AUSTRALIA 6[illegible]96

P/00/001 28/5/91
Section 29

67

Patents Act 1990

PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

I/We, being the person(s) identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow.

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[54] Invention Title: HETEROCYCLICALLY SUBSTITUTED PIPERAZINOALKYLBENZOXAZINE AND PIPERAZINOALKYLBENZOTHIAZINE COMPOUNDS AND PROCESSES FOR THEIR PREPARATION AND MEDICAMENTS CONTAINING THESE COMPOUNDS

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BASIC CONVENTION APPLICATION(S) DETAILS

[31] Application Number	[33] Country	Country Code	[32] Date of Application
P40 37 427.0	Germany	DE	24th November 1990

Drawing number recommended to accompany the abstract .....

By my/our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

.....
Ian A. Scott

21st November 1991
(Date)

Registered Patent Attorney

Section 29 (1)
Regulation 3.1 (2)

AUSTRALIA

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NOTICE OF ENTITLEMENT

We, KALI-CHEMIE PHARMA GMBH, of Hans-Bockler-Allee 20, 3000 Hannover 1, GERMANY, being the applicant in respect of Application No. 88091/91 state the following:-

Part 1

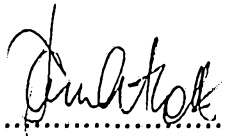
The Person nominated for the grant of the patent has entitlement from the actual inventors by assignment.

Part 3

The person nominated for the grant of the patent is the applicant of the basic application listed on the patent request form.

The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS



16 September 1993

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AU9188091

(12) PATENT ABRIDGMENT (11) Document No. AU-B-88091/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 644496

(54) Title
HETEROCYCLICALLY SUBSTITUTED PIPERAZINOALKYLBENZOXAZINE AND PIPERAZINOALKYLBENZOTHIAZINE COMPOUNDS AND PROCESSES FOR THEIR PREPARATION AND MEDICAMENTS CONTAINING THESE COMPOUNDS

(51)[5] International Patent Classification(s)
C07D 413/12 A61K 031/54 C07D 265/36 C07D 279/16
C07D 417/12 A61K 031/535

(21) Application No. : 88091/91 (22) Application Date : 22.11.91

(30) Priority Data

(31) Number (32) Date (33) Country
4037427 24.11.90 DE GERMANY

(43) Publication Date : 28.05.92

(44) Publication Date of Accepted Application : 09.12.93

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(56) Prior Art Documents
AU 84711/91 C07D 413/12
AU 68531/87 C07D 265/36

(57)
The compounds I and their pharmacologically acceptable acid addition salts are characterised by interesting pharmacological properties and have anti-inflammatory and anti-allergic effects. In particular the compounds show an activity profile favourable for the treatment of asthmatic disorders with low toxicity and good compatability.

Asthma is a chronic inflammatory lung disease which is characterised by a episodally occurring reversible obstruction of the respiratory passages. It is generally assumed that the initiation of asthmatic symptons and crisis originates from a parenchymal and interstitial cell type known as a mast cell. These mast cells contain pre-formed inflammation mediators and spasmogens, in particular histamine. They are also capable of de novo synthesis of a variety of mediators originating from membrane lipids. Mast cells also act in combination with a number of associated cells which are all capable of synthesising inflammatory and pro-inflammatory mediators.

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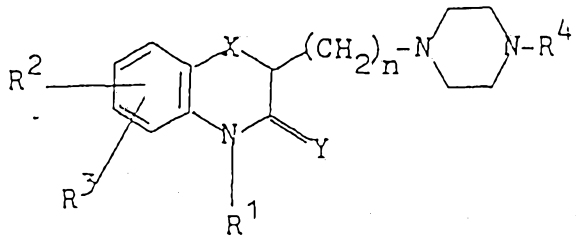
1. A compound of the general formula I:



wherein
X denotes oxygen or sulphur,
Y denotes oxygen or sulphur,
R^1 denotes hydrogen or lower alkyl,
R^2 denotes hydrogen, lower alkyl, halogen, lower alkoxy, hydroxy, nitro or trifluoromethyl, and
R^3 denotes hydrogen, lower alkyl, halogen or lower alkoxy, or
R^2 and R^3 are bonded to neighbouring carbon atoms and together denote an alkylenedioxy group having 1-2 carbon atoms,
n is a whole number from 0 to 4, and
R^4 is a 6-membered unsaturated heterocycle containing 1 or 2 nitrogen atoms not directly bonded to the piperazine ring, which heterocycle may optionally be substituted by 1-2 substituents, bonded to carbon atoms, from the group of lower alkyl, lower alkoxy and halogen,
and physiologically acceptable acid addition salts thereof.

P/00/011 28/5/91
Regulation 3.2(2)

AUSTRALIA

Patents Act 1990

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ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

Application Number:

Lodged:

Invention Title: HETEROCYCLICALLY SUBSTITUTED PIPERAZINOALKYLBENZOXAZINE AND PIPERAZINOALKYLBENZOTHIAZINE COMPOUNDS AND PROCESSES FOR THEIR PREPARATION AND MEDICAMENTS CONTAINING THESE COMPOUNDS

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

Heterocyclically substituted piperazinooalkylbenzoxazine and piperazinoalkylbenzothiazine compounds and processes for their preparation and medicaments containing these compounds

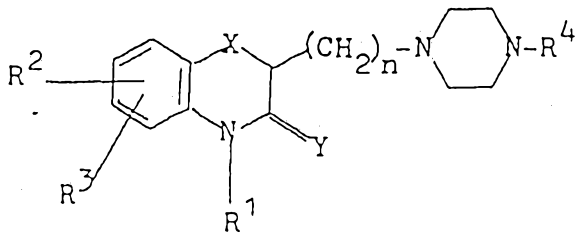
The present invention relates to novel benzoxazin-3-one and benzothiazin-3-one derivatives which carry in the 2-position a piperazinoalkyl radical substituted by a heterocycle, the corresponding 3-thione derivatives and salts thereof, as well as pharmaceutical formulations containing these compounds and processes for preparation of these compounds.

