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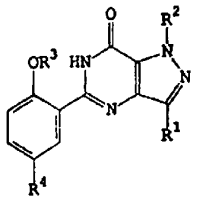
(54) Title: MEDICAMENT FOR TREATMENT OF NEUROPATHIES

(54) Bezeichnung: ARZNEIMITTEL ZUR BEHANDLUNG VON NEUROPATHIEN



(I)

(57) Abstract: Compounds of formula (I) in which R^1 = C_{1-6} alkyl, optionally halosubstituted; R^2 = H, C_{1-4} alkyl, optionally halosubstituted or replaced by halogen; R^3 = C_{2-4} alkyl, optionally halosubstituted; R^4 = $SO_2NR^5R^8$, CO_2R^7 or halogen. C_{2-4} alkenyl, optionally substituted with NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO^2R^7 or halogen, C_{2-4} alkanoyl, optionally substituted with NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7 or halogen; R^5 and R^6 = independently H or C^{1-4} alkyl, or, together with the N atom to which they are attached, a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring optionally substituted with one or two C_{1-4} alkyl groups; R^7 =H, C^{1-4} alkyl, optionally fluorosubstituted, and R^8 =H, C^{1-3} alkyl or hydroxyalkyl with 1 - 4 C atoms, or the pharmaceutically acceptable salts thereof are useful for the chemotherapeutic treatment of neuropathies.

(57) Zusammenfassung: Verbindungen der Formel (I), in der R^1 = C_{1-6}-Alkyl, gegebenenfalls mit Halogen substituiert, R^2 = Wasserstoff, C_{1-4}-Alkyl, gegebenenfalls mit Halogen substituiert oder durch Halogen ersetzt, R^3 = C_{2-4}-Alkyl, gegebenenfalls mit Halogen substituiert, R^4 = $SO_2NR^5R^8$, CO_2R^7 oder Halogen, C_{2-4}-Alkenyl, gegebenenfalls substituiert mit NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7 oder Halogen, C_{2-4}-Alkeyl, gegebenenfalls substituiert mit NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7 oder Halogen, C_{2-4}-Alkanoyl, gegebenenfalls substituiert mit NR^5, R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7 oder Halogen, R^5 und R^6 unabhängig voneinander Wasserstoff oder C_{1-4}-Alkyl bedeuten oder zusammen mit dem Stickstoffatom, an dem sie hängen, einen Pyrrolidino-, Piperidino-, Morpholino-, 4-(NR^8)-1-Piperazinyl- oder 1-Imidazolylring bedeuten, der gegebenenfalls mit ein oder zwei C_{1-4}-Alkylgruppen substituiert ist, R^7 = Wasserstoff, C_{1-4}-Alkyl, gegebenenfalls mit Fluor substituiert, und R^8 = Wasserstoff, C_{1-3}-Alkyl oder Hydroxyalkyl mit 1 - 4 C-Atomen bedeutet, sowie die pharmazeutisch akzeptablen Salze solcher Verbindung eignen sich zur chemotherapeutischen Behandlung von Neuropathien.

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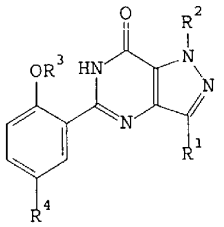
Vor Ablauf der für Änderungen der Ansprüche geltenden Frist; Veröffentlichung wird wiederholt, falls Änderungen eintreffen.

Zur Erklärung der Zweibuchstaben-Codes, und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

Pharmaceutical Agent for Treatment of Neuropathies

The present invention relates to pharmaceutical agents for treatment of neuropathies, such as, e.g., peripheral diabetic polyneuropathies and gastropareses, as well as general degenerative, toxic, metabolic, ischemic and other autonomous forms of neuropathies in the narrower, namely neurological sense.

Surprisingly, it has been found that compounds of formula (I)



(I)

known, for example, from WO 93/07149 as such and for use as a pharmaceutical agent for cardiovascular disorders, in which

R^1 = C_{1-6}alkyl, optionally substituted by halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted by halogen,

R^3 = C_{2-4}alkyl, optionally substituted by halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen or C_{1-4}alkyl, and

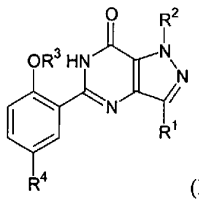
R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl with 1 - 4 C atoms, as well as pharmaceutically acceptable salts of such compounds (I), are suitable for chemotherapeutic treatment of neuropathies of the type mentioned above.

In the above definitions, halogen represents fluorine, chlorine, or bromine, fluorine being preferred.

Compounds which correspond or are analogous to this formula, including its salts, and preparation processes of such compounds and salts are known in the art, e.g. from EP 0 463 756, where they have been proposed for prophylactic or therapeutic treatment of cardiovascular diseases. The cardiovascular activity of formula (I) compounds is based on the fact that these compounds are effective and selective inhibitors for cyclic 3',5'-monophosphate phosphodiesterase (cGMP PDE).

