EUROPEAN PATENT SPECIFICATION

(19) European Patent Office
(11) EP 0 662 957 B1
(21) Application number: 93919147.4
(22) Date of filing: 24.08.1993
(45) Date of publication and mention of the grant of the patent: 05.11.1997 Bulletin 1997/45
(51) Int Cl.6: C07D 207/08, C07D 207/09, C07D 207/16, C07D 401/12, C07D 403/12, A61K 31/50, A61K 31/505, A61K 31/53, A61K 31/40
(86) International application number: PCT/EP93/02264

(54) 1,4-DISUBSTITUTED PIPERAZINES USEFUL IN THE THERAPY OF THE ASTHMA AND OF THE INFLAMMATION OF THE RESPIRATORY TRACT
1,4-DISUBSTITUIERTE PIPERAZINE ZUR BEHANDLUNG VON ASTHMA UND ENTZÜNDUNGEN DER ATEMWEGE
PIPERAZINES 1,4-DISUBSTITUEES UTILES DANS LE TRAITEMENT DE L'ASTHME ET D'INFLAMMATIONS DES VOIES RESPIRATOIRES

(84) Designated Contracting States: AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT SE
(30) Priority: 30.09.1992 IT MI922263
(43) Date of publication of application: 19.07.1995 Bulletin 1995/29
(73) Proprietor: BOEHRINGER MANNHEIM ITALIA S.P.A.
20126 Milano (IT)

(72) Inventors:
- LONG, Giorgio
  I-20126 Milano (IT)
- SPINELLI, Silvano
  I-20126 Milano (IT)
- ROZZI, Antonella
  I-20126 Milano (IT)
- D’ALO’, Simonetta
  I-20126 Milano (IT)
- GALLICO, Licia
  I-20126 Milano (IT)

(74) Representative: Weber, Manfred, Dr.
c/o Boehringer Mannheim GmbH,
Patentabteilung,
Sandhoferstrasse 116
68298 Mannheim (DE)

(56) References cited:
EP-A- 0 288 575
EP-A- 0 461 012
WO-A-92/18478
- CHEMICAL ABSTRACTS, vol. 97, no. 23, 6 December 1982, Columbus, Ohio, US; abstract no. 198218, 'Aminquinazoline derivatives'
- CHEMICAL ABSTRACTS, vol. 109, no. 19, 1988, Columbus, Ohio, US; abstract no. 170371, 'Studies in potential fumaricides,'

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

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).
The present invention relates to heterocyclic amines, a process for the preparation thereof and pharmaceutical compositions containing them.

More particularly, the invention relates to compounds of formula (I):

\[
\begin{align*}
\text{N} & \quad \text{B} & \quad \text{N} & \quad \text{D} \\
\text{CO} & \quad \text{CR}_{\text{RA}} \text{RB} & \quad \text{n} & \quad \text{COOH}
\end{align*}
\]

(I)

the single enantiomeric and diastereomeric forms thereof, the mixtures thereof and the salts thereof with pharmaceutically acceptable acids and bases, wherein:

B is a -CO- or -CH_{2}CO- group; D is an heterocycle selected from the group consisting of [2,6-bis(pyridin-1-yl)-4,pyrimidinyl], [4,6-bis(pyridin-1-yl)-1,3,5-triazin-2-yl], [3,6-bis(diethylaminopyridin-2-yl] and [3-ethylaminopyridin-2-yl]; Ra, which is the same as Rb, is hydrogen or methyl and n is 1.

The acid and basic groups can be salted respectively with pharmaceutically acceptable bases and acids. The non toxic salts thus obtained fall within the scope of the invention, as well as the single enantiomers, diastereomers, diastereomeric mixtures and racemates of the compounds of formula (I). Compounds (I) can be salted with both inorganic and organic acids which are pharmaceutically acceptable, such as hydrochloric, hydrobromic, hydroiodic, phosphoric, metaphosphoric, nitric or sulfuric, acetic, oleic, tartaric, citric, benzoic, glycolic, gluconic, glucuronic, succinic, maleic, fumaric acids, etc. The carboxy group can be salted with bases of various nature, with the only proviso that the salts are pharmaceutically acceptable. Examples of said salts comprise those with: ammonium, sodium, potassium, calcium, magnesium, aluminium, iron, zinc, copper, or salts with pharmaceutically acceptable organic bases such as arginine, lysine, histidine, methyleneamine, ethylamine, dimethylamine, dibenzylamine, morpholine, phenylglycin and D-glucosamine.

Prolinamides with piperazinquinazoline are described to be ACE-inhibitors (Sankyo Co., JP 82 91,987; C.A., 97 198218w, 1982). N-Carbamoylprolinamides with N-methylpiperazine are known to be filaricidal (Indian J. Chem., Sect. B, 1987, 26B(8), 748-751).

The compounds of the invention showed useful pharmacological properties, particularly as far as the treatment of bronchial hyper-reactivity is concerned.

Bronchial hyper-reactivity is a clinical symptom of asthma and it is believed to be a direct consequence of an abnormal and latent contractility and sensitivity of the bronchial mucosa.

Bronchial hyper-reactivity can cause acute asthma after physical practice, and/or after exposure to external stimuli such as the inhalation of fog, pollutants, allergens and autacoids.

The bronchial hyper-reactivity conditions may be simulated by an experimental model consisting in the PAF infusion (600 µg/l) in male guinea-pigs weighing 400-450 g, kept under forced ventilation under urethane and pancuronium bromide anaesthesia.

PAF, which is one of the most important mediators involved in the inflammatory process of the airways, after infusion for 1 hour, causes an hyperreactivity reaction (bronchocostriction) to specific and different substances.