1,4-Benzoxazin-3-one derivatives which carry a phenylpiperazinoalkyl radical in the 2-position are known from EP-A-0233728. These compounds have pronounced hypotensive and vasodilative effects.

The object of the present invention is to develop novel pharmaceutical active ingredients which can be used as anti-allergic agents. Furthermore, the object of the invention is to prepare novel benzoxazine derivatives having valuable pharmacological properties.

It has now been found that the novel heterocyclically substituted compounds defined by formula I below show anti-inflammatory and anti-allergic effects, exhibiting a favourable activity profile with low toxicity and good tolerance. Compounds of the invention are thus suitable as anti-inflammatory and/or anti-allergic agents for the treatment of inflammatory and allergic diseases.

The present invention therefore relates to novel compounds of the general formula I :



wherein
X denotes oxygen or sulphur,
Y denotes oxygen or sulphur,
R^1 denotes hydrogen or lower alkyl,
R^2 denotes hydrogen, lower alkyl, halogen, lower alkoxy, hydroxy, nitro or trifluoromethyl, and
R^3 denotes hydrogen, lower alkyl, halogen or lower alkoxy, or
R^2 and R^3 are bonded to neighbouring carbon atoms and together denote an alkylenedioxy group having 1-2 carbon atoms,
n is a whole number from 0 to 4, and
R^4 is a 6-membered unsaturated heterocycle containing 1 or 2 nitrogen atoms not directly bonded to the piperazine ring, which heterocycle may optionally be substituted by 1-2 substituents, bonded to carbon atoms, from the group of lower alkyl, lower alkoxy and halogen, and physiologically acceptable acid addition salts thereof.

In as far as the substituents R^2 and R^3 in the compounds of the formula I and the substituents in the radical R^4 represent or contain lower alkyl groups, these may be straight or branched and contain in particular 1 - 4, preferably 1 - 2, carbon atoms and represent in particular methyl or methoxy. In as far as the substituents represent halogen, in particular fluorine,

chlorine or bromine, preferably chlorine, are used. The benzene ring of the ring structure may advantageously be unsubstituted. In as far as the benzene ring is substituted by a substituent R^2 or also by two substituents R^2 and R^3, lower alkyl substituents, for example methyl substituents, are particularly suitable.

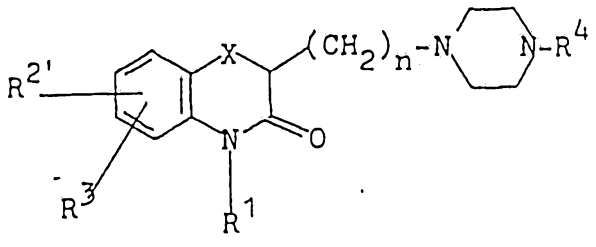
The substituent R^1 advantageously represents hydrogen. If R^1 denotes lower alkyl, it may be straight-chain or branched and may contain 1 - 4, in particular 1 - 2, carbon atoms.

In the compounds of the formula I n is 0 - 4. An alkylene chain having 3 or 4 members has proved to be particularly favourable.

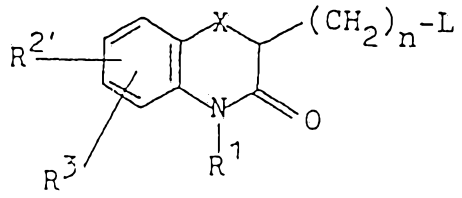
The substituent R^4 may represent an unsaturated heterocycle containing one or two nitrogen atoms, for example a heteroaryl group. Suitable radicals R^4 are, for example pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl radicals, in particular pyridyl radicals. If R^4 represents a pyridyl group, a pyrid-2-yl group, which may optionally be substituted, is preferably used. Suitable examples are pyridyl radicals unsubstituted or substituted by lower alkyl, in particular methyl. The 4-methylpyrid-2-yl radical proves to be particularly favourable.

The novel compounds of the formula I and acid addition salts thereof may be obtained by the following reactions which can be carried out in a manner known per se.

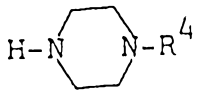
a) to prepare compounds of the general formula Ia



wherein X, R^1, R^2, R^3, n and R^4 have the above meaning, compounds of the general formula II:

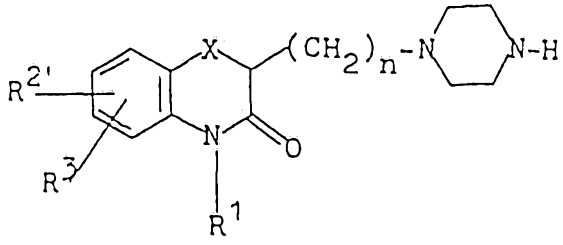


wherein X, R^1, R^3 and n have the above meaning, and $R^{2'}$ has the meaning given for R^2, but wherein a hydroxy group is protected by a subsequently splittable protective group, and L is an aminolytically splittable radical, in particular halogen, are reacted with piperazine derivatives of the general formula III:



wherein R^4 has the above meaning, or

b) compounds of the general formula IV:



