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(54) Title: NEW 1,2,4-TRIAZOLE-3-CARBOXAMIDE DERIVATIVES

(57) Abstract: The invention relates to new 1,2,4-triazole-3-carboxamide derivatives, as well as to their use for the treatment of diseases in which cannabinoid receptors are involved.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

NEW 1,2,4-TRIAZOLE-3-CARBOXAMIDE DERIVATIVES

FIELD OF THE INVENTION

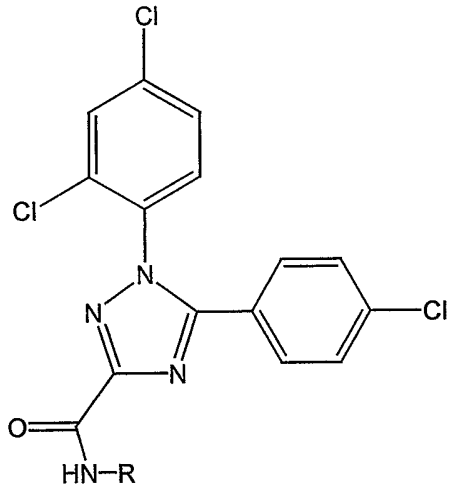
The present invention refers to new 1,2,4-triazole-3-carboxamide derivatives and to their use as medical products intended to human and/or veterinary therapy, for the treatment of several diseases in which cannabinoid receptors are involved.

BACKGROUND OF THE INVENTION

Cannabinoid receptors belong to the family of G-protein coupled receptors. Nowadays, there have been identified and cloned two types of cannabinoid receptors CB_1 and CB_2 (Howlett A. C. *et al.*, Pharmacol. Rev., 2002, 54, 161-202). These receptors are involved in the modulation of different functions, such as memory, cognition, appetite, immune responses, pain, etc., and, therefore, the compounds which interact with said receptors will be useful in those therapeutic fields in which they are involved (R.G. Pertwee, Exp. Opin. Invest. Drugs., 2000, 9 7-19).

Cannabinoid ligands with a large variety of structures have been disclosed (P. Goya et al., Exp. Opin. Ther. Pat., 2000, 10 1529-1538). An aim of great interest during the last years has been the structure-activity relationship studies of said compounds (Reggio H. P. *et al.*, Cur. Pharm. Design, 2003, 9 1607-1633). In 1994, it was identified the first antagonist of CB_1 cannabinoid receptor, SR141716A, a pyrazole-3-carboxamide derivative (Rinaldi-Carmona M. *et al.*, FEBS Lett., 1994, 350 240-244). Nowadays, SR141716A is the object of clinical assays as appetite suppressor (Drugs R D, 2002, 3 65-66).

Triazole derivatives with cannabinoid properties are disclosed in the literature (WO-03082833) (Dyck B. *et al.*, Bioorg. Med. Chem. Lett., 2004, 14 1151-1154). Dyck B. *et al.* in Bioorg. Med. Chem. Lett., 2004, 14 1151 disclose triazole-3-carboxamide derivatives of formula:



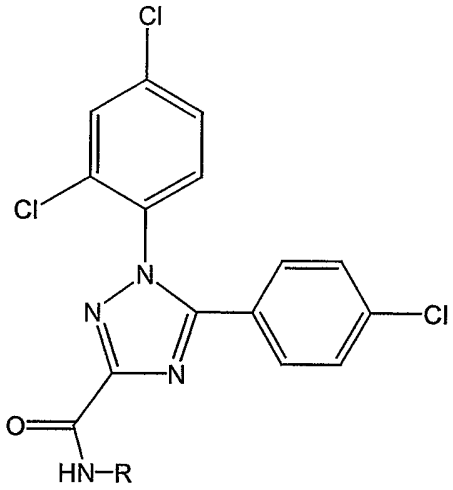
in which R represents 3-azabicyclo[3.3.0]octan-3-yl, 1-homopiperidyl or $CH_2CH_2N(3\text{-}CF_3C_6H_4)CH_2CH_2$.