The activity of the compounds of the invention, in the considered pharmacological model, is shown by the prevention of the PAF-induced hyper-reactivity, measured as increase of the pulmonary insufflatory pressure (measured according to the modified procedure of Konzett and Rossler, Naun. Schmied. Arch. Exper. Pathol. Pharmacol. 191, 71, 1970).

The compounds of the invention, which are administered 10 minutes before the PAF administration in dosages which vary between 2 and 50 µg/kg, demonstrate a protective action which lasts at least 4-6 hours and results in a reduction of the PAF-induced hypereactivity. Such pharmacological effects are dose related.

From what has been shown above it is clear that the compounds of the invention can be used in human therapy in the treatment of asthmatic and obstructive conditions of the respiratory tract, in the treatment of inflammatory phlogosis. For the intended therapeutic uses, the compounds of the invention will be administered in the form of pharmaceutical compositions which can be prepared with conventional excipients and techniques such as, for example, those

The daily dose will depend on several factors such as the gravity of the pathology and the condition of the patient: it will normally consist of 1 to 50 mg of a compound of formula (I) for a patient weighing 70 kg, one or more times a day.

The compounds of formula (I) are prepared by reacting a compound of formula (II)

wherein B and D are as above defined, with a compound of formula (III)

wherein Rα, Rβ and n have the above described meanings; R is a C₁⁻C₆⁻alkyl, benzyl, allyl group or any other group which can easily be removed; E is halogen (chlorine, bromine), N-imidazolyl, OH, O-hydroxy succinimidy or, taken together with the carbonyl group, it forms a mixed anhydride with a carboxylic or sulfonic acid (for example, trifluoromethanesulfonic acid), to give compounds of formula (Ia)

Compounds of formula (Ia) can be transformed into the compounds of formula (I) by means of conventional reactions such as:

a) when R is C₁⁻C₆⁻alkyl, hydrolysis with mineral bases such as sodium, potassium, lithium hydroxides at various concentrations and in various solvents (such as methanol, ethanol, dimethylformamide);

b) when R is allyl or benzyl, catalytic hydrogenation with various catalysts (such as palladium on charcoal in various concentrations, nikkel-Raney, palladium tetrakis (triphenylphosphine), and the like) and in various solvents (such as methanol, ethanol, toluene, methylene chloride) or by means of hydrogen transfer procedures, such as those with ammonium formate, cyclohexene or sodium hypophosphate in the presence of palladium on charcoal in solvents such as water, lower alcohols or mixtures thereof.

The reaction of compound (II) with compound (III) is usually carried out in an inert solvent and in the presence of a suitable base. In case E=CO⁻ is a carboxylic group (E=OH), the reaction is carried out in an inert solvent and in the presence of condensing agents such as carbodiimides, isocyanites, and the like.

The preparation of the compounds of formula (II) is carried out starting from an acid of formula (IV)
wherein \( R' \) is a suitable protecting group which can be removed compatibly with the reactions described below and with the functional groups present in the molecule. Convenient protecting groups of formula \( R' \) can be: tert-butoxycarbonyl, methoxycarbonyl, 9-fluorenylecarboxylic, 2,2,2-trichloroethoxycarbonyl, allyloxycarbonyl, benzylxycarbonyl. Compounds of formula (IV) are commercially available or they can be prepared from proline by means of conventional and widely known reactions, which are reported in literature. If said compounds are not commercially available as the enantiomerically pure forms thereof, they can be resolved with conventional methods such as salification with optically active bases and separation of the diastereomeric salts.

The transformation of the products of formula (IV) in those of formula (V)

wherein \( R' \) has the above defined meanings, can be effected with conventional reactions. Particularly:

a) the synthesis of compounds of formula (Va):

starting from compounds of formula (IV), can be carried out by transformation of the carboxy group into a succinimido ester, acid chloride, mixed anhydride, imidazolide or other reactive derivatives of the carboxy group and condensation thereof with an amine of formula (VI)

b) the synthesis of compounds of formula (Vb):
in which X = O, starting from compounds of formula (IV), can be performed by reduction of the carboxy group or of a corresponding mixed anhydride or a carboxy ester derivative thereof to primary alcohol (CH₂OH), which can be converted into a carbamate by reaction with carbonyldimidazole and subsequently with an amine of formula (VI). The reduction of the carboxy group of proline or of a mixed anhydride thereof to alcohol can conveniently be carried out with reducing agents such as diborane or a borohydride of an alkali or alkaline-earth metal.

The transformation of compounds of formula (V) into compounds of formula (II) can be performed by conventional removing methods which are specific and selective for the used protecting group and particularly, in the case of BOC-derivatives, with trifluoroacetic acid or trimethylsilyl iodide.

Compounds of formula (III) are obtained according to conventional processes reported in literature.

The following examples and preparations further illustrate the invention. The concentrations are expressed as % in w/v. The described compounds should be considered as racemic mixtures, if not otherwise stated by means of the symbols (+) and (-). The malonic acid monoalkyl- or monobenzyl esters and the acyl chlorides thereof are known in literature or anyhow they can be prepared according to conventional methods which are widely reported in literature.

