutta, A.K. *et al., Med. Chem. Res.* **1994**, *5*, 54. Lan, R. *et al., J. Med. Chem.* **1999**, *42*, 769. Nakamura-Palacios, E.M. *et al., CNS Drug Rev.* **1999**, *5*, 43). CP-272871 is a pyrazole derivative, like SR141716A, but less potent and less CB_1 receptor subtype-selective than SR141716A (Meschler, J.P. *et al., Biochem. Pharmacol.* **2000**, *60,* 1315). Aminoalkylindoles have been disclosed as CB_1 receptor antagonists. A representative example is Iodopravadoline (AM-630), which was introduced in 1995. AM-630 is a moderately active CB_1 receptor antagonist, but sometimes behaves as a weak partial agonist (Hosohata, K. *et al., Life Sc.* **1997**, *61*, PL115). Researchers from Eli Lilly described aryl-aroyl substituted benzofurans as selective CB_1 receptor antagonists (*e.g.* LY-320135) (Felder, C.C. *et al., J. Pharmacol. Exp. Ther.* **1998**, *284,* 291). 3-Alkyl-5,5'-diphenylimidazolidinediones were described as cannabinoid receptor ligands, which were indicated to be cannabinoid antagonists (Kanyonyo, M. *et al., Biorg. Med.Chem. Lett.* **1999**, *9,* 2233). Aventis Pharma claimed diarylmethyleneazetidine analogs as CB_1 receptor antagonists (Mignani, S. *et al.,* Patent FR 2783246, 2000; *Chem. Abstr.* **2000**, *132,* 236982). Tricyclic pyrazoles were claimed by Sanofi-Synthelabo as CB_1 antagonists (Barth, F. *et al.,* Patent WO 0132663, 2001; *Chem. Abstr.* **2001**, *134,* 340504). Interestingly, many CB_1 receptor

antagonists have been reported to behave as inverse agonists *in vitro* (Landsman, R.S. *et al., Eur. J. Pharmacol.* **1997**, *334*, R1). Reviews provide a nice overview of the cannabinoid research area (Mechoulam, R. *et al., Prog. Med. Chem.* **1998**, *35*, 199. Lambert, D.M. *Curr. Med. Chem.* **1999**, *6*, 635. Mechoulam, R. *et al., Eur. J. Pharmacol.* **1998**, *359*, 1. Williamson, E.M. and Evans, F.J. *Drugs* **2000**, *60*, 1303. Pertwee, R.G. *Addiction Biology* **2000**, *5*, 37. Robson, P. *Br. J. Psychiatry* **2001**, *178*, 107. Pertwee, R. G. *Prog. Neurobiol.* **2001**, *63*, 569. Goya, P and Jagerovic, N. *Exp. Opin. Ther. Patents* **2000**, *10*, 1529. Pertwee, R. G. *Gut* **2001**, *48*, 859).

It has now surprisingly been found that potent and selective antagonism of cannabinoid-CB_1 receptors is present in the novel 4,5-dihydro-1H-pyrazole derivatives of the formula (Ia) or (Ib), prodrugs thereof, tautomers thereof and salts thereof



(Ia) (Ib)

wherein

- R and R_1 independently represent phenyl, thienyl or pyridyl which groups may be substituted with 1, 2 or 3 substituents Y, which can be the same or different, from the group 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 and acetyl, or R and/or R_1 represent naphtyl,
- R_2 represents hydrogen, hydroxy, C_{1-3}-alkoxy, acetyloxy or propionyloxy,
- R_3 represents a hydrogen atom or a branched or unbranched C_{1-8} alkyl group or a C_{3-7} cycloalkyl group which alkyl group or cycloalkyl group may be substituted with a hydroxy group,
- R_4 represents a hydrogen atom or a branched or unbranched C_{1-8} alkyl, C_{3-8} cycloalkyl, C_{2-10} heteroalkyl, C_{3-8} nonaromatic heterocycloalkyl or C_{4-10} nonaromatic heterocycloalkyl-alkyl moiety which moieties may contain one or more heteroatoms from the group (O, N, S), which moieties may be substituted with a keto group, trifluoromethyl group, C_{1-3} alkyl group, hydroxy, amino, monoalkylamino, or dialkylamino group or a fluoro atom, or R_4 represents an amino, hydroxy, phenoxy or benzyloxy group or R_4 represents a branched or

unbranched C_{1-8} alkoxy, C_{3-8} alkenyl, C_{5-8} cycloalkenyl or C_{6-9} cycloalkenylalkyl group which groups may contain a sulphur, nitrogen or oxygen atom, a keto group or $-SO_2-$ group which C_{1-8} alkoxy, C_{3-8} alkenyl, C_{5-8} cycloalkenyl or C_{6-9} cycloalkenylalkyl groups may be substituted with a hydroxy group, a trifluoromethyl group, an amino group, a monoalkylamino group or dialkylamino group or a fluoro atom, or R_4 represents a phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl group wherein the aromatic rings may be substituted with 1, 2 or 3 of the substituents Y, wherein Y has the meaning as indicated above, or

R_4 represents a group NR_8R_9 with the proviso that R_3 represents a hydrogen atom or a methyl group and wherein R_8 and R_9 are the same or different and represent C_{1-4} alkyl or C_{2-4} trifluoroalkyl or R_8 and R_9 - together with the nitrogen atom to which they are bonded - form a saturated or un-saturated heterocyclic moiety having 4 to 8 ring atoms which heterocyclic moiety may contain an oxygen or sulphur atom or a keto group or $-SO_2-$ group or an additional nitrogen atom, which saturated or unsaturated heterocyclic moiety may be substituted with a C_{1-4} alkyl group or

R_3 and R_4 - together with the nitrogen atom to which they are bonded - form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety may contain one or more atoms from the group (O, N, S) or a keto group or $-SO_2-$ group, which moiety may be substituted with a C_{1-4} alkyl, hydroxyalkyl, phenyl, thienyl, pyridyl, amino, monoalkylaminoalkyl, dialkylaminoalkyl, monoalkylamino, dialkylamino, aminoalkyl, azetidinyl, pyrrolidinyl, piperidinyl or hexahydro-1H-azepinyl group,

– R_5 and R_6 independently of each other represent a hydrogen atom or a branched or unbranched C_{1-8} alkyl or alkenyl group which groups may contain one or more heteroatoms from the group (O, N, S), a keto group or a $-SO_2-$ group and which groups may be substituted with a hydroxy or amino group, or R_5 and R_6 independently of each other represent a C_{3-8} cycloalkyl group or C_{3-8} cycloalkenyl group which may contain one or more ring heteroatoms from the group (O, N, S) or the $-SO_2-$ group and which groups may be substituted with a hydroxy group, alkyl (C_{1-3}), the $-SO_2-$ group, the keto group, amino group, monoalkylamino group (C_{1-3}) or dialkylamino group (C_{1-3}), or

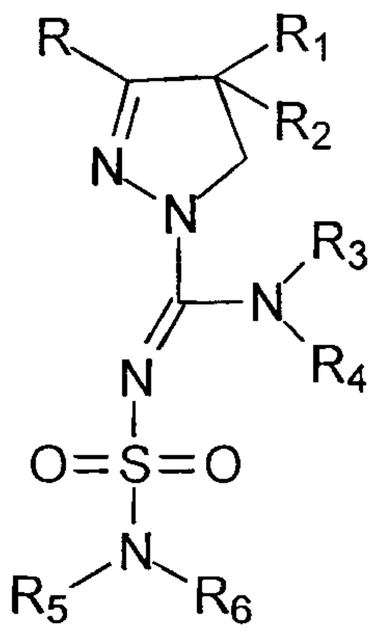
R_5 represents a naphtyl group or a phenyl group which phenyl group may be substituted with 1, 2 or 3 substituents Y wherein Y has the meaning as described hereinabove, with the proviso that R_6 represents a hydrogen atom, or a branched or unbranched alkyl group (C_{1-5}) which alkyl group may contain one or more heteroatoms from the group (O, N, S) or the $-SO_2-$ group and which alkyl group may be substituted with a hydroxy, keto or amino group, or

R_5 and R_6 - together with the nitrogen atom to which they are bonded - form a monocyclic, bicyclic or tricyclic alkyl or alkenyl group which may contain ring heteroatoms from the group (O, N, S), the keto or the SO_2 group and which

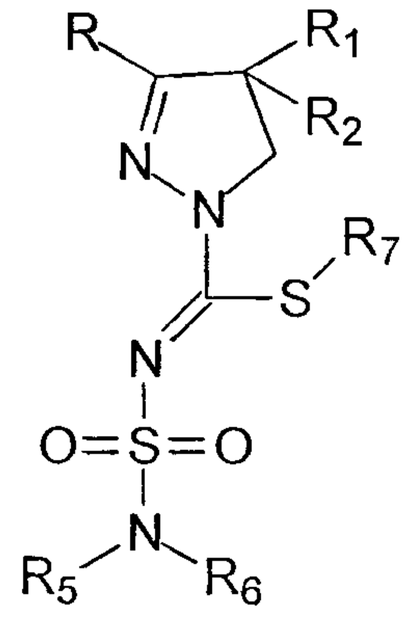
monocyclic, bicyclic or tricyclic alkyl or alkenyl group may be substituted with a hydroxy group, alkyl (C_{1-3}) group, SO_2 group, keto group, amino group, monoalkylamino group (C_{1-3}), dialkylamino group (C_{1-3}), pyrrolidinyl group or piperidinyl group, which monocyclic, bicyclic or tricyclic alkyl or alkenyl group may contain an annelated phenyl group which annelated phenyl group may be substituted with 1 or 2 substituents Y, wherein Y has the meaning as described herein above,

- R_7 represents branched or unbranched C_{1-3} alkyl.