These compounds have affinity for CB_1 cannabinoid receptors. However, these ligands are less potent in front of CB_1 receptor than the reference pyrazole SR141716A.

DESCRIPTION OF THE INVENTION

The object of the present invention is to provide new 1,2,4-triazole-3-carboxamide derivatives, which have affinity for cannabinoid receptors, and more particularly, for CB_1 receptors.

Therefore, the present invention refers to a 1,2,4-triazole-3-carboxamide derivative of general formula (I):



(I)

in which R represents a group which is selected from piperidino, morpholino, cyclohexyl and 1-adamantyl.

The process for preparing a 1,2,4-triazole-3-carboxamide derivative of general formula (I), according to the first aspect of the invention, can be carried out according to that shown in the Reaction Scheme.

The synthetic route described in said Scheme consist, firstly, on the preparation of ethyl 1-(2,4-dichlorophenyl)-5-(4-chlorophenyl)-1,2,3-triazole-3-carboxilate from 2,4-dichloroaniline and 4-chlorobenzoyl chloride. For that, 2,4-dichloroaniline was submitted to diazotization conditions in presence of tetrafluoroboric acid. The resulting diazonium salt reacts with ethyl acetoacetate, producing the ethyl 2-(2,4-dichlorophenyl)hidrazono-3-oxobutanoate. This is treated with bromine, and, subsequently, with ammonium hydroxide, obtaining the ethyl 2-[*N'*-(2,4-dichlorophenyl) hidrazinyl]-2-iminoacetate. This iminoacetate is cycled by reaction with 4-chlorobenzoyl chloride in presence of piridine, obtaining ethyl 1-(2,4-dichlorophenyl)-5-(4-chlorophenyl)-1,2,4-triazole-3-carboxilate.

The 1,2,4-triazole-3-carboxamide derivatives object of the present invention are obtained from the corresponding ethylcarboxilate in one-pot procedure. In a heterocyclic series, the transformation of the ester in the amide generally involves three steps: hydrolysis of the ester in acid medium followed by the formation of the acid chloride and, finally, the reaction with an amine.

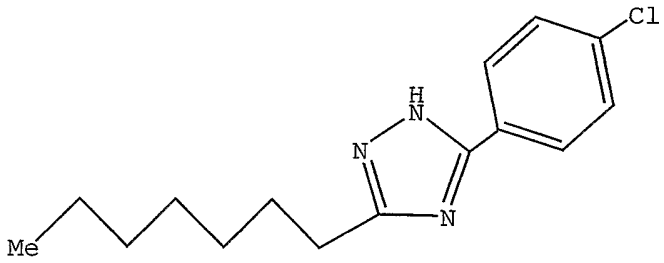
An alternative process for obtaining 1,2,4-triazole-3-carboxamide derivatives of general formula (I) would be that described by A. Benderly *et al.*, Tetrahedron Lett., 1988, 29 739-740, in which it is disclosed the preparation of hydrazides from esters in mild conditions. Briefly, said process consists on *in situ* formation of an aluminium complex by reacting trimethylaluminium with the corresponding amines or hydrazines, which reacts, subsequently, with ethyl 1-(2,4-dichlorophenyl)-5-(4-chlorophenyl)-1,2,3-triazole-3-carboxilate.

Reaction Scheme

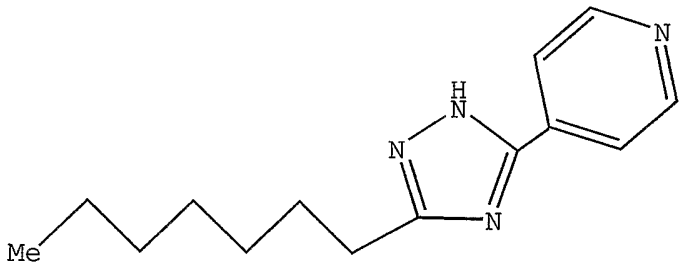
(a) i) $NaNO_2$, HBF_4, 0 °C.; ii) ethyl acetoacetate, NaOAc, EtOH, H_2O, 0 °C; (b) i) Br_2, NaOAc, AcOH; ii) NH_4OH, acetone; (c) 4-clorobenzoyl chloride, piridine, 1,4-dioxane, reflux; (d) piridine, 1,4-dioxane, reflux; (e) 1-aminopiperidine, 4-aminomorpholine, ciclohexylamine or 1-aminoadamantane, $Al(Me)_3$, N_2, CH_2Cl_2, 40 °C.

