(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 235 796 B2

(12) **NEW EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the opposition decision:
12.03.1997 Bulletin 1997/11

(45) Mention of the grant of the patent:
06.05.1992 Bulletin 1992/19

(21) Application number: **87102983.1**

(22) Date of filing: **03.03.1987**

(51) Int Cl.[6]: **C07D 313/12**, C07D 405/06, C07D 405/12, A61K 31/335

(54) **Dibenz [b,e] oxepin derivative and antiallergic and antiinflammatory agent**

Dibenzo[b,e]oxepin-Derivate sowie antiallergische und entzündunghemmende Mittel

Dérivés de dibenzo[b,e]oxépine et agent anti-allergique et anti-inflammatoire

(84) Designated Contracting States:
BE CH DE ES FR GB IT LI NL

(30) Priority: **03.03.1986 JP 45676/86**

(43) Date of publication of application:
09.09.1987 Bulletin 1987/37

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GB-A- 1 018 995	**US-A- 3 509 176**

- **JOURNAL OF MEDICINAL CHEMISTRY, vol. 21, no. 7, July 1978, pages 633-639, American Chemical Society; "Novel arabinofuranosyl derivatives of cytosine resistant to enzymatic deamination and possessing potent antitumor activity"**

Remarks:

The file contains technical information submitted after the application was filed and not included in this specification

EP 0 235 796 B2

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Description

Background of the Invention

Heretofore, it has been known that 11-unsubstituted, 11-hydroxy or 11-oxodibenz[b,e]oxepin derivative is used for antiinflammatory agents [J. Med. Chem., 21, 633 - 639 (1978)].

Further, it is known that dibenz[b,e]oxepin derivative wherein substitutents Ra and Rb at 11-position have the following definitions, is employed in the treatment and control of allergic conditions (USP 4.282.365).

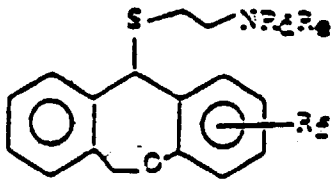
Ra: H, CH, lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, arylthio, NH_2, NHCHO or imidazolyl;

Rb: H or lower alkyl;

or Ra and Rb taken together are = 0, = CH-Rc wherein Rc is H or aryl.

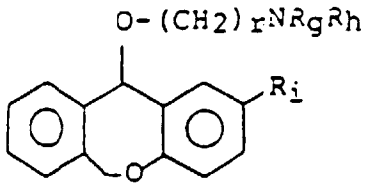
Furthermore, it is known that 11-(4-methylpiperazino) dibenz[b,e]oxepin derivative has an antiasthmatic activity (USP 4.396.550 USP 4.465,835, EP-A-38564).

It is also known that dibenz[b,e]oxepin derivative having the following formula:



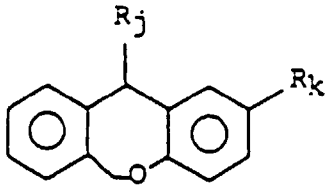
wherein Rd and Re are lower alkyl and Rf is lower alkyl or halogen, has an antiasthmatic activity (EP-A-85870).

Dibenz[b,e]oxepin derivative having an antiallergic activity and having the following structural formula:



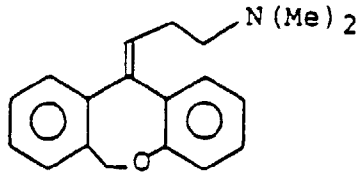
wherein Rg and Rh are alkyl, r is 2 or 3 and Ri is alkyl or halogen is known (JP-A-227879/84).

Dibenz[b,e]oxepin derivative having an antiallergic activity and having the following structural formula:

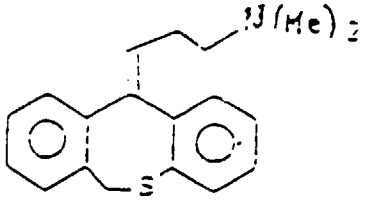


wherein Rj is 4-alkylpiperazino, 3-quinuclidylamino or -Xa-$(CH_2)_s$-$NR_\ell R_m$ wherein Xa is -NH-, -S- or -O-, s is 2 or 3 and R_ℓ and R_m are alkyl, and R_k is CN, 5-tetrazolyl, $CONH_2$ or CO_2R_n wherein R_n is H, alkyl or 1-(ethoxycarbonyloxy) ethyl is known (EP-A-130555).