In one compound aspect, the invention provides a compound of the general formula (1a) or (1b):



(Ia)



(Ib)

wherein:

R and R_1 independently represent: (i) phenyl, thienyl or pyridyl, each optionally substituted with 1, 2 or 3 substituents Y, which independently represent (C_{1-3})-alkyl, (C_{1-3})-alkoxy, hydroxy, a halogen atom, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, (C_{1-2})mono- or dialkylamino, (C_{1-2})-mono- or dialkylamido, (C_{1-3})-alkylsulfonyl, dimethylsulfamido, (C_{1-3})-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl or acetyl, or (ii) naphthyl;

R_2 represents, H, hydroxy, (C_{1-3})-alkoxy, acetyloxy or propionyloxy;

R_3 represents: (i) H, or (ii) a branched or unbranched (C_{1-8})-alkyl or (C_{3-7})-cycloalkyl, each optionally substituted with hydroxy;

R_4 represents: (i) H, amino, hydroxy, phenoxy or benzyloxy, (ii) a branched or unbranched (C_{1-8})-alkyl, (C_{3-8})-cycloalkyl, (C_{2-10})-heteroalkyl, (C_{3-8})-nonaromatic heterocycloalkyl or (C_{4-10})-nonaromatic heterocycloalkyl-alkyl, each optionally containing one or more heteroatoms which are O, N or S, and each optionally substituted with a keto group, trifluoromethyl, (C_{1-3})-alkyl, hydroxy, amino, (C_{1-3})-monoalkylamino, (C_{1-3})-dialkylamino, F, amino, hydroxy, phenoxy or benzyloxy, (iii) a branched or unbranched (C_{1-8})-alkoxy, (C_{3-8})-alkenyl, (C_{5-8})-cycloalkenyl or (C_{6-9})-cycloalkenylalkyl, each optionally containing S, N, O, a keto group or $-SO_2-$, and each optionally substituted with hydroxy, trifluoromethyl, amino, (C_{1-3})-monoalkylamino, (C_{1-3})-dialkylamino or F, (iv) phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl, wherein each aromatic ring is optionally substituted with 1, 2 or 3 of the substituents Y as defined above, or (v) NR_8R_9, with the proviso that R_3 represents H or methyl, wherein R_8 and R_9 independently represent (C_{1-4})-alkyl or (C_{2-4})-trifluoroalkyl, or R_8 and R_9, together with the nitrogen atom to which they are bonded, form a saturated or un-saturated heterocyclic moiety having 4 to 8 ring atoms, which heterocyclic moiety optionally contains: (α) O, S, a keto group or $-SO_2-$, or (β) an additional N, and which heterocyclic moiety is optionally substituted with (C_{1-4})-alkyl; or

R_3 and R_4, together with the nitrogen atom to which they are bonded, form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety optionally contains one or more O, N, S, a keto group or $-SO_2-$, and which heterocyclic moiety is optionally substituted with (C_{1-4})-alkyl, hydroxy-(C_{1-3})-alkyl, phenyl, thienyl, pyridyl, amino, (C_{1-3})-monoalkylamino-(C_{1-3})-alkyl, (C_{1-3})-dialkylamino-(C_{1-3})-alkyl, (C_{1-3})-monoalkylamino, (C_{1-3})-dialkylamino, amino-(C_{1-3})-alkyl, azetidinyl, pyrrolidinyl, piperidinyl or hexahydro-1H-azepinyl;

R_5 and R_6 independently represent: (i) H, (ii) a branched or unbranched (C_{1-8})-alkyl or (C_{2-8})-alkenyl, each optionally containing one or more O, N, S, a keto group or $-SO_2-$, and each optionally substituted with hydroxy or amino, or (iii) (C_{3-8})-cycloalkyl or (C_{3-8})-cycloalkenyl, each optionally containing one or more ring

O, N, S or -SO_2-, and each optionally substituted with hydroxy, (C_{1-3})-alkyl, -SO_2-, a keto group, amino, (C_{1-3})-monoalkylamino or (C_{1-3})-dialkylamino; or

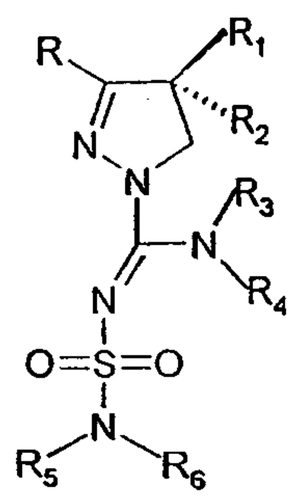
R_5 represents: (i) a naphthyl, or (ii) phenyl, which is optionally substituted with 1, 2 or 3 substituents Y as defined above, with the proviso that R_6 represents H, or a branched or unbranched (C_{1-5})-alkyl, which optionally contains one or more O, N, S or -SO_2-, and which is optionally substituted with hydroxy, a keto group or amino; or

R_5 and R_6, together with the nitrogen atom to which they are bonded, form a monocyclic, bicyclic or tricyclic alkyl or alkenyl having 4 to 14 ring atoms, each optionally containing a ring O, N, S, a keto group or SO_2, each optionally substituted with hydroxy, (C_{1-3})-alkyl, SO_2, a keto group, amino, (C_{1-3})-monoalkylamino, (C_{1-3})-dialkylamino, pyrrolidinyl or piperidinyl, and each optionally containing an annelated phenyl group, which is optionally substituted with 1 or 2 substituents Y, as defined above; and

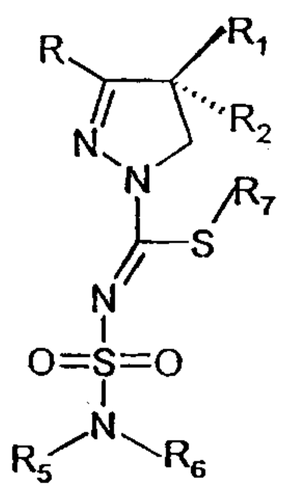
R_7 represents branched or unbranched (C_{1-3})-alkyl;

or a tautomer, stereoisomer or salt thereof.

At least one centre of chirality is present (at the C_4 position of the 4,5-dihydro-1H-pyrazole moiety) in the compounds of the formula (Ia) and (Ib). The invention relates both to racemates, mixtures of diastereomers and the individual stereoisomers of the compounds having formula (Ia) or (Ib). Particular compounds of interest of formula (Ia) or (Ib) have the absolute stereoconfiguration at the C_4 position of the 4,5-dihydro-1H-pyrazole moiety as represented by the formulas (1a*) and (1b*):



(1a*)



(1b*)

The invention also relates both to the E isomer, Z isomer and E/Z mixtures of compounds having formula (Ia) or (Ib).

The compounds of the invention can be brought into forms suitable for administration by means of usual processes using auxiliary substances and/or liquid or solid carrier materials.

In a composition aspect, the invention provides a pharmaceutical composition, comprising: at least one pharmaceutically acceptable carrier, at least one pharmaceutically acceptable auxiliary substance or a combination of two or more thereof; and at least one compound as defined above, or a pharmacologically acceptable salt thereof, as the active ingredient.

Due to the potent CB_1 antagonistic activity the compounds according to the invention are suitable for use in the treatment of psychiatric disorders such as psychosis, anxiety, depression, attention deficits, memory disorders, cognitive disorders, appetite disorders, obesity, addiction, appetence, drug dependence and neurological disorders such as neurodegenerative disorders, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, stroke, Parkinson's disease, Alzheimer's disease, epilepsy, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, neuroinflammatory disorders, plaque sclerosis, viral encephalitis, demyelinisation related disorders, as well as for the treatment of pain disorders,

including neuropathic pain disorders, and other diseases involving cannabinoid neurotransmission, including the treatment of septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, respiratory diseases, gastrointestinal disorders, gastric ulcers, diarrhoea and cardiovascular disorders.