Another aspect of the present invention are the following 1,2,4-triazole-3-carboxamide derivatives:

(a)



(b)



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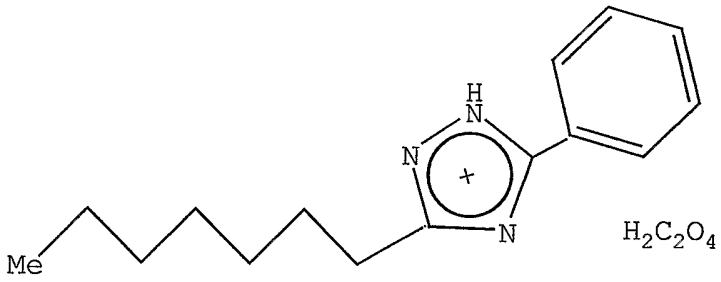

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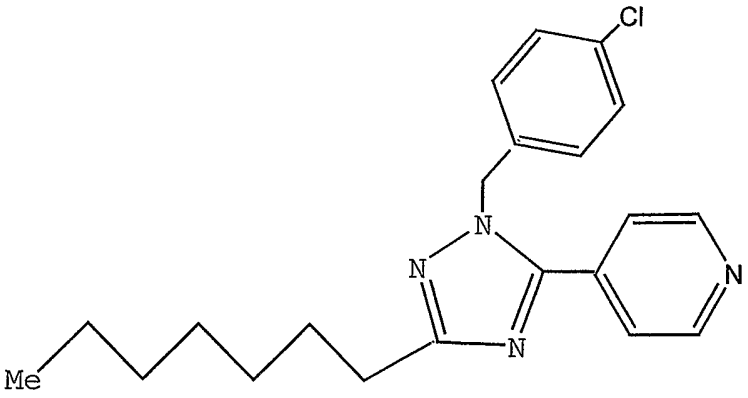
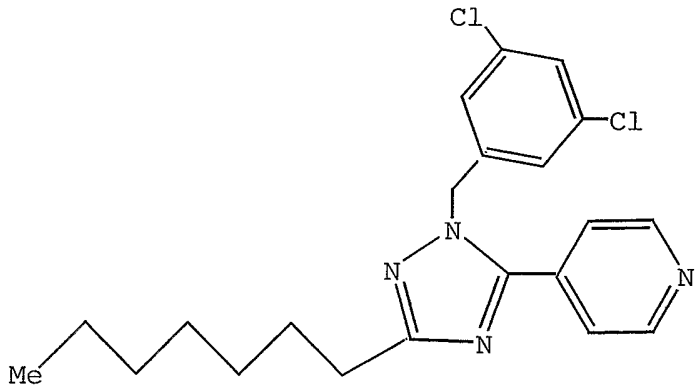
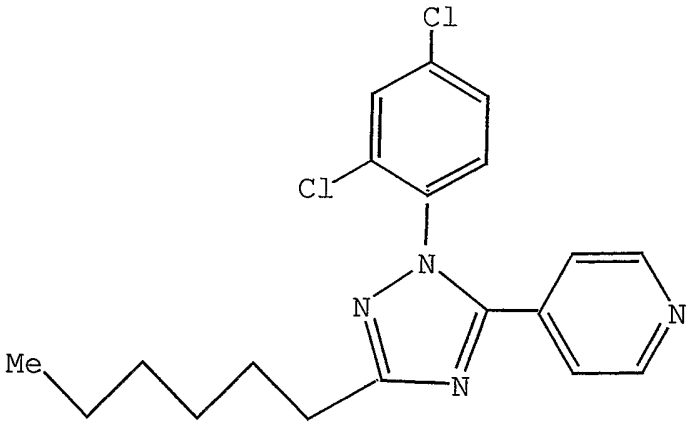


