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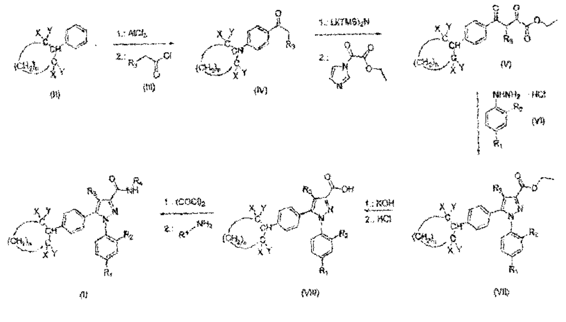
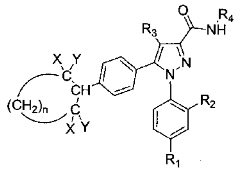
# (54) Title: NOVEL CB1 ANTAGONISTS AND THEIR PREPARATION

**(57) Abstract:** The invention relates to new compounds of general formula (I) acting as CB1 antagonists and to their preparation. The compounds according to this invention can be used for the treatment of obesity, behavioral addictions, psychiatric and metabolic disorders.





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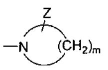

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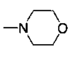

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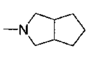

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# Novel CB1 antagonists and their preparation

## Introduction

The present invention relates to new compounds of general formula (I) acting as CB1 antagonists and to their preparation. The compounds according to this invention can be used for the treatment of obesity, behavioral addictions, psychiatric and metabolic disorders.

## Background of the invention

Terpenoids of *Cannabis sativa* have been used for several thousand years as folk medicines, but their use has been banned since 1930s because of their addictive potential. A new era started in 1990s in the pharmacology of cannabionoids when the endocannabinoid system has been discovered. Identification of the receptors CB1 (1990) and CB2 (1992) made it possible to develop selective agonists and antagonists and to study the endocannabinoid system (Howlett et al., 2002).

Rimonabant, a diaryl-pyrazole derivative, has been published in the patent EP 576 357 as the first potent and selective CB1 antagonist. In animal models the CB1 antagonists and inverse agonists are effective in the treatment of depression, anxiety, schizophrenia, nicotine, alcohol- and cocaine addiction, obesity, metabolic syndrome and related disorders, such as dyslipidemia and type II diabetes etc.

The molecules of diaryl-pyrazole structure are important among the CB1 antagonists under development (Muccioli et al.: Current Medicinal Chemistry (2005), 12, 1361-94). The majority of the published CB1 antagonists belong to this structural group. Their activity and medicinal application have been proven in clinical tests. The first and best known representative of this class, the above mentioned rimonabant (Acomplia®) was active and well tolerated in clinical trials of obese patients and average weight loss of 3.4 kg and 6.6 kg have observed at one year treatment in doses of 5 mg and 20 mg, resp. (LF Van Gaal et al, RIO-Europe Study (2005), Lancet, 365, 1389-1397).

Treatment of diseases e.g. obesity, connected to potential field of application of CB1 antagonists often needs lifelong drug therapy. Because of high comorbidity in this condition application of several drugs at the same time is very common in clinical practice therefore there is a high risk of drug interaction incidents.

Therefore obvious need emerged for introduction of medication having good pharmacokinetic parameters resulting in less drug-drug interactions.

Compounds metabolized intensively before entering systemic circulation (first-pass effect) are highly prone to drug-drug interactions. A compound that metabolized in 80% can evoke pharmacological effect by only the remaining 20% that reaches the circulation. A co-administered enzyme inhibitor can multiply the plasma level of an enzyme substrate so much that it can reach toxic concentration. Therefore, higher metabolic stability means less capability for drug-drug interactions.

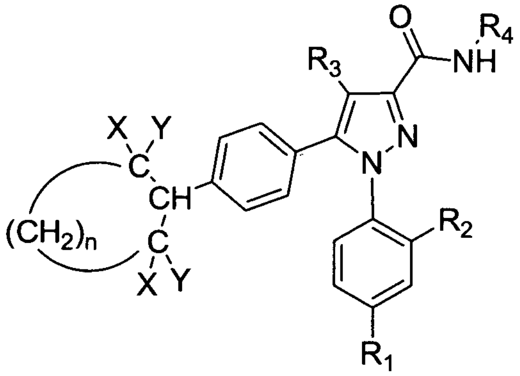
High metabolic stability not only results in less capability to drug-drug interactions but it has additional advantages considering drug safety. (See: Venkatakrishnan K. et.al.: Drug metabolism and drug interactions: application and clinical value of in vitro models. Current Drug Metabolism 4, 423-459, 2003). Lower dose of a metabolically stable compound is needed to evoke the desired pharmacological effects; besides, less accumulation of metabolites occurs as well. Metabolisms of several xenobiotics results in formation of toxic metabolites.

Tremendous information is available on the mechanisms of action of diaryl-pyrazoles but their pharmacokinetic is under investigation. Only one reference has been published on the metabolism of diaryl-pyrazoles (Zhang et al., 2001); therefore, it was reasonable to study the in vitro metabolism of rimonabant. Our results showed, that in human, rat and mouse liver microsomes the rimonabant has weak/moderate metabolic stability (mouse=35%; rat=37%; human=52%).

Accordingly, potent and *in vivo* effective but higher metabolic stability diaryl–pyrazole analogues may bring remarkable improvement in the effectiveness of therapies recently used.

## Summary of the invention

The present invention relates to new compounds of formula (I),



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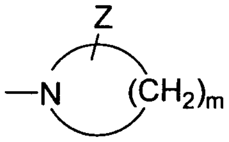

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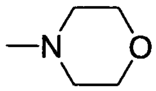

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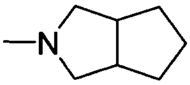


wherein

- n is an integer from 0 to 3,
- X and Y are each independently hydrogen, halogen, or $C_1$-$C_5$ alkyl group,
- $R_1$ and $R_2$ are each independently hydrogen, halogen, $C_1$-$C_4$ alkyl group or $C_1$-$C_4$ alkylmercapto group,
- $R_3$ is hydrogen, $C_1$-$C_4$ alkyl group or $C_1$-$C_4$ alkoxy group,

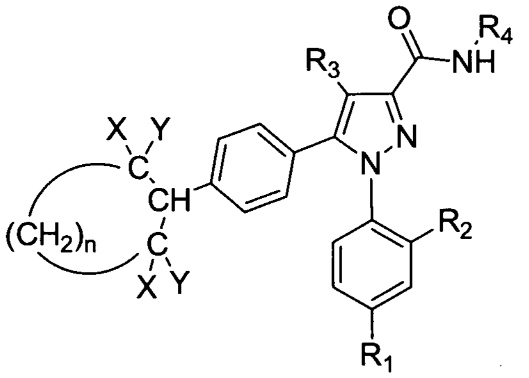
- $R_4$ is a cycloalkyl ring having about 3 to about 6 members ring, optionally substituted with a hydroxy group or a group having formula a.), b.) and c.) where
- m is an integer from 4 to 6,
- Z is hydrogen, halogen, $C_1$-$C_4$ alkyl, hydroxy, trifluoromethyl or methoxymethyl group,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof.

The invention also relates to the process of their synthesis as well as the pharmaceutical composition containing the same and the use for diseases or disorders associated with cannabinoid system e.g. psychiatric disorders such as schizophrenia (Weiser and Noy; Dialogues in Clinical Neuroscience Vol.7 No.1. 2005), depression (Witkin; Trends Pharmacol Sci. 2005 Dec 26(12):609-17) anxiety, (Griebel; Biol Psychiatry. 2005 Feb 1 57(3):261-7.), Huntington's chorea (Lastres-Becket; Neuroreport. 2003 May 6 14(6):813-6.), Alzheimer's disease (Mazzola Eur J Pharmacol. 2003 Sep 23 477(3):219-25.), metabolic syndrome and related disorders such as obesity and being overweight (van Gaal; Lancet. 2005 Apr 16-22 365(9468):1389-97), dyslipidemia (Despres; N Engl J Med. 2005 Nov 17 353(20):2121-34.), type II diabetes (Despres; N Engl J Med. 2005 Nov 17 353(20):2121-34.) or atherosclerosis (Gomaraschi; IDrugs. 2005 Jul 8(7):555-9.), dependence and addictive disorders such as nicotine, cocaine, opioid, alcohol, methamphetamine dependence (Fattore; Brain Res Brain Res Rev. 2006 Jul 11), social dependence, such as pathological gambling or every other diseases in which cannabinoid system plays a special role e.g. different type of cancers (Sarnataro; Mol Pharmacol. 2006 Oct 70(4):1298-306. Epub 2006 Jul 5.), cirrhosis (Gabbay; Liver Int. 2005 Oct 25 (5):921-6.) or hemorrhagia (Cainazzo; Eur J Pharmacol. 2002 Apr 19 441(1-2):91-7).

