(CONVENTION. By one or more persons and/or a Company.)

Form 4

LODGED AT SUB-OFFICE
17 APR 1986
Melbourne

599024

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

CONVENTION APPLICATION FOR A PATENT

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 2.5.90

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es).

~~We~~ / ~~I~~ (1) CIBA-GEIGY AG,

of Klybeckstrasse 141, 4002 Basle, Switzerland

(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled: (2)

FLUORINATED BENZYLTRIAZOLES

(3) Here insert number(s) of basic application(s)

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3)

1663/85-5

(4) Here insert Name of basic Country or Countries, and basic date or dates

for a patent or similar protection made in (4) Switzerland

on 18th April 1985

AUSTRALIAN PATENT OFFICE

ADDRESS FOR SERVICE ALTERED

~~My~~ / Our address for service is ~~Messrs. Edwd. Waters & Sons, Patent Attorneys,~~ 50 Queen Street, Melbourne, Victoria, Australia. ARTHUR S. CAVE & CO SYDNEY N.S.W.

DATED this 16th day of April 1986.

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association.

(5) CIBA-GEIGY AG

by

W. F. Dancer

Reg'd. Patent Attorney

To:

THE COMMISSIONER OF PATENTS.

Edwd. Waters & Sons, Melbourne.

AU Case 4-15323/14247/+ FORM 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952 - 1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made by CIBA-GEIGY AG for a patent for an invention entitled:

Fluorinated benzyltriazoles

We, Arnold Seiler and Ernst Altherr of CIBA-GEIGY AG, Klybeckstrasse 141, 4002 Basle, Switzerland
do solemnly and sincerely declare as follows:

1. We are authorised by the applicant for the patent to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 on the Act was(~~were~~) made in Switzerland on April 18, 1985

by CIBA-GEIGY AG, 4002 Basle, Switzerland.

3. René Meier, Rickenbacherstrasse 76, 4463 Buus, Switzerland

is(~~are~~) the actual inventor(s) of the invention and the facts upon which the applicant is entitled to make the application are as follows:
The said applicant is the assignee of the actual inventor(s).

4. The basic application(s) referred to in paragraph 2 of this Declaration was(~~were~~) the first application(s) made in a Convention country in respect of the invention the subject of the application.

DECLARED at Basle, Switzerland on March 24, 1986

CIBA-GEIGY AG

pp Seiler pp Meier

To: The Commissioner of Patents

(12) PATENT ABRIDGMENT (11) Document No. AU-B-56319/86
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 599024

(54) Title
FLUORINATED BENZYL TRIAZOLES

International Patent Classification(s)
(51)[4] C07D 249/04 A61K 031/41

(21) Application No. : 56319/86 (22) Application Date : 17.04.86

(30) Priority Data

(31) Number	(32) Date	(33) Country
1663/85	18.04.85	CH SWITZERLAND

(43) Publication Date : 23.10.86

(44) Publication Date of Accepted Application : 12.07.90

(71) Applicant(s)
CIBA-GEIGY AG

(72) Inventor(s)
RENE MEIER

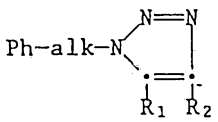
(74) Attorney or Agent
ARTHUR S. CAVE & CO.

(56) Prior Art Documents
AU 566730 22807/83 C07D 249/04
GB 1511195
EP 114347

(57) ANTI - CONVULSANT.

CLAIM

1. A novel fluorinated 1-(α-phenylalkyl)-1H-1,2,3-triazole of the formula



(I),

wherein Ph is an o-fluorinated phenyl radical which may be additionally substituted by up to 2 chlorine atoms inclusive, by 1 fluorine atom and 1 chlorine atom, or by up to 2 fluorine atoms inclusive, alk is methyiene, R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)-alkylcarbamoyl, and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl.

599024

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number: 56319/86.
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

This document contains the amendments made under Section 49 and is correct for printing.

Name of Applicant : CIBA-GEIGY AG

Address of Applicant : Klybeckstrasse 141, 4002 Basle, Switzerland

Actual Inventor: RENE MEIER

Address for Service : ARTHUR S. CAVE & CO. SYDNEY NSW
~~EDWD. WATERS & SONS,~~
~~50 QUEEN STREET, MELBOURNE~~, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

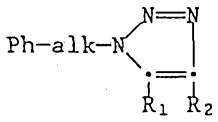
FLUORINATED BENZYLTRIAZOLES

The following statement is a full description of this invention, including the best method of performing it known to :- us

4-15323/14247/+
AU

Fluorinated benzyltriazoles

The present invention relates to novel fluorinated 1-(α-phenylalkyl)-1H-1,2,3-triazoles of formula



(I),

wherein Ph is an o-fluorinated phenyl radical which may be additionally substituted by up to 2 chlorine atoms inclusive, by 1 fluorine atom and 1 chlorine atom, or by up to 2 fluorine atoms inclusive, alk is methylene, R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)-alkylcarbamoyl, and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, to a process for the preparation of said compounds, to pharmaceutical compositions containing said compounds and to the use of said compounds.