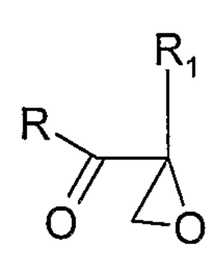
The affinity of the compounds of the invention for cannabinoid CB_1 receptors was determined using membrane preparations of Chinese hamster ovary (CHO) cells in which the human cannabinoid CB_1 receptor is stably transfected in conjunction with [^{3}H]CP-55,940 as radioligand. After incubation of a freshly prepared cell membrane preparation with the [^{3}H]-ligand, with or without addition of compounds of the invention, separation of bound and free ligand was performed by filtration over glassfiber filters. Radioactivity on the filter was measured by liquid scintillation counting.

The cannabinoid CB_1 antagonistic activity of compounds of the invention was determined by functional studies using CHO cells in which human cannabinoid CB_1 receptors are stably expressed. Adenylyl cyclase was stimulated using forskolin and measured by quantifying the amount of accumulated cyclic AMP. Concomitant activation of CB_1 receptors by CB_1 receptor agonists (*e.g.* CP-55,940 or (R)-WIN-55,212-2) can attenuate the forskolin-induced accumulation of cAMP in a concentration-dependent manner. This CB_1 receptor-mediated response can be antagonised by CB_1 receptor antagonists such as the compounds of the invention.

Intermediates having formula (II) (see below) can be obtained according to methods known, for example: a) Francotte, E.; Tong, Z. *Chem. Abstr.* **126**, 213598; b) Rempfler, H. and Kunz, W. *Chem. Abstr.* **113**, 40432; c) Rempfler, H. and Kunz, W. *Chem. Abstr.* **107**, 217473.

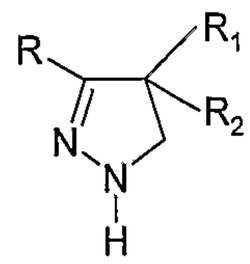
Intermediates having formula (III) wherein R_2 represents hydrogen (see below) can be obtained according to methods known, for example: a) EP 0021506; b) DE 2529689, c) Grosscurt, A.C. et al., *J. Agric. Food Chem*. **1979**, 27, (2), 406.

Intermediates having formula (III) wherein R_2 represents a hydroxy group can be obtained by reacting a compound having formula (II) with hydrazine or hydrazine hydrate



(II)

This reaction, preferably carried out in an organic solvent such as ethanol, yields a compound having formula (III) wherein R_2 represents a hydroxy group.

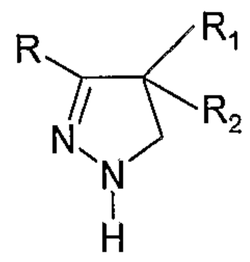


(III)

Suitable synthetic routes for the compounds of the invention are the following:

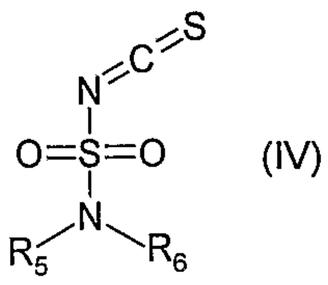
Synthetic route A

Step 1: reaction of a compound having formula (III)



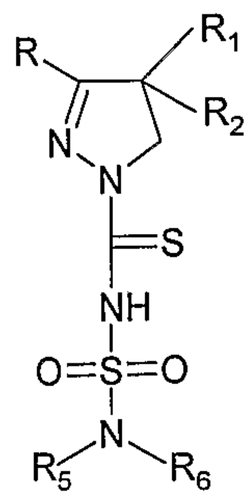
(III)

with a compound having formula (IV).



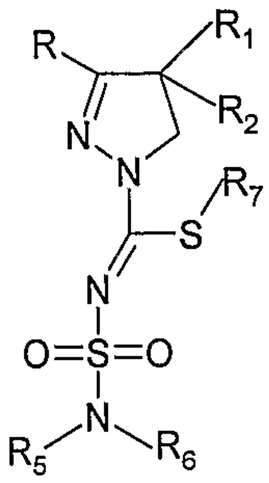
(IV)

This reaction is preferably carried out in an organic solvent, such as for example dichloromethane, and yields a compound having formula (V) wherein R, R_1, R_2, R_5 and R_6 have the meaning as described above for compound (Ia), and which are new.



(V)

Step 2: reaction of a compound having formula (V) with a compound R_7-X, wherein X represents a leaving group, for example an iodide group, and R_7 has the meaning as described above for (Ib) gives a compound having formula (Ib).



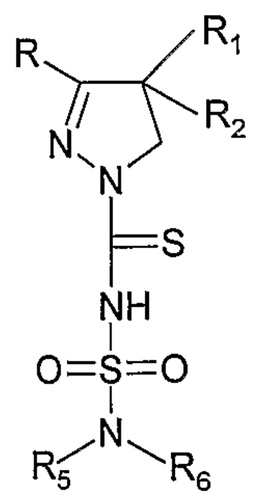
(Ib)

This reaction is preferably carried out in the presence of a base, for example triethylamine.

Step 3: reaction of a compound having formula (Ib) with an amine having formula HNR_3R_4 wherein R_3 and R_4 have the meanings as described above, analogous to the method described in *Synth. Commun.* **1996**, 26, (23), 4299.
This reaction gives a compound having formula (Ia).

Synthetic route A1

Step 1: Reaction of a compound having formula (V)



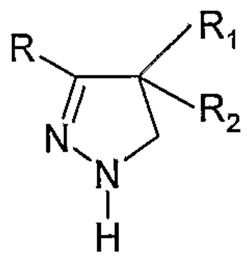
(V)

with an amine having formula HNR_3R_4 wherein R_3 and R_4 have the meanings as described above in the presence of a mercury(II) salt, for example $HgCl_2$, gives a compound having formula (Ia).

This reaction is preferably carried out in an organic solvent, such as for example acetonitrile, analogous to the method described in *Synth. Commun.* **1996**, *26*, (23), 4299.

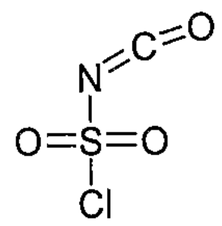
Synthetic route A2

Step 1: reaction of a compound having formula (III)



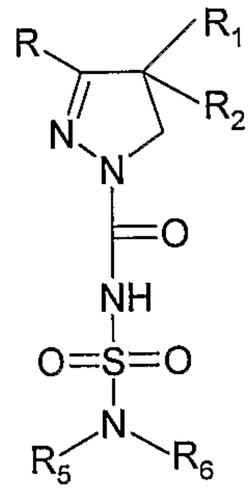
(III)

with a isocyanate derivative having formula (VI), followed by treatment with an amine HNR_5R_6



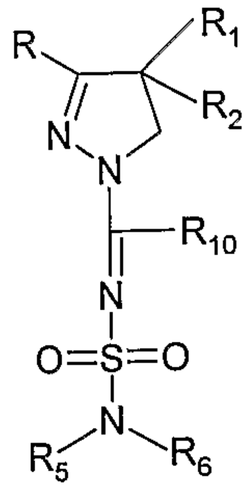
(VI)

This reaction is preferably carried out in an organic solvent like dichloromethane, and yields a compound having formula (VII). Compounds having formula (VII) wherein R, R_1, R_2, R_5 and R_6 have the meaning as described herein above for compound (Ia) are new.



(VII)

Step 2: reaction of a compound having formula (VII) with a halogenating agent, such as for example PCl_5, gives a compound having formula (VIII)



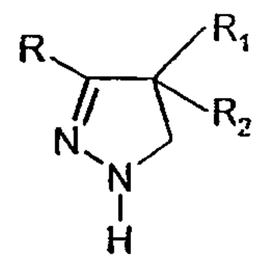
(VIII)

wherein R_{10} represents a halogen atom, for example a chloro atom. This reaction is preferably carried out in an organic solvent such as chlorobenzene.
Compounds having formula (VIII) wherein R, R_1, R_2, R_5 and R_6 have the meanings as described above for compound (Ia) and wherein R_{10} represents a halogen atom, are new.

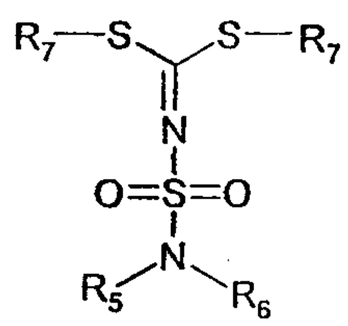
Step 3: reaction, preferably carried out in an inert organic solvent such as dichloromethane, of a compound having formula (VIII) with an amine having formula HNR_3R_4 wherein R_3 and R_4 have the meanings as described above gives a compound having formula (Ia).

Synthetic route A3

Step 1: reaction of a compound having formula (III)


(III)

with a compound having formula (IX)


(IX)

gives a compound having formula (Ib), (see e.g. *Chem. Ber.* **1966**, *99*, 2885 and *Chem. Ztg.* **1984**, *108*, (12), 404).

In a use aspect, the invention provides use of a compound, salt or composition of the invention for the preparation of a medicament for the treatment of a disorder involving cannabinoid neurotransmission.

In a further use aspect, the invention provides use of a compound, salt or composition of the invention for the treatment of a disorder involving cannabinoid neurotransmission.