## Detailed description of the invention

The present invention relates to new compounds of formula (I),



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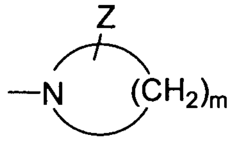

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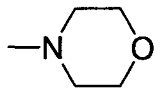

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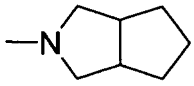


wherein

- n is an integer from 0 to 3,
- X and Y are each independently hydrogen, halogen, or $C_1$-$C_5$ alkyl group,
- $R_1$ and $R_2$ are each independently hydrogen, halogen, $C_1$-$C_4$ alkyl group or $C_1$-$C_4$ alkylmercapto group,
- $R_3$ is hydrogen, $C_1$-$C_4$ alkyl group or $C_1$-$C_4$ alkoxy group,

- $R_4$ is a cycloalkyl ring having about 3 to about 6 members ring, optionally substituted with a hydroxy group or a group having formula a.), b.) and c.) where
- m is an integer from 4 to 6,
- Z is hydrogen, halogen, $C_1$-$C_4$ alkyl, hydroxy, trifluoromethyl or methoxymethyl group,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof. .The invention also relates to the process of the synthesis of compounds of formula (I).

In compounds of formula (I) the meaning of halogen is fluoro, chloro, bromo and iodo atom, in the meaning of $R_1$ and $R_2$ preferably fluoro, chloro and bromo atom.

In compounds of formula (I) the meaning of the alkyl group or the alkyl group at the alkoxy group is methyl, ethyl, n-propyl, n-butyl or its branched isomers such as isopropyl, *tert*-butyl, *sec*-butyl etc.

Synthesis of compounds of formula (I)

The synthesis of compounds of formula (I) can be shown on Scheme 1.

The reaction of compound of formula (II), wherein the meaning of X, Y and n is the same as mentioned before and compound of formula (III), wherein the meaning of $R_3$ is the same as mentioned before in the presence of $AlCl_3$ give compound of formula (IV), wherein X, Y, n and $R_3$ is the same as mentioned before, which is reacted with imidazol-1-yl-oxo-acetic acid ethyl ester in the presence of lithium bis(trimethylsilyl)amide to yield the diketon esters (V), wherein the meaning of X, Y, n and $R_3$ is the same as mentioned before, then reacting the obtained compound of formula (V) with the appropriate substituted phenyl hydrazine hydrochloride (VI), wherein the meaning of $R_1$ and $R_2$ is the same as mentioned before to give compounds of formula (VII), wherein the meaning of X, Y, n, $R_1$, $R_2$ and $R_3$ is the same as mentioned before, then hydrolyzing the ester groups of compounds of formula (VII) with KOH to give compounds having formula (VIII) wherein the meaning of X, Y, n, $R_1$, $R_2$ and $R_3$ is the same as mentioned before, which is reacted with oxalyl chloride, then reacted with compounds of formula (IX), wherein the meaning of $R_4$ is the same as above mentioned to yield compounds of formula (I).

The invention also relates to the process of their synthesis as well as the pharmaceutical composition containing the same and the use for diseases or disorders associated with cannabinoid system e.g. psychiatric disorders such as schizophrenia (Weiser and Noy; Dialogues in Clinical Neuroscience Vol.7 No.1. 2005), depression (Witkin; Trends Pharmacol Sci. 2005 Dec 26(12):609-17) anxiety, (Griebel; Biol Psychiatry. 2005 Feb 1 57(3):261-7.), Huntington's chorea (Lastres-Becket; Neuroreport. 2003 May 6 14(6):813-6.), Alzheimer's disease (Mazzola Eur J Pharmacol. 2003 Sep 23 477(3):219-25.), metabolic syndrome and related disorders such as obesity and being overweight (van Gaal; Lancet. 2005 Apr 16-22 365(9468):1389-97), dyslipidemia (Despres; N Engl J Med. 2005 Nov 17 353(20):2121-34.), type II diabetes (Despres; N Engl J Med. 2005 Nov 17 353(20):2121-34.) or atherosclerosis (Gomaraschi; IDrugs. 2005 Jul 8(7):555-9.), dependence and addictive disorders such as nicotine, cocaine, opioid, alcohol, methamphetamine dependence (Fattore; Brain Res Brain Res Rev. 2006 Jul 11), social dependence, such as pathological gambling or every other diseases in which cannabinoid system plays a special role e.g. different type of cancers (Sarnataro; Mol Pharmacol. 2006 Oct 70(4):1298-306. Epub 2006 Jul 5.), cirrhosis (Gabbay; Liver Int. 2005 Oct 25(5):921-6.) or hemorrhagia (Cainazzo; Eur J Pharmacol. 2002 Apr 19 441(1-2):91-7).

Compounds of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof may be administered by any convenient method, for example by oral, parenteral buccal, sublingual, nasal, rectal or transdermal administration and the pharmaceutical compositions adapted accordingly.

Pharmaceutical compositions containing compounds of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof when given orally can be formulated as liquids or solids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

Liquid formulations of compounds of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof generally consist of a suspension or solution of a compound of formula (I) in an appropriate liquid carrier(s), for example an aqueous solvent, such as water, ethanol or glycerin or a non-aqueous solvent, such as polyethylene glycol or an oil. The pharmaceutical composition can also contain a suspending agent, preservative, flavoring and coloring agents.

A composition in the solid form of tablet can be prepared using any suitable pharmaceutical carrier(s), which are commonly used in practice, such as magnesium stearate, starch, lactose, saccharose, cellulose etc.

A composition in the solid form of capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatine capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatine capsule.

Typical parenteral compositions consist of a solution or suspension of the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilized and then reconstituted with a suitable solvent just prior to administration.

Compositions of the present invention for nasal administration containing the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof may conveniently be formulated as aerosols, drops, gels and powders. Aerosol formulations of the present invention typically comprise a solution or fine suspension of the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof in a physiologically acceptable aqueous or non-aqueous solvent and are usually presented in a single or multidose quantities in sterile form is a sealed container, which can take the form of a cartridge or refill for use with an atomizing device. Alternatively, the sealed container may be a unitary dispensing device, such as a single dose nasal inhaler or an aerosol dispenser fitted with a metering valve which is intended for disposal once the contents of the container have been exhausted. Where the dosage form comprises an aerosol dispenser, it will contain a propellant which can be a compressed gas, such as compressed air or an organic propellant, such as a fluorochlorohydrocarbon. The aerosol dosages form can also take the form of a pump-atomizer.

Compositions containing the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof suitable for buccal or sublingual administration include tablets, lozenges and pastilles, wherein the active ingredient is formulated with a carrier, such as sugar and acacia, tragacanth or gelatine and glycerine etc.

Composition of the present invention containing the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof for rectal administration are conveniently in the form of suppositories containing a conventional suppository base, such as cocoa butter.

Composition of the present invention containing the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof for transdermal administration include ointments, gels and patches.

The compositions of the present invention containing the compound of formula (I) and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof are preferably in the unit dose form, such as tablet, capsule or ampoule.

The compounds of formula (I) of our invention are *in vitro* and *in vivo* effective CB1 antagonists and their metabolic stability better than the common diaryl-pyrazoles stability, so the compositions containing the compounds of formula (I) as active ingredient are effective in lower dose and has lower capability for drug-drug interactions because of their higher metabolic stability than the known CB1 antagonists till now.

**Biological evaluation**

The *in vitro* CB1 affinity of compounds of formula (I) was measured on [$^3$H]SR-141716A radioligand binding assay, their metabolic stability assessed using human, rat and mouse liver microsomes and their *in vivo* efficacy was determined by CB1 agonist induced hypothermia test.

1. *In vitro* [$^3$H]SR-141716A radioligand binding at CB1
receptors

For the evaluation of *in vitro* CB1 affinities of compounds radioligand binding assay using [$^3$H]SR-141716A binding to rat cerebellum membrane preparation was employed. The assay was set up according to the methods of Thomas et al. (1998) and Devane et al. (1988). Aliquots of 200 μg rat brain membrane preparation were incubated at 30°C for 60 min in the presence of 0.04 nM [$^3$H]SR-141716A in a thermostated shaker. Incubation was stopped by rapid vacuum filtration, filters were washed then radioactivity remaining on the filters was detected by scintillation spectrometry. Nonspecific binding was determined in the presence of 1 μM unlabelled SR-141716A. Data were analyzed and $IC_{50}$ values calculated using sigmoid fitting with the software Origin 6.0 then equilibrium inhibition coefficients ($K_i$) calculated using the Cheng-Prusoff equation (Cheng and Prusoff, 1973).

