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Declaration under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:
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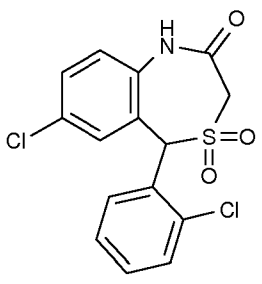
(54) Title: CYCLIC SULFONES USEFUL AS MITOCHONDRIAL SODIUM-CALCIUM EXCHANGERS



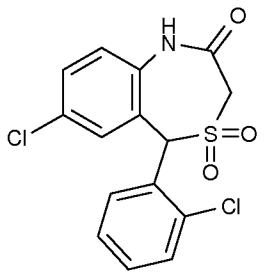
(I)

(57) Abstract: The invention relates to novel heterocyclic compounds of the formula (I), in free base form or in acid addition salt form, to their preparation, to their use as medicaments and to medicaments comprising them.

BENZOTHIAZEPINES AS ANTAGONISTS FOR THE MITOCHONDRIAL SODIUM-CALCIUM EXCHANGER

The present invention relates to novel heterocyclic compounds, to their preparation, to their use as medicaments and to medicaments comprising them.

More particularly the invention relates to a compound of the formula



(I),

in free base form or in acid addition salt form.

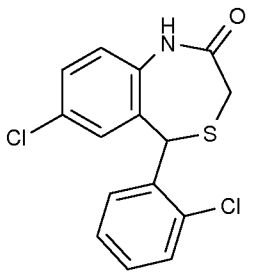
E. g. on account of the asymmetrical carbon atom present in a compound of the formula I, a compound of the formula I may exist in pure optically active form or in the form of a mixture of optical isomers, e. g. in the form of a racemic mixture. All of such pure optical isomers and all of their mixtures, including the racemic mixtures, are part of the present invention.

A compound of the formula I may exist in free base form or in acid addition salt form. All of such free compounds and salts are part of the present invention.

A compound of the formula I may exist in tautomeric form. All of such tautomers are part of the present invention.

In especially preferred embodiments, the invention relates to one or more than one of the compounds of the formula I mentioned in the Examples, in free base form or in acid addition salt form.

In a further aspect, the invention relates to a process for the preparation of a compound of the formula I, in free base form or in acid addition salt form, comprising the steps of reacting a compound of the formula



(II),

in free base form or in acid addition salt form, with an oxidizing agent, optionally followed by the cleavage of any protecting group(s) optionally present, and of recovering a so obtainable compound of the formula I in free base form or in acid addition salt form.

The process steps can be effected according to conventional methods, for example as described in the Examples.

As oxidizing agent in the oxidizing step can be used, for example, ozone, a dioxirane derivative, such as dimethyldioxirane, an oxidizing pyridinium salt, such as pyridinium chlorochromate, a peroxide, such as H_2O_2 or tert.-butylhydroperoxide, an inorganic peracid or a salt thereof, such as $KHSO_5$, a composition comprising an inorganic peracid or a salt thereof, such as OXONE®, or an organic peracid, such as peracetic acid or meta-chloroperbenzoic acid.

The oxidizing step can be carried out in the presence of a solvent, which is preferably inert under the reaction conditions employed.

The cleavage of a protecting group may be carried out in accordance with known procedures.

The working-up of a reaction mixture and the purification of a compound of the formula I thus obtainable may be carried out in accordance with known procedures.

An acid addition salt of a compound of the formula I may be produced from the corresponding free base in known manner, and vice-versa.

The starting materials of the formula II are known or may be prepared according to conventional procedures starting from known compounds.

A compound of the formula I can also be prepared by further conventional processes, which processes are further aspects of the invention.

The compounds of the formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as "agents of the invention", exhibit valuable pharmacological properties when tested in vitro and in animals, and are therefore useful as medicaments.

The agents of the invention are inhibitors of the mitochondrial sodium-calcium exchanger (mNCE), which is an important component of the mitochondrial Ca-homeostasis in excitable tissues. Therefore, the agents of the invention can be used for the treatment and/or prevention of disorders or diseases influenced by the malfunction of the mitochondrial Ca-handling capacity.