It is not known and - respectively - is improbable on the basis of what is known, that this inhibitor effect plays a significant role in neuropathies of the type mentioned. Also, the efficacy of formula (I) compounds for treatment of neuropathies has, in fact, not been determined on the basis of theoretical considerations, but in an empirical manner, and was neither anticipated nor predictable.

Accordingly, a first aspect of the present invention provides the use of a compound of formula (I):



(I)

in which

R^1 = C_{1-6}alkyl, optionally substituted with halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted with halogen or replaced with halogen,

R^3 = C_{2-4}alkyl, optionally substituted with halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

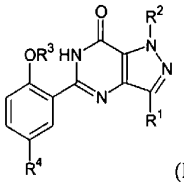
NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen or C_{1-4}alkyl, optionally, substituted with fluorine, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl with 1 - 4 C atoms, or of a pharmaceutically acceptable salt of such a compound for production of a pharmaceutical agent for treatment of neuropathies.

A second aspect of the present invention provides a chemotherapeutic method for treatment of neuropathies characterised by application to a patient of a pharmaceutical agent which consists, at least in part, of a compound of formula (I):



(I)

in which

R^1 = C_{1-6}alkyl, optionally substituted with halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted with halogen or replaced with halogen,

R^3 = C_{2-4}alkyl, optionally substituted with halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen or C_{1-4}alkyl, optionally, substituted with fluorine, and

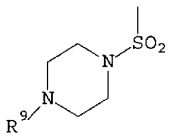
R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl having 1 - 4 C atoms, or of a pharmaceutically acceptable salt of such a compound.

The pharmaceutical agent used in the treatment of neuropathies is characterised in that it consists, at least in part, of at least one compound of formula (I), or at least one pharmaceutically acceptable salt of such a compound, and that it may contain standard auxiliary agents, adjuvants, and carriers, as well as, optionally, additional pharmaceutically active substances.

Examples of pharmaceutically acceptable salts of compounds and additional methods of synthesis are also known from the above-noted EP 0 463 756 and, furthermore, from WO 93/07149, as well as from WO 93/06104 and WO 94/05661.

For production of pharmaceutical agents according to the invention, active agents of formula I may be formulated as solid or liquid products with standard adjuvants and carrier substances.

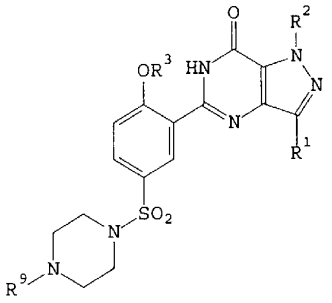
In a preferred group of compounds (I), R^4 represents a group of formula (II):



(II)

particularly if R^1, R^2, R^3, and R^9, respectively, represent alkyl groups with 1 - 4 C atoms, preferably, methyl or ethyl, which, optionally, may be substituted or replaced by halogen, preferably, fluorine.

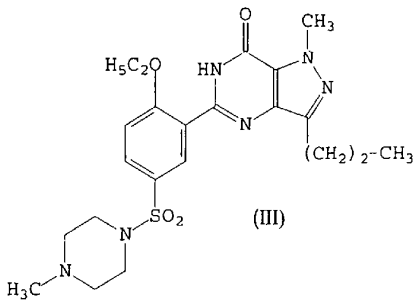
Such compounds correspond to formula (Ia):



(Ia)

in which groups R^1 to R^3 and R^9 have the above-specified meaning.

A preferred specific compound for pharmaceutical agents in accordance with the invention corresponds to formula (III):



(III)

and is the compound known in the art under the generic name sildenafil for treatment of erectile dysfunctions.

Formula (III) compounds and their pharmaceutically acceptable salts can also be prepared in a known manner, e.g., in accordance with the method disclosed in EP 0 463 756.

It is to be expected that effective dosages for treatment of neuropathies will generally be in a similar or lower range as with known medical indications of compounds (1) and (3), respectively, i.e., they will typically be in the range from 1 - 100 mg/day, more specifically, 5 - 50 mg/day, and, typically, 25 - 50 mg/week.

The invention will be explained further by means of examples which are not limiting.

Example 1

A male patient (age 66 years) had been suffering from diabetes mellitus, type 2, for 9 years. While blood glucose values (HbA1c between 6 and 7%) were good, symptoms of a diabetic polyneuropathy appeared, namely vibration sensing of 2/8, no filament sensing, and a reduced hot/cold differentiation. Because of a simultaneous erectile dysfunction he was treated with sildenafil in its commercially available preparation (tablets) at 50 mg/week in a single administration.