References:

Cheng Y. and Prusoff W.H. Biochem Pharmacol 22(23): 3099-3108, 1973

Devane W.A., Dysarz F.A., Johnson M.R., Melvin L.S. and Howlett M.C. Mol Pharmacol 34 (5): 605-613, 1988

Thomas B.F., Gilliam A.F., Burch D.F., Roche M.J. and Seltzmand H.H. JPET 285 (1): 285-292, 1998)

## 2. *In vitro* metabolic stability in rat, human and mouse liver microsomes

Microsomes: Rat liver microsomes (Gedeon Richter, pool of 10); human liver microsomes (Xenotech, USA; pool of 50), CD-1 mouse liver microsomes (Gedeon Richter, pool of 10).

Method: Metabolic stability of the test compounds was assessed using liver microsomes (see: Houston J.B.: Utility of in vitro drug metabolism data in predicting in vivo metabolic clearance Biochemical Pharmacology 47, 1469-1479, 1994).

Metabolic stabilities were determined by incubation of test compounds with liver microsomes under first order reaction conditions. Consumption of test compound was monitored in time and unchanged test compound was quantified using high performance liquid chromatography. Intrinsic clearance ($CL_{int}$) was calculated from the consumption-time curves by determination of the actual rate of enzyme reaction under first order conditions. Metabolic bioavailability ($F_M$) was calculated comparing the intrinsic clearance to the hepatic blood flow. The metabolic bioavailability obtained is the highest possible bioavailability of the test compounds that is limited by the rate of liver metabolism.

Calculation of Metabolic Bioavailability: $\mathbf{F_M = (1 - E_H) \times 100}$; $\mathbf{E_H = CL_{int} / (CL_{int} + HBF)}$ where $\mathbf{CL_{int} = V_{max} / K_m}$ or if $\mathbf{[S] << K_m}$ than $\mathbf{CL_{int} = v / [S]}$

$\mathbf{CL_{int}}$ = intrinsic clearance; $\mathbf{F_M}$ = metabolic bioavailability; $\mathbf{E_H}$ = hepatic extraction ratio; $\mathbf{V_{max}}$ = maximal rate of enzyme reaction; $\mathbf{K_m}$ = affinity constant of a substrate; **[S]** = substrate concentration; **v** = actual rate of enzyme reaction under first order conditions; **HBF** = hepatic blood flow

## 3. *In vivo* CB1 agonist induced hypothermia

CD1 mice weighted ~30g was treated orally with various doses of the test compounds (pretreatment time = 60 min, n=8/group). 15 minutes hence, CB1 agonist (WIN 55,212-2, 3 mg/kg, pretreatment time = 45 min) was given intraperitoneally, and after 45 minutes, body temperatures was measured rectally. From the mean body temperatures of the different groups, „inhibition percentage" was calculated (see below), and the results were plotted as the dependent variable of the logarithm of the dose. ED50 values were calculated using linear regression (Microcal Origin 6.0, linear plot).

Calculation of the inhibition percentages: **inh%=100×(Mx-Ma)/(Mc-Ma)**; where **Mx** = mean body temperature of a group treated with a dose of the test compound and later with the agonist; **Ma** = mean body temperature of the group treated with the vehicle of the test compound and later with the agonist; **Mc** = mean body temperature of the group treated with vehicle of the test compound and later with the vehicle of the agonist.

## Biological results

The CB1 affinity of compounds of formula (I) on radioligand binding assay were the same (Ki=5.6 nM) or better (2.7 nM < Ki < 62 nM) as compared to rimonabant as main reference.

The results of *in vitro* metabolic stability tests are summarized in Table 1.

| Test compound | metabolic stabilities | | | | | |
|---|---|---|---|---|---|---|
| | rat liver microsomes | | human liver microsomes | | mouse liver microsomes | |
| | $CL_{INT}$ | $F_M$ % | $CL_{INT}$ | $F_M$ % | $CL_{INT}$ | $F_M$ % |
| rimonabant | 3.1 | 37 | 1.09 | 52 | 3.22 | 35 |
| Compound of Example 1 | 2.14 | 46 | 0.87 | 58 | 3.28 | 34 |
| Compound of Example 2 | 1.72 | 51 | 0.26 | 82 | 0.41 | 80 |
| Compound of Example 3 | 0.38 | 83 | 0.16 | 88 | 0.68 | 71 |
| Compound of Example 4 | 0.01 | 99 | 0.01 | 99 | 0.01 | 99 |

Table 1

The results show, that rimonabant has weak/moderate metabolic stability. The metabolic stability of examples (1-4) covered by general structure (I) improved in parallel to the increasing size of cycloalkyl rings and reached the highest possible value of 99% in example 4.

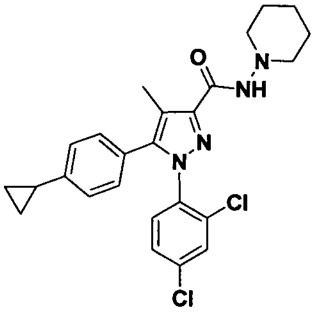
Results of the hypothermia test show that compounds of formula (I) are in vivo potent CB1 antagonist compounds. The obtained results show that oral efficacy of compounds of formula (I) are the same (ED50=0.41mg/kg) or better (3 mg/kg > ED50 > 0.1 mg/kg) as compared to rimonabant.

## Examples

The invention is illustrated by the following not limiting examples.

Example 1.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide**



a.:

1-(4-cyclopropylphenyl)propan-1-one

To a stirred suspension of $AlCl_3$ (33.3 g, 0.25 mol) in trichloroethylene (50 ml) propionyl chloride (0.25 mol, 19.4 ml) was added dropwise at 0-5 °C. After stirring for 0.5 h the reaction mixture was cooled to -50 °C and cyclopropylbenzene (25 g, 0.21 mol) was added dropwise. The obtained mixture was stirred for 1 h at -50 °C then poured into a mixture of ice (250 g) and cc. HCl (30 ml). The organic layer was washed with $NaHCO_3$ (10% solution in water), dried over anh. $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography using dichloromethane/hexane as eluent.

Yield: 14 g (38%)

b.:

4-(4-cyclopropylphenyl)-3-methyl-2,4-dioxo-butyric acid ethyl ester

In a -70 °C solution of lithium bis(trimethylsilyl)amide (91 ml, 91 mmol) in methyl *t*-butyl ether (223 ml) under argon atmosphere 1-(4-cyclopropylphenyl)propan-1-one (14 g, 0.08 mol) dissolved in methyl *t*-butyl ether (116 ml) was added. The reaction mixture was allowed to warm to -10 °C then imidazol-1-yl-oxo-acetic acid ethyl ester (13.5 g, 0.08 mol) dissolved in methyl *t*-butyl ether (70 ml) was added. The so obtained mixture was stirred for 16 h at ambient temperature then a mixture of cc. HCl (50 ml) and water (50 ml) was added. The organic layer was separated and dried over anh. $MgSO_4$. The obtained crystalline product was used in the next step without further purification.

Yield: 19.7 g (90%)

c.:

5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1-*H*-pyrazole-3-carboxylic acid ethyl ester

To a stirred solution of 4-(4-cyclopropylphenyl)-3-methyl-2,4-dioxo-butyric acid ethyl ester (19.7 g, 0.072 mol) in ethanol (230 ml) 2,4-dichlorophenylhydrazine hydrochloride (15.4 g, 0.072 mol) was added at ambient temperature, followed by addition of a mixture of cc. HCl (10 ml) and water (10 ml). The obtained suspension was refluxed for 3 h, then concentrated *in vacuo*. The residue was purified by column chromatography using dichloromethane as eluent.

Yield: 9.3 g (31%)

d.:

5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1-*H*-pyrazole-3-carboxylic acid

To a stirred suspension of 5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1-*H*-pyrazole-3-carboxylic acid ethyl ester (9.3 g, 0.022 mol) in methanol (28 ml) KOH (2.9 g, 0.051 mol) dissolved in water (28 ml) was added. The obtained suspension was refluxed for 2 h, then acidified with 3 M HCl. The precipitated product was collected by filtration and washed with water.

Yield: 8.9 g (96%)

e.:

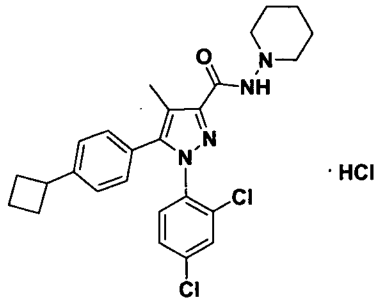
5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide

To a stirred suspension of 5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-1-*H*-pyrazole-3-carboxylic acid (8.9 g, 0.021 mol) and DMF (0.36 ml) in dichloromethane (278 ml) oxalyl chloride (3.8 ml, 0.043 mol) was added dropwise with cooling. The mixture was stirred for 2 h at room temperature then evaporated *in vacuo* and dissolved in dichloromethane (80 ml). The so obtained solution was added dropwise to a stirred mixture of N-amino-piperidine (3.4 ml, 0.032 mol) and triethyl amine (4.5 ml, 0.032 mol) in dichloromethane (150 ml) at 0-5°C. The resulting mixture was allowed to warm to ambient temperature and stirred for 14-16 h then evaporated *in vacuo*. The residue was purified by column chromatography using dichloromethane/ethyl acetate as eluent.