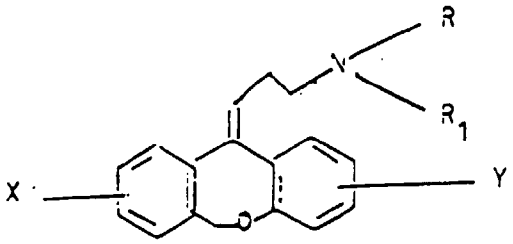
Doxepin having an antidepressant activity and having the following structural formula is known [Drugs, 13. 161 (1977)].



Dothiepin having an antidepressant activity and having the following structural formula is known [Arz.-Forsch., 13 1039 (1963); ibid., 14 100 (1964)].



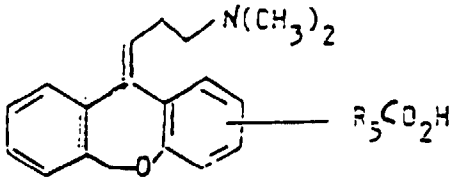
It is also known that dibenz [b,e] oxepin derivatives having the formula :



wherein :

R is hydrogen or methyl ;
R_1 is a lower alkyl, lower alkenyl or lower cycloalkyl ;
X and Y are each hydrogen, lower alkyl, lower alkoxy, lower alkylthio, chloro, fluoro, trifluoromethyl, lower acyl or dialkylsulfonamido, have an antidepressent activity (GB 1,018,955).

It is known that dibenz [b,e] oxepin derivatives of formula :

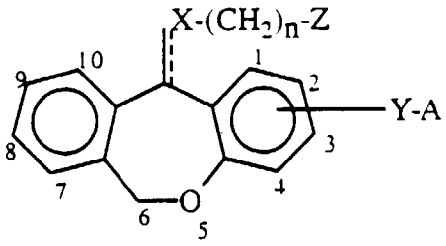


wherein R_5 is a single bond or -CH=CH-, have an anti-asthmatic activity (EP 214779).

As the compound having both an anti-allergic activity and an anti-inflammatory activity, steroids are known.

It is always desired that a novel compound having an antiallergic activity and an antiinflammatory activity be developed.

The present invention relates to a dibenz[b, e]oxepin derivative represented by the formula (I):



(I)

wherein

A represents a carboxyl, a straight or branched (C_1-C_6) alkoxy carbonyl group, -CONHOH or -$CONR_1R_2$ wherein R_1 and R_2 are the same or different and represent hydrogen atom or a straight or a branched (C_1-C_6) alkyl

Y represents -(CH_2)-, -CHR_3-$(CH_2)_m$- wherein R_3 represents a straight or branched (C_1-C_4) alkyl, and m is 1, 2, 3 or 4, which is the substituent at 2- or 3-position of the mother nucleus and the left side of the group Y is bound to benzene nucleus.

X represents =N-, =CH-;

n is o, 1, 2, 3 or 4;

Z represents 4-methylpiperazino, 4-methylhomopiperazino, piperidino, pyrrolidino, thiomorpholino, morpholino or -NR_6R_7 wherein R_6 and R_7 are the same or different and represent hydrogen atom or a straight or branched (C_1-C_4) alkyl a ---- means double bond; and the pharmaceutically acceptable salts thereof.

The present invention further pertains to pharmaceutical composition containing an effective amount of Compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient, and a carrier or an excipient.

The present compound (I) is useful for treatment of allergic conditions and inflammation diseases.

DETAILED DESCRIPTION OF THE INVENTION

In the definition of each group of formula (I), the lower alkyl group includes straight or branched chain alkyl groups having 1 to 6 carbon atoms, for example, methyl, ethyl, n-propyl, iso-propyl, n-butyl, etc.

In the definition of the group A, lower alkyl moiety of lower alkoxymethyl group and lower alkoxycarbonyl group has the same meaning as previously defined.

The lower alkoxymethyl group includes methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxymethyl, etc. and the lower alkoxycarbonyl group includes methoxycarbonyl, ethoxycarbonyl, etc.

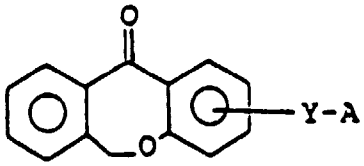
In the definition of the group A, the lower alkyl moiety of lower alkanoyl group and lower alkanyoloxymethyl group has the same meaning as previously defined.

The lower alkanoyl group includes formyl, acetyl, etc. and the lower alkanoyloxymethyl group includes formylo-cymmethyl, acetyloxymethyl.

The pharmaceutically acceptable salt of compound (I) includes pharmaceutically acceptable acid addition salt, metal salt, ammonium salt, organic amine addition salt, amino acid addition salt, etc..