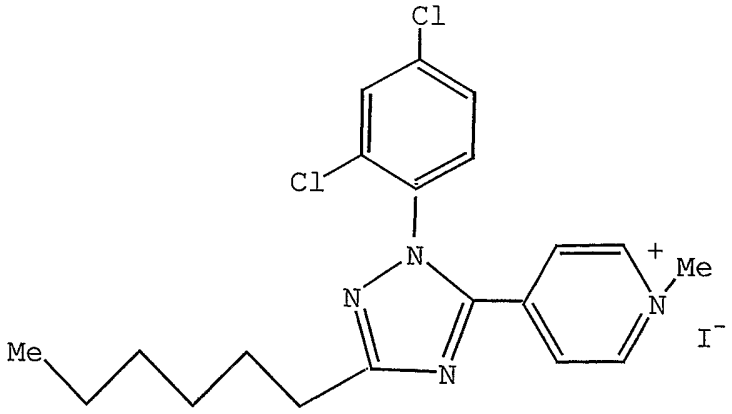
(e)



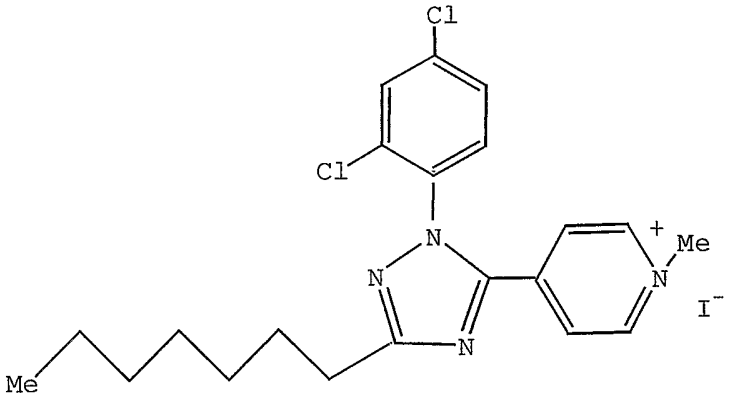
(f)



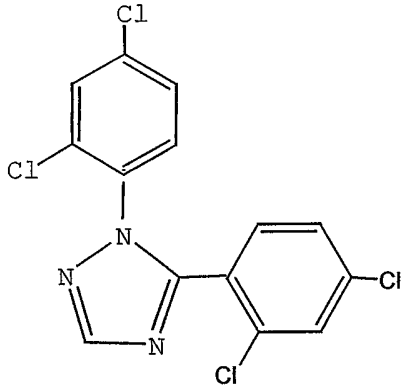
(g)



(h)



(i)



Derivatives (a)-(i) can be obtained following procedures well known for the person skilled in the art, such as those disclosed in the applications WO 04/26301 and WO 03/082833.

The inventors of the present invention have proved that the compounds of general formula (I), according to the first aspect of the invention have affinity for cannabinoid receptors.

In the present invention, the concept of "affinity for cannabinoid receptors" is determined assessing the binding of a derivative of general formula (I), according to the first aspect of the invention, to the cannabioid receptors, in particular CB_1 receptors, by displacement of radioligands *in vitro*. Said assessment is performed

following well known protocols for the person skilled in the art.

The characterization of the cannabinoid activity of the new derivatives, described in the present invention, was performed assessing their ability to displace the radioligand [^{3}H]-CP55940 from CB_1 cannabinoid receptors. The compounds of the present invention showed a significant affinity for the CB_1 cannabinoid receptor. At a concentration of 10^{-6} M, the derivatives of general formula (I), in which R represents a piperidino, morpholino and cyclohexyl group, displace the radioligand [^{3}H]-CP55940 at 31.7, 32.1 y 55.9% respectively. When R represents a 1-adamantyl group in the derivative of general formula (I), it was proved that said compound showed a greater affinity with a displacement of 77.5% (K_i = 498.2 nM).