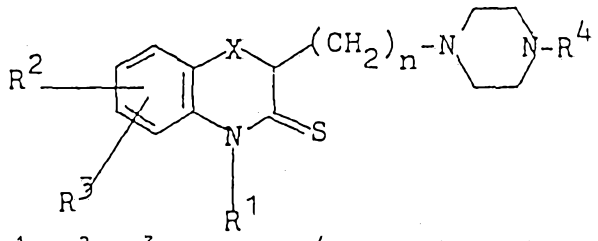
wherein X, R^1, $R^{2'}$, R^3 and n have the above meaning, are reacted with compounds of the general formula V:

$$R^4\text{-}L'$$

wherein R^4 has the above meaning and L' denotes halogen,

and then any hydroxy protective group is split off again, or

c) compounds of the general formula Ia are converted to compounds of the general formula Ib



wherein X, R^1, R^2, R^3, n and R^4 have the above meaning, and

optionally compounds of the general formula I obtained wherein R^1 denotes hydrogen, are alkylated to form compounds of the general formula I, wherein R^1 denotes lower alkyl, and/or in compounds of the general formula I obtained, wherein R^2 denotes methoxy, the methoxy group is split to form the hydroxy group, and optionally free compounds of the formula I are converted into their acid addition salts or the acid addition salts are converted into the free compounds of the formula I.

The reaction of compounds of the formula II with compounds of the formula III according to process variant a) may be carried out in accordance with methods conventional per se for alkylating amines.

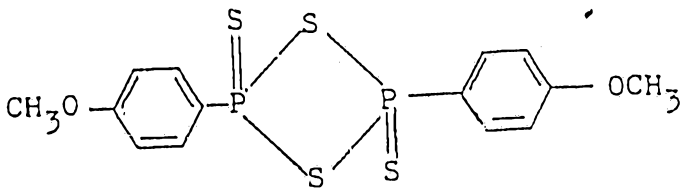
The reaction is advantageously carried out under basic conditions in an organic solvent which is inert under the reaction conditions.

Halogens, such as chlorine, bromine or iodine, preferably bromine or chlorine, or also an acyloxy radical O-Z, wherein Z represents a lower alkanoyl radical or an organic sulphonic acid radical, for example the radical of a lower alkanesulphonic acid, such as for example

methanesulphonic acid, or of aromatic sulphonic acids, such as benzenesulphonic acid or benzenesulphonic acids substituted by lower alkyl or by halogen, for example toluenesulphonic acids or bromobenzenesulphonic acids, are suitable as aminolytically splittable radicals L in the compounds of the formula II. Aprotic solvents in particular, for example aromatic hydrocarbons, such as toluene, xylene or benzene, cyclic ethers, such as dioxane, dimethylformamide or lower alkanols, such as ethanol, or mixtures of the above-mentioned solvents are suitable as inert organic solvents. The process is advantageously carried out at elevated temperatures, for example temperatures between 50 and 150°C, preferably boiling temperature of the solvent. The reaction is advantageously carried out with addition of an organic or inorganic base. However, an excess of the compound of the formula III may also be used and this may be used as an internal base. Examples of suitable organic bases are tertiary organic amines, in particular tertiary lower alkyl amines, such as triethylamine, tripropylamine, N-lower alkyl morpholines or N-lower alkyl piperidines. Suitable inorganic bases are in particular alkali metal carbonates or alkali metal carbonates. The reaction time may be between 2 and 8 hours depending on the reaction conditions. Ether protective groups known per se, which are then split off again solvolytically or hydrogenolytically in a manner known per se, for example lower alkyl or benzyl groups, may be selected as protective groups for any hydroxy group R^2.

The reaction of compounds of the formula IV with compounds of the formula V according to process variant b) may be carried out according to methods conventional per se for alkylating amines. It may be carried out, for example in the manner described for reacting compounds of the formula II with compounds of the formula III.

The conversion of the 3-one group of the compounds of the formula Ia into the 3-thione group of the compounds of the formula Ib according to process variant c) may be carried out according to methods conventional per se for exchange of oxygen for sulphur in oxo compounds. Hence the compounds of the formula Ib may be prepared in a manner known per se, for example by treating the compounds of the formula Ia with a phosphorus pentasulphide (for example P_4S_{10}) or also according to the method described by Lawesson et al. (see Bull. Soc. Chim. Belg. 87, 525-534 (1978)) by reacting with 2,4-bis-(methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide of the formula VI



(= known as Lawesson's reagent). The deoxosulphuration is advantageously carried out in an organic solvent which is inert under the reaction conditions, for example an aromatic hydrocarbon, such as xylene or toluene, at elevated temperatures, for example temperatures between 50 and 150°C, advantageously at boiling temperature of the reaction mixture. When the reaction is completed the sulphurised compounds of the phosphorus derivatives may be separated by filtration.

Compounds of the formula I obtained wherein R^1 denotes hydrogen, may optionally be alkylated subsequently in a manner known per se to form the corresponding N-alkyl compounds. Suitable alkylating agents are alkyl halides, in particular iodides, alkyl sulphates or alkyl sulphonates. A compound of the formula I containing an amide or thiamide group is advantageously initially

reacted with a strong base, such as for example an alkali metal hydride, alkali metal amide or alkali metal alcoholate, in a inert polar organic solvent and then reacted further with the alkylating agent. The reaction may be carried out at a temperature of 0°C up to the boiling temperature of the solvent. Dimethylformamide or cyclic ethers, such as tetrahydrofuran or dioxane, are suitable as solvents depending on the base used, or, if the base is a metal alcoholate, also the corresponding alcohols. Hence the reaction may be carried out, for example advantageously in dimethylformamide using sodium hydride.