A total of 3 halogen atoms may be present in the phenyl nucleus, which halogens may be, in addition to the o-fluoro substituent, 1 or 2 chlorine atom(s), 1 chlorine atom and 1 fluorine atom or 1 or 2 fluorine atom(s). A single additional halogen atom is located preferably in 6-position.

N-(C_2-C_5)Alkanoylcarbamoyl is for example N-acetylcarbamoyl or N-pivaloylcarbamoyl; N,N-di(C_1-C_4)alkylcarbamoyl is for example N,N-dimethylcarbamoyl or N,N-diethylcarbamoyl.

The compounds of the formula I have valuable pharmacological properties, in particular a pronounced anticonvulsive activity, which may be observed e.g. in mice in the form of a marked metrazole antagonism in the dosage range from about 30 to 300 mg/kg p.o. as well as in mice and rats in the form of a distinct protective action against convulsions induced by electroshock in the dosage range from about 1 to 25 mg/kg p.o.. In this assay, the following values are obtained for the effective dose ED_{50} in mg/kg p.o. (administration 1 hour beforehand):

1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide: 17 (mice) and 8 (rats);
1-(o-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide: 17 (mice, rats);
1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide: 4 (mice, rats);
1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide: 7 (mice) and 10 (rats);
1-(o-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide: 11 (mice) and 10 (rats);
1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide: 11 (mice);
1-(2,5-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide: 6 (mice);
1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-(N-acetyl)carboxamide: 17 (mice);
1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-(N-acetyl)dicarboxamide: 6 (mice); and
1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-(N,N-dimethyl)dicarboxamide: 31 (mice).

In the Australian patent application no. 22807/83 there are disclosed anticonvulsively active 1-phenylalkyl-1H-1,2,3-triazole-4-carboxamides and -4,5-dicarboxamides substituted in the phenyl moiety by, among other things, halogen. All of the 5-unsubstituted compounds specifically mentioned in said Australian patent application are bearing as halogen substituent chlorine, whereas, if the halogen substituent is fluorine, the triazole ring is bearing an amino group in the 5-position. Compared with the known compounds according to said Australian patent application, the 1-benzyl-1H-1,2,3-triazole-4-carboxamides and -4,5-dicarboxamides

according to the present invention, which are always substituted in the phenyl ring by fluorine, have the advantage of a better activity or of a longer duration of action, respectively. Thus the following ED_{50} values were obtained in the above assay:
1-(o-chlorobenzyl)-1H-1,2,3-triazole-4-carboxamide: 26 (mice) and 25 (rats); and
1-(o-chlorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide: 40 (mice) and 43 (rats).

The compounds of the present invention are therefore better suited for the treatment of convulsions of different provenance, for example epilepsy, and may be used as anticonvulsive, e.g. antiepileptic, agents.

The invention relates in particular to compounds of formula (I), wherein Ph is o-fluorinated phenyl which may be additionally substituted by 1 chlorine atom, by 1 fluorine atom and 1 chlorine atom, or by up to 2 fluorine atoms inclusive, and is e.g. o-fluorophenyl, 2,3-, 2,4-, 2,5- or 2,6-difluorophenyl, 2-chloro-6-fluorophenyl, and also 2,4,6-trifluorophenyl; alk is methylene; R_1 is hydrogen, or is a radical R_2; and R_2 is carbamoyl or, less preferably, N,N-di(C_1-C_4alkyl)carbamoyl such as N,N-dimethylcarbamoyl; for example compounds of formula (I), wherein Ph is o-fluorophenyl, 2,3-, 2,4-, 2,5- or 2,6-difluorophenyl or 6-chloro-2-fluorophenyl, alk is methylene, R_1 is hydrogen or unsubstituted carbamoyl, and R_2 is unsubstituted carbamoyl.

More particularly, the invention relates to compounds of formula (I), wherein Ph is o-fluorophenyl or 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen or unsubstituted carbamoyl and R_2 is unsubstituted carbamoyl.

Most particularly, the invention relates to compounds of formula (I), wherein Ph is 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen, or is a radical R_2, and R_2 is carbamoyl or, less preferably, N-(C_2-C_5)alkanoyl-carbamoyl such as N-acetylcarbamoyl, or is N,N-di(C_1-C_4)alkylcarbamoyl such as N,N-dimethylcarbamoyl.

First and foremost, the invention relates to compounds of formula (I), wherein Ph is o-fluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl or 2-chloro-6-fluorophenyl, alk is methylene and R_1 and R_2 are both carbamoyl; and further to compounds of formula (I), wherein Ph is 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen or carbamoyl and R_2 is carbamoyl.