**EXAMPLE 1**

A solution containing 2.5 g of BOC-L-proline in anhydrous THF (10 ml) is added, at a temperature of 0°C, under inert gas atmosphere and with stirring, with 2.9 g of N-hydroxysuccinimide dissolved in 10 ml of THF. Seid solution is added dropwise with a solution of 2.1 ml of morpholinoethylsulfini)nitride in 5 ml of THF and stirring is continued at room temperature for 2 hours; the reaction mixture is acidified with 1N hydrochloric acid to acid pH (pH paper) and is extracted with ethyl acetate (3x10 ml). The combined organic extracts are concentrated under vacuum to crystallize the BOC-L-proline succinimido ester, which is separated by filtration, to obtain 2.6 g, m.p. 125-130 °C. 1 g of the BOC-L-proline succinimido ester is dissolved in acetonitrile (7 ml), at room temperature and under inert gas atmosphere, then, under stirring, 0.97 g of N-[4,6-bis(pyridolin-1-yl)-1,3,5-triazin-2-yl]piperazine dissolved in acetonitrile (5 ml) are added. After 5 hours the reaction mixture is concentrated under vacuum to small volume, then it is added with a sodium bicarbonate saturated solution to slightly basic pH. The mixture is extracted with ethyl acetate (3x10 ml), then the combined extracts are concentrated to small volume under vacuum. By addition of ethyl ether, 1.5 g of (-)-N-[pyrrolidin-1-tertbutoxycarbonyl-2-yl]carbonyl]-N'[4,6-bis(pyridolin-1-yl)-1,3,5-triazin-2-yl]piperazine precipitate, m.p. 148 °C after recrystallization from diisopropyl ether, [α]D -20.25° (c=2.01 in EtOH).

**EXAMPLE 2**

By reacting a solution of the BOC-proline N-hydroxysuccinimido ester in acetonitrile with a suitable N-substituted piperazine, according to the procedure described in example 1, the following N,N'-disubstituted piperazines are obtained:

(-)-N'-[(pyrrolidin-1-tertbutoxycarbonyl-2-yl]carbonyl]-N-[2,6-bis(pyridolin-1-yl]pyrimidin-4-yl)piperazine, m.p. 168-170°C, [α]D -20.7° (c=2 in EtOH),

(+)-N'-[(pyrrolidin-1-tertbutoxycarbonyl-2-yl]carbonyl]-N-[2,6-bis(pyridolin-1-yl]pyrimidin-4-yl)piperazine,

[α]D +20.2° (c=2.03 in EtOH),

N'-[(pyrrolidin-1-tertbutoxycarbonyl-2-yl]carbonyl]-N-[2,6-bis(pyridolin-1-yl]pyrimidin-4-yl)piperazine, m.p. 125°C,

(-)-N'-[(pyrrolidin-1-tertbutoxycarbonyl-2-yl]carbonyl]-N-[3,6-bis(diethylamino)pyridin-2-yl]piperazine, [α]D =-19.3° (c=2.07 in EtOH),

(+)-N'-[(pyrrolidin-1-tertbutoxycarbonyl-2-yl]carbonyl]-N-[3,6-bis(diethylamino)pyridin-2-yl]piperazine,

[α]D +19.5° (c=2.01 in EtOH),

**EXAMPLE 3**

2.54 ml of trifluoroacetic acid are added, under stirring and inert gas atmosphere, to a solution of 1.4 g of (-)-N'-[pyrrolidin-1-tertbutoxycarbonyl-2-y]carbonyl]-N-[4,6-bis(pyrrolidin-1-yl)-1,3,5-triazin-2-yl]pipera-zine in 10 ml of methylene chloride. After 3 hours at room temperature, the reaction mixture is added with 1N NaOH to basic pH, then it is extracted with methylene chloride and repeatedly washed with water. The combined organic extracts are dried over sodium sulfate and the solvent is evaporated off under reduced pressure. The crude product is crystallized from ethyl ether, to give 950 mg of (-)-N'-[pyrrolidin-2-yl]carbonyl]-N-[4,6-bis(pyrrolidin-1-yl)-1,3,5-triazin-2-yl]pipera-zine, m.p. 143°C, [α]D = -65.75° (c=0.23 in EtOH).

**EXAMPLE 4**

By reacting the N,N'-disubstituted piperazine described in example 2 according to the procedure described in example 3, the following N'-substituted N'-[pyrrolidin-2-yl]carbonyl]pipera-zines are obtained:

(-)-N'-[pyrrolidin-2-yl]carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)]pyrimidin-4-yl]pipera-zine, m.p. 172-174°C, [α]D = -56.6° (c=1.88 in EtOH),
(+)-N'-[pyrrolidin-2-yl]carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)]pyrimidin-4-yl]pipera-zine, m.p. 148-151°C, [α]D = +53.5° (c=0.2 in EtOH),
N'-[pyrrolidin-2-yl]carbonyl]-N-[2,6-bis(2-pyrrolidinyl)pyrimidin-4-yl]pipera-zine, m.p. 137°C,
(-)-N'-[pyrrolidin-2-yl]carbonyl]-N-[3,6-bis(diethylamino)pyridin-2-yl]pipera-zine, oil [α]D = -43.9° (c=2.56 in EtOH),
(+)-N'-[pyrrolidin-2-yl]carbonyl]-N-[3,6-bis(diethylamino)pyridin-2-yl]pipera-zine, [α]D = +48.4° (c=0.21 in EtOH),

**EXAMPLE 5**

0.8 g of (-)-N'-[pyrrolidin-2-yl]carbonyl]-N-[4,6-bis(pyrrolidin-1-yl)-1,3,5-triazin-2-yl]pipera-zine dissolved in 20 ml of acetonitrile are added, at 0°C and under stirring, with 0.22 g of potassium bicarbonate and with a solution of 0.28 ml of ethyl malonyl chloride in 5 ml of acetonitrile. After 4 hours at room temperature and under stirring, the reaction mixture is added with water (50 ml) and extracted repeatedly with ethyl acetate (3x20 ml). The combined organic extracts are dried over sodium sulfate and the solvent is evaporated off under reduced pressure. The residue (0.86 g) is purified by silica gel chromatography (eluent hexane/AcOEt 1:1) to give 0.6 g of (-)-N'-[1-ethoxymalonoyl]pyrrolidin-2-yl) carbonyl]-N-[4,6-bis(pyrrolidin-1-yl)-1,3,5-triazin-2-yl]pipera-zine, m.p. 115°C, [α]D = -23.95° (c=0.2 in EtOH).