Therefore, a second aspect of the present invention refers to a derivative of general formula (I), according to the first aspect of the invention to use as a medicament, preferably as antagonist of cannabinoid receptors and, more preferably, as antagonist of CB_1 receptors.

It was observed, furthermore, that the 1,2,4-triazole-3-carboxamide derivatives of general formula (I), act suppressing the appetite, reducing the dyskinesia caused by L-dopa in Parkison patients, permitting the treatment of acute schizophrenia and improving the cognitive and memory dysfunctions associated to the Alzheimer disease.

In a preferred embodiment, the present invention refers to a pharmaceutical composition which comprises at least one compound of general formula (I), according to the first aspect of the invention, and at least one pharmaceutically acceptable diluent and/or adjuvant to use as a medicament, more preferably to use as antagonist of

cannabionid receptors and, even more preferably, to use as antagonist of CB_1 receptors.

Said pharmaceutical composition can be adapted to its topical, oral or parenteral application, among others.

The diluent and/or adjunvant will be selected depending on the desired application of the pharmaceutical composition.

Because of the affinity of the compounds of the present invention for the cannabinoid receptors, said compounds can be used as active principles in medicaments for the treatment of diseases associated with cannabinoid receptors.

In the present invention by "disease associated with the cannabinoid receptors" is meant a pathological state which is started by the lack of modulation in the cannabinoid receptors.

Therefore, a third aspect of the invention refers to the use of at least one 1,2,4-triazole-3-carboxamide derivative of general formula (I), according to the first aspect of the invention, for the manufacture of a medicament for the treatment and/or prevention of diseases in which cannabinoid receptors are involved, preferably CB_1 receptors and, more preferably, being selected said disease from: glaucoma, bronchial asthma and chronic bronchitis; allergies, such as the contact dermatitis or allergic conjunctivitis; arthritis; pain; diseases associated with organ transplants; motor diseases related to Tourette syndrome; Parkinson disease or Huntington chorea; malignant glioma; multiple sclerosis; emesis related to anti-cancer chemotherapy; appetite.

Now there are included the following illustrative and no limitative examples.

EXAMPLES OF EMBODIMENT OF THE INVENTION

In the examples are used the following abbreviations:

ac: aqueous
AcOEt: ethyl acetate
AcOH: acetic acid
$Al(Me)_3$: trimethylaluminium
Anal.: Elemental analysis
Br_2: bromine
CH_2Cl_2: dichloromethane
EtOH: ethanol
Et_2O: ethyl ether
g: gram
HBF_4: boron tetrahidrofluoride
HCl: hydrochloric acid
H_2O: water
int. rel.: relative intensity
K_2CO_3: potassium carbonate
min: minutes
ml: mililitre
µl: microlitre
$NaNO_2$: sodium nitrite
NaOAc: sodium acetate
NaOH: sodium hydroxide
Na_2SO_4: sodium sulphate
NH_4OH: ammonium hydroxide
P.f.: melting point
t.a.: room temperature

Example 1.- Preparation and obtaining of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1*H*-1,2,4-triazole-3-carboxamide

A) Ethyl 2-(2,4-Dichlorophenyl)hidrazono-3-oxobutanoate

To a solution of HBF_4 (13 ml, 48%) in H_2O(13 ml), 8.00 g. of 2,4-dichloroaniline are added. It is cooled in an ice bath and a cold solution of 3.41 g. of $NaNO_2$ in H_2O (5 ml) is added on it. The mixture is stirred 30 min. at 0°C, and it is stirred continuously until t.a. is reached. The resulting diazonium salt is filtered, washed with HBF_4 ac., EtOH and Et_2O, and dried. A solution of the salt in 250 ml of EtOH is added to 6.25 ml of a solution at 0°C of ethyl acetoacetate, EtOH (25 ml), 11.12 g. of NaOAc and H_2O (25 ml) and the mixture is stirred at this temperature for 1 h. The resulting solid is filtered, washed with H_2O, dried and recrystallized with cyclohexane, obtaining 4.89 g. of desired product. P.f. = 118-121 °C. EM (ES^+) m/z (Rel. Int.): 303 (100 %) $[M+H]^+$. Anal. ($C_{12}H_{12}Cl_2N_2O_3$) % theoretical (% experimental) C: 47.54 (47.80); H: 3.99 (4.21); N: 9.24 (9.43).