The compounds of formula (I) can be prepared by methods which are known per se, for example by

a) reacting a compound of the formula

$$Ph - alk - N_3 \qquad (II)$$

with a compound of formula

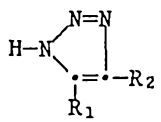
$$R_1 - \underset{Y_1}{C} = \underset{Y_2}{C} - R_2 \qquad (III),$$

wherein Y_1 is hydroxy and Y_2 is hydrogen, or Y_1 and Y_2 together form an additional bond, or with a salt and/or tautomer thereof, or

b) reacting a compound of formula

$$Ph - alk - Z \qquad (IV),$$

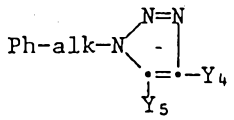
wherein Z is reactive esterified hydroxy, with a 1H-1,2,3-triazole derivative of formula



(V)

or with a salt thereof, or

c) for the preparation of a compound of the formula I, wherein either R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and R_2 is carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl or R_1 is carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and R_2 is carbamoyl, N-(C_2-C_5)-alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, in a compound of formula



(VI),

wherein Y_4 is a radical Y_A which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and Y_5 is a group R_1 or a radical Y_B which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, or Y_4 is a group R_2 and Y_5 is a radical Y_B which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, converting Y_A and/or Y_B into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, if necessary, separating a mixture of isomers obtained into the individual isomers and isolating the isomer of formula (I), and, if desired, converting a compound of the formula I obtained according to the process into another compound of formula (I) and/or resolving a mixture of enantiomers or diastereoisomers obtained according to the process into the individual components.

Suitable starting materials of formula (III) for process variant a) and tautomers thereof are e.g. compounds of formulae R_1-C≡C-R_2 (IIIa) and R_1-C(=O)-CH_2-R_2 (IIIb). Salts thereof are e.g. alkali metal salts, such as sodium salts, of compounds of formula (IIIa), which can be obtained therefrom and from alkali metal alcoholates, e.g. sodium methanolate.

The reaction of compound II with compound III is carried out in known manner, conveniently in an inert solvent and, if necessary, in the presence of a condensing agent and/or at elevated temperature. Examples of inert solvents are aromatic or araliphatic hydrocarbons such as benzene or toluene, or ethers such as tert-butoxymethane, tetrahydrofuran or dioxane.

Preferred embodiments of this process are for example the reaction of an azide of formula (II) with a compound of formula (IIIa) in benzene or dioxane, in the temperature range from 60° to 120°C, preferably at boiling temperature.

The starting materials of formula (III) and some of those of formula (II) are known. Novel starting materials of formula (II) can be prepared by methods analogous to those employed for obtaining the known compounds, for example by reacting a compound of formula Ph-alk-Z (IV), wherein Z is reactive esterified hydroxy such as halogen, e.g. chlorine, bromine or iodine, or sulfonyloxy such as C_1-C_4-alkanesulfonyloxy or unsubstituted or substituted benzenesulfonyloxy such as methanesulfonyloxy, ethanesulfonyloxy, benzenesulfonyloxy, p-toluenesulfonyloxy or p-bromosulfonyloxy, or fluorosulfonyloxy, with an alkali metal azide, e.g. with sodium azide, for example in dimethylsulfoxide or dimethylformamide, or by reacting an alcohol corresponding to the formula IV (Z = hydroxy), in the presence of triphenylphosphane and an azodicarboxylate, e.g. diethyl azodicarboxylate, with hydrazoic acid, for example in toluene.

In starting materials IV for process variant b), reactive esterified hydroxy is e.g. halogen, for example chlorine, bromine or iodine, or sulfonyloxy such as C_1-C_4-alkanesulfonyloxy or unsubstituted or substituted benzenesulfonyloxy such as methanesulfonyloxy, ethanesulfonyloxy, benzenesulfonyloxy, p-toluenesulfonyloxy or p-bromosulfonyloxy, or fluorosulfonyloxy.

Salts of compounds (V) are e.g. alkali metal salts or alkaline earth metal salts thereof such as sodium, potassium or calcium salts.

The reaction is carried out in conventional manner, for example in the presence of a basic condensing agent or conveniently by using the component of formula (V) in salt form, if necessary with heating, preferably in a solvent or diluent. Examples of basic condensing agents are those that form salts with the component of formula (V), e.g. alkali metal alcoholates such as sodium methanolate or sodium ethanolate or alkali metal amides or alkaline earth metal amides such as sodium amide

or lithium diisopropylamide. As already mentioned, the conversion of the component of formula (V) into a salt thereof is best carried out beforehand, e.g. by reaction with one of the above-mentioned bases. Preferred solvents for carrying out the reaction in the presence of an alcoholate are the corresponding alcoholates. For carrying out the reaction in the presence of amides, it is preferred to use e.g. aprotic organic solvents such as C_1-C_4alkyl amides of phosphoric acid, e.g. hexamethylphosphoramide, alkanoic acid amides such as dimethylformamide, or di(C_1-C_4)alkylsulfoxides such as dimethylsulfoxide. Isomers obtained as by-products in the process of the invention may be separated from the desired compounds of formula (I).