**EXAMPLE 6**

According to the procedure described in example 5, starting from the N,N'-disubstituted piperazines described in example 4 and from the malonic acids monocarboxylic chloride, optionally 2,2 disubstituted, the following piperazines are prepared:

(-)-N'-[1-ethoxymalonoyl]pyrrolidin-2-yl)carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)]pyrimidin-4-yl]pipera-zine, m.p. 170-172°C, [α]D = -26.5° (c=2.19 in EtOH),
(+)-N'-[1-ethoxymalonoyl]pyrrolidin-2-yl)carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)]pyrimidin-4-yl]pipera-zine, m.p. 133-135°C, [α]D = +26.5° (c=2.14 in EtOH),
N'-[1-ethoxymalonoyl]pyrrolidin-2-yl)carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)]pyrimidin-4-yl]pipera-zine, m.p. 127-129°C,
(-)-N'-[1-ethoxymalonoyl]pyrrolidin-2-yl)carbonyl]-N-[3,6-bis(diethylamino)pyridin-2-yl]pipera-zine, m.p. hydrochloride 80-85°C, [α]D = -20.6° (free base, c=2.09 in EtOH),
(+)-N'-[1-ethoxymalonoyl]pyrrolidin-2-yl)carbonyl]-N-[3,6-bis(diethylamino)pyridin-2-yl]pipera-zine, [α]D = +20.1° (c=2.01 in EtOH),
N'-[1-ethoxymalonoyl]pyrrolidin-2-yl)carbonyl]-N-[3-ethylaminopyridin-2-yl]pipera-zine,
(-)-N'-[1-benzyloxyalonoxy]pyrrolidin-2-yl)carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)]pyrimidin-4-yl]pipera-zine, m.p. 144-145°C, [α]D = -26.5° (c=0.23 in EtOH),
N'-[1-benzyloxyalonoxy]pyrrolidin-2-yl)carbonyl]-N-[4,6-bis(pyrrolidin-1-yl)-1,3,5-triazin-2-yl]pipera-zine,
N'-[1-benzyloxyalonoxy]pyrrolidin-2-yl)carbonyl]-N-[3,6-bis(diethylamino)pyridin-2-yl]pipera-zine,
N'-[1-benzyloxyalonoxy]pyrrolidin-2-yl)carbonyl]-N-[3-ethylaminopyridin-2-yl]pipera-zine,
(-)-N'-[1-(2',2'-dimethylbenzoxoxyalonoxy)]pyrrolidin-2-yl)carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)]pyrimidin-4-yl]pipera-zine, m.p. 104-106°C, [α]D = -43.2° (c=0.24 in EtOH),
N'-[1-(2',2'-dimethylbenzoxoxyalonoxy)]pyrrolidin-2-yl)carbonyl]-N-[3,6-bis(diethylamino)pyridin-2-yl]pipera-zine,
EXAMPLE 7

A solution of 0.5 g of (-)-N'-[(1-ethoxy)malonyl]pyrrolidin-2-yl]carbonyl]-N-[4,6-bis(pyrrrolidin-1-y1]-1,3,5-triazin-2-yl]piperazine in 5 ml of methanol is added, under stirring and inert gas atmosphere, with 80 μl of sodium hydroxide (35% aqueous solution). Stirring is continued for 20 more hours, then the reaction mixture is brought to neutrality by addition of sodium bicarbonate, filtered over celite and the solvent is evaporated off under reduced pressure. The crude product (0.52 g) is purified by silica gel chromatography (eluent methylene chloride/methanol 9:1) to obtain 0.43 g of (-)-N'[1-(1'-malonyl)pyrrolidin-2-yl]carbonyl]-N-[4,6-bis(pyrrrolidin-1-y1]-1,3,5-triazin-2-yl]piperazine, m.p. 208-211°C, [α]D=-21.7° (c=0.3 in EtOH).

EXAMPLE 8

1.5 g of (-)-N'-[(1-benzyloxy)malonyl]pyrrolidin-2-yl]carbonyl]-N-[2,6-bis(pyrrrolidin-1-y1]pyrimidin-4-yl]piperazine are dissolved in a mixture of 20 ml of methanol and 6 ml of toluene, then 1.5 g of 10% palladium on charcoal are carefully added, under nitrogen protection. The resulting reaction mixture is subjected to catalytic hydrogenation under atmospheric pressure, using an apparatus such as the one described in VOGEL’S Textbook of Practical Organic Chemistry, fifth Edition, Longman Scientific & Technical (USA John Wiley & Sons, Inc.), 1989, pages 89-92. After 10 minutes the reaction is filtered through a celite plug to remove the catalyst and the solvent is evaporated off under reduced pressure. By recrystallization of the crude product from ethyl ether (5 ml), 1.1 g of (-)-N'[1-(1'-malonyl)pyrrolidin-2-yl]carbonyl]-N-[2,6-bis(pyrrrolidin-1-y1]pyrimidin-4-yl]piperazine are obtained, m.p. 205-207°C, [α]D=-19.25° (c=0.21 in EtOH).