In compounds of the formula I wherein R' denotes methoxy, the methoxy group may be split to form the hydroxy group in a manner known per se using methods suitable for splitting methoxyaryl ethers. For example, splitting of ether may be carried out by treating with hydrogen iodide in a solvent which is inert under the reaction conditions, for example acetanhydride, or with iodotrimethylsilane or boron tribromide.

The compounds of the formula I may be isolated from the reaction mixture and purified in a manner known per se. Acid addition salts may be converted to the free bases in conventional manner and the latter are converted, if required, in known manner to pharmacologically acceptable acid addition salts.

Suitable pharmacologically acceptable acid addition salts of the compounds of the formula I are, for example their salts with inorganic acids, for example hydrohalic acids, in particular hydrochloric acid, sulphuric acid or phosphoric acids, or with organic acids, for example lower aliphatic monocarboxylic acids or dicarboxylic acids, such as maleic acid, fumaric acid, lactic acid, tartaric acid or acetic acid, or sulphonic acids, for

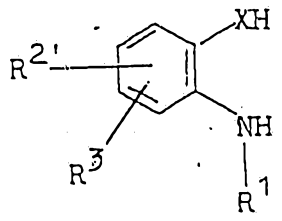
example lower alkyl sulphonic acids, such as methanesulphonic acid, or benzenesulphonic acids optionally substituted in the benzene ring by halogen or lower alkyl, such as p-toluenesulphonic acid, or cyclohexylaminesulphonic acid.

The compounds of the formula I contain a centre of chirality in position-2 of the benzoxazine or benzothiazine structure and may be present in two optically active enantiomeric forms or as a racemate.

The present invention includes both the racemic mixtures as well as the pure optical isomers of the compounds of the formula I.

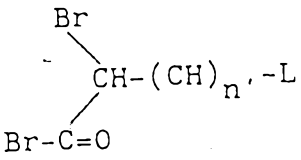
If racemates of the compounds of the formulae II or IV are used in the synthesis, the compounds of the formula I are obtained in the form of racemates. Optically active compounds of the formula I may be obtained starting from optically active forms of the compounds of the formulae II or IV. The optically active compounds of the formula I may be obtained from the racemic mixtures in a manner known per se, for example by chromatographic separation on chiral separating materials, or by reacting with suitable optically active acids, for example tartaric acid or 10-camphorsulphonic acid, and then separating into their optically active antipodes by fractional crystallisation of the salts obtained.

The starting compounds of the formula II may be obtained starting from 2-aminophenol derivatives of the formula VII

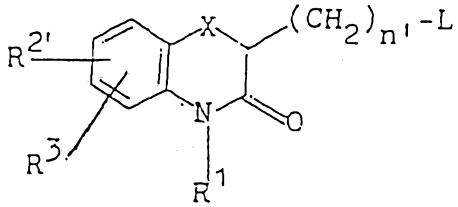


wherein R^1, $R^{2'}$, R^3 and X have the above meaning.

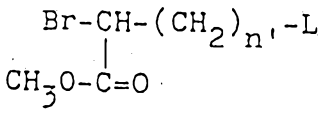
Hence the compounds of the formula VII may be condensed in a manner known per se using a β-bromo-acylbromide of the formula VIII:



wherein L has the above meaning and n' denotes 1 - 4, to form compounds of the formula IIa:



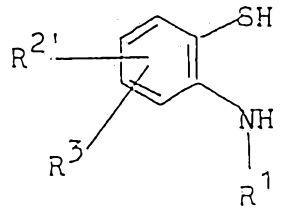
wherein R^1, $R^{2'}$, R^3, X, n' and L have the above meaning. The condensation may be carried out in a solvent which is inert under the reaction conditions, for example a halogenated hydrocarbon, such as chloroform, in the presence of a base, for example alkali metal hydrogen carbonates or alkali metal carbonates, and is advantageously carried out in the presence of a transfer catalyst, for example benzyltrimethylammonium chloride. The compounds of the formula VII may also be reacted with methyl β-bromo-alkanecarboxylates of the formula IX:



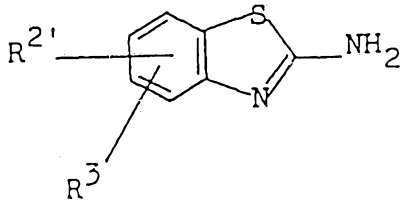
wherein n' and L have the above meaning, to form compounds of the formula IIa in a manner known per se.

The reaction may be carried out, for example in dimethylformamide in the presence of an inorganic base, for example an alkali metal carbonate.