The starting compounds (IV) and (V), if not already known, may be prepared in conventional manner. Thus compounds of formula (IV) may be obtained by reactively esterifying an appropriate alcohol (IV; Z = hydroxy), for example with thionyl chloride, phosphorus tribromide or a sulfonyl chloride. Compounds (V) may be prepared by reacting trimethylsilyl azide or hydrazoic acid with a compound of formula

R_1-C≡C-R_2 (IIIa) or R_1-C(=O)-CH_2-R_2 (IIIb),

wherein R_1 is preferably carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, and removing the silyl group by mild hydrolysis from a 1-trimethylsilyltriazole derivative, where obtained, if desired after N-alkylating or N-alkanoylating a carbamoyl group R_2 and/or R_1 as described below for compounds of formula (I). It is, however, also possible to react trimethylsilyl azide with a compound of formula

Y_5-C≡C-Y_4 (VIIa) or R_1-C(=O)-CH_2-Y_4 (VIIb),

wherein Y_4 is a radical Y_A which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, for example esterified carboxy such as C_1-C_4alkoxycarbonyl, or cyano, and Y_5 is hydrogen or preferably a radical Y_B which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and which is preferably identical with Y_A, and to convert Y_A and/or Y_B into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, in the case of esterified

carboxy e.g. by ammonolysis (reaction with ammonia) and, in the case of cyano, e.g. by hydrolysis, with simultaneous removal of the trimethylsilyl group.

In process variant c), radicals Y_A and/or Y_B which are convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl are, for example, carboxyl groups which are in the free or salt form or in the anhyride form, amidino groups or esterified carboxyl groups, or also cyano groups.

Esterified carboxyl groups are e.g. carboxyl groups which are esterified with a C_1-C_4alkanol or a C_1-C_4alkylmercaptan, i.e. C_1-C_4alkoxycarbonyl or C_1-C_4alkylthiocarbonyl groups. However, they may also be esterified with any other alcohol or mercaptan, e.g. with an unsubstituted or substituted phenol or thiophenol.

Carboxyl groups in salt form are e.g. carboxyl groups which are in the form of ammonium salts derived from ammonia or a di(C_1-C_4)alkylamine, and also in the form of metal salts, e.g. alkali metal salts or alkaline earth metal salts.

Carboxyl groups in anhydride form are e.g. carboxyl groups in halide form such as chlorocarbonyl, but may also be formed by dehydration with a reactive carboxylic acid and are e.g. alkoxycarbonyloxycarbonyl or trifluoroacetoxycarbonyl.

The conversion of the groups Y_A and/or Y_B into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl is effected in known manner, starting from carboxyl groups which are free, esterified or in anhydride form and amidino groups, by solvolysis, i.e. hydrolysis, or by ammonolysis or aminolysis (reaction with ammonia or a di(C_1-C_4)alkylamine respectively).

For example, by means of hydrolysis cyano groups or amidino groups Y_A and/or Y_B can be converted into carbamoyl. The hydrolysis of cyano groups is carried out e.g. in the presence of a basic hydrolysing agent such as an alkali metal hydroxide, e.g. sodium or potassium hydroxide, if necessary in the presence of a peroxy compound, e.g. hydrogen peroxide.

The hydrolysis of amidino groups is carried out e.g. in the presence of an acid hydrolysing agent such as a mineral acid, sulfonic acid or carboxylic acid, for example in the presence of sulfuric acid, phosphoric acid, hydrochloric acid or another hydrohalic acid, p-toluenesulfonic acid or another organic sulfonic acid, or of a C_1-C_4alkanoic acid such as acetic acid, preferably in catalytic amounts.

By means of ammonolysis or aminolysis it is possible to convert carboxyl groups which are in the free, esterified or anhydride form into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl. The reaction is performed, if necessary, in the presence of a condensing agent and preferably in an inert solvent. Suitable condensing agents are basic condensing agents, preferably ammonia or an excess of the amine employed for the aminolysis, starting from carboxyl in anhydride form, and also alkali metal hydroxides or alkali metal carbonates or tertiary organic nitrogen bases such as tri(C_1-C_4)alkylamines or tertiary heteroaromatic nitrogen bases such as triethylamine or pyridine. Free carboxyl groups can be converted into carbamoyl by dehydration of the ammonium salts obtained as intermediates, e.g. by heating or by treatment with dehydrating agents such as acid anhydrides, e.g. phosphorus pentoxide and the like, or of carbodiimides, e.g. N,N'-dicyclohexylcarbodiimide. A particularly preferred embodiment of this process variant comprises reacting a compound of formula VI, wherein Y_4 is esterified carboxy and Y_5 is hydrogen or esterified carboxy, with an excess of ammonia or of a di(C_1-C_4)alkylamine.