EXAMPLE 9

Following the procedures described in example 7 or in example 8, starting from the suitable esters described in example 6, the following carboxylic acids are prepared:

N'-[(1'-malonyl)pyrrolidin-2-yl]carbonyl]-N-[3,6-bis(diethylamino)pyridin-2-yl]piperazine, m.p. sodium salt, 188-191°C.
N'-[(1'-malonyl)pyrrolidin-2-yl]carbonyl]-N-[3-ethylaminopyridin-2-yl]piperazine, m.p. sodium salt 171-174°C, (-)-N'[(1'-malonyl)pyrrolidin-2-yl]carbonyl]-N-[2,6-bis(pyrrrolidin-1-y1]pyrimidin-4-yl]piperazine, m.p. 160-163°C, [α]D=-25.4° (c=0.2 in EtOH).
N'-[(1'-malonyl)pyrrolidin-2-yl]carbonyl]-N-[4,6-bis(pyrrrolidin-1-y1]-1,3,5-triazin-2-yl]piperazine, m.p. 160-181°C.
N'-[(1'-malonyl)pyrrolidin-2-yl]carbonyl]-N-[3,6-bis(diethylamino)pyridin-2-yl]piperazine, m.p. sodium salt 189-192°C.
N'[(1'-malonyl)pyrrolidin-2-yl]carbonyl]-N-[3-ethylaminopyridin-2-yl]piperazine, m.p. potassium salt 206-208°C.

EXAMPLE 10

A solution of BOC-(L)-proline in 60 ml of anhydrous THF, cooled at -10°C with brine, is added with 6.1 ml of triethylamine and 1 g of 4 A molecular sieves, then, keeping the temperature below -5°C, a solution of 4.16 ml of ethyl chloroforamate in 5 ml of anhydrous THF is dropped therein. After 30 minutes under stirring, the reaction mixture is filtered to remove the triethylammonium chloride precipitate and the filtrate is concentrated under reduced pressure to a volume of 30 ml. The resulting solution is dropped into a suspension of 7.5 g of sodium borohydride in 50 ml of anhydrous THF, cooled at -10°C with brine. After 2 hours the reaction mixture is added with 200 ml of an aqueous saturated solution of sodium dihydrogen phosphate, keeping the temperature at 0°C with water/ice, then it is extracted with ethyl acetate (3x50 ml). The combined organic extracts are washed repeatedly with an aqueous saturated solution of sodium bicarbonate (3x30 ml), dried over sodium sulfate and the solvent is evaporated off under reduced pressure. The residue, by crystallization from hexane, yields 6.1 g of BOC-(L)-prolinol, m.p. 59-60°C, [α]D=-54.9° (c=0.2 in EtOH).

EXAMPLE 11

A solution of 3 g of BOC-(L)-prolinol in 100 ml of anhydrous THF, cooled at 0°C with water/ice, under stirring and inert gas atmosphere, is added with 2.9 g of carbonyldimidazole in portions, then the reaction mixture is warmed to room temperature and stirring is continued for 3 hours. Said solution is added with 4.5 g of N-[2,6-bis(pyrrrolidin-1-y1]
pyrimidin-4-yl)piperazine in portions and stirring is continued for 18 hours. The reaction mixture is added with 400 ml of an aqueous saturated solution of sodium dihydrogen phosphate and extracted with ethyl acetate (3x100 ml). The combined organic extracts are dried over sodium sulfate and the solvent is evaporated off under reduced pressure. The residue (7.5 g) is purified by silica gel chromatography (eluent hexane/ethyl acetate 7:3), to obtain 5.5 g of (S)-N-[(1-[tert-butylcarbonyl]pyrrolidin-2-yl)methoxy]carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)pyrimidin-4-yl]piperazine, m.p. 142°C, [α]D = -32° (c=0.25 in EtOH).

EXAMPLE 12

17.4 ml of trifluoroacetic acid are dropped into a solution of 10 g of (S)-N-[(1-[tert-butylcarbonyl]pyrrolidin-2-yl)methoxy]carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)pyrimidin-4-yl]piperazine in 300 ml of methylene chloride. After about 18 hours, the reaction mixture is added with 400 ml of a 1N sodium hydroxide aqueous solution and extracted with methylene chloride (3x150 ml). The combined organic extracts are washed with water (2x100 ml), dried over sodium sulfate and the solvent is evaporated off under reduced pressure. By crystallization of the residue from diisopropyl ether/ethyl acetate 9:1, 6.5 g of (S)-N-[(pyrrolidin-2-yl)methoxy]carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)pyrimidin-4-yl]piperazine are obtained, m.p. 137-138°C, [α]D = -8.7° (c=0.23 in EtOH).

EXAMPLE 13

A solution of 3.4 g of 2,2-dimethylmalonic acid mono-benzyl ester in 75 ml of anhydrous dimethylformamide, cooled at 0°C with stirring and inert gas atmosphere, is added with 3.77 g of 1-hydroxybenzotriazole, 1.55 ml of N-methylmorpholine, 6 g of (S)-N-[(3-benzyloxy-2',2'-dimethylmalon-1'-yl)pyrrolidin-2-yl]methyl]oxycarbonyl]-N-[2,6-bis(pyrrolidin-1-yl)pyrimidin-4-yl]piperazine and finally 5.35 g of N-[(3-dimethylaminopropyl]-N-ethylcarbodiimide hydrochloride dissolved in 25 ml of dimethylformamide, in this succession. The mixture is left to warm to room temperature, then stirring is continued for 18 more hours. The solvent is evaporated off under reduced pressure, then the reaction mixture is added with 200 ml of a sodium bicarbonate saturated aqueous solution and extracted with ethyl acetate (3x100 ml). The combined organic extracts are dried over sodium sulfate and the solvent is evaporated off under reduced pressure. 10.2 g of a crude product are obtained, which is purified by silica gel chromatography (300 g of silica: eluent petroleum ether/ethyl acetate 1:1), to obtain 6.5 g of (S)-N-[(1-[3-benzyloxy-2',2'-dimethylmalon-1'-yl)pyrrolidin-2-yl]methyl]oxycarbonyl]-N-[2,6-bis(pyrrolidin-1-yl)pyrimidin-4-yl]piperazine, as a light brown foam. 6.45 g of (S)-N-[(1-[3-benzyloxy-2',2'-dimethylmalon-1'-yl)pyrrolidin-2-yl]methyl]oxycarbonyl]-N-[2,6-bis(pyrrolidin-1-yl)pyrimidin-4-yl]piperazine are dissolved in a mixture of 100 ml of methanol and 40 ml of toluene. Said solution is carefully added with 0.65 g of 10% palladium on charcoal and the resulting reaction mixture is subjected to catalytic hydrogenation under atmospheric pressure using an apparatus such as the one described in Vogel's Textbook of Practical Organic Chemistry, fifth Edition, Longman Scientific & Technical (USA John Wiley & Sons, Inc.). 1989, pages 89-92. After 10 minutes the reaction is filtered through a celite plug to remove the catalyst and the solvent is evaporated off under reduced pressure. By crystallization of the crude product from diisopropyl ether, 5.5 g of (S)-N-[(1-[2',2'-dimethylmalon-1'-yl)pyrrolidin-2-yl]methyl]oxycarbonyl]-N-[2,6-bis(pyrrolidin-1-yl)pyrimidin-4-yl]piperazine are obtained, m.p. 159-160°C, [α]D = -49.8° (c=0.21 in EtOH).