Yield: 8.6 g (80%)

Example 2.

**5-(4-cyclobutylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide hydrochloride**

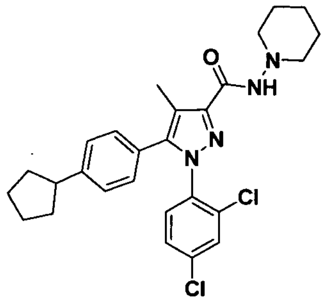


This compound was synthesized according to the method described in example 1 using 4-cyclobutylbenzene in step „a”, which can be prepared by a known method starting from commercially available 2-phenyl-1,4-butanediol (W. F. BAILEY, P. R. GAGNIER, and J. J. PATRICIA., Journal of Organic Chemistry 49, (12) 2098-2107 (1984).

$^1$H NMR(DMSO): 1.90-2.01 m (1H); 1.99-2.11 m (2H); 2.21-2.29 m (1H); 2.27 s (3H); 3.28-3.41 m (4H); 3.44-3.55 m (1H); 7.13-7.18 m (2H); 7.23-7.27 m (2H); 7.59 d (1H); 7.77 d (1H); 7.79 d (1H)

Example 3.

**5-(4-cyclopentylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide**

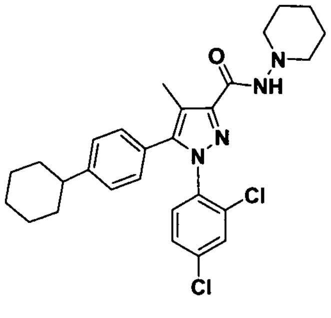


This compound was synthesized according to the method described in example 1 using 4-cyclopentylbenzene in step „a", which can be prepared by the reaction of cyclopentanol and benzene (W. F. BAILEY, P. R. GAGNIER, and J. J. PATRICIA., Journal of Organic Chemistry 49, (12) 2098-2107 (1984).

$^1$H NMR(DMSO): 1.44-1.56 m (4H); 1.57-1.67 m (2H); 1.70-1.79 m (2H); 1.84-1.92 m (4H); 1.95-2.04 m (2H); 2.30 s (3H); 2.89-3.01 m (1H); 3.39-3.51 m (4H); 7.13-7.18 m (2H); 7.26-7.30 m (2H); 7.59 dd (1H); 7.78 d (1H); 7.79 d (1H); 11.60 br s (1H)

Example 4.

**5-(4-cyclohexylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide**

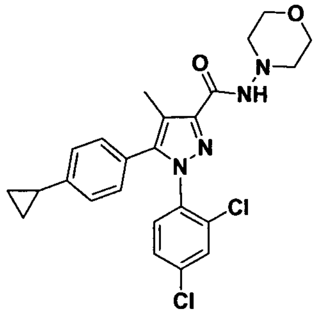


This compound was synthesized according to the method described in example 1 using commercially available 4-cyclohexylbenzene in step „a".

$^1$H NMR(DMSO): 1.16-1.26 m (1H); 1.29-1.41 m (4H); 1.46-1.56 m (2H); 1.64-1.73 m (1H); 1.73-1.81 m (4H); 1.82-1.88 m (4H); 2.28 s (3H); 2.43-2.50 m (1H); 3.34-3.48 m (4H); 7.12-7.17 m (2H); 7.21-7.28 m (2H); 7.58 dd (1H); 7.76 d (1H); 7.79 d (1H); 11.38 br s (1H)

Example 5.

**5-(4-cyclohexylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-morpholin-1-yl-1-*H*-pyrazole-3-carboxamide**

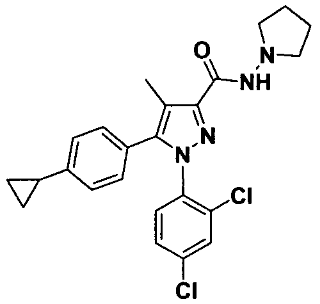


This compound was synthesized according to the method described in example 1 using commercially available 4-aminomorpholine in step „e".

$^1$H NMR(DMSO): 0.63-0.70 m (2H); 0.90-0.98 m (2H); 1.81-1.92m (1H); 2.21 s (3H); 2.81-2.87 m (4H); 3.61-3.68 m (4H); 7.06 m (4H); 7.56 dd (1H); 7.71 d (1H); 7.75 d (1H); 9.25 s (1H)

Example 6.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-pyrrolidine-1-yl-1-*H*-pyrazole-3-carboxamide**

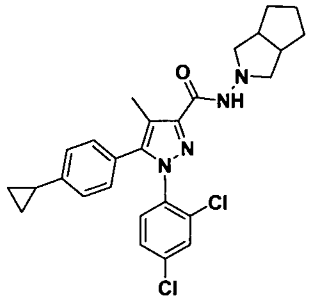


This compound was synthesized according to the method described in example 1 using commercially available 1-aminopyrrolidine in step „e".

$^1$H NMR(DMSO): 0.63-0.71 m (2H); 0.90-0.99 m (2H); 1.68-1.78 m (2H); 1.81-1.93m (1H); 2.21 s (3H); 2.83-2.95 m (4H); 7.05 m (4H); 7.55 dd (1H); 7.71 d (1H); 7.74 d (1H); 9.03 s (1H)

Example 7.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-hexahydro-cyclopenta[c]pyrrole-2-yl-1-*H*-pyrazole-3-carboxamide**

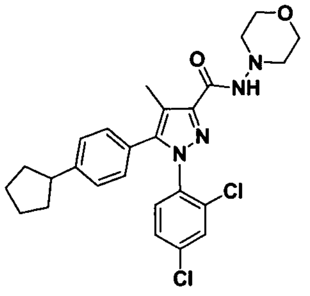


This compound was synthesized according to the method described in example 1 using commercially available 3-amino-3-azabicyclo[3.3.0]octane in step „e”.

$^1$H NMR(DMSO): 0.63-0.71 m (2H); 0.90-0.97 m (2H); 1.36-1.51 m (3H); 1.54-1.74 m (3H); 1.81-1.93 m (1H); 2.20 s (3H); 2.45-2.54 m (2H); 2.54-2.60 m (2H); 3.01-3.09 m (2H); 7.05 m (4H); 7.55 dd (1H); 7.69 d (1H); 7.74 d (1H); 8.88 s (1H)

Example 8.

**5-(4-cyclopentylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-morpholin-1-yl-1-*H*-pyrazole-3-carboxamide**

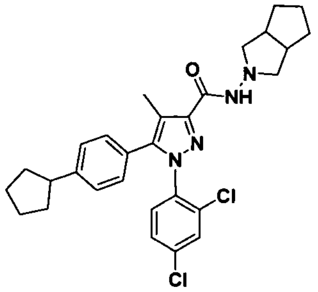


This compound was synthesized according to the method described in example 3 using commercially available 4-aminomorpholine in step „e”.

$^1$H NMR(DMSO): 1.47-1.57 m (2H); 1.60-1.70 m (2H); 1.71-1.82 m (2H); 1.98-2.06 m (2H); 2.29 s (3H); 2.91-3.02 m (1H); 3.08-3.18 m (4H); 3.78-3.85 m (4H); 7.07-7.11 m (2H); 7.20-7.23 m (2H); 7.49 dd (1H); 7.61 d (1H); 7.62 d (1H); 10.14 br s (1H)

Example 9.

**5-(4-cyclopentylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-hexahydro-cyclopenta[c]pyrrole-2-yl-1-*H*-pyrazole-3-carboxamide**

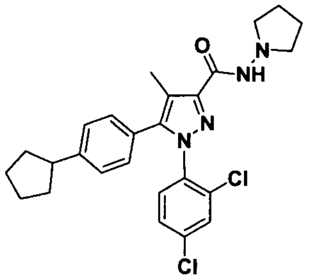


This compound was synthesized according to the method described in example 3 using commercially available 3-amino-3-azabicyclo[3.3.0]octane in step „e".

$^1$H NMR(DMSO): 1.42-1.80 m (12H); 1.95-2.05 m (2H); 2.28 s (3H); 2.80-2.89 m (2H); 2.89-3.01 m (1H); 3.17-3.28 m (2H); 3.96-4.04 m (2H); 7.13-7.17 m (2H); 7.25-7.30 m (2H); 7.61 dd (1H); 7.78 d (1H); 7.81 d (1H)

Example 10.

**5-(4-cyclopentylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-pyrrolidine-1-yl-1-*H*-pyrazole-3-carboxamide**

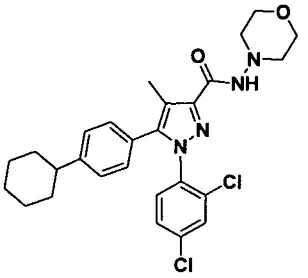


This compound was synthesized according to the method described in example 3 using commercially available 1-aminopyrrolidine in step „e".