In a commercial package aspect, the invention provides a commercial package comprising a compound, salt or composition of the invention and associated therewith instructions for the use thereof in the treatment of a disorder involving cannabinoid neurotransmission.

The preparation of the compounds is illustrated in the following examples.

Example 1

3-(4-Chlorophenyl)-N'-(((ethyl)propylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine

Part A: To a stirred solution of ((ethyl)propylamino)sulfonyl isothiocyanate (5.98 gram, 25.4 mmol) in dry dichloromethane in a nitrogen atmosphere is added of 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (6.52 gram, 25.4 mmol). After stirring for 90 minutes the resulting solution is concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2, silicagel, R_f ~0.45). The resulting solid is recrystallized from diethyl ether to give 3-(4-chlorophenyl)-N-

(((ethyl)propylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyra-zole-1-thiocarboxamide (6.57 gram, 56 % yield). Melting point: 144-146 °C.

Part B: To a stirred suspension of 3-(4-chlorophenyl)-N-(((ethyl)propyl-amino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (2.32 gram, 5 mmol) in acetonitrile (20 mL) is added cold methylamine (4 mL). To the resulting solution is added a solution of $HgCl_2$ (1.5 gram) in acetonitrile (10 mL). The resulting black suspension is stirred for four hours. The precipitate is removed by filtration. The filtrate is concentrated *in vacuo*, dissolved in dichloromethane and successively washed with aqueous 0.5 N NaOH solution and water, dried over Na_2SO_4, filtered and concentrated *in vacuo.* The resulting oil is crystallized from diethyl ether to give 3-(4-chlorophenyl)-N'-(((ethyl)propylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (1.78 gram, 77 % yield). Melting point (MP):129-131 °C.

In an analogous manner the compounds having formula (Ia) listed below have been prepared:

2. 3-(4-Chlorophenyl)-N'-(((ethyl)methylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 112-115 °C.
3. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(2-hydroxyethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 104-106 °C.
4. 3-(4-Chlorophenyl)-N-(2-hydroxyethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 490 (MH^+).
5. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(2-(morpholin-4-yl)ethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 547 (MH^+))
6. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(2-(morpholin-4-yl)ethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
7. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(2-(dimethylamino)ethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine.MS (ESI+): 505 (MH^+)).
8. 3-(4-Chlorophenyl)-N-(3-(dimethylamino)propyl)-N'-((dimethylamino)sulfo-nyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
9. 3-(4-Chlorophenyl)-N-(2-(piperidin-1-yl)ethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 557 (MH^+)).
10. 3-(4-Chlorophenyl)-N-(2-(morfolin-4-yl)ethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MS (ESI+): 559 (MH^+)); MP: 174-176 °C.
11. 3-(4-Chlorophenyl)-N-(2-(dimethylamino)ethyl)-N'-((dimethylamino)sulfo-nyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
12. 3-(4-Chlorophenyl)-N-(2-(diethylamino)ethyl)-N'-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
13. 3-(4-Chlorophenyl)-N-(3-(dimethylamino)propyl)-N'-((diethylamino)sulfo-nyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine.MS(ESI+):519 (MH^+).

14. 3-(4-Chlorophenyl)-N-(2-(diethylamino)ethyl)-N'-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine hemifumarate. MP: 182-185 °C.
15. 3-(4-Chlorophenyl)-N-(2-(dimethylamino)ethyl)-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
16. 3-(4-Chlorophenyl)-N-(2-(diethylamino)ethyl)-N'-((pyrrolidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
17. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-(1-methylpiperidin-4-yl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
18. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(2-hydroxyethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 123-126 °C.
19. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous. R_f ~ 0.4 (diethyl ether).
20. 3-(4-Chlorophenyl)-N'-(((ethyl)propylamino)sulfonyl)-N-Methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 129-131 °C.
21. 3-(4-Chlorophenyl)-N-methyl-N'-((pyrrolidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous. R_f ~ 0.3 (MTBE).
22. 3-(4-Chlorophenyl)-N-methyl-N'-(((methyl)propylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 132-134 °C.
23. 3-(4-Chlorophenyl)-N,N-dimethyl-N'-((pyrrolidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous. R_f ~ 0.25 (MTBE).
24. 3-(4-Chlorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 175-177 °C.
25. 3-(4-Chlorophenyl)-N'-((hexahydro-1H-azepin-1-yl)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
26. 3-(4-Chlorophenyl)-N'-((dipropylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 141-142 °C.
27. 3-(4-Chlorophenyl)-N'-(((isopropyl)methylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 134-136 °C.
28. 3-(4-Chlorophenyl)-N-methyl-N'-((octahydroazocin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 165-168 °C.
29. 3-(4-Chlorophenyl)-N-ethyl-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
30. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 166-168 °C.

Example 31

3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-propyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine

Part A: To a stirred solution of chlorosulfonyl isocyanate (1.73 mL, 20 mmol) in dry dichloromethane (20 mL) is very slowly added a solution of 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (5.13 gram, 20 mmol) in dry dichloromethane (125 mL) at – 5 °C. After stirring for 30 minutes the reaction mixture is allowed to attain

room temperature and stirred for another 2 hours. After cooling to 0 °C liquid dimethylamine (5 mL) is added and the resulting solution is stirred for another hour at 0 °C and for 2 hours at room temperature. The solution is washed with water, filtered over hyflo and concentrated *in vacuo*. Flash chromatography (MTBE, R_f ~ 0.3) gives 3-(4-chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (4.75 g, 58 %). MP: 210-212 °C.

Part B: A mixture of 3-(4-chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (1.47 gram, 3.62 mmol) and phosphorus pentachloride (0.80 gram, 3.84 mmol) in chlorobenzene (20 mL) is heated at reflux temperature for 1 hour. After thorough concentration *in vacuo*, the formed 3-(4-chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidoyl chloride is suspended in dry dichloromethane and reacted with cold *n*-propylamine (1.0 mL) at 0 °C. After stirring for 1 hour, the mixture is dissolved in ethyl acetate and washed with water and concentrated *in vacuo*. The residue is purified by column chromatography (dichloromethane/acetone = 19/1 (v/v), R_f ~ 0.35) to give an oil (0.82 g). Crystallisation from diethyl ether, followed by recrystallisation from ethanol gives 3-(4-chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-propyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (0.38 gram, 23 % yield). MP: 127-129°C.

In an analogous manner the compounds having formula (Ia) listed below have been prepared:

32. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(2-fluoroethyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 128-131 °C.
33. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-4-phenyl-N-(2,2,2-trifluoroethyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 158-159 °C.
34. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methoxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 170-172 °C.

Example 35

3-(4-Chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester

Part A: To a stirred solution of (piperidin-1-yl)sulfonyl isothiocyanate (54.77 g, 266 mmol) in dry dichloromethane (900 mL) in a nitrogen atmosphere is added 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (68.3 gram, 266 mmol). After stirring for 16 hours an additional amount of dichloromethane is added. The resulting solution is twice washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. After addition of MTBE, the residue crystallizes. The crystalline material is collected and washed with MTBE to give 3-(4-chlorophenyl)-4-phenyl-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (77.6 gram, 63 % yield).

Part B: To a stirred solution of 3-(4-chlorophenyl)-4-phenyl-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-thiocarboxamide (30 gram, 64.9 mmol) in acetone (1 L) is added triethylamine (18.0 mL, 130 mmol). To the resulting yellow solution is added methyl iodide (9.12 g, 64 mmol) and the resulting solution is stirred

for 16 hours at room temperature. The formed precipitate is removed by filtration. The filtrate is washed with water, concentrated *in vacuo* to give a yellow solid. Recrystallisation from MTBE gives 3-(4-chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester (27.9 gram, 90% yield). MP: 192-194 °C.

In an analogous manner the compounds having formula (Ib) listed below have been prepared:

36. 3-(4-Chlorophenyl)-N-((dimethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 159-160 °C.
37. 3-(4-Chlorophenyl)-N-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 141-143 °C.
38. 3-(4-Chlorophenyl)-4-phenyl-N-((1,2,3,4-tetrahydroisoquinolin-2-yl)sulfonyl) -4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 143-145 °C.
39. 3-(4-Chlorophenyl)-N-(((ethyl)phenylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 143-146 °C.
40. 3-(4-Chlorophenyl)-N-((diethylamino)sulfonyl)-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
41. 3-(4-Chlorophenyl)-N-((diethylamino)sulfonyl)-4-(pyridin-4-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
42. 3-(4-Chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-(3-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
43. 3-(4-Chlorophenyl)-N-((dimethylamino)sulfonyl)-4-(3-(trifluoromethyl) phenyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
44. 3-(4-Chlorophenyl)-N-(((ethyl)methylamino)sulfonyl)-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester.MP:133-136 °C.
45. 3-(4-Chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 182-185 °C.
46. 3-(4-Chlorophenyl)-N-((morpholin-4-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 202-204 °C.
47. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP:205-207°C.
48. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP:196-198°C.
49. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-((dimethylamino)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP:181-183°C.
50. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP:231-233°C.
51. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP:221-225°C.

52. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-((dimethylamino)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP:181-185°C.

53. 3-(4-Chlorophenyl)-N-((1,1-dioxidothiomorpholin-4-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 216-217 °C.

54. 3-(5-Chlorothien-2-yl)-N-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.

Example 55

3-(4-Chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine

To a cooled mixture (< 0 °C) of 3-(4-chlorophenyl)-N-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester (10.0 gram, 21 mmol) in methanol (75 mL) is added cold methylamine (15 mL). The resulting mixture is allowed to attain room temperature and stirred for 3 hours at 50 °C. After cooling to room temperature the mixture is concentrated *in vacuo*, dissolved in dichloromethane, washed twice with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Subsequent flash chromatography (EtOAc/MeOH/NH_4OH (25 % aq.) = 95/5/0.5 (v/v)), followed by recrystallisation from diisopropyl ether gives 3-(4-chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine (7.87 gram, 81 % yield) as a white solid. MP: 175-177 °C.

In an analogous manner the compounds having formula (Ia) listed below - including those in table 1 - have been prepared:

56. 3-(4-Chlorophenyl)-N-cyclopropyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 142-144 °C.
57. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 180-182 °C.
58. 3-(5-Chlorothien-2-yl)-N'-((diethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 122-123 °C.
59. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 169-170 °C.
60. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-(1-methylpiperidin-4-yl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 144-146 °C.
61. 3-(4-Chlorophenyl)-N-cyclopropyl-N'-((diethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 150-151 °C.
62. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-ethyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 116-119 °C.
63. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N,N-dimethyl-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 135-137 °C.
64. N'-((Diethylamino)sulfonyl)-N,N-dimethyl-3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 159-160 °C.
65. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-isopropyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 81-85 °C.
66. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-ethyl,N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
67. 3-(4-Chlorophenyl)-N-ethyl,N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 178 °C.
68. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-ethyl-4-hydroxy-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 162-165 °C.
69. 3-(4-Chlorophenyl)-N-methyl-N'-((1,2,3,4-tetrahydroisoquinolin-2-yl)sulfo-nyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. Amorphous.
70. 3-(4-Chlorophenyl)-N'-(((ethyl)phenylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 145-147 °C.

71. N'-((Diethylamino)sulfonyl)-3-(4-chlorophenyl)-N-methyl-4-(pyridin-4-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 109-111 °C.
72. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 157-159 °C.
73. 3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 85-89 °C.
74. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-(pyridin-4-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 178-182 °C.
75. 3-(4-Chlorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-(3-(trifluoro-methyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 168-170 °C.
76. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-(3-(trifluoro-methyl)phenyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 65-68 °C.
77. 3-(4-Chlorophenyl)-N'-(((ethyl)methylamino)sulfonyl)-N-methyl-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 125-128 °C.
78. 3-(4-Chlorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4-(pyridin-3-yl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 174-177 °C.
79. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-methyl-N'-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 223-235 °C.
80. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 214-216 °C.
81. 3-(4-Chlorophenyl)-4-(2,6-difluorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 260-263 °C.
82. 3-(4-Chlorophenyl)-4-(3-fluorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 170 °C.
83. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-methyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 223-225 °C.
84. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-4-(2-fluorophenyl)-N-methyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 173-175 °C.
85. 3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-4-(3-fluorophenyl)-N-methyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 110 °C.
86. 3-(4-Chlorophenyl)-4-(2-fluorophenyl)-N-methyl-N'-((morpholin-4-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 165-168 °C.
87. 3-(4-Chlorophenyl)-N'-((1,1-dioxidothiomorpholin-4-yl)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 268-271 °C.
88. 3-(4-Chlorophenyl)-N'-((4-hydroxypiperidin-1-yl)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. MP: 80 °C.

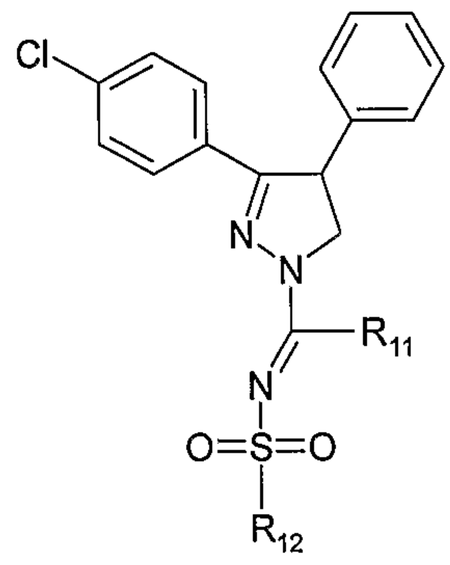


Table 1

Example:	R_{11}	R_{12}	MP (°C)	Salt form
89:	4-Methyl-1,4-diazepan-1-yl	Dimethylamino	197-200	0.5 Fumarate
90:	1,4-Diazepan-1-yl	Piperidin-1-yl	Amorphous	
91:	1,4-Diazepan-1-yl	Dimethylamino	Amorphous	
92:	4-Methyl-1,4-diazepan-1-yl	Piperidin-1-yl	159-164	

93:	4-Methylpiperazin-1-yl	Dimethylamino	191-193	

Example 94

3-(4-Chlorophenyl)-N-((4-methylpiperazin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester

Part A: A stirred mixture of 3-(4-chlorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole (3.21 gram, 11.3 mmol), [(4-methylpiperazin-1-yl)sulfonyl]dithioimido- carbonic acid dimethyl ester (3.08 gram, 12.0 mmol) and pyridine (25 mL) is heated at 100 °C for 24 hours in a nitrogen atmosphere. After cooling to room temperature the mixture is concentrated *in vacuo*, water is added and the resulting mixture is extracted with dichloromethane. The dichloromethane extract is washed twice with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Subsequent flash chromatographic purification gives 3-(4-chlorophenyl)-N-((4-methylpiperazin-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester (4.24 gram, 76 % yield) as an amorphous solid. (R_f ~ 0.1, EtOAc/methanol = 95/5 (v/v)).

In an analogous manner the compounds having formula (Ib) listed below have been prepared:

95. 3-(4-Chlorophenyl)-N-(((2-(dimethylamino)ethyl)ethylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester.
MP: 158 °C.
96. N-((Diethylamino)sulfonyl)-3-(4-fluorophenyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
R_f ~ 0.4 (MTBE).
97. 3-(4-Chlorophenyl)-N-(([1,4']bipiperidin-1'-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. MP: 245 °C.
98. 3-(4-Chlorophenyl)-N-(((1-methylpiperidin-4-yl)methylamino)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Oil. R_f ~ 0.15 (methanol/dichloromethane = 5/95 (v/v)).
99. 3-(4-Chlorophenyl)-N-((4-methyl-1,4-diazepan-1-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboximidothioic acid methyl ester. Amorphous.
R_f ~ 0.10 (methanol/dichloromethane = 5/95 (v/v)).

Example 100

(-)-(4S)-3-(4-Chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine

(-)-(4S)-3-(4-Chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-dihydro-1H-pyrazole-1-carboxamidine (3.8 gram, 8.3 mol)) ($[\alpha^{25}_D]$ = -139 °, c = 0.006, MeOH) was obtained as an amorphous solid via chiral chromatographic separation of racemic 3-(4-chlorophenyl)-N-methyl-4-phenyl-N'-((piperidin-1-yl)sulfonyl)-4,5-

dihydro-1H-pyrazole-1-carboxamidine (7.87 gram, 17.1 mmol) using a chiral stationary phase Chiralpak AD. The mobile phase consisted of methanol/diethylamine = 999/1 (v/v).

In an analogous manner the optically pure compounds listed below have been prepared from the corresponding racemates:

101. (-)-(4S)-3-(4-Chlorophenyl)-N'-((diethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (Chiral stationary phase: Chiralcel OD). Mobile phase consisted of hexane/2-propanol = 80/20 (v/v). ($[\alpha^{25}_D]$ = -147 °, c = 0.01, MeOH). Amorphous.

102. (-)-(4S)-3-(4-Chlorophenyl)-N'-((dimethylamino)sulfonyl)-N-methyl-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine (Chiral stationary phase: Chiralpak AD). The mobile phase consisted of methanol/diethylamine = 999/1 (v/v). ($[\alpha^{25}_D]$ = -171 °, c = 0.005, MeOH). Amorphous.

103. (-)-(4S)-3-(4-Chlorophenyl)-N-methyl-N'-((morpholin-4-yl)sulfonyl)-4-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamidine. ($[\alpha^{25}_D]$ = -144 °, c = 0.01, MeOH). (Chiral stationary phase: Chiralpak AD). The mobile phase consisted of ethanol. Amorphous.