The starting materials of formula (VI), if not known, may be prepared in conventional manner, for example by reacting an azide of formula

$$Ph - alk - N_3 \qquad (II)$$

with a compound of formula

$$Y_5-C\equiv C-Y_4 \qquad (VIIa) \qquad \text{or} \qquad R_1-C(=O)-CH_2-Y_4 \qquad (VIIb),$$

for example as described in process variant a). If necessary, directly obtained esters or nitriles of formula (VI) (Y_4 and/or Y_5 = esterified carboxy or cyano) can be hydrolysed under basic conditions, e.g. with aqueous alcoholic sodium hydroxide solution, to the corresponding acid, and acids of formula (VI) (Y_4 and/or Y_5 = carboxy), which are obtained directly or by hydrolysis of corresponding esters or nitriles, can be converted e.g. with thionyl chloride into the acid chlorides.

In compounds of formula (I) obtained according to the process it is possible to convert N-unsubstituted carbamoyl into N-(C_2-C_5)alkanoyl-carbamoyl by treatment with an alkanoylating agent.

Alkanoylating agents are e.g. C_1-C_4alkanecarboxylic acid anhydrides such as acetic anhydride or the mixed anhydride of formic and acetic acid, or C_1-C_4alkanecarboxylic acid chlorides such as acetyl chloride. The reaction with these compounds is carried out in conventional manner, if necessary in the presence of a base, e.g. triethylamine or pyridine, or in the presence of a mineral acid, e.g. sulfuric acid, if an acid anhydride is used as alkanoylating agent.

The separation of mixtures of isomers, exemplary of which are mixtures of enantiomers and diasteroisomers of compounds of formula (I) containing at least one asymmetrical carbon atom, as well as mixtures of compounds of formula (I) and isomers thereof, is effected in known manner. Diastereo-isomers and mixtures of compounds of formula (I) and isomers thereof may be separated e.g. on the basis of the different physical properties of the components by conventional methods of separation such as fractional crystallisation, chromatographic methods and the like. A suitable method of separating mixtures of enantiomers is for example fractional crystallisation from an optically active solvent or chromatography over an optically active stationary and/or mobile phase. It is, however, also possible to separate a mixture of enantiomers into the corresponding diastereoisomeric acyl derivatives, for example by reaction with an optically active acid chloride, to separate said diastereoisomers into the indivudual components and to isolate the pure enantiomers therefrom, for example by mild treatment with an acid.

The compounds of formula (I) may be used for example in the form of pharmaceutical compositions that contain a therapeutically effective amount of active ingredient, optionally together with inorganic or organic, solid or liquid pharmaceutically acceptable carriers that are suitable for enteral, e.g. oral, or parenteral administration. Hence the compositions employed are tablets or gelatin capsules which contain the active ingredient together with diluents, e.g. lactose, dextrose, saccharose, mannitol, sorbitol, cellulose and/or glycine, and/or lubricants, e.g. silica, talcum, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Tablets also contain binders, e.g. magnesium aluminium silicate, starches such as maize, corn, rice or arrow root starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone and, if desired, disintegrators, e.g. starches, agar, alginic acid or a salt thereof such as sodium alginate, and/or effervescent mixtures, or adsorption agents, colourants, flavouring matters and sweeteners. The compounds of formula (I) may also be used in the form of compositions for parenteral administration or of infusion solutions. Such solutions are preferably isotonic aqueous solutions or suspensions which, e.g. in the case of lyophilised formulations that contain the active ingredient alone or together with a carrier, e.g. mannitol, may be prepared prior to use. The pharmaceutical compositions may be sterilised and/or may contain adjuvants, e.g. preservatives, stabilisers, wetting agents and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The pharmaceutical compositions of the invention may, if desired contain further pharmacologically active substances, are prepared in a manner known per se, e.g. by conventional mixing, granulating, confectioning, dissolving or lyophilising methods, and contain from about 0.1 to 100 %, preferably from about 1 to 50 % (lyophilisates up to 100 %), of active ingredient.

The invention also relates to the use of compounds of formula (I), preferably in the form of pharmaceutical compositions. The dosage may depend on different factors, such as the mode of application, species, age and/or the individual condition of the patient. The daily doses for

oral administration are in the range from about 1 to 50 mg/kg, in single doses of about 1 to 25 kg/mg, and for warm-blooded animals having a body weight of about 70 kg preferably in daily doses of about 0.070 to 3.5 g.