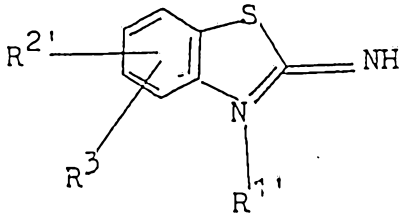
Compounds of the general formula VIIa:



wherein R^1, $R^{2'}$ and R^3 have the above meaning, are known or may be obtained in a manner known per se starting from compounds of the general formula XIII:



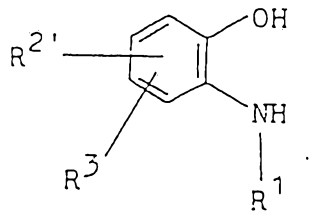
wherein $R^{2'}$ and R^3 have the above meaning. Compounds of the formula XIII may be alkylated in a manner known per se to introduce an alkyl radical R^1 to form compounds of the general formula XIV:



wherein $R^{2'}$ and R^3 have the above meaning and $R^{1'}$ denotes lower alkyl.

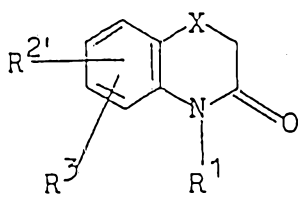
Compounds of the formula XIII and XIV may be converted to compounds of the formula VIIa in a manner known per se by thermal splitting in aqueous alkaline medium, for example by heating in alkali metal hydroxide solution.

Compounds of the general formula VIIb:

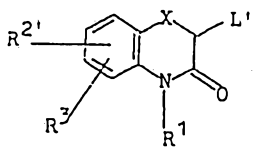


wherein R^1, $R^{2'}$ and R^3 have the above meaning, are known or may be obtained according to methods known per se or analogously to methods known per se. 2-Alkylaminophenol compounds (R^1 = lower alkyl) may be obtained starting from the corresponding 2-aminophenol compounds. For this they are initially acylated, whereby both the phenolic hydroxy group and the amino group are provided with a protective acyl group. In the ester amide compounds obtained the amide group is alkylated in a manner known per se, by reacting the compounds with an alkylating agent, for example a lower alkyl halide, alkyl sulphate or alkyl sulphonate, in the presence of a strong base, for example an alkali metal hydride or alkali metal hydroxide, optionally in the presence of a transfer catalyst, for example benzyltrimethylammonium chloride. The reaction may take place, for example under the conditions given above for the subsequent alkylation of compounds of the formula I. When the alkylation is completed the protective acyl groups may then be split off again in a manner known per se by acid or alkaline hydrolysis.

Compounds of the formula II, wherein n is 0, may be obtained starting from compounds of the formula X:



wherein R^1, $R^{2'}$, R^3 and X have the above meaning. Hence to prepare compounds of the formula IIb



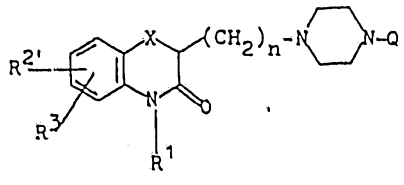
wherein R^1, $R^{2'}$ and R^3 have the above meaning and L' denotes halogen, it is possible to introduce a halogen substituent L', in particular chlorine, into compounds of the formula X in a manner known per se, by treatmeant with a halogenating agent, for example sulphuryl chloride. The chlorination may be carried out in a solvent which is inert under the reaction conditions, for example a halogenated hydrocarbon, such as dichloromethane.

Compounds of the formula X are known or may be obtained in a manner known per se, for example by condensing compounds of the formula VII using chloroacetyl chloride. The condensation may be carried out under the reaction conditions cited for the preparation of compounds of the formula IIa.

Compounds of the formula IV have not yet been described hitherto in the literature and are novel valuable intermediate products for the preparation of pharmacologically active compounds, for example the compounds of the formula I.

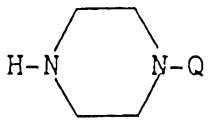
Compounds of the formula IV may be obtained according to methods known per se, by reacting, for example compounds of the formula II with an excess of piperazine. The reaction may be carried out according to methods conventional per se for alkylating amines, for example under the conditions described above for the reaction of compounds of the formula II with compounds of the formula III.

Compounds of the formula IV may also be obtained from compounds of the general formula XI



wherein R^1, $R^{2'}$, R^3, X and n have the above meaning and Q is an amine protective group, by splitting off the amine protective group in a manner known per se. Suitable amine protective groups are the usual protective groups known per se for the protection of an amino function, for example hydrolytically splittable acyl groups or hydrogenolytically splittable benzyl groups. Suitable protective groups are, for example known from E. McOmie "Protective Groups in Organic Chemistry"; Plenum Press, London (1971), page 44 ff. The formyl group and protective lower carbalkoxy groups are particularly suitable. They may be split off in a manner known per se by acid or alkaline hydrolysis.

Compounds of the formula XI may be obtained in a manner known per se, for example by reacting compounds of the formula II with compounds of the formula XII:



wherein Q has the above meaning. The reaction may be carried out according to methods conventional for the alkylation of amines, for example under the reaction conditions described for the reaction of compounds of the formula II with compounds of the formula III.

Compounds of the formula III are known or may be prepared according to methods known per se, for example by reacting compounds of the formula V with an excess of piperazine or with a compound of the formula XII and then splitting off the protective group Q again.

The compounds I and their pharmacologically acceptable acid addition salts are characterised by interesting

pharmacological properties and have anti-inflammatory and anti-allergic effects. In particular the compounds show an activity profile favourable for the treatment of asthmatic disorders with low toxicity and good compatability.

Asthma is a chronic inflammatory lung disease which is characterised by a episodally occurring reversible obstruction of the respiratory passages. It is generally assumed that the initiation of asthmatic symptons and crisis originates from a parenchymal and interstitial cell type known as a mast cell. These mast cells contain pre-formed inflammation mediators and spasmogens, in particular histamine. They are also capable of de novo synthesis of a variety of mediators originating from membrane lipids. Mast cells also act in combination with a number of associated cells which are all capable of synthesising inflammatory and pro-inflammatory mediators.