The agents of the invention are, therefore, useful, e. g., for the treatment and/or prevention of neurological, vascular or metabolic disorders or diseases, such as neurodegenerative diseases, e. g. Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease, multiple sclerosis (MS), Down's syndrome, memory impairment, cognitive impairment, dementia, neuronal degeneration, brain inflammation, myasthenia gravis, nerve trauma, brain trauma, progressive supranuclear palsy, amyotrophic lateral sclerosis (ALS), amyotrophic lateral sclerosis- (ALS)-like syndrome, aging, Leber's hereditary optic neuropathy (LHON) syndrome, Leigh's syndrome, mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome, familial bilateral striatal necrosis (FBSN) syndrome, growth retardation, aminoaciduria, lactic acidosis and early death (GRACILE) syndrome, myoclonic epilepsy with ragged-red fibers (MERRF) syndrome, neuropathy, ataxia and retinitis pigmentosa (NARP) syndrome, progressive external ophtalmoplegia (PEO) syndrome, Kearns-Sayre (KS) syndrome, sudden infant death (SID) syndrome, dominant optic atrophy, mtDNA depletion (MD) syndrome, Barth 's syndrome, mitochondrial neurogastrointestinal encephalomyopathy, Mohr-Tranebjaerg's syndrome, Friedreich's ataxia, Wilson's disease, pathological conditions following ischemia-reperfusion damage (such as cardiac ischemia or stroke), pathological conditions following epileptic seizures, Niemann-Pick type C disease, diabetes (such as type 1 diabetes, type 2 diabetes or juvenile onset diabetes) or atherosclerosis.

For the above-mentioned indications, the appropriate dosage of an agent of the invention will of course vary depending upon, for example, the compound employed, the host, the mode of

administration or the nature and severity of the condition being treated and/or prevented. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of an agent of the invention of from about 0.1 to about 100, preferably from about 1 to about 50, mg/kg of animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range of from about 10 to about 2000, preferably from about 10 to about 200, mg of an agent of the invention conveniently administered, for example, in divided doses up to four times a day or in sustained release form.

The agent of the invention may be administered by any conventional route, in particular enterally, preferably orally, for example in the form of tablets or capsules, or parenterally, for example in the form of injectable solutions or suspensions.

In accordance with the foregoing, the present invention also provides an agent of the invention for use as a medicament, e. g. for the treatment and/or prevention of disorders or diseases influenced by the malfunction of the mitochondrial Ca-handling capacity.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutical carrier or diluent. Such compositions may be manufactured in conventional manner. Unit dosage forms contain, for example, from about 1 to about 1000, preferably from about 1 to about 500, mg of an agent of the invention.

An agent of the invention can be administered alone or as a combination with at least one other pharmaceutical agent, which combination is effective in the treatment and/or prevention of conditions mentioned above.

The pharmaceutical combination may be in the form of a unit dosage form, whereby each unit dosage will comprise a predetermined amount of the active components, in admixture with suitable pharmaceutical carriers or diluents. Alternatively, the combination may be in the form of a package containing the active components separately, e. g. a pack or dispenser-device adapted for the concomitant or separate administration of the active agents, wherein these agents are separately arranged.

Moreover the present invention provides the use of an agent of the invention for the manufacture of a medicament for the treatment and/or prevention of disorders or diseases influenced by the malfunction of the mitochondrial Ca-handling capacity.

In still a further aspect, the present invention provides a method for the treatment and/or prevention of disorders or diseases influenced by the malfunction of the mitochondrial Ca-handling capacity in a subject in need of such treatment and/or prevention, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

The following Examples illustrate the invention, but do not limit it.