$^1$H NMR(DMSO): 1.42-1.53 m (2H); 1.57-1.67 m (2H); 1.68-1.78 m (2H); 1.94-2.02 m (2H); 2.04-2.13 m (4H); 2.28 s (3H); 2.91-3.00 m (1H); 3.69-3.76 m (4H); 7.13-7.19 m (2H); 7.25-7.29 m (2H); 7.62 dd (1H); 7.77 d (1H); 7.78 d (1H)

Example 11.

**5-(4-cyclophexylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-morpholin-1-yl-1-*H*-pyrazole-3-carboxamide**

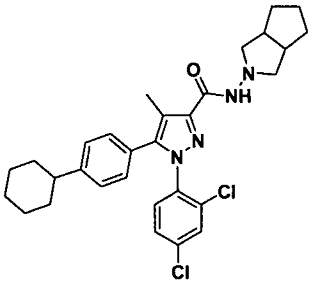


This compound was synthesized according to the method described in example 4 using commercially available 4-aminomorpholine in step „e".

$^{1}$H NMR(DMSO): 1.17-1.27 m (1H); 1.33-1.41 m (4H); 1.68-1.75 m (1H); 1.77-1.85 m (4H); 2.27 s (3H); 2.42-2.51 m (1H); 2.88-2.95 m (4H); 3.69-3.75 m (4H); 7.05-7.08 m (2H); 7.13-7.18 m (2H); 7.44 dd (1H); 7.54-7.57 m (2H); 9.02 s (1H)

Example 12.

**5-(4-cyclohexylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-hexahydro-cyclopenta[c]pyrrole-2-yl-1-*H*-pyrazole-3-carboxamide**

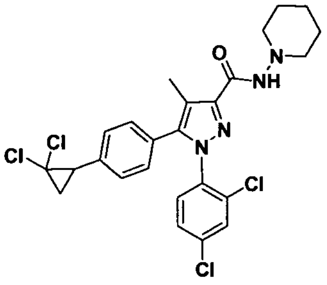


This compound was synthesized according to the method described in example 4 using commercially available 3-amino-3-azabicyclo[3.3.0]octane in step „e".

$^{1}$H NMR(DMSO): 1.14-1.26 m (1H); 1.26-1.40 m (4H); 1.53-1.81 m (11H); 2.27 s (3H); 2.44-2.52 m (1H); 2.80-2.93 m (2H); 3.17-3.29 m (2H); 3.96-4.06 m (2H); 7.12-7.18 m (2H); 7.22-7.28 m (2H); 7.60 dd (1H); 7.77 d (1H); 7.80 d (1H)

Example 13.

**5-[4-(2,2-dichlorocyclopropyl)-phenyl]-1-(2,4-dichlorophenyl)-4-methyl-N-pyperidine-1-yl-1-*H*-pyrazole-3-carboxamide**

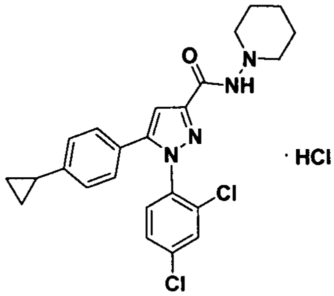


This compound was synthesized according to the method described in example 1 using commercially available 2,2-dichloro-cyclopropylbenzene in step „a".

$^1$H NMR(DMSO): 1.27-1.37 m (2H); 1.52-1.65 m (4H); 2.00-2.20 m (2H); 2.28 s (3H); 2.75-2.82 m (4H); 3.96-4.04 m (2H); 7.16-7.22 m (2H); 7.28-7.34 m (2H); 7.55 dd (1H); 7.72 d (1H); 7.73 d (1H); 9.02 s (1H)

Example 14.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide hydrochloride**

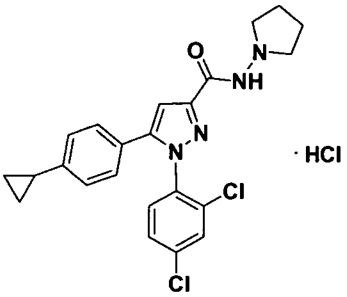


This compound was synthesized according to the method described in example 1 using acetyl chloride in step „a".

$^1$H NMR(DMSO): 0.64-0.69 m (2H); 0.91-0.98 m (2H); 1.42-1.51 m (2H); 1.76-1.83 m (4H); 1.84-1.92 m (1H); 3.25-3.35 m (4H); 7.03-7.08 m (2H); 7.10-7.15 m (2H); 7.24 s (1H); 7.65 dd (1H); 7.81 d (1H); 7.87 d (1H); 11.21 s (1H)

Example 15.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-*N*-pyrrolidine-1-yl-1-*H*-pyrazole-3-carboxamide hydrochloride**

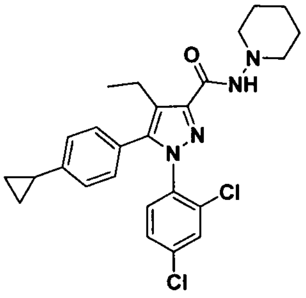


This compound was synthesized according to the method described in example 14 using commercially available 1-aminopyrrolidine in step „e".

$^1$H NMR(DMSO): 0.63-0.70 m (2H); 0.92-0.98 m (2H); 1.85-1.93 m (1H); 1.95-2.05 m (4H); 3.47-3.63 m (4H); 7.01-7.08 m (2H); 7.11-7.15 m (2H); 7.28 br s (1H); 7.66 dd (1H); 7.81 d (1H); 7.88 d (1H); 11.80 s (1H)

Example 16.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-ethyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide**

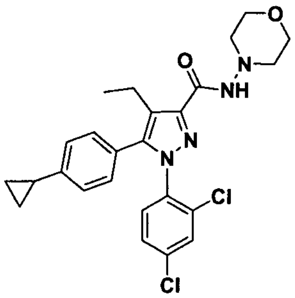


This compound was synthesized according to the method described in example 1 using butyryl chloride in step „a".

$^1$H NMR(DMSO): 0.64-0.69 m (2H); 0.91-0.97 m (2H); 1.07 t (3H); 1.30-1.38 m (2H); 1.52-1.65 m (4H); 1.82-1.92 m (1H); 2.62 q (2H); 2.74-2.81 m (4H); 7.03-7.09 m (4H); 7.51 dd (1H); 7.71 d (1H); 7.73 d (1H); 9.01 s (1H)

Example 17.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-ethyl-*N*-morpholin-1-yl-1-*H*-pyrazole-3-carboxamide**

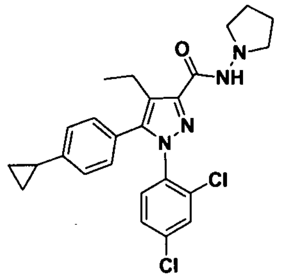


This compound was synthesized according to the method described in example 16 using commercially available 4-aminomorpholine in step „e".

$^1$H NMR(DMSO): 0.64-0.67 m (2H); 0.91-0.98 m (2H); 1.07 t (3H); 1.82-1.92 m (1H); 2.62 q (2H); 2.80-2.88 m (4H); 3.60-3.69 m (4H); 7.04-7.10 m (4H); 7.54 dd (1H); 7.72 d (1H); 7.74 d (1H); 9.28 s (1H)

Example 18.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-ethyl-*N*-pyrrolidin-1-yl-1-*H*-pyrazole-3-carboxamide**

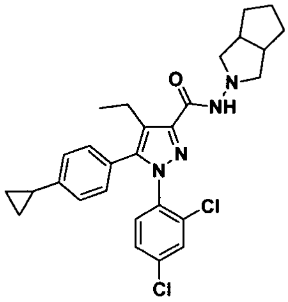


This compound was synthesized according to the method described in example 16 using commercially available 1-aminopyrrolidine in step „e".

$^1$H NMR(DMSO): 0.64-0.67 m (2H); 0.91-0.97 m (2H); 1.07 t (3H); 1.71-1.79 m (4H); 1.82-1.92 m (1H); 2.62 q (2H); 2.85-2.94 m (4H); 7.03-7.09 m (4H); 7.53 dd (1H); 7.70 d (1H); 7.73 d (1H); 9.03 s (1H)

Example 19.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-ethyl-*N*-hexahydro-cyclopenta[c]pyrrole-2-yl-1-*H*-pyrazole-3-carboxamide**

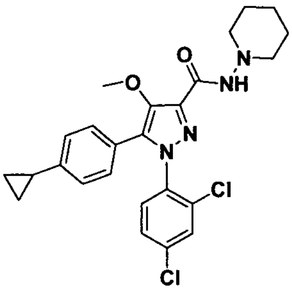


This compound was synthesized according to the method described in example 16 using commercially available 3-amino-3-azabicyclo[3.3.0]octane in step „e".