B) Ethyl 2-[*N'*-(2,4-Dichlorophenyl)hidrazino]-2-iminoacetate

To a solution of 1.44 g of the compound obtained in the previous step A and 3.52 g of NaOAc in AcOH (35 ml), 243 µl of Br_2 are added dropwise.

After stirring the solution 30 min. at t.a., it is poured onto 100 ml. of H_2O, and it is extracted with CH_2Cl_2 (3x50 ml). The organic phase is dried over Na_2SO_4 anhydrous, the solvent is removed in vacuum, and the obtained residue is dissolved in 50 ml of acetone. On this reaction mixture a solution of 4 ml of 30% NH_4OH in 10 ml of acetone is added dropwise, and the mixture is stirred

at t.a. for 1 h. After this time, the solvent is removed, the residue is dissolved in 100 ml of 10% HCl and is washed with toluene (3 x 50 ml). The aqueous phase is basified with NaOH until pH 8, precipitating a solid. This solid is filtered and suspended in hot EtOH. The solid impurity is filtered. The liquid phase is treated with active carbon for 30 min, it is filtered on celite and the solvent is removed in vacuum, obtaining 1.76 g of the desired product. P.f. = 82-87 °C. EM (ES^+) m/z (int. rel.): 276 (100 %) $[M+H]^+$. Anal. ($C_{10}H_{11}Cl_2N_3O_2$) % theoretical (% experimental) C: 43.50 (43.61); H: 4.02 (4.30); N: 15.22 (15.25).

C) Ethyl 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-1*H*-1,2,4-triazole-3-carboxilate

A mixture of 0.60 g of the compound obtained in the previous step B, 0.20 ml of pyridine, and 0.32 ml of 4-chlorobenzoyl chloride is dissolved in 50 ml of 1,4-dioxane and it is stirred at reflux for 3 h. Then, the solvent evaporates, the obtained residue is dissolved in 120 ml of CH_2Cl_2 and it is washed with HCl 1M (3 x 50 ml), H_2O (50 ml), saturated solution of K_2CO_3 (3 x 50 ml) and H_2O again (50 ml). The organic phase is dried over anhydrous Na_2SO_4, the solvent is removed, and the obtained residue is purified by medium pressure chromatography, using cyclohexane/AcOEt (8:1) as eluent. 0.31 g. of desired product are isolated. P.f. = 113-118 °C. EM (ES^+) m/z (rel. Int.): 296 (90 %) $[M+H]^+$. Anal. ($C_{17}H_{12}Cl_3N_3O_2.1.25H_2O$) % theoretical (% experimental) C: 48.71 (48.74); H: 3.48 (3.37); N: 10.02 (9.98).

D) 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-(piperidin-1-yl)-1*H*-1,2,4-triazole-3-carboxamide

To a solution of 0.32 ml of 1-aminopiperidine in dry CH_2Cl_2 (3-5 ml) under N_2 atmosphere, a solution of 1.50 ml of a 2M solution of $Al(Me)_3$ in heptane is added. The mixture is stirred at t.a. and under N_2 atmosphere for 1