Examples

Abbreviations

BSA	bovine serum albumin
DMSO	dimethylsulfoxide
EDTA	ethylene diamine tetraacetic acid
h	hour(s)
Hepes	2-[4-(2-hydroxyethyl)-1-piperazino]-ethanesulfonic acid
^{1}H-NMR	proton nuclear magnetic resonance spectrometry
min	minute(s)
MS	mass spectrometry
rt	room temperature
sec	second(s)
Tris	α,α,α-tris-(hydroxymethyl)-methylamine hydrochloride

Example 1: 2-Chloro-9-(2-chlorophenyl)-8,8-dioxo-5,7,8,9-tetrahydro-8lambda*6*-thia-5-aza-benzocyclohepten-6-one

To a stirred solution of 2-chloro-9-(2-chlorophenyl)-5,9-dihydro-8-thia-5-aza-benzocyclohepten-6-one (200 mg, 0.62 mmol) in dichloromethane (5 ml) meta-chloroperbenzoic acid (319 mg, 0.93 mmol) is added at rt. After 45 min, the mixture is taken up in dichloromethane, washed with saturated $Na_2S_2O_3$-solution and with saturated Na_2CO_3-solution, dried over

Na_2SO_4 and concentrated. The residue is recrystallized from methanol / dichloroethane (5ml / 1ml) yielding the title compound in the form of a white solid.
^{1}H-NMR (400 MHz, DMSO-D_6): 4.27 (d, J = 13.7 Hz, 1H), 4.46 (d, J = 13.3 Hz, 1H), 5.96 (s, 1H), 7.08 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.6 Hz, 1H), 7.58 - 7.72 (m, 4H), 8.27 (dd, J = 7.8 Hz and 1.6 Hz, 1H).
MS: $[M + NH_4]^+$ = 372.9, 374.9.

Example 2: Isolation of rat brain mitochondria

The method is adapted from the method of Rosenthal et al. [J. Cereb. Blood Flow Metab., 7, 752 - 758 (1987)].

Solutions
MSH+: 225 mM mannitol, 75 mM sucrose, 5 mM Hepes, 0.5 mM EDTA, 1 mg / ml of BSA (essentially free fatty acid free); final pH = 7.3.
MSH-: Equal to MSH+, but without EDTA.
Nagarse solution: 5 mg of nagarse (bacterial protease type XXIV from Sigma, St. Louis, USA, catalogue # P-8038) dissolved in 1 ml of MSH+.
Digitonin solution: 10% W/V in DMSO.

Procedure
The entire procedure is performed on ice. Remove the whole brain from the rat (1 brain = 2 g). Add the tissue to cold MSH+ in a beaker on ice. Cut the tissue into small pieces using scissors and wash the tissue 2 times with MSH+. Transfer the tissue into a 20 ml Dounce homogenizer and set level to about 9 ml with MSH+. Add 1 ml of freshly made Nagarse solution. Homogenize (6 strokes with a loose and 6 strokes with a tight pestle). Add MSH+ to make about 30 ml / brain and centrifuge at 2000g / 3 min. Keep the supernatant. Resuspend the pellet in about 30 ml of MSH+ and centrifuge again at 2000g / 3 min. Pool the supernatants and centrifuge at 12000g / 8 min. Suspend the pellet (composed mainly of mitochondria and synaptosomes) in 20 ml of MSH+ / brain. Add 20 µl of digitonin solution and incubate for 2 min on ice. Centrifuge at 12000g / 10 min. Resuspend the pellet in 10 ml of MSH- and centrifuge at 12000g / 10 min. Resuspend the final pellet in 1.5 ml of MSH- / brain. The protein concentration is determined using the Pierce BCA assay (Pierce, Rockford IL, USA). A typical yield is 10 - 15 mg of mitochondrial protein / rat brain (i. e. the final mitochondrial suspension is about 8 mg / ml). The mitochondria are kept on ice and are used within 2 - 3 h.

Example 3: Measurement of the Na-Ca exchanger of rat brain mitochondria

The method is basically as described by Chiesi et al. [Biochem. Pharmacol., 37, 4399 - 4403 (1988)] and adapted to a microtiter plate format.

Incubation medium

120 mM KCl, 20 mM Tris (pH = 7.4), 5 µM rotenone, 10 mM K-succinate, 1 µM Oregon Green (from Molecular Probes).