The invention is illustrated by the following Examples.

Example 1: 73.5 g (0.25 mole) of dimethyl 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate are dissolved in 1000 ml of methanol. Then 250 g of ammonia are introduced into the autoclave under pressure and the reaction mixture is kept for 24 hours at 100°C. The batch is then cooled and the crystallised product is filtered with suction, washed with methanol and recrystallised from dioxane/toluene, affording 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 197°-199°C.

The starting material may be prepared as follows:
A solution of 40 g (0.282 mole) of dimethyl acetylenedicarboxylate in 500 ml of toluene is added dropwise to a solution of 41.5 g (0.255 mole) of o-fluorobenzyl azide in 50 ml of toluene, which solution has been heated to 90°C. After a further 5 hours at 90°C, the toluene is stripped off, the reaction mixture is cooled and the crystalline product is filtered with suction. Recrystallisation from a 1:1 mixture of diethyl ether/petroleum ether yields dimethyl 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate with a melting point of 49°-51°C.

Example 2: 59 g (0.26 mole) of 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4,5-carboxylic acid and 300 ml of thionyl chloride are heated for 1 hour to reflux. Excess thionyl chloride is distilled off in vacuo and the residual 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid chloride is dissolved in 500 ml of toluene. The solution is added dropwise at 5°-10°C to 500 ml of a concentrated aqeous ammonia solution. The precipitated product is filtered with suction, washed with water and recrystallised from ethanol, affording 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide with a melting point of 220°-222°C.

The starting material may be prepared as follows:
A solution of 50 g (0.33 mole) of o-fluorobenzyl azide, 23.1 g (0.33 mole) of propinecarboxylic acid and 400 ml of toluene is stirred for 24 hours at 70°C. After the reaction mixture has cooled to room temperature, the precipitated product is filtered with suction and washed first with toluene and then with diethyl ether, affording 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid with a melting point of 151°C (dec.).

Example 3: Following the procedure described in Example 1, 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 203°-205°C (recrystallisation from methanol) is obtained from 2,6-difluorobenzyl azide and dimethyl acetylenedicarboxylate via dimethyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate.

Example 4: Following the procedure described in Example 2, 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide with a melting point of 237°-240°C (recrystallisation from ethanol) is obtained from 2,6-difluorobenzyl azide via 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid, with a melting point of 160-162°C (recrystallisation from acetonitrile; decomposition).

Example 5: The following compounds can also be prepared in accordance with the procedures described in Examples 1-4:
1-(2,3-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide,
1-(2,4-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide and
1-(2,5-difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide.

Example 6: Following the procedure described in Example 2, 1-(6 chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide with a melting point of 274°-276°C (recrystallisation from glacial acetic acid) is obtained from 1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4-carboxylic acid.

The starting material may be prepared as follows:
A mixture of 98 g (0.678 mole) of 6-chloro-2-fluorotoluene, 91.5 g (0.678 mole) of sulfuryl chloride and 0.2 g of dibenzoyl peroxide is stirred for 3 hours at 100°-110°C and then distilled, affording 6-chloro-2-fluorobenzyl chloride with a boiling point in the range from 78°-82°C.

123 g of (0.687 mole) of 6-chloro-2-fluorobenzyl chloride are added dropwise at 20°-40°C to a suspension of 47 g (0.722 mole) of sodium azide in 400 ml of dimethylsulfoxide. The mixture is stirred for 4 hours at room temperature, then diluted with ice-water and extracted with cyclohexane. The solvent is removed by distillation and the residue is distilled, affording 6-chloro-2-fluorobenzyl azide (bp_{15} = 99°-100°C).

27.5 g (0.15 mole) of 6-chloro-2-fluorobenzyl azide and 10.5 g (0.15 mole) of propinecarboxylic acid in 300 ml of toluene are heated for 3 hours to 90°C. After cooling, the crystals are filtered with suction and recrystallised from acetonitrile to give 1-(6-chloro-2-fluoro-benzyl)-1H-1,2,3-triazole-4-carboxylic acid with a melting point of 182°C (dec.).

Example 7: Following the procedure described in Example 1, 1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 214°-216°C (recrystallisation from glacial acetic acid) is obtained from 6-chloro-2-fluorobenzyl azide and dimethyl acetylenedicarboxylate via dimethyl 1-(6-chloro-2-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicar-boxylate.

Example 8: Following the procedure described in Example 1, 1-(2,5-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 191°-192°C (recrystallisation from dioxane/toluene) is obtained from 2,5-difluorobenzyl azide (bp_{15} = 82°-84°C) via dimethyl 1-(2,5-di-fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate.