EXAMPLE 14

Following the procedures described in the examples 11, 12 and 13, starting from the suitable N-substituted piperazines and from the suitable malonic acids monoaalkyl or mono-benzyl esters, optionally 2,2-disubstituted, the following N,N'-disubstituted piperazines are obtained:

(S)-N-[(1-[1'-malonyl]pyrrolidin-2-yl)methoxy]carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)pyrimidin-4-yl]piperazine, m.p. 169-170°C, [α]D = -38.1° (c=0.2 in EtOH),

N-[(1-[1'-malonyl]pyrrolidin-2-yl)methoxy]carbonyl]-N-[3,6-bis(diethylamino)pyrrolidin-2-yl]piperazine, m.p. sodium salt 198-199°C,

N-[(1-[1'-malonyl]pyrrolidin-2-yl)methoxy]carbonyl]-N-[3-ethylaminopyrrolidin-2-yl]piperazine, m.p. sodium salt 200-201°C,

N-[(1-[2',2'-dimethyl-1'-malonyl]pyrrolidin-2-yl)-methoxy]carbonyl]-N-[4,6-bis(pyrrolidin-1-yl)-1,3,5-triazin-2-yl] piperazine, m.p. 172-173°C,

N-[(1-[2',2'-dimethyl-1'-malonyl]pyrrolidin-2-yl)-methoxy]carbonyl]-N-[3,6-bis(diethylamino)pyrrolidin-2-yl]piperazine,

N-[(1-[2',2'-dimethyl-1'-malonyl]pyrrolidin-2-yl)-methoxy]carbonyl]-N-[3-ethylaminopyrrolidin-2-yl]piperazine, m.p. potassium salt 220-225°C.
Claims

1. Compounds of general formula (I)

![Chemical Structure (I)]

the single enantiomeric and diastereomeric forms thereof, the mixtures thereof and the salts thereof with pharmaceutically acceptable acids and bases, wherein:

- B is a -CO- or -CH₂OCC- group;
- D is an heterocycle selected in the group consisting of [2,6-bis(pyrrrolidin-1-yl)-4-pyrimidinyl], [4,6-bis(pyrrrolidin-1-yl)1,3,5-triazin-2-yl], [3,6-bis(diethylamino)pyridin-2-yl] and [3-ethylaminopyridin-2-yl];
- Ra, which is the same as Rb, is hydrogen or methyl;
- and n is the integer 1.

2. A compound according to claim 1, selected in the group consisting of:

- (-)-N'-(1-(1'-malonyl)pyrrrolidin-2-yl)carbonyl)-N-[2,6-bis(pyrrrolidin-1-yl)pyrimidin-4-yl]piperazine,
- (-)-N'-(1-(2',2'-dimethyl-1'-malonyl)pyrrrolidin-2-yl)carbonyl)-N-[2,6-bis(pyrrrolidin-1-yl)pyrimidin-4-yl]piperazine;
- (-)-N'-(1-(1'-malonyl)pyrrrolidin-2-yl)carbonyl)-N-[4,6-bis(pyrrrolidin-1-yl)1,3,5-triazin-2-yl]piperazine;
- (-)-N'-(1-(2',2'-dimethyl-1'-malonyl)pyrrrolidin-2-yl)methoxy carbonyl)-N-[2,6-bis(pyrrrolidin-1-yl)pyrimidin-4-yl]piperazine;
- (-)-N'-(1-(1'-malonyl)pyrrrolidin-2-yl)methoxy carbonyl)-N-[2,6-bis(pyrrrolidin-1-yl)pyrimidin-4-yl]piperazine;
- N'-(1-(2',2'-dimethyl-1'-malonyl)pyrrrolidin-2-yl)methoxy carbonyl)-N-[4,6-bis(pyrrrolidin-1-yl)1,3,5-triazin-2-yl]piperazine.

3. A compound according to claim 2, wherein such compound is:

- (-)-N'-(1-(2',2'-dimethyl-1'-malonyl)pyrrrolidin-2-yl)methoxy carbonyl)-N-[2,6-bis(pyrrrolidin-1-yl)pyrimidin-4-yl]piperazine.