As long as no allergy-inducing conditions are present, the mast cells are in a quasi non-involved waiting position. The key to the allergic reactions lies in the presence of high concentrations of circulating IgE antibodies. When these antibodies become fixed to a corresponding antigen, they activate both the degranulation and release of pre-formed mediators as well as the de novo synthesis of other mediators.

Since asthma is an inflammatory obstructive lung disease, the therapy is based on essentially two approaches: alleviating the symptomatic complaints by administering bronchodilators, such as β-sympathomimetic agents, xanthine derivatives and anti-cholinergic agents; administration of anti-inflammatory active ingredients, such as disodium cromoglycate and steroids; and target therapy directed at specific mediators, such as for example histamine. Treatment to alleviate the symptomatic

complaints is adequate in about 50 % of the asthmatics, but does not contribute anything to alleviating the causes, that is the inflammation. Anti-inflammatory active ingredients may controll the inflammation, but often have undesirable side-effects and are often co-administered with bronchodilators at the same time. On its own targeted therapy for a specific mediator is totally inadequate, since there are plethora of mediators.

The compounds of the invention are characterised in that they have an anti-inflammatory effect and act targeted against one or more of the three types of mediator, histamine, leucotrienes and platelet activating factor, which participate not only in acute bronchospasms but also in maintaining the chronic inflammation, or are also active against the respective target cells via mediator-specific receptors.

The anti-inflammatory and anti-allergic properties of the compounds can be shown in vitro and in vivo by pharmacological standard test methods.

Description of the test methods

1. Determination of the inhibition of the passive cutaneous anaphylaxis (P.C.A.) and of the anaphylactoid cutaneous reaction induced by histamine.

The P.C.A. reaction is carried out according to the methods described by Goose et al. (J.N. Immunology 16 (1969), 749) and by Martin et al. (Arch. Pharmacol. 316 (1981), 186).

The IgE-rich ovoalbumin antiserum used in the test is obtained from immunised Brown-Norway rats. For

immunisation the rats are given an intraperitoneal injection of a mixture of 100 µg of ovoalbumin with a Bordetella pertussis suspension (Vaxicoq®, Manufacturer: Institute Merieux, containing 5 x 10^9 organisms and 1.25 mg $Al(OH)_3$). After 20 days the animals receive a further intraperitoneal injection of a solution of 10 µg of ovoalbumin in 0.5 ml of physiological saline solution for reimmunisation. After a further four days the blood is removed from the animals and the blood is centrifuged. The antiserum thus obtained is stored at -20°C until it is used.

The determination of the inhibition of the passive cutaneous anaphylaxis and of the anaphylactoid cutaneous reaction induced by histamine is carried out as follows:

Sprague-Dawley rats having a body weight of 150 - 180 g are injected intradermally in one flank with 50 µl of a 1:75 dilution of the IgE-rich ovoalbumin antiserum in physiological saline solution for passive sensitisation to ovoalbumin.

24 hours after sensitisation a solution of 8.25 mg/kg of ovoalbumin and 26.4 mg/kg of a blue dye (Evans's Blue) is administered to the rats intravenously according to Martin et al. to trigger passive cutaneous anaphylaxis. The ovoalbumin challenge results in a local anaphylactic reaction at the point where the antiserum had been injected.

To determine the histamine-induced anaphylactoid skin reaction, the animals are injected intradermally in the flank opposite to the antiserum administration with 50 µl of a physiological saline solution containing 0.8 mg/ml of histamine directly before the intravenous injection of the solution containing the ovoalbumin and the blue dye.

On the day of investigation the test substances are dissolved in distilled water, which contains 1 vol.% of dimethylformamide and 1 vol.% of Tween^{R}20 (= polyoxyethylene(20)sorbitanmonolaurate). One hour before the challenging ovoalbumin administration, each animal receives 2 x 10^{-5} mole/kg of test substance administered orally each in 0.5 ml of solution. A control group receives only the solvent for comparison.

The edematous anaphylactic (P.C.A.) and anaphylactoid (histamine-induced) reactions caused by the challenging intravenous ovoalbumin injection, and which are manifested by edema formation, swelling and exsudation of blue dye, are evaluated 30 minutes after challenge by the intravenous ovoalbumin injection. This is done by visual determination of the extent to which the blue dye emerges at the site of the edema formed. The percentage inhibition of anaphylactic and anaphylactoid reactions induced by the test substances is determined in comparison with the reactions of the control animals not treated with test substance with the aid of comparison scales.

The results from the above test methods obtained using compounds of the formula I are shown in Table A below. The example numbers given for the compounds of the formula I relate to the following preparative examples.

Table A

Test substance Example No.	Inhibiting effect on cutaneous anaphylactic and anaphylactoid reactions in the rat % inhibition for dose of 2 x 10^{-5} mole/kg per os	
	Passive cutaneous anaphylaxis (P.C.A.)	Histamine-induced anaphylactoid reaction
22	69	45
7	70	40
9	60	30
1	88	55
8	73	60
12	80	50
13	55	30
15	60	30
16	50	45
17	70	35
11	55	20
10	70	35
3	80	55
18	80	53
19	80	60
21	78	55
24	80	60
25	50	15
27	60	35
28	65	40

2. Determination of the minimum toxic dose.

Maximum doses of 300 mg/kg of the test substance are administered orally to male mice 20-25 g in weight. The animals are observed carefully for 3 hours for toxicity symptoms. In addition, all symtoms and deaths are recorded over a period of 24 hours after administration.