h. Then a solution of 240 mg. of the compound obtained in the previous step C in dry CH_2Cl_2 (3-6 ml) is added dropwise, and it is stirred continuously at 35-50 °C (external t.) for 21 h. Then, the solution is poured onto HCl 1N (20-30 ml). The formed biphasic solution is stirred at 40°C (external t.) for 30 min. Then it is cooled, and it is extracted with CH_2Cl_2 (3 x 20 ml). The organic phase is dried over Na_2SO_4, the solvent is removed, and the obtained residue is purified by medium pressure chromatography [cyclohexane/AcOEt (25:1)-cyclohexane/AcOEt (3:1)]. 214 mg. of desired product are obtained. P.f.= 115-118 °C. EM (ES^+) m/z (rel. int.): 450 (99 %) $[M+H]^+$. Anal. ($C_{20}H_{18}Cl_3N_5O$) % theoretical (% experimental) C: 53.29 (53.25); H: 4.03 (4.20); N: 15.54 (15.38).

Example 2.- Preparation and obtaining of 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-morpholino-1*H*-1,2,4-triazole-3-carboxamide

A) 5-(4-Chlorophenyl)-1-(2,4-dichlorophenyl)-*N*-morpholino-1*H*-1,2,4-triazole-3-carboxamide

The desired compound is prepared according to the embodiment described in step D of the Example 1, from 0.18 ml of 4-aminomorpholine, 0.95 ml of an hexane solution of $Al(Me)_3$ 2M, and 150 mg of the obtained compound in step C of the Example 1 with a reaction time of 2.5 h (instead of 21 h of Example 1). The raw material is purified by toluene recrystallization. 161 mg of the desired compound are obtained. P.f.= 193-195 °C. EM (ES^+) m/z (rel. Int.): 452 (100%) $[M+H]^+$. Anal. ($C_{19}H_{16}Cl_3N_5O_2.0.5C_6H_5CH_3$) % theoretical (% experimental) C: 54.18 (53.62); H: 4.04 (4.41); N: 14.04 (14.38).

Example 3.- Preparation and obtaining of 5-(4-chlorophenyl)-*N*-cyclohexyl-1-(2,4-dichlorophenyl)-1*H*-1,2,4-triazole-3-carboxamide

A) 5-(4-Chlorophenyl)-*N*-cyclohexyl-1-(2,4-dichlorophenyl)-1*H*-1,2,4-triazole-3-carboxamide

The desired compound is prepared according to the embodiment described in step D in the Example 1, from 0.18 ml cyclohexylamine, 0.76 ml of an hexane solution of $Al(Me)_3$ 2M, and 120 mg of the compound obtained in step C of Example 1 with a reaction time of 4.5 h (instead of 21 h of Example 1). The raw material is purified by toluene recrystallization and flash chromatography [cyclohexane/AcOEt (2:1)]. 83 mg of the desired compound are obtained. P.f.= 181-185 °C. EM (ES^+) m/z (rel. int.): 449 (100 %) $[M+H]^+$. Anal. ($C_{21}H_{19}Cl_3N_4O$) % theoretical (% experimental) C: 56.08 (55.96); H: 4.26 (4.35); N: 12.46 (12.18).

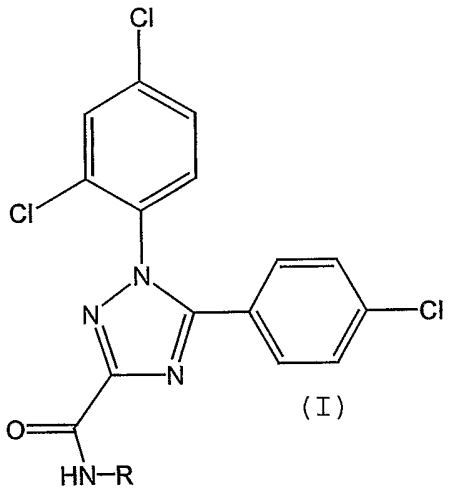
Example 4.- Preparation and obtaining of 5-(4-chlorophenyl)-*N*-(1-adamantyl)-1-(2,4-dichlorophenyl)-1*H*-1,2,4-triazole-3-carboxamide

A) 5-(4-Chlorophenyl)-*N*-(1-adamantil)-1-(2,4-dichlorophenyl)-1*H*-1,2,4-triazole-3-carboxamide