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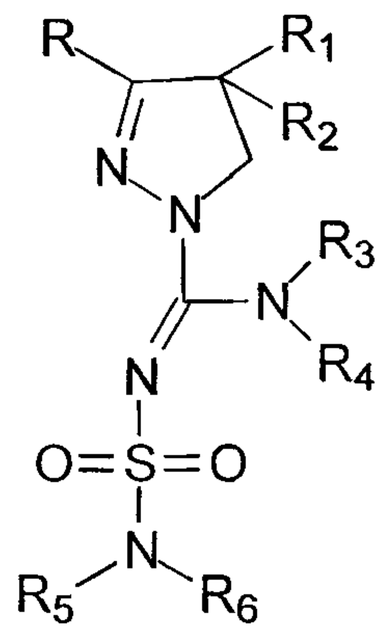
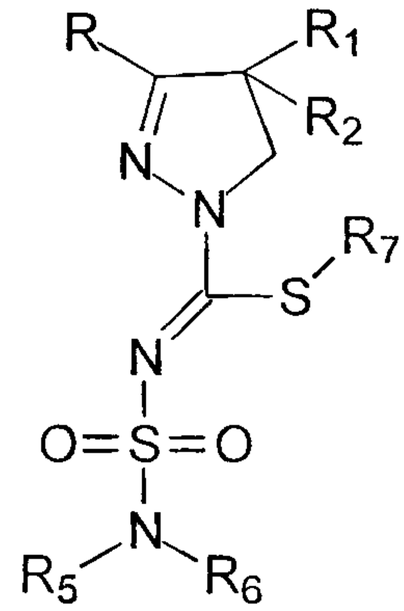
CLAIMS:

1. A compound of the general formula (1a) or (1b):



(Ia)



(Ib)

wherein:

R and R_1 independently represent: (i) phenyl, thienyl or pyridyl, each optionally substituted with 1, 2 or 3 substituents Y, which independently represent (C_{1-3})-alkyl, (C_{1-3})-alkoxy, hydroxy, a halogen atom, trifluoromethyl, trifluoromethylthio, trifluoromethoxy, nitro, amino, (C_{1-2})mono- or dialkylamino, (C_{1-2})-mono- or dialkylamido, (C_{1-3})-alkylsulfonyl, dimethylsulfamido, (C_{1-3})-alkoxycarbonyl, carboxyl, trifluoromethylsulfonyl, cyano, carbamoyl, sulfamoyl or acetyl, or (ii) naphthyl;

R_2 represents, H, hydroxy, (C_{1-3})-alkoxy, acetyloxy or propionyloxy;

R_3 represents: (i) H, or (ii) a branched or unbranched (C_{1-8})-alkyl or (C_{3-7})-cycloalkyl, each optionally substituted with hydroxy;

R_4 represents: (i) H, amino, hydroxy, phenoxy or benzyloxy, (ii) a branched or unbranched (C_{1-8})-alkyl, (C_{3-8})-cycloalkyl, (C_{2-10})-heteroalkyl, (C_{3-8})-nonaromatic heterocycloalkyl or (C_{4-10})-nonaromatic heterocycloalkyl-alkyl, each optionally containing one or more heteroatoms which are O, N or S, and each optionally substituted with a keto group, trifluoromethyl, (C_{1-3})-alkyl, hydroxy, amino, (C_{1-3})-monoalkylamino, (C_{1-3})-dialkylamino, F, amino, hydroxy, phenoxy or benzyloxy, (iii) a branched or unbranched (C_{1-8})-alkoxy, (C_{3-8})-alkenyl, (C_{5-8})-cycloalkenyl or (C_{6-9})-cycloalkenylalkyl, each optionally containing S, N, O, a keto group or $-SO_2-$,

and each optionally substituted with hydroxy, trifluoromethyl, amino, (C_{1-3})-monoalkylamino, (C_{1-3})-dialkylamino or F, (iv) phenyl, benzyl, pyridyl, thienyl, pyridylmethyl or phenethyl, wherein each aromatic ring is optionally substituted with 1, 2 or 3 of the substituents Y as defined above, or (v) NR_8R_9, with the proviso that R_3 represents H or methyl, wherein R_8 and R_9 independently represent (C_{1-4})-alkyl or (C_{2-4})-trifluoroalkyl, or R_8 and R_9, together with the nitrogen atom to which they are bonded, form a saturated or un-saturated heterocyclic moiety having 4 to 8 ring atoms, which heterocyclic moiety optionally contains: (α) O, S, a keto group or $-SO_2-$, or (β) an additional N, and which heterocyclic moiety is optionally substituted with (C_{1-4})-alkyl; or

R_3 and R_4, together with the nitrogen atom to which they are bonded, form a saturated or unsaturated, monocyclic or bicyclic heterocyclic moiety having 4 to 10 ring atoms, which heterocyclic moiety optionally contains one or more O, N, S, a keto group or $-SO_2-$, and which heterocyclic moiety is optionally substituted with (C_{1-4})-alkyl, hydroxy-(C_{1-3})-alkyl, phenyl, thienyl, pyridyl, amino, (C_{1-3})-monoalkylamino-(C_{1-3})-alkyl, (C_{1-3})-dialkylamino-(C_{1-3})-alkyl, (C_{1-3})-monoalkylamino, (C_{1-3})-dialkylamino, amino-(C_{1-3})-alkyl, azetidinyl, pyrrolidinyl, piperidinyl or hexahydro-1H-azepinyl;

R_5 and R_6 independently represent: (i) H, (ii) a branched or unbranched (C_{1-8})-alkyl or (C_{2-8})-alkenyl, each optionally containing one or more O, N, S, a keto group or $-SO_2-$, and each optionally substituted with hydroxy or amino, or (iii) (C_{3-8})-cycloalkyl or (C_{3-8})-cycloalkenyl, each optionally containing one or more ring O, N, S or $-SO_2-$, and each optionally substituted with hydroxy, (C_{1-3})-alkyl, $-SO_2-$, a keto group, amino, (C_{1-3})-monoalkylamino or (C_{1-3})-dialkylamino; or

R_5 represents: (i) a naphthyl, or (ii) phenyl, which is optionally substituted with 1, 2 or 3 substituents Y as defined above, with the proviso that R_6 represents H, or a branched or unbranched (C_{1-5})-alkyl, which optionally contains one or more O, N, S or $-SO_2-$, and which is optionally substituted with hydroxy, a keto group or amino; or

R_5 and R_6, together with the nitrogen atom to which they are bonded, form a monocyclic, bicyclic or tricyclic alkyl or alkenyl having 4 to 14 ring atoms, each

optionally containing a ring O, N, S, a keto group or SO_2, each optionally substituted with hydroxy, (C_{1-3})-alkyl, SO_2, a keto group, amino, (C_{1-3})-monoalkylamino, (C_{1-3})-dialkylamino, pyrrolidinyl or piperidinyl, and each optionally containing an annelated phenyl group, which is optionally substituted with 1 or 2 substituents Y, as defined above; and

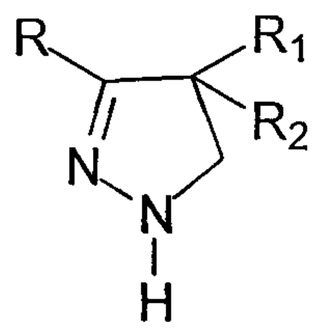
R_7 represents branched or unbranched (C_{1-3})-alkyl;

or a tautomer, stereoisomer or salt thereof.

2. A pharmaceutical composition, comprising: at least one pharmaceutically acceptable carrier, at least one pharmaceutically acceptable auxiliary substance or a combination of two or more thereof; and at least one compound as claimed in claim 1, or a pharmacologically acceptable salt thereof, as the active ingredient.