$^1$H NMR(DMSO): 0.63-0.69 m (2H); 0.91-0.97 m (2H); 1.06 t (3H); 1.36-1.52 m (3H); 1.54-1.74 m (3H); 1.82-1.92 m (1H); 2.54-2.64 m (4H); 3.01-3.07 m (2H); 7.02-7.09 m (4H); 7.53 dd (1H); 7.70 d (1H); 7.74 d (1H); 8.90 s (1H)

Example 20.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methoxy-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide**

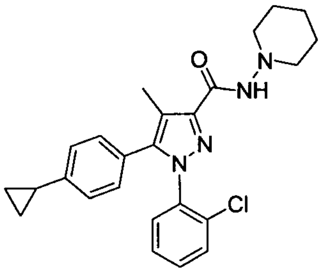


This compound was synthesized according to the method described in example 1 starting from 2-methoxy-1-(4-cyclopropylphenyl)-ethanone (step "b").

$^1$H NMR (500 MHz, DMSO-$d_6$, 25 °C) δ 9.03 (s, 1H); 7.78 (d, $J$ = 2.3 Hz, 1H); 7.75 (d, $J$ = 8.5 Hz, 1H); 7.59 (dd, $J$ = 8.5, 2.3 Hz, 1H); 7.13-7.02 (m, 4H); 3.75 (s, 3H); 2.84-2.73 (m, 4H); 1.91-1.82 (m, 1H); 1.63-1.52 (m, 4H); 1.39-1.29 (m, 2H); 0.97-0.90 (m, 2H); 0.70-0.63 (m, 2H) ppm.

Example 21.

**5-(4-cyclopropylphenyl)-1-(2-chlorophenyl)-4-methyl-N-piperidin-1-yl-1*H*-pyrazole-3-carboxamide**

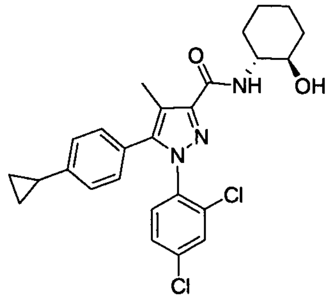


This compound was synthesized according to the method described in example 1 using commercially available 2-chloro-phenylhydrazine hydrochloride in step „c".

$^1$H NMR(CDCl3): 0.64-0.69 m (2H); 0.92-0.99 m (2H); 1.38-1.47 m (2H); 1.71-1.79 m (4H); 1.79-1.87 m (1H); 2.37 s (3H); 2.83-2.89 m (4H); 6.93-7.02 m (4H); 7.25-7.35 m (3H); 7.37-7.7.43 m (1H); 7.68 s (1H)

Example 22.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-((1R,2R)-2-hydroxy-cyclohexyl)-1*H*-pyrazole-3-carboxamide**

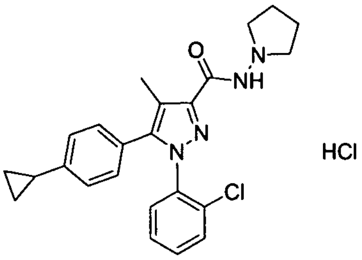


This compound was synthesized according to the method described in example 1 using commercially available *trans*-2-amino-cyclohexanol in step „e".

$^1$H NMR(DMSO): 0.63-0.68 m (2H); 0.90-0.96 m (2H); 1.13-1.30 m (4H); 1.56-1.65 m (2H); 1.82-1.92 m (3H); 2.22 s (3H); 3.35-3.43 m (1H); 3.52-3.61 m (1H); 4.58 d (1H); 7.05 m (4H); 7.54 dd (1H); 7.68 d (1H); 7.68 s (1H); 7.74 d (1H)

Example 23.

**5-(4-cyclopropylphenyl)-1-(2-chlorophenyl)-4-methyl-N-pyrrolidin-1-yl-1*H*-pyrazole-3-carboxamide hydrochloride**

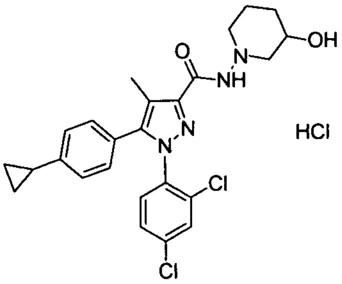


This compound was synthesized according to the method described in example 22 using commercially available 1-aminopyrrolidine in step „e".

$^1$H NMR(CDCl$_3$): 0.64-0.69 m (2H); 0.93-0.99 m (2H); 1.79-1.87 m (1H); 2.23-2.31 m (4H); 2.33 s (3H); 3.86-3.93 m (4H); 6.94-7.03 m (4H); 7.29-7.41 m (4H); 9.50 br s (1H)

Example 24.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(3-hydroxy-piperidin)-1-yl-1*H*-pyrazole-3-carboxamide hydrochloride**

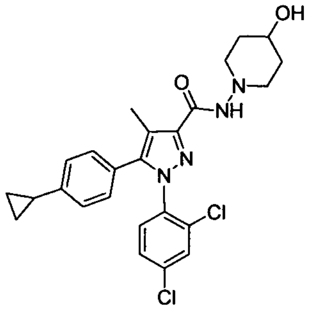


This compound was synthesized according to the method described in example 1 using 3-hydroxy-1-aminopiperidine in step „e".

$^1H$ NMR($CDCl_3$): 0.64-0.72 m (2H); 0.93-1.01 m (2H); 1.65-1.96 m (4H); 2.30 s (3H); 2.33-2.44 m (1H); 3.61-4.12 m (4H); 4.34-4.43 m (1H); 6.92-7.01 m (4H); 7.24-7.38 m (4H); 10.29 br s (1H)

Example 25.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(4-hydroxy-piperidin)-1-yl-1*H*-pyrazole-3-carboxamide hydrochloride**

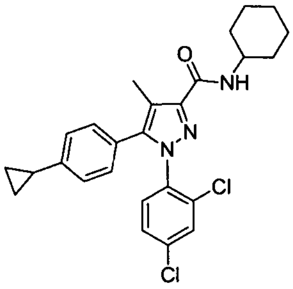


This compound was synthesized according to the method described in example 1 using 4-hydroxy-1-aminopiperidine in step „e".

$^1H$ NMR(DMSO): 0.65-0.69 m (2H); 0.91-0.97 m (2H); 1.44-1.55 m (2H); 1.70-1.78 m (2H); 1.83-1.91 m (1H); 2.20 s (3H); 2.66-2.74 m (2H); 2.88-2.91 m (2H); 3.44-3.51 m (2H); 4.59 d (1H); 7.04 m (4H); 7.55 dd (1H); 7.70 d (1H); 7.74 d (1H); 8.99 br s (1H)

Example 26.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-cyclohexyl-1*H*-pyrazole-3-carboxamide**

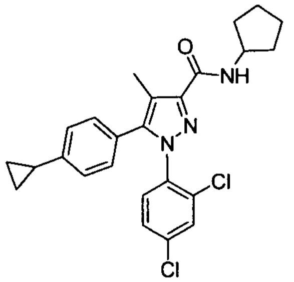


This compound was synthesized according to the method described in example 1 using commercially available cyclohexylamine in step „e".

$^1$H NMR(DMSO): 0.64-0.70 m (2H); 0.90-0.98 m (2H); 1.20-1.41 m (6H); 1.54-1.81 m (4H); 1.83-1.91 m (1H); 2.21 s (3H); 3.70-3.81 m (1H); 7.06 m (4H); 7.55 dd (1H); 7.71 d (1H); 7.75 d (1H); 7.84 d (1H)

Example 27.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-cyclopentyl-1*H*-pyrazole-3-carboxamide**

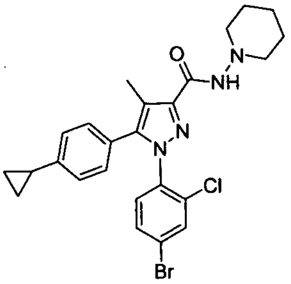


This compound was synthesized according to the method described in example 1 using commercially available cyclopenylamine in step „e".

$^1$H NMR(DMSO): 0.64-0.69 m (2H); 0.91-0.97 m (2H); 1.46-1.72 m (7H); 1.76-1.92 m (3H); 2.22 s (3H); 4.17-4.28 m (1H); 7.06 m (4H); 7.56 dd (1H); 7.70 d (1H); 7.75 d (1H); 7.94 d (1H)

Example 28.

**5-(4-cyclopropylphenyl)-1-(2-chloro-4-bromophenyl)-4-methyl-N-piperidin-1-yl-1*H*-pyrazole-3-carboxamide**

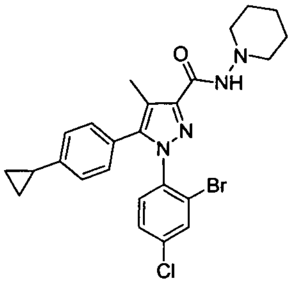


This compound was synthesized according to the method described in example 1 using commercially available 4-bromo-2-chloro-phenylhydrazine hydrochloride in step „c".