The desired compound is prepared according to the embodiment described in step D in the Example 1, from 145 mg 1-adamantanylamine, 0.48 ml of an hexane solution of $Al(Me)_3$ 2M and 76 mg of the compound obtained in step C in the Example 1 with a reaction time of 26 h (instead of 21 h. in the Example 1). The raw material is purified by flash chromatography [cyclohexane/AcOEt (4:1)]. 75 mg. of the desired compound are obtained. P.f.= 185-189 °C. EM (ES^+) m/z (rel. int.): 501 (100 %) $[M+H]^+$. Anal. ($C_{25}H_{23}Cl_3N_4O$) % theoretical (% experimental) C: 59.83 (59.67); H: 4.62 (4.90); N: 11.16 (10.87).

CLAIMS

1. 1,2,4-triazole-3-carboxamide derivative of general formula (I):



(I)

wherein R represents a group selected from piperidino, morpholino, cyclohexyl and 1-adamantyl.

2. Derivative according to claim 1 for use as a medicament.

3. Derivative according to claim 2 for use as antagonist of cannabinoid receptors.

4. Derivative according to any of claims 2-3 for use as antagonist of CB_1 receptors.

5. Pharmaceutical composition comprising at least one derivative according to claim 1, and at least one pharmaceutically acceptable diluent and/or adjuvant for use as a medicament.

6. Pharmaceutical composition according to claim 5 for use as antagonist of cannabinoid receptors.

7. Pharmaceutical composition according to claim 6 for use as antagonist of CB_1 receptors.

8. Use of a derivative of 1,2,4-triazole-3-carboxamide of general formula (I), according to claim 1 for the manufacture of a medicament for the treatment and/or

prevention of dysfunctions related with cannabinoid receptors.

9. Use according to claim 8, wherein said dysfunction is one selected from: glaucoma, bronchial asthma and chronic bronchitis, for allergies as contact dermatitis, allergic conjunctivitis, for arthritis, for pain, for diseases or disorders caused by organ transplant, for motor diseases related to Tourette syndrome, Parkinson disease or Huntingdon chorea, for malign gliomas, for multiple sclerosis, for emisis related to anticancer chemotherapy, and for appetite.

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INTERNATIONAL SEARCH REPORT

Inter | Application No
PCT/IB2005/002720

A. CLASSIFICATION OF SUBJECT MATTER
C07D249/10 A61K31/4196 A61P11/06 A61P27/06 A61P19/02

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 A61K A61P

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, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/106614 A1 (LANGE ET. AL.) 3 June 2004 (2004-06-03) page 1, paragraph 1 - page 2, paragraph 19; claims; examples 1,3,6	1-9
X	B. DYCK ET. AL.: "Potent imidazole and triazole CB1 receptor antagonists related to SR141716" BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 14, 2004, pages 1151-1154, XP002359079 cited in the application table 2	1-9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in 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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 December 2005	02/01/2006

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Helps, I

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INTERNATIONAL SEARCH REPORT

Intern: Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	J.L. LANGE ET. AL.: "Bioisosteric Replacements of the Pyrazole moiety of Rimonabant: Synthesis, Biological Properties, and molecular Modelling Investigations of Thiazoles, Triazoles, and Imidazoles as Potent and Selective CB1 Cannabinoid Receptor Antagonists. page 1824," JOURNAL OF MEDICINAL CHEMISTRY, vol. 48, no. 6, 24 March 2005 (2005-03-24), pages 1823-1838, XP002359080 Page 1824, Scheme 2, compound 28 -----	1-9

INTERNATIONAL SEARCH REPORT

tion on patent family members

Intern: Application No
PCT/IB2005/002720

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2004106614 A1	03-06-2004	AU 2003299024 A1	08-04-2004
		BR 0312020 A	22-03-2005
		CA 2491394 A1	01-04-2004
		CN 1671377 A	21-09-2005
		WO 2004026301 A1	01-04-2004
		HR 20050053 A2	30-04-2005