Twelve months after start of therapy, a largely normal neurologic situation was reached, namely a vibration sensing of 5/8, intact filament sensing, and hot/cold differentiation. Subjectively, the patient noted disappearance of sensory misperceptions of temperature.

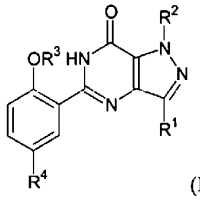
Example 2

A 61-year-old female patient had been suffering from diabetes mellitus, type 1, for about 35 years. Complications included a retinopathy and a painful neuropathy. Under intensified insulin therapy, blood glucose metabolism data were in a sub-optimum range (HbA1c around 8%). Thus, the patient suffered from a painful neuropathy and was treated unsuccessfully with various conventional medicaments.

After medication with sildenafil (50 mg/week, each in a single administration of the entire week's dosage), a lasting improvement of symptomatic pain was achieved in the course of the following three months. Objectifiable diagnostic data were improved as well.

The claims defining the invention are as follows:

1. The use of a compound of formula (I):



(I)

in which

R^1 = C_{1-6}alkyl, optionally substituted with halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted with halogen or replaced with halogen,

R^3 = C_{2-4}alkyl, optionally substituted with halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

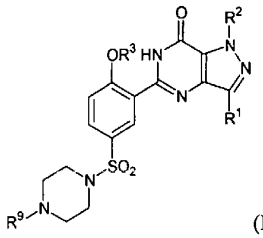
NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen or C_{1-4}alkyl, optionally, substituted with fluorine, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl with 1 - 4 C atoms, or of a pharmaceutically acceptable salt of such a compound for production of a pharmaceutical agent for treatment of neuropathies.

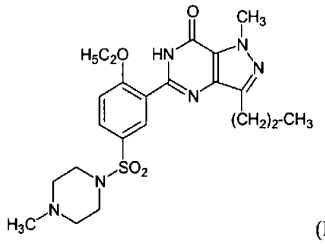
2. The use according to claim 1 wherein the compound is a compound of formula (Ia):



(Ia)

in which the groups R^1 to R^3 have the meaning specified in claim 1, and R^9 is an alkyl group having 1 - 4 C atoms which, optionally, are substituted or replaced by halogen; or a pharmaceutically acceptable salt of such a compound.

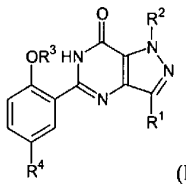
3. The use according to claim 1 wherein the compound is a compound of formula (III)



(III)

or a pharmaceutically acceptable salt of such a compound.

4. A chemotherapeutic method for treatment of neuropathies characterised by application to a patient of a pharmaceutical agent which consists, at least in part, of a compound of formula (I):



(I)

in which

R^1 = C_{1-6}alkyl, optionally substituted with halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted with halogen or replaced with halogen,

R^3 = C_{2-4}alkyl, optionally substituted with halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

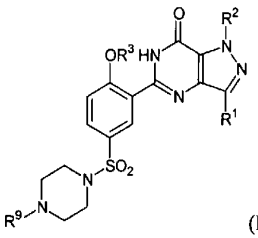
NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen or C_{1-4}alkyl, optionally, substituted with fluorine, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl having 1 - 4 C atoms, or of a pharmaceutically acceptable salt of such a compound.

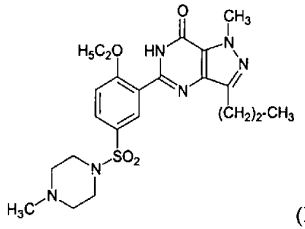
5. The method according to claim 4 wherein the agent consists, at least in part, of a compound of formula (Ia):



(Ia)

in which the groups R^1 to R^3 have the meaning specified in claim 1, and R^9 is an alkyl group having 1 - 4 C atoms which, optionally, are substituted or replaced by halogen; or of a pharmaceutically acceptable salt of such a compound.

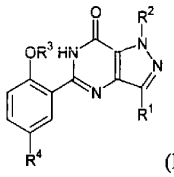
6. The method according to claim 4 wherein the agent consists, at least in part, of a compound of formula (III):



(III)

or of a pharmaceutically acceptable salt of such a compound.

7. A chemotherapeutic method for treatment of neuropathies characterised by application to a patient of a pharmaceutical agent which consists, at least in part, of a compound of formula (I):



(I)

in which

R^1 = C_{1-6}alkyl, optionally substituted with halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted with halogen or replaced with halogen,

R^3 = C_{2-4}alkyl, optionally substituted with halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen or C_{1-4}alkyl, optionally, substituted with fluorine, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl having 1 - 4 C atoms, or of a pharmaceutically acceptable salt of such a compound, substantially as hereinbefore described with reference to Example 1 or Example 2.

Dated 7 December, 2004

Lilly ICOS LLC

Patent Attorneys for the Applicant/Nominated Person

SPRUSON & FERGUSON

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