$^1$H NMR($CDCl_3$): 0.65-0.73 m (2H); 0.93-1.01 m (2H); 1.39-1.46 m (2H); 1.70-1.78 m (4H); 1.79-1.87 m (1H); 2.35 s (3H); 2.81-2.91 m (4H); 6.99 m (4H); 7.18 d (1H); 7.41 dd (1H); 7.57 d (1H); 7.63 s (1H)

Example 29.

**5-(4-cyclopropylphenyl)-1-(2-bromo-4-chlorophenyl)-4-methyl-N-piperidin-1-yl-1*H*-pyrazole-3-carboxamide**

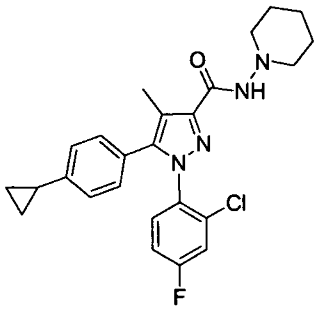


This compound was synthesized according to the method described in example 1 using commercially available 2-bromo-4-chloro-phenylhydrazine hydrochloride in step „c”.

$^1$H NMR($CDCl_3$): 0.66-0.71 m (2H); 0.94-1.01 m (2H); 1.37-1.46 m (2H); 1.71-1.79 m (4H); 1.80-1.88 m (1H); 2.36 s (3H); 2.82-2.89 m (4H); 6.96-7.02 m (4H); 7.22 d (1H); 7.30 dd (1H); 7.60 d (1H); 7.65 s (1H)

Example 30.

**5-(4-cyclopropylphenyl)-1-(2-chloro-4-fluorophenyl)-4-methyl-N-piperidin-1-yl-1*H*-pyrazole-3-carboxamide**

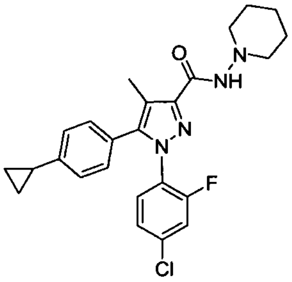


This compound was synthesized according to the method described in example 1 using commercially available 4-fluoro-2-chloro-phenylhydrazine hydrochloride in step „c”.

$^1H$ NMR(DMSO): 0.64-0.72 m (2H); 0.90-0.98 m (2H); 1.29-1.38 m (2H); 1.52-1.62 m (4H); 1.84-1.90 m (1H); 2.20 s (3H); 2.74-2.81 m (4H); 7.03-7.09 m (4H); 7.35 ddd (1H); 7.57 dd (1H); 7.75 dd (1H); 8.99 s (1H)

Example 31.

**5-(4-cyclopropylphenyl)-1-(2-fluoro-4-chlorophenyl)-4-methyl-N-piperidin-1-yl-1*H*-pyrazole-3-carboxamide**

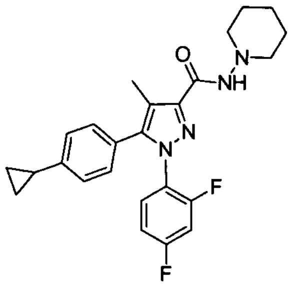


This compound was synthesized according to the method described in example 1 using commercially available 2-fluoro-4-chloro-phenylhydrazine hydrochloride in step „c".

$^1H$ NMR($CDCl_3$): 0.63-0.73 m (2H); 0.95-1.03 m (2H); 1.39-1.46 m (2H); 1.72-1.79 m (4H); 1.80-1.88 m (1H); 2.35 s (3H); 2.82-2.91 m (4H); 6.96-7.03 m (4H); 7.08 dd (1H); 7.17 dd (1H); 7.31 dd (1H); 7.65 s (1H)

Example 32.

**5-(4-cyclopropylphenyl)-1-(2,4-difluorophenyl)-4-methyl-N-piperidin-1-yl-1*H*-pyrazole-3-carboxamide**

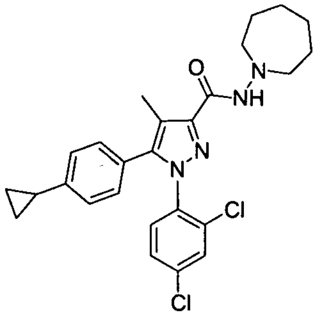


This compound was synthesized according to the method described in example 1 using commercially available 2,4-difluoro-phenylhydrazine hydrochloride in step „c".

$^{1}$H NMR(DMSO): 0.65-0.70 m (2H); 0.91-0.98 m (2H); 1.28-1.37 m (2H); 1.54-1.63 m (4H); 1.84-1.92 m (1H); 2.19 s (3H); 2.72-2.82 m (4H); 7.03-7.08 m (4H); 7.19-7.25 m (1H); 7.35-7.42 m (1H); 7.66-7.73 m (1H); 9.02 s (1H)

Example 33.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-azepan-1-yl-1-*H*-pyrazole-3-carboxamide**

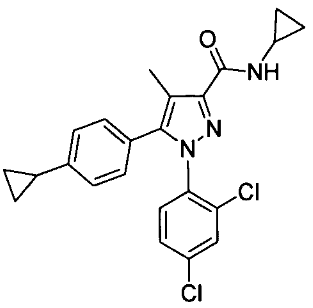


This compound was synthesized according to the method described in example 1 using commercially available 1-aminohomopiperidine in step „e".

$^{1}$H NMR(DMSO): 0.64-0.72 m (2H); 0.91-0.98 m (2H); 1.53-1.59 m (4H); 1.60-1.69 m (4H); 1.84-1.92 m (1H); 2.20 s (3H); 2.95-3.03 m (4H); 7.05 m (4H); 7.55 dd (1H); 7.69 d (1H); 7.75 d (1H); 9.26 s (1H)

Example 34.

**5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-cyclopropyl-1*H*-pyrazole-3-carboxamide**

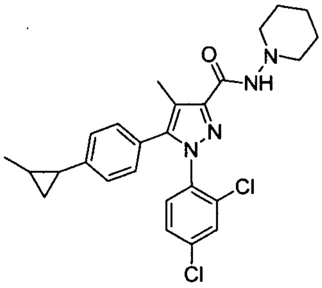


This compound was synthesized according to the method described in example 1 using commercially available cyclopropylamine in step „e".

$^1$H NMR(DMSO): 0.58-0.70 m (6H); 0.90-0.98 m (2H); 1.83-1.92 m (1H); 2.22 s (3H); 2.79-2.87 m (1H); 7.06 m (4H); 7.54 dd (1H); 7.68 d (1H); 7.75 d (1H); 8.18 d (1H)

Example 35.

**5-(4-methyl-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide**

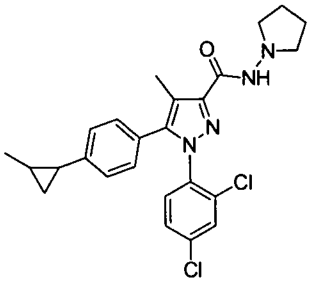


This compound was synthesized according to the method described in example 1 using methyl-cyclopropylbenzene in step „a", which can be prepared by a known method starting from commercially available methylstyrene (S. E. DENMARK and J. P. EDWARDS, Journal of Organic Chemistry 56, (25) 6974-6981 (1991).

$^1$H NMR(DMSO): 0.70-0.78m (1H); 0.83-0.89 m (1H); 1.00-1.08 m (1H); 1.12 s (3H); 1.30-1.39 m (2H); 1.52-1.63 m (5H); 2.19 s (3H); 2.74-2.82 m (4H); 6.99-7.07 m (4H); 7.55 dd (1H); 7.71 d (1H); 7.74 d (1H); 9.00 s (1H)

Example 36.

**5-(4-methyl-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-pyrrolidin-1-yl-1-*H*-pyrazole-3-carboxamide**

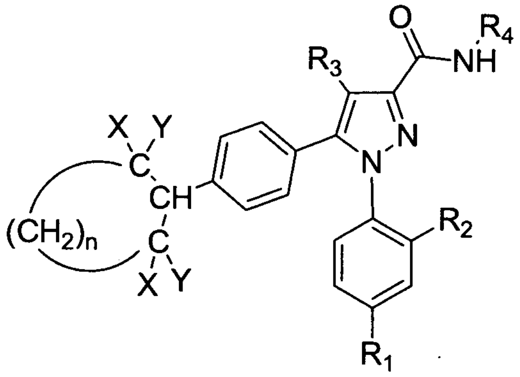


This compound was synthesized according to the method described in example 35 using commercially available 1-amino-pyrrolidine in step „e".