4. A process for the preparation of the compounds of claims 1-3, characterized in that a compound of formula (II)

![Chemical Structure (II)]

wherein B and D are as defined above, is reacted with a compound of formula (III)
wherein Ra, Rb and n have the above described meanings; R is a C₇-C₈-alkyl, benzy1, allyl group or any other group which can easily be removed; E is halogen (chlorine, bromine), N-imidazolyl, OH, O-hydroxysuccinimidy1 or, taken together with the carbonyl group, it forms a mixed anhydride with a carboxylic or sulfonic acid, to give compounds of formula (Ia)

which are transformed into the compounds of formula (I) by means of transformation of the -COOR group into a -COOH group.

5. A process according to claim 4, characterized in that the compounds of formula (Ia)

wherein B, D, Ra, Rb and n are as defined above and R is C₇-C₈-alkyl, are transformed into the compounds of formula (I) by means of hydrolysis with mineral bases in suitable concentrations and in a suitable solvent.

6. A process according to claim 4, characterized in that the compounds of formula (Ia)

wherein B, D, Ra, Rb and n are as defined above and R is ally1 or benzy1, are transformed into the compounds of
formula (I) by means of catalytic hydrogenation.

7. A process according to claim 6, characterized in that hydrogenation is carried out with a catalyst selected from palladium on charcoal in various concentrations, nickel-Raney, palladium tetrakis(triphenylphosphine) in a suitable solvent or by means of hydrogen transfer procedures.

8. Pharmaceutical compositions containing a compound of claims 1-3 as the active ingredient.

9. The use of the compounds of claims 1-3 for the preparation of a medicament having antiasthmatic and antiinflammatory effects on the respiratory tract.

Patentansprüche

1. Verbindungen der allgemeinen Formel (I)

\[
\begin{align*}
\text{N} & \quad \text{B} \quad \text{N} \quad \text{D} \\
\text{CO} & \quad \text{CRaRb} \quad \text{COOH}
\end{align*}
\]

(I)

deren einzelne enantiomere und diastereomere Formen, deren Mischungen und deren Salze mit pharmazeutisch annehmbaren Säuren und Basen, worin:

B eine -CO- oder -CH\(_2\)CO-Gruppe ist;
D ein Heterocyclus ist, ausgewählt aus der Gruppe bestehend aus [2,6-Bis(pyrrolidin-1-yl)-4-pyrimidinyl], [4,6-Bis(pyrrolidin-1-yl)-1,3,5-triazin-2-yl], [3,6-Bis(di-ethylamino)pyridin-2-yl] und [3-Ethylaminopyridin-2-yl];
Ra, welches das gleiche wie Rb ist, Wasserstoff oder Methyl ist; und
n die ganze Zahl 1 ist.

2. Verbindung nach Anspruch 1, ausgewählt aus der Gruppe bestehend aus:

\[
\begin{align*}
\text{(-)-N} & \text{'-}[1 \cdot (1' \cdot \text{Malonyl}) \text{pyrrolidin-2-yl}] \text{carbonyl}] - N \cdot [2,6-\text{bis(pyrrolidin-1-yl)pyrimidin-4-yl}] \text{piperazin;}
\text{(-)-N} & \text{'-}[1 \cdot (2' \cdot 2' \cdot \text{Dimethyl-1' -malonyl}) \text{pyrrolidin-2-yl}] \text{carbonyl}] - N \cdot [2,6-\text{bis(pyrrolidin-1-yl)pyrimidin-4-yl}] \text{piperazin;}
\text{(-)-N} & \text{'-}[1 \cdot (1' \cdot \text{Malonyl}) \text{pyrrolidin-2-yl}] \text{carbonyl}] - N \cdot [4,6-\text{bis(pyrrolidin-1-yl)-1,3,5-triazin-2-yl}] \text{piperazin;}
\text{(-)-N} & \text{'-}[1 \cdot (2' \cdot 2' \cdot \text{Dimethyl-1' -malonyl}) \text{pyrrolidin-2-yl}] \text{me-thyloxy carbonyl}] - N \cdot [2,6-\text{bis(pyrrolidin-1-yl)pyrimidin-4-yl}] \text{piperazin;}
\text{(-)-N} & \text{'-}[1 \cdot (1' \cdot \text{Malonyl}) \text{pyrrolidin-2-yl}] \text{methyl oxycarbonyl}] - N \cdot [2,6-\text{bis(pyrrolidin-1-yl)pyrimidin-4-yl}] \text{piperazin;}
\text{N'} & \text{'}-[1 \cdot (2' \cdot 2' \cdot \text{Dimethyl-1' -malonyl}) \text{pyrrolidin-2-yl}] \text{methyl oxycarbonyl}] - N \cdot [4,6-\text{bis(pyrrolidin-1-yl)-1,3,5-triazin-2-yl}] \text{piperazin.}
\end{align*}
\]

3. Verbindung nach Anspruch 2, wobei die Verbindung \text{(-)-N} \text{'}-[(1 \cdot (2' \cdot 2' \cdot \text{Dimethyl-1' -malonyl}) \text{pyrrolidin-2-yl}) \text{methyl oxycarbonyl}] - N \cdot [2,6-\text{bis(pyrrolidin-1-yl)pyrimidin-4-yl}] \text{piperazin ist.}

4. Verfahren zur Herstellung der Verbindungen nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß eine Verbindung der Formel (II)
 worin B und D wie vorstehend definiert sind, umgesetzt wird mit einer Verbindung der Formel (III)

worin Ra, Rb und n die vorstehend beschriebenen Bedeutungen haben; R eine C₁-C₆-Alkyl-, Banzyl-, Allyl-Gruppe oder irgendeine andere Gruppe ist, die sich leicht abspalten lässt; E Halogen (Chlor, Brom), N-Imidazolyl, OH, O-Hydroxysuccinimidyl ist oder zusammengenommen mit der Carbonyl-Gruppe ein gemischtes Anhydrid mit einer Carbon- oder Sulfonsäure bildet, um Verbindungen der Formel (Ia)

zu ergeben, die durch Umwandlung der -COOR-Gruppe in eine -COOH-Gruppe in die Verbindungen der Formel (I) umgewandelt werden.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß die Verbindungen der Formel (Ia)

worin B, D, Ra, Rb und n wie vorstehend definiert sind und R C₁-C₆-Alkyl ist, durch Hydrolyse mit Mineralbasen in geeigneten Konzentrationen und in einem geeigneten Lösungsmittel in die Verbindungen der Formel (I) umgewandelt werden.

6. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß die Verbindungen der Formel (Ia)
worin B, D, Rα, Rβ und n wie vorstehend definiert sind und R ist Allyl oder Benzyl ist, durch katalytische Hydrierung in die Verbindungen der Formel (I) umgewandelt werden.


8. Pharmazeutische Zusammensetzungen, enthaltend als wirksamen Bestandteil eine Verbindung nach den Ansprüchen 1 bis 3.

9. Verwendung von Verbindungen nach den Ansprüchen 1 bis 3 zur Herstellung eines Medikaments mit antiasthmatischer und entzündungshemmender Wirkung auf die Atemwege.

Revendications

1. Composés de formule générale (I):

leurs formes énantiomères et diastéréoisomères simples, leurs mélanges et leurs sels avec des acides et des bases acceptables sur le plan pharmaceutique, dans lesquels:

B est un groupe -CO- ou -CH₂OOC-;
D est un hétérocycle choisi dans le groupe formé par le [2,6-bis(pyrrrolidin-1-yl)-4-pyrimidinyle], le [4,6-bis-(pyrrolidin-1-yl)-1,3,5-triazin-2-y], le [3,6-bis(diéthylamino)pyriddin-2-y] et le [3-déthylaminopyridin-2-y];
Rα, qui est identique à Rβ, est un atome d'hydrogène ou un groupe méthyle;

et n est le nombre entier 1.

2. Composé selon la revendication 1, choisi dans le groupe formé par:

- la (-)-N’-[[1-(1'-malonyl)pyrrolidin-2-y]carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)pyrimidin-4-y]pipérazine;
- la (-)-N’-[[1-(2',2'-diméthyl-1'-malonyl)]pyrrolidin-2-y]carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)pyrimidin-4-y]pipérazine;
- la (-)-N’-[[1-(1'-malonyl)pyrrolidin-2-y]carbonyl]-N-[4,6-bis-(pyrrolidin-1-yl)-1,3,5-triazin-2-y]pipérazine;
- la (-)-N’-[[1-(2',2'-diméthyl-1'-malonyl)]pyrrolidin-2-y)méthoxy carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)pyrimidin-4-y]pipérazine;
- la (-)-N’-[[1-(1'-malonyl)pyrrolidin-2-y)méthoxy carbonyl]-N-[2,6-bis(pyrrolidin-1-yl)pyrimidin-4-y]pipérazi-
Composé selon la revendication 2, dans lequel un tel composé est :

- la N'\{-\{1-(2',2'-diméthyl-1'-malonyl)pyrrolidin-2-yl\}méthylloxycarbonyl\}N-[4,6-bis(pyrrolidin-1-yl)-1,3,5-triazin-2-yl]pipérazine.

Procédé pour la préparation des composés selon l'une quelconque des revendications 1 à 3, caractérisé en ce qu'un composé de formule (II)

\[ \text{N} \quad \text{B} \quad \text{N} \quad \text{D} \]

dans laquelle B et D sont tels que définis ci est mis à réagir avec un composé de formule (III)

\[ \text{O} \quad \text{CRaRb} \quad \text{n-COOR} \]

dans laquelle Ra, Rb et n ont les significations décrites ci-dessus ; R est un groupe alkyle en C_2 à C_6, benzyle, allyle ou tout autre groupe qui peut facilement être retiré ; E est un atome d'halogène (chloré, bromé), un groupe N-imidazolyle, OH, O-hydroxysuccinimidylé ou, pris conjointement avec le groupe carbonyl, il forme un anhydride mixte avec un acide carboxylique ou sulfonique, pour donner les composés de formule (Ia)

\[ \text{CO} \quad \text{CRaRb} \quad \text{n-COOR} \]

qui sont transformés en composés de formule (I) à l'aide de la transformation du groupe -COOR en un groupe -COOH.

Procédé selon la revendication 4, caractérisé en ce que les composés de formule (Ia)
dans laquelle B, D, Ra, Rb et n sont tels que définis ci-dessus et R est un groupe alkyle en C₁ à C₉, sont transformés
en composés de formule (I) à l'aide d'une hydrolyse avec des bases minérales à des concentrations appropriées
et dans un solvant approprié.

6. Procédé selon la revendication 4, caractérisé en ce que les composés de formule (Ia)


dans laquelle B, D, Ra, Rb et n sont tels que définis ci-dessus et R est un groupe allyle ou benzyle, sont transformés
en composés de formule (I) à l'aide d'une hydrogénation catalytique.

7. Procédé selon la revendication 6, caractérisé en ce que l'hydrogénation est effectuée avec un catalyseur choisi
parmi le palladium sur charbon de bois à diverses concentrations, le nickel de Raney, la tétrakis(triphénylphos-
phine) de palladium dans un solvant approprié ou à l'aide de procédés de transfert d'hydrogène.

8. Compositions pharmaceutiques contenant un composé selon l'une quelconque des revendications 1 à 3, en tant
que principe actif.

9. Utilisation des composés selon l'une quelconque des revendications 1 à 3 pour la préparation d'un médicament
ayant des effets anti-asthmatiques et anti-inflammatoires sur les voies respiratoires.