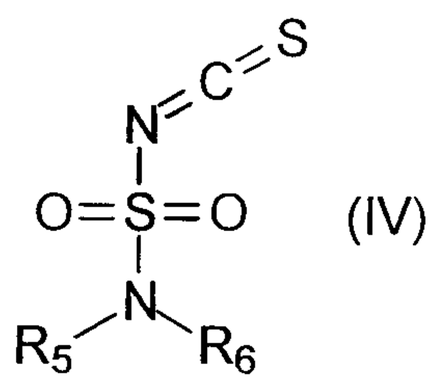
3. A process for the preparation of a compound of the general formula (Ib) as defined in claim 1, comprising:

(1) reacting, in an organic solvent, a compound of the general formula (III):



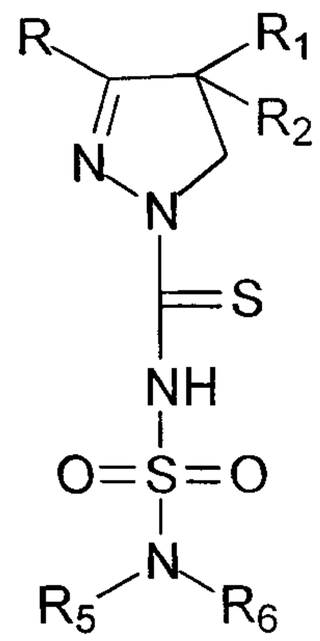
(III)

wherein R, R_1 and R_2 are as defined in claim 1, with a compound of the general formula (IV):



(IV)

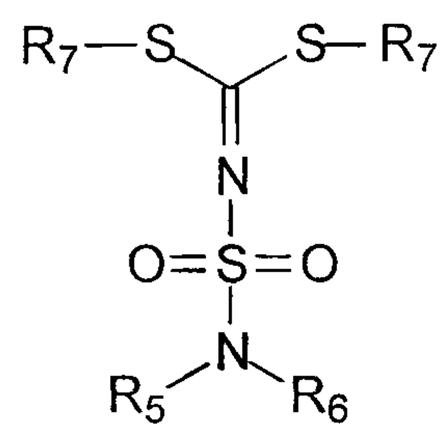
wherein R_5 and R_6 are as defined in claim 1, to give a compound of the general formula (V):



(V)

wherein R, R_1, R_2, R_5 and R_6 are as defined in claim 1, which, in the presence of a base, is reacted with a compound of the general formula: R_7-X, wherein R_7 is as defined in claim 1, and X represents a leaving group; or

(2) reacting a compound of the general formula (III) as defined in step (1) with a compound of the general formula (IX):



(IX)

wherein R_5, R_6 and R_7 are as defined in claim 1.

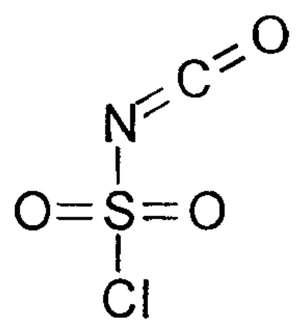
4. The process according to claim 3, wherein X is I^-.

5. A process for the preparation of a compound of the general formula (Ia) as defined in claim 1, comprising:

(1) reacting a compound of the general formula (1b) as defined in claim 1, with an amine of the general formula: HNR_3R_4, wherein R_3 and R_4 are as defined in claim 1; or

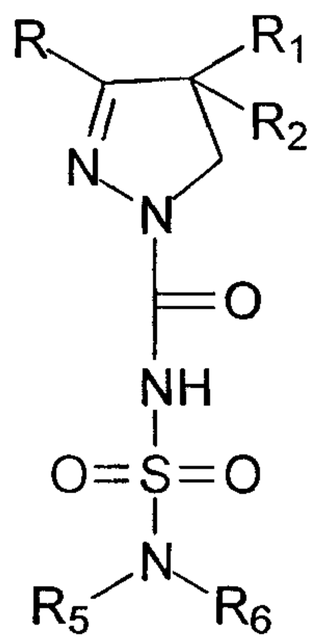
(2) reacting a compound of the general formula (V) as defined in claim 4, with an amine of the general formula: HNR_3R_4, wherein R_3 and R_4 are as defined in claim 1, in the presence of a Hg^{++} salt; or

(3) reacting a compound of the general formula (III) as defined in claim 4, with a compound of the formula (VI):



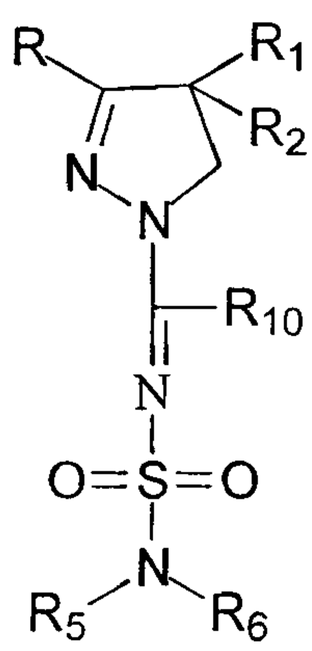
(VI)

followed by treatment in an organic solvent with an amine of the general formula: HNR_5R_6, wherein R_5 and R_6 are as defined in claim 1, to give a compound of the general formula (VII):



(VII)

wherein R, R_1, R_2, R_5 and R_6 are as defined in claim 1, which, in an organic solvent, is reacted with a halogenating agent to give a compound of the general formula (VIII):

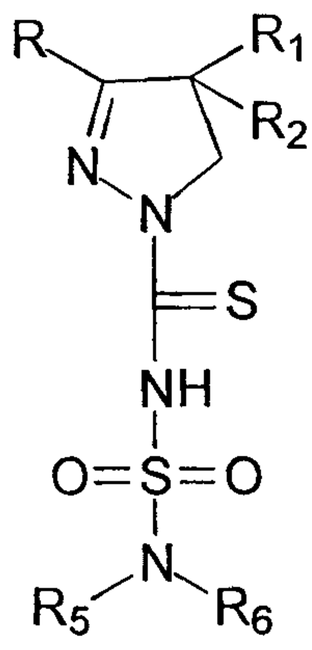


(VIII)

wherein R, R_1, R_2, R_5 and R_6 are as defined in claim 1, and R_{10} represent a halogen atom, which, in an inert organic solvent, is reacted with an amine of the general formula: HNR_3R_4, wherein R_3 and R_4 are as defined in claim 1.

6. The process according to claim 5, wherein the halogenating agent is PCl_5.

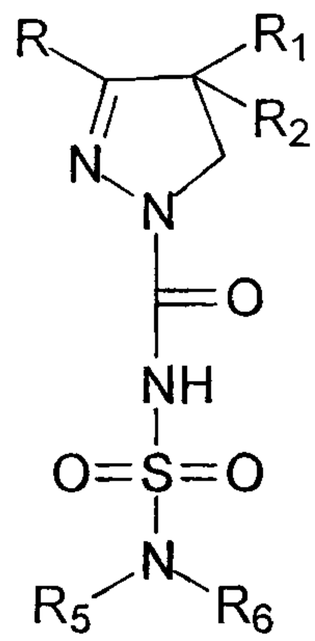
7. A compound of the general formula (V):



(V)

wherein R, R_1, R_2, R_5 and R_6 are as defined in claim 1.

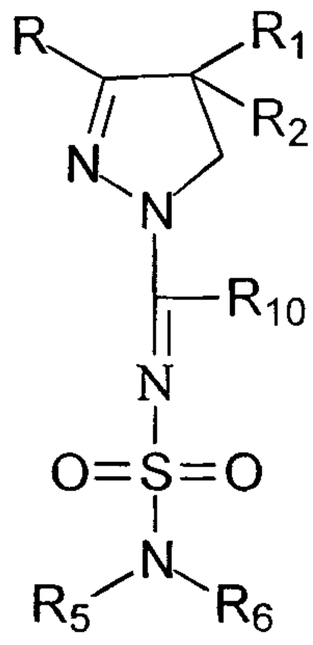
8. A compound of the general formula (VII):



(VII)

wherein R, R_1, R_2, R_5 and R_6 are as defined in claim 1.

9. A compound of the general formula (VIII):



(VIII)

wherein R, R_1, R_2, R_5 and R_6 are as defined in claim 1, and R_{10} represents a halogen atom.

10. Use of a compound as claimed in claim 1, or a pharmacologically acceptable salt thereof, or a composition as claimed in claim 2, for the preparation of a medicament for the treatment of a disorder involving cannabinoid neurotransmission.

11. Use of a compound as claimed in claim 1, or a pharmaceutically acceptable salt thereof, or a composition as claimed in claim 2, for the treatment of a disorder involving cannabinoid neurotransmission.

12. The use as claimed in claim 10 or 11, wherein said disorder is a psychiatric disorder, psychosis, anxiety, depression, an attention deficit, a memory disorder, a cognitive disorder, an appetite disorder, obesity, addiction, appetence, drug dependence, a neurodegenerative disorder, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, Parkinson's disease, Alzheimer's disease, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, a neuroinflammatory disorder, plaque sclerosis, viral encephalitis, a demyelinisation related disorder, a pain disorder, a neuropathic pain disorder, septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, a respiratory disease, a gastrointestinal disorder, a gastric ulcer, diarrhoea or a cardiovascular disorder.

13. A compound as claimed in claim 1, or a pharmacologically acceptable salt thereof, or a composition as claimed in claim 2, for use in the preparation of a medicament for the treatment of a disorder involving cannabinoid neurotransmission.

14. A compound as claimed in claim 1, or a pharmacologically acceptable salt thereof, or a composition as claimed in claim 2, for use in the treatment of a disorder involving cannabinoid neurotransmission.

15. A compound, salt or composition as claimed in claim 13 or 14, wherein said disorder is a psychiatric disorder, psychosis, anxiety, depression, an attention deficit, a memory disorder, a cognitive disorder, an appetite disorder, obesity, addiction, appetence, drug dependence, a neurodegenerative disorder, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, Parkinson's disease, Alzheimer's disease, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, a neuroinflammatory disorder, plaque sclerosis, viral encephalitis, a demyelinisation related disorder, a pain disorder, a neuropathic pain disorder, septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, a respiratory disease, a gastrointestinal disorder, a gastric ulcer, diarrhoea or a cardiovascular disorder.