Procedure

In a typical experiment 96-well microtiter plates (flat bottom) are used. The experiment is performed at rt. Distribute in a 96-well plate 5 µl / well of 2 µM ruthenium red [in 120 mM KCl and 20 mM Tris (pH = 7.4)] and the compounds (in DMSO) to be analyzed (1 µl / well). The controls receive the same amount of vehicle. Prepare the mitochondrial suspension (30 µl of freshly prepared brain mitochondria are diluted in 1 ml of incubation medium). After 4 min, when the energized mitochondria have accumulated all endogenous and contaminating Ca, 90 µl / well of mitochondrial suspension are distributed to the wells of the microtiter plate, which is then placed in a fluorimeter equipped with a syringe. The syringe is filled with 200 mM NaCl, and the fluorimeter is programmed to deliver 10 µl / well (final concentration: 20 mM) from the syringe and to make 20 measurements (once every 3 sec). Measure the Ca-release induced by the addition of Na by monitoring the Oregon Green fluorescence (485 nm and 538 nm monochromators for excitation and emission, respectively).

Data analysis

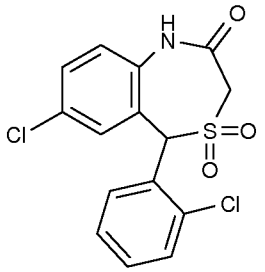
The evaluation of the exponentially decaying Ca-efflux curves is done by fitting and calculating the initial decay rates. To assess the efficacy of a compound, the concentration dependency curves of Ca-efflux rates are fitted using the Levenberg / Marqwardt equation to obtain IC_{50} values.

The agents of the invention show IC_{50} values below 20 µM in this test.

Specifically, the agent of the invention described in Example 1 shows an IC_{50} value of 3.8 µM in this test.

Claims

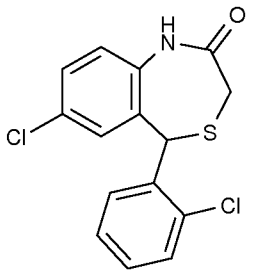
1. A compound of the formula



(I),

in free base form or in acid addition salt form.

2. A process for the preparation of a compound as defined in claim 1 of the formula I, in free base form or in acid addition salt form, comprising the steps of reacting a compound of the formula



(II),

in free base form or in acid addition salt form, with an oxidizing agent, optionally followed by the cleavage of any protecting group(s) optionally present, and of recovering a so obtainable compound of the formula I in free base form or in acid addition salt form.

3. A compound as defined in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, for use as a medicament.

4. A compound as defined in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, for use in the treatment and/or prevention of disorders and diseases influenced by the malfunction of the mitochondrial Ca-handling capacity.

5. A pharmaceutical composition comprising a compound as defined in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, as active ingredient and a pharmaceutical carrier or diluent.

6. The use of a compound as defined in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, as a medicament for the treatment and/or prevention of disorders and diseases influenced by the malfunction of the mitochondrial Ca-handling capacity.

7. The use of a compound as defined in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, for the manufacture of a medicament for the treatment and/or prevention of disorders and diseases influenced by the malfunction of the mitochondrial Ca-handling capacity.

8. A method for the treatment and/or prevention of disorders and diseases influenced by the malfunction of the mitochondrial Ca-handling capacity in a subject in need of such treatment and/or prevention, which comprises administering to such subject a therapeutically effective amount of a compound as defined in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form.

9. A combination comprising a therapeutically effective amount of a compound as defined in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, and a second drug substance, for simultaneous or sequential administration.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/059394

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D281/10 A61K31/554 A61P3/00 A61P25/00 A61P9/00

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, BEILSTEIN Data, WPI Data, 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.
X	PEI Y ET AL: "Efficient Syntheses of Benzothiazepines as Antagonists for the Mitochondrial Sodium-Calcium Exchanger : Potential Therapeutics for Type II Diabetes" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 68, no. 1, 20 November 2002 (2002-11-20), pages 92-103, XP002260407 ISSN: 0022-3263 compound 1A	1-9
A	WO 2004/041286 A (MITOKOR INC [US]; YU JINGHUA [US]; GHOSH SOUMITRA S [US]; PEI YAZHONG) 21 May 2004 (2004-05-21) examples 1-5	1-9

☐ 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	Date of mailing of the international search report
19 October 2007	05/11/2007

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	Bakboord, Joan

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/059394

Box 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. [X] Claims Nos.: 8
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 8 is directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound.

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 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 all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers 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.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2007/059394

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004041286 A	21-05-2004	AU 2003286755 A1	07-06-2004