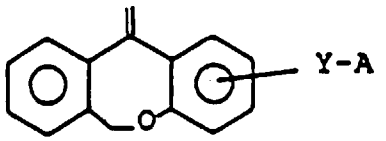
The pharmaceutically acceptable acid addition salt of compound (I) includes inorganic acid salts such as hydrochloride, sulfate, phosphate, etc., and organic acid salts such as acetate, maleate, fumarate, tartrate, citrate, etc.. The pharmaceutically acceptable metal salt includes alkalimetal salts such as sodium salt, potassium salt, etc., alkaline earch metal salts such as magnesium salt, calcium salt, etc., and aluminium salt, zinc salt, etc.. The pharmaceutically acceptable organic amine addition salt includes addition salt of morpholine and piperidine and the pharmaceutically acceptable amino acid addition salt includes addition salt of lysine, glysine, phenylalanine, etc..

Compound (I) is prepared by using a compound represented by the formula (II):



(II)

wherein Y and A have the same meanings as previously defined or a compound represented by the formula (III):



(III)

wherein Y and A have the same meanings as previously defined as the starting compound. Compound (II) is disclosed in J. Med. Chem., 19. 941 (1976), ibid., 20, 1499 (1977) and JP-A-21679/83.

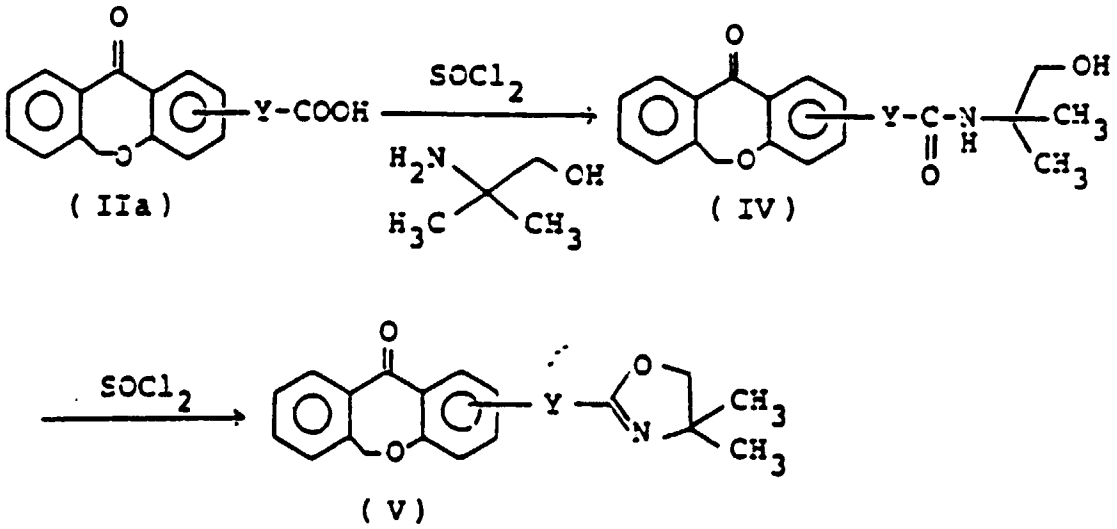
Compound (III) wherein -Y-A is -COOH is disclosed in JP-A-21679/83 and the other Compounds (III) can be prepared according to the method described in the publication though they do not occur in the publication.

The process for preparing Compound (I) is explained, depending on the kind of the group X.

Process A

[Synthesis of Compound (I) wherein X is = CH- (Part 1)]

The carboxy group of Compound (IIa) is protected according to the following reaction scheme.



In the formula, Y has the same meaning as previously defined, and Compound (IIa) is included in Compound (II) (compounds with an alphabet suffix following formula number are likewise included in compounds with common formula no.)

Compound (IIa) is reacted with 1 to 5 equivalents of thionyl chloride and 1 to 5 equivalents of 2-amino-2-methyl-1-propanol on the basis of Compound (IIa) in an inert solvent such as methylene chloride, if necessary in the presence of a base such as triethylamine at a temperature of from 0°C to room temperature for 1-24 hours to form Compound (IV). Compound (IV) can also be obtained by reacting Compound (IIa) with thionyl chloride in advance and then with 2-amino-2-methyl-1-propanol.

Compound (IV) is reacted with 1-5 equivalents of thionyl chloride in an inert solvent such as methylene chloride, toluene and benzene at a temperature of from 0°C to room temperature for I - 24 hours to form Compound (V).

Compounds (Ia) and (Ib) can be prepared from Compound (V) according to the following reaction scheme.

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