16. A commercial package comprising a compound as claimed in claim 1, or a pharmacologically acceptable salt thereof, or a composition as claimed in claim 2, and associated therewith instructions for the use thereof in the treatment of a disorder involving cannabinoid neurotransmission.

17. The commercial package as claimed in claim 16, wherein said disorder is a psychiatric disorder, psychosis, anxiety, depression, an attention deficit, a memory disorder, a cognitive disorder, an appetite disorder, obesity, addiction, appetence, drug dependence, a neurodegenerative disorder, dementia, dystonia, muscle spasticity, tremor, epilepsy, multiple sclerosis, traumatic brain injury, Parkinson's disease, Alzheimer's disease, Huntington's disease, Tourette's syndrome, cerebral ischaemia, cerebral apoplexy, craniocerebral trauma, stroke, spinal cord injury, a neuroinflammatory disorder, plaque sclerosis, viral

encephalitis, a demyelinisation related disorder, a pain disorder, a neuropathic pain disorder, septic shock, glaucoma, cancer, diabetes, emesis, nausea, asthma, a respiratory disease, a gastrointestinal disorder, a gastric ulcer, diarrhoea or a cardiovascular disorder.

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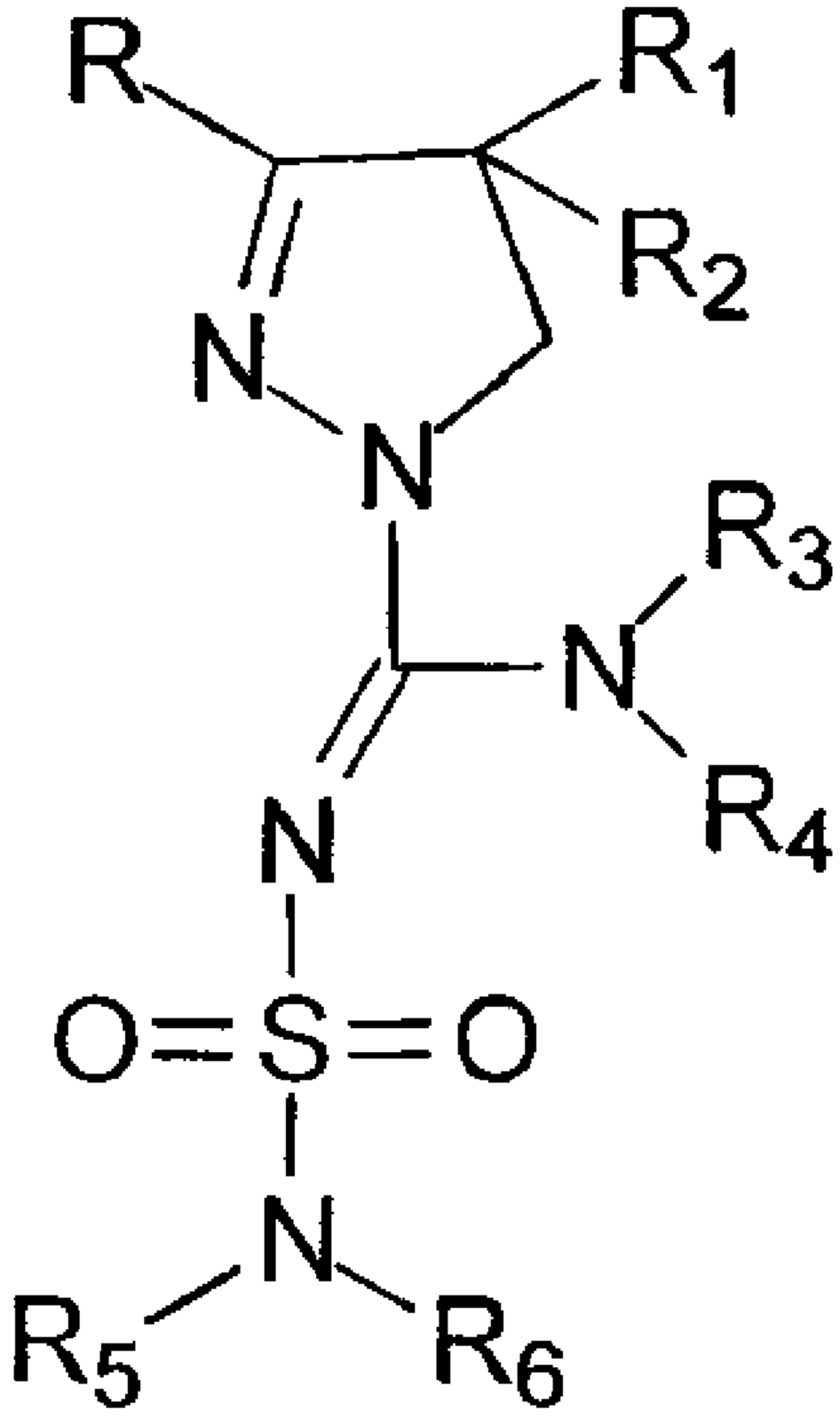
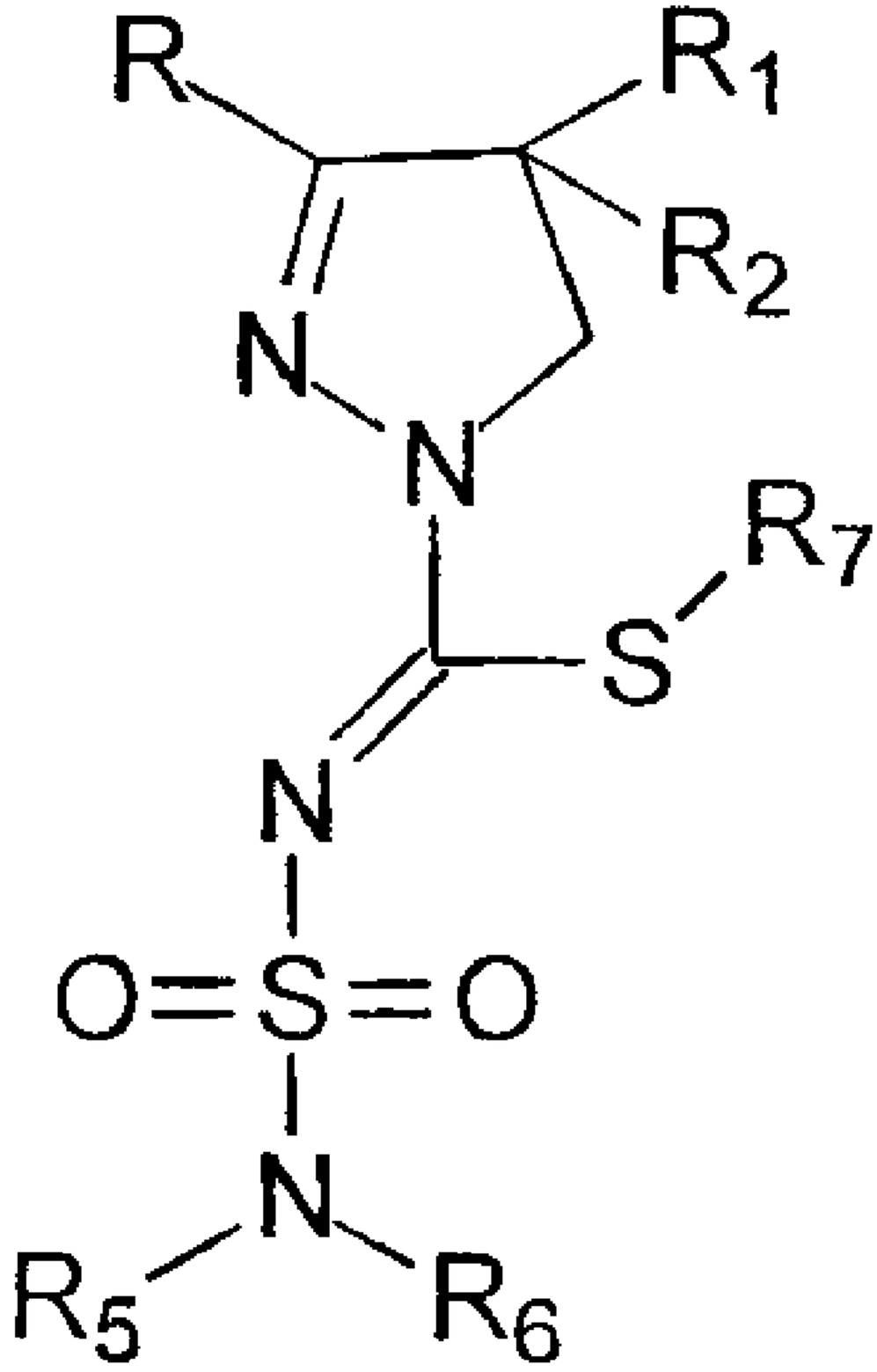
PATENT AGENTS



(Ia)



(Ib)