Associated symptoms are also observed and recorded. If death or severe toxic symptoms are observed, further mice are administered increasingly lower doses. The lowest dose, which produces death or severe toxic symptoms, is given as the minimum toxic dose in Table B below.

Table B

Test substance Example No.	Minimum toxic dose mg/kg of mouse per os
1	300
22	300
8	100
9	300
2	> 300
11	> 300
12	300
13	100
16	300

3. Examination of the anti-histamine-(H_1) effect based on histamine-(H_1)-receptor antagonism in vitro.

To examine the histamine-(H_1)-receptor antagonism of the substances, the inhibiting effect thereof on histamine induced contractions of the smooth muscle is determined in vitro on the isolated organ. Isolated strips of organ from the ileum are suitable for this. In an organ bath of physiological saline solution they react to addition of histamine by contracting. Addition of the compounds of the invention reduces this contraction of the smooth muscle of the ileum strips induced by addition of histamine. The extent of regression of the contraction is an indication of the anti-histamine-(H_1) effectiveness of the compounds. The investigation is ——————→

carried out analogously to the method described originally by Magnus (Pflügers Arch. 102, 123 (1904)).

Method description for the determination of the inhibiting effect on the contraction induced by a 5 x 10^{-6} molar histamine concentration on the isolated smooth muscle of the guinea pig ileum.

For the test segments of the ileum 1.5 cm long from Dunkin Hartley guinea pigs having a body weight of 300 - 500 g are used.

Each strip is placed in an organ bath of 10 ml of physiological saline solution according to Krebs-Henseleit and attached to an apparatus conventional for isotonic measurement of changes in length of the ileum strips (automated Celaster measuring apparatus), so that the tissue is under 1 g of tension. The bath is kept at a pH value of 7.4 and gassed with a mixture of 5 % CO_2 and 95 % O_2. After an equilibration phase, an isotonic contraction of the tissue is induced by adding histamine in a final concentration of 5 x 10^{-6} mole/litre, and after a contact time of 30 seconds is washed out again. Only those tissues where three reproducible contractions are obtained at 10 minute intervals are used in the subsequent test. The test substances are then added in a final concentration of 10^{-6} mole/litre, and after 30 seconds contact time histamine is added again up to a concentration of 5 x 10^{-6} mole/litre. The resulting contractions are measured over 30 seconds. The tissue is then washed several times over a period of 10 minutes. A contraction challenge is then again applied by adding histamine. The resulting contractions are again measured over 30 seconds. The difference between the amplitude of the contraction obtained by histamine addition ———— alone and the amplitude of the contraction ————

obtained in the presence of the test substance is determined and calculated as % inhibition.

The following Table C shows the results obtained with the test substances according to the method described above. The inhibiting effects on the contractions induced by histamine 30 seconds after administration of the test substance and on the contractions induced by the addition of histamine carried out 10 minutes later are given in the table.

Table C

Test substance Example No.	in vitro (H_1)-receptor antagonism % inhibiting effect on histamine-induced contractions of the ileum at histamine concentration 5×10^{-6} mole/l and test substance concentration 10^{-6} mole/l	
	after 30 seconds	after 10 minutes
7	85	74
8	42	5
13	42	15
16	30	27
11	32	35
2	51	60
10	42	36
3	66	28
18	78	83
19	60	42
21	50	89
23	70	83
24	70	86
25	50	32
27	16	72
28	38	45

4. Determination of the anti-P.A.F. activity in vitro.

P.A.F. (= Platelet Activating Factor) is a phospholipid mediator which has many activities. The activation of platelet aggregation leads to the induction of protracted broncho-contractions and hyper-reactivity of the air paths.

The effect of the test substances on platelet aggregation induced by adding P.A.F. in a platelet suspension obtained from rabbit's blood is examined in this test according to the method described by Mikashima et al. (Jap. J. Pharmacol. 44 (1987) 387-391).

A suspension of platelets originating from rabbit's blood, which contains 4 x 10^9 platelets/ml in a modified Tyrode buffer solution (= Tyrode solution* with addition of 1.3 mM/l of $CaCl_2$ and 2.5 g/l of gelatine) adjusted to pH 7.4, is used. The platelets are obtained from 10 ml blood samples from three rabbits in each case (New Zealand hybrids, body weight 3 - 4 kg). For this the blood samples are treated with ethylenediamine tetraacetic acid and washed according to the method of Artley et al. (Brit. J. Hämatol. 19 (1970), 7-17). A platelet-rich plasma is then initially separated off by centrifuging (20 minutes at 400 x g). The platelets are separated from the plasma by centrifuging again for 15 minutes at 1,400 x g. After centrifuging the platelets remaining as sediment are resuspended in a Tyrode buffer solution (but without calcium). 0.4 mmole of lysine acetylsalicylate is then added and after 15 minutes the

* Tyrode solution = aqueous solution containing 136.9 mmoles NaCl, 2.68 mmoles KCl, 2.31 mmoles $CaCl_2$, 1.0 mmole $MgCl_2$, 11.9 mmoles $NaHCO_3$, 1.45 mmoles NaH_2PO_4 and 5.55

platelets are sedimented again. The sediment is resuspended in the above-mentioned modified Tyrode buffer solution, and the number of platelets in the suspension obtained is adjusted to the desired content.