Example 9: Following the procedure described in Example 1, 1-(2,4-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 183°-185°C (recrystallisation from dioxane/toluene) is obtained from 2,4-difluorobenzyl azide (bp_{15} = 80°-83°C) via dimethyl 1-(2,4-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate with a melting point of 75°-76°C (recrystallisation from cyclohexane).

Example 10: Following the procedure described in Example 1, N,N-dimethyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 130°-133°C (recrystallisation from (tert-butoxymethane) is obtained by reaction with dimethylamine.

Example 11: Following the procedure described in Example 1, 1-(2,3-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide with a melting point of 183°-185°C (recrystallisation from ethyl acetate/benzene) is obtained from 2,3-difluorobenzyl azide and dimethyl acetylenedicarboxylate via dimethyl 1-(2,3-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxylate.

Example 12: 2.81 g (10 millimoles) of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide, 20 ml of acetic anhydride and 2 drops of sulfuric acid are heated for 3 hours to 80°C. After cooling, the mixture is stirred for 1 hour at 20°-25°C and the precipitated product is filtered with suction and washed with water. Recrystallisation from methanol gives 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4,5-di-(N-acetyl)carboxamide with a melting point of 136°-138°C.

Example 13: Following the procedure described in in Example 12, 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-(N-acetyl)carboxamide with a melting point of 205°-207°C (recrystallisation from dioxane/toluene) is also obtained.

Example 14: Tablets which each contain 50 mg of 1-(o-fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide may be prepared as follows:

Composition (for 10,000 tablets)

active ingredient	500.0 g
lactose	500.0 g
potato starch	352.0 g
gelatin	8.0 g
talcum	60.0 g
magnesium stearate	10.0 g
silica (highly dispersed)	20.0 g
ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of potato starch and this mixture is moistened with an alcoholic solution of the gelatin and granulated through a sieve. After drying, the granulate is mixed with the remainder of the potato starch, the talcum, the magnesium stearate and the highly disperse silica and the mixture is compressed to tablets weighing 145.0 g each and containing 50.0 mg of active ingredient. If desired, the tablets may be provided with a breaking notch for a finer adjustment of the dose.

Example 15: Film-coated tablets each containing 100 mg of 1-(o-fluoro-benzyl)-1H-1,2,3-triazole-4-carboxamide may be prepared as follows:

Composition (for 1000 tablets)

active ingredient	100.00 g
lactose	100.00 g
corn starch	70.00 g
talcum	8.50 g
calcium stearate	1.50 g
hydroxypropylmethyl cellulose	2.36 g
shellac	0.64 g
water	q.s.
methylene chloride	q.s

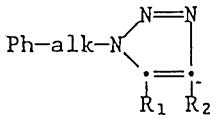
The active ingredient, the lactose and 40 g of the corn starch are mixed and moistened with a paste prepared from 15 g of corn starch and water (with heating) and the mixture is granulated. The granulate is dried and

mixed with the remainder of the corn starch, talcum and the calcium stearate. The mixture is compressed to tablets weighing 280 g. The tablets are then coated with a solution of the hydroxypropylmethyl cellulose and the shellac in methylene chloride. The tablets have a final weight of 283 g.

Example 16: Tablets and coated tablets containing another compound of Examples 1-13 can also be prepared as described in Examples 14 and 15.

The Claims defining the invention are as follows:

1. A novel fluorinated 1-(α-phenylalkyl)-1H-1,2,3-triazole of the formula



(I),

wherein Ph is an o-fluorinated phenyl radical which may be additionally substituted by up to 2 chlorine atoms inclusive, by 1 fluorine atom and 1 chlorine atom, or by up to 2 fluorine atoms inclusive, alk is methylene, R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)-alkylcarbamoyl, and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl.

2. A compound according to claim 1, wherein Ph is an o-fluorinated phenyl radical which may be additionally substituted by 1 chlorine atom, by 1 fluorine atom and 1 chlorine atom, or by up to 2 fluorine atoms inclusive, alk is methylene, R_1 is hydrogen, or is a radical R_2; and R_2 is carbamoyl or N,N-di(C_1-C_4alkyl)carbamoyl.

3. A compound according to claim 1, wherein Ph is o-fluorophenyl, 2,3-, 2,4-, 2,5- or 2,6-difluorophenyl or 6-chloro-2-fluorophenyl, alk is methylene, R_1 is hydrogen or carbamoyl and R_2 is carbamoyl.

4. A compound according to claim 1, wherein Ph is o-fluorophenyl or 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen or carbamoyl and R_2 is carbamoyl.

5. A compound according to claim 1, wherein Ph is 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen, or a radical R_2, and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl.

6. A compound according to claim 1, wherein Ph is o-fluorophenyl, 2,5-difluorophenyl, 2,6-difluorophenyl or 2-chloro-6-fluoro-phenyl, alk is methylene and R_1 and R_2 are both carbamoyl.