$^1$H NMR(DMSO): 0.70-0.78m (1H); 0.83-0.89 m (1H); 1.00-1.09 m (1H); 1.12 s (3H); 1.53-1.62 m (1H); 1.69-1.79 m (4H); 2.20 s (3H); 2.84-2.93 m (4H); 6.99-7.07 m (4H); 7.55 dd (1H); 7.70 d (1H); 7.75 d (1H); 9.03 s (1H)

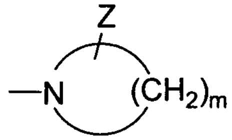
## CLAIMS:

1. New compounds of formula (I),

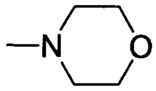


(I)

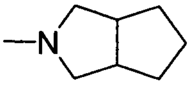
a.)



b.)



c.)



wherein

- n is an integer from 0 to 3,
- X and Y are each independently hydrogen, halogen, or $C_1$-$C_5$ alkyl group,
- $R_1$ and $R_2$ are each independently hydrogen, halogen, $C_1$-$C_4$ alkyl group or $C_1$-$C_4$ alkylmercapto group,
- $R_3$ is hydrogen, $C_1$-$C_4$ alkyl group or $C_1$-$C_4$ alkoxy group,

- $R_4$ is a cycloalkyl ring having about 3 to about 6 members ring, optionally substituted with a hydroxy group or a group having formula a.), b.) and c.) where
- m is an integer from 4 to 6,
- Z is hydrogen, halogen, $C_1$-$C_4$ alkyl, hydroxy, trifluoromethyl or methoxymethyl group,

and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof.

2. 5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-pyrrolidine-1-yl-1-*H*-pyrazole-3-carboxamide,

5-(4-cyclopropylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide

5-(4-cyclobutylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide

5-(4-cyclopentylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide

5-(4-cyclohexylphenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidin-1-yl-1-*H*-pyrazole-3-carboxamide

3. Process for the synthesis of compounds of claims 1-2, characterized by
   a) reacting compound of formula (II), wherein the meaning of X, Y and n is the same as mentioned before with compound of formula (III), wherein the meaning of $R_3$ is the same as mentioned before to give compound of formula (IV), wherein X, Y, n and $R_3$ is the same as mentioned before,
   b) which is reacted with imidazol-1-yl-oxo-acetic acid ethyl ester in the presence of lithium bis(trimethylsilyl)amide to yield the diketon esters (V), wherein the meaning of X, Y, n and $R_3$ is the same as mentioned before,
   c) then reacting the obtained compound of formula (V) with the appropriate substituted phenyl hydrazine hydrochloride (VI), wherein the meaning of $R_1$ and $R_2$ is the same as mentioned before to give compounds of formula(VII), wherein the meaning of X, Y, n, $R_1$, $R_2$ and $R_3$ is the same as mentioned before,

d) then hydrolyzing the ester groups of compounds of formula (VII) with KOH to give compounds having formula (VIII) as defined in claim 1,

e) which is reacted with oxalyl chloride, then reacted with compounds of formula (IX), wherein the meaning of $R_4$ is the same as above mentioned to yield compounds of formula (I).

4. Pharmaceutical composition containing a compound of claims 1-2 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof as well as one or more pharmaceutically acceptable adjuvant and auxiliary material.

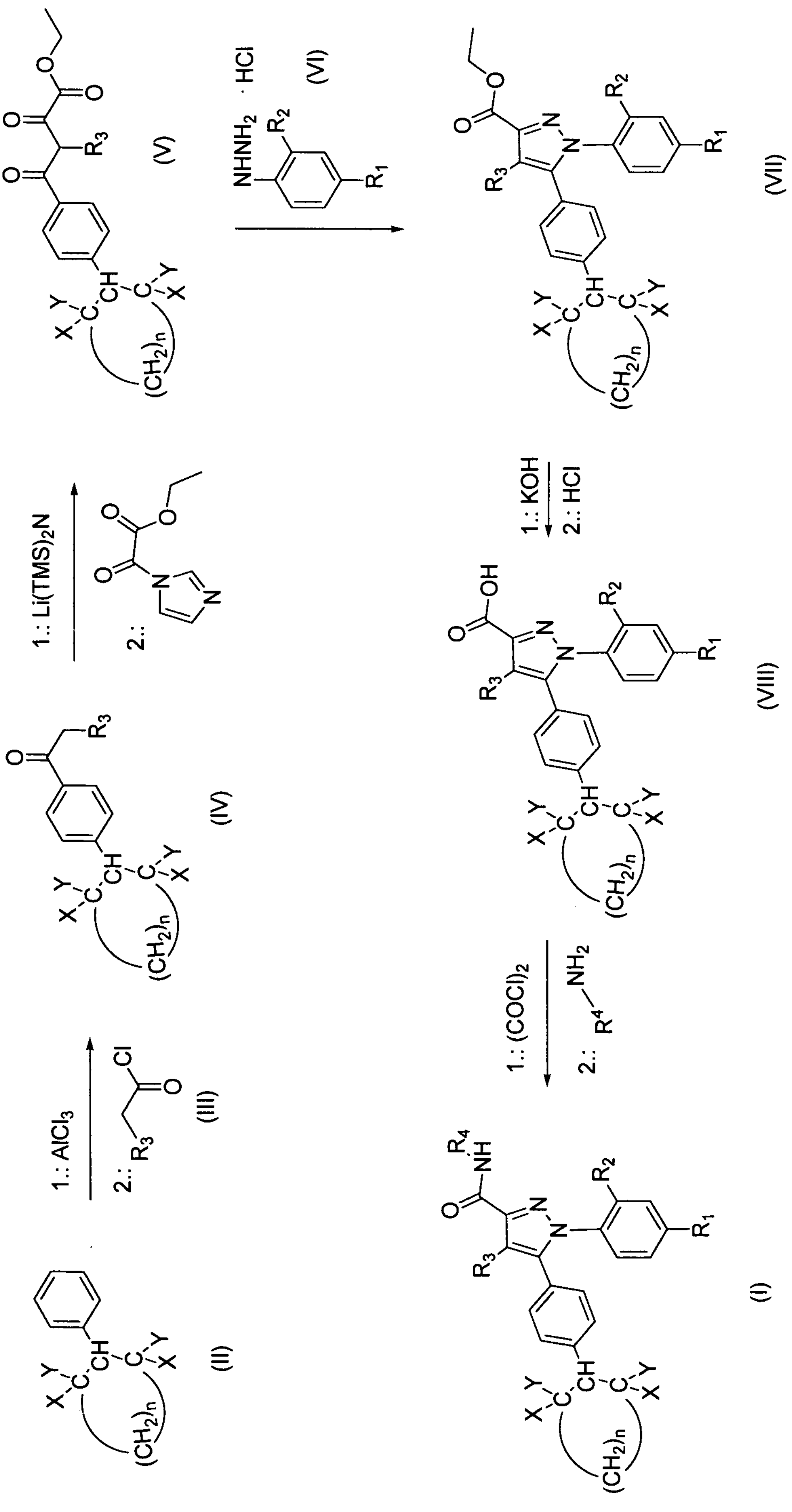
5. Use of a compound of claims 1-2 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof for manufacturing a pharmaceutical composition for treating and/or preventing condition requiring influence on cannabinoid receptor.

6. A use according to claim 5, wherein the cannabinoid receptor is cannabinoid CB1 receptor.

7. Method of treating and/or preventing condition requiring influence on cannabinoid receptor, characterized by administering to a mammal to be treated – including human – effective amount/amounts of a compound of claims 1-2 and/or geometric isomers and/or stereoisomers and/or diastereomers and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof.

8. A method according to claim 7, wherein the cannabinoid receptor is cannabinoid CB1 receptor.

Scheme 1.


(II)
1.: AlCl3
2.: R3 (III)
(IV)
1.: Li(TMS)2N
2.:
(V)
NHNH2 · HCl
R2
R1
(VI)
(VII)
1.: KOH
2.: HCl
(VIII)
1.: (COCl)2
2.: R4–NH2
(I)
X
Y
C
CH
(CH2)n
R3
R4
NH
N
OH
O

# INTERNATIONAL SEARCH REPORT

International application No
PCT/HU2007/000126

**A. CLASSIFICATION OF SUBJECT MATTER**
INV. C07D401/12 C07D231/14

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | WO 2004/058744 A (SANOFI SYNTHELABO [FR]; MISCORIA GILLES [FR]; RINALDI MURIELLE [FR]; S) 15 July 2004 (2004-07-15)<br>claims 1,5<br>----- | 1,4,5,7 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

| | |
|---|---|
| Date of the actual completion of the international search<br>11 March 2008 | Date of mailing of the international search report<br>28/03/2008 |
| Name and mailing address of the ISA/<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31–70) 340–2040, Tx. 31 651 epo nl,<br>Fax: (+31–70) 340–3016 | Authorized officer<br>Bader, Karl Günther |

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box II.1

Although claims 7,8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box II.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU2007/000126

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/HU2007/000126

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