A 40 x 10^{-9} molar P.A.F. solution is used as reagent. This solution is made from a 1.8 x 10^{-3} molar stock solution in chloroform. For this a 10 µl sample of the stock solution is evaporated to dryness and redissolved in 180 µl of the modified Tyrode solution, to which 0.25 % of delipidated bovine serum albumin had been added. 10^{-5} molar working solutions are then prepared from this and stored frozen. Samples of these solutions are diluted appropriately for the tests.

To carry out the test 50 µl of the platelet suspension and 10 µl of a 40 x 10^{-5} molar solution of the compound under assay are added to 330 µl of the modified Tyrode buffer solution with stirring (1,000 rpm) in an aggregation tube provided with a small magnetic stirrer. This corresponds to a final concentration of test substance of 10^{-5} mole/l. After 90 seconds preincubation time 10 µl of the P.A.F. formulation are added. The aggregation occurring in the aggregation tubes is measured for 4-5 minutes with the aid of a computerised aggregometer.

The aggregation occurring in the test tubes containing only platelet suspension is rated as 0 %, whereas the aggregation occurring in test tubes containing platelet suspension and P.A.F. formulation is rated as 100 %. The aggregation still taking place during the inhibition, caused by adding the test substances, of the P.A.F. induced platelet aggregation amplification is measured, and the resulting aggregation inhibition is calculated therefrom in %.

The results obtained according to the above method using the compounds of the formula I are shown in Table D below.

Table D

Test substance Example No.	Anti-P.A.F. activity in vitro. % inhibition of the P.A.F.-induced aggregation of platelets from rabbit's blood at a test substance concentration of 10^{-5} mole/l
22	42
9	51
8	48
11	96
2	60
18	76
21	37
10	74
27	35
28	45

5. In vitro determination of cyclooxygenase inhibition and 5-lipoxygenase inhibition.

After activating a cell arachidonic acid contained in cell membranes is metabolised in two ways. Leucotrienes, inter alia leucotriene C_4, are formed under the action of the enzyme 5-lipoxygenase (= 5-LO), and prostanoids are formed under the action of the enzyme cyclooxygenase (= CO). These metabolites are secreted from the cell in in vitro systems.

To investigate the cyclooxygenase-inhibiting and the 5-lipoxygenase-inhibiting properties, the inhibitory activity of the test substances on the biosynthesis of

acid derivatives leucotriene C_4 (= LTC_4) and 6-keto-prostaglandin $F_{1\alpha}$ (= 6-keto-$PGF_{1\alpha}$) is determined in vitro on peritoneal macrophage cells of the mouse. For this the contents of LTC_4 and 6-keto-$PGF_{1\alpha}$ in a culture medium from peritoneal macrophage cells of the mouse are determined by zymosan stimulation, as described by Scott et al. (J. Exp. Med. 152 (1980), 324-335) and by Fradin et al. (Prostaglandins, 33 (1987), 579-589).

A cell suspension containing peritoneal cells of male mice 8 - 10 weeks old is obtained in a manner known per se. A solution marketed under the denomination RPMI 1640 (Manufacturer Messrs. Gibco) is used as cell culture medium, to which heparin (10 international units/ml) and antibiotics are added according to the formula of Bonney et al. (Biochem. J. 176 (1978) 422-433). The cell suspension is adjusted to a cell concentration of 10^6 cells per ml and distributed evenly on cluster dishes containing 24 1 ml cluster dishes (wells). These are kept for two hours in a humidified incubator filled with air enriched with 7 % CO_2. Cells not adhering to the titre well walls are then removed by washing. The remaining macrophage cells adhering to the walls are incubated for about 12 hours in a suspension medium, to which 0.1 % of bovine serum albumin (BSA = Bovine Serum Albumin) is added. The suspension medium is then replaced by a salt solution of Hanks (= Hanks' Balanced Salt Solution = HBSS) with 10 mmoles of Hepes (= hydroxyethylpiperazinoethanesulphonic acid), to which a 0.1 % strength solution of the test substances in aqueous, 1 % strength dimethyl formamide or only the solvent had been added. 15 minutes later the arachidonic acid metabolism is stimulated by adding 10 particles of zymosan (= glycoprotein mixture, isolated from cell walls of beer yeast, Saccharomyces cerevisiae, Manufacturer Sigma Chemical Co., Munich) per titre cell. After 2 hours samples of the supernatant liquid in each case are

examined for their 6-keto-$PGF_{1\alpha}$ and LTC_4 content by means of an enzyme immunoassay (= EIA). This EIA is carried out according to the method by Pradelles et al. (Analytical Chem. 57 (1985), 1170-1173). The determination of LTC_4 and the determination of 6-keto-$PGF_{1\alpha}$ are each carried out in comparison with a comparative scale on suitable dilutions of the samples (1 : 50 to 1 : 250 for the LTC_4 determination and 1 : 250 to 1 : 1,250 for the 6-keto-$PGF_{1\alpha}$ determination). To determine the inhibiting effect of a 10^{-5} molar concentration of the compounds, the amount of reference eicosanoids is determined and the inhibiting effect is calculated therefrom in % inhibition compared to the measurements of the zymosan controls. The results obtained using this test are shown in Table E below.

Table E

Test substance Example No.	In vitro % inhibition activity in zymosan-stimulated peritoneal macrophage cells of the mouse at a concentration of 10^{-5} mole/l on the release of	
	6-keto-$PGF_{1\alpha