7. A compound according to claim 1, wherein Ph is 2,6-difluorophenyl, alk is methylene, R_1 is hydrogen or carbamoyl and R_2 is carbamoyl.

8. 1-(o-Fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide.

9. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide.

10. 1-(o-Fluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide.

11. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide.

12. 1-(6-Chloro-2-fluoro-benzyl)-1H-1,2,3-triazole-4-carboxamide.

13. 1-(6-Chloro-2-fluoro-benzyl)-1H-1,2,3-triazole-4,5-dicarboxamide.

14. 1-(2,5-Difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide.

15. 1-(2,4-Difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide.

16. 1-(2,3-Difluorobenzyl)-1H-1,2,3-triazole-4-carboxamide.

17. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4,5-(N,N-dimethyl)-dicarboxamide.

18. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4-(N-acetyl)carboxamide.

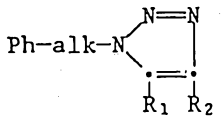
19. 1-(2,6-Difluorobenzyl)-1H-1,2,3-triazole-4,5-(N-acetyl)dicarboxamide.

20. 1-(2,3-Difluorobenzyl)-1H-1,2,3-triazole-4,5-dicarboxamide.

21. A pharmaceutical composition containing a compound according to any one of claims 1, 2, 5 and 15 to 20 together with conventional pharmaceutical excipients and/or carriers.

22. A pharmaceutical composition containing a compound according to any one of claims 3, 4 and 6 to 14 together with conventional pharmaceutical excipients and/or carriers.

23. A process for the preparation of a novel fluorinated 1-(α-phenylalkyl)-1H-1,2,3-triazole of formula



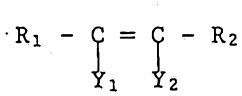
(I),

wherein Ph is an o-fluorinated phenyl radical which may be additionally substituted by up to 2 chlorine atoms inclusive, by 1 fluorine atom and 1 chlorine atom, or by up to 2 fluorine atoms inclusive, alk is methylene, R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)-alkylcarbamoyl, and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, which process comprises

a) reacting a compound of the formula

Ph - alk - N_3 (II)

with a compound of formula



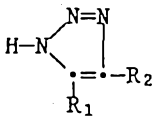
(III),

wherein Y_1 is hydroxy and Y_2 is hydrogen, or Y_1 and Y_2 together form an additional bond, or with a salt and/or tautomer thereof, or

b) reacting a compound of formula

Ph - alk - Z (IV),

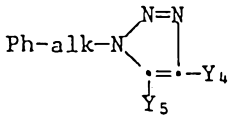
wherein Z is reactive esterified hydroxy, with a 1H-1,2,3-triazole derivative of formula



(V)

or with a salt thereof, or

c) for the preparation of a compound of the formula I, wherein either R_1 is hydrogen, carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and R_2 is carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl or R_1 is carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and R_2 is carbamoyl, N-(C_2-C_5)alkanoylcarbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, in a compound of formula



(VI),

wherein Y_4 is a radical Y_A which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl and Y_5 is a group R_1 or a radical Y_B which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, or Y_4 is a group R_2 and Y_5 is a radical Y_B which is convertible into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, converting Y_A and/or Y_B into carbamoyl or N,N-di(C_1-C_4)alkylcarbamoyl, if necessary, separating a mixture of isomers obtained into the individual isomers and isolating the isomer of formula (I), and, if desired, converting a compound of the formula I obtained according to the process into another compound of formula (I) and/or resolving a mixture of enantiomers or diastereoisomers obtained according to the process into the individual components.

24. A process according to claim 23, which process comprises reacting a compound of formula VI, wherein Y_4 is esterified carboxy and Y_5 is hydrogen or esterified carboxy, with an excess of ammonia or of a di(C_1-C_4)alkylamine.

25. A process according to claim 23, substantially as described hereinbefore in any one of Examples 1 to 5.

26. A process according to claim 23, substantially as described hereinbefore in any one of Examples 6 to 18.

27. A method of treating convulsions of different provenance in the human or animal body, which comprises administering to a subject in need of such treatment a compound according to any one of claims 1, 2, 5 and 15 to 20 or a pharmaceutical preparation according to claim 21.

28. A method of treating convulsions of different provenance in the human or animal body, which comprises administering to a subject in need of such treatment a compound according to any one of claims 3, 4 and 6 to 14 or a pharmaceutical preparation according to claim 22.

29. A fluorinated 1-(α-phenylalkyl)-1H-1,2,3-triazole compound of the formula I represented in Claim 1, said compound substantially as herein described with reference to any one of Examples 1 to 13.

30. A pharmaceutical composition substantially as herein described with reference to any one of Examples 14 to 16.

DATED this 10th day of April, 1990.

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By Its Patent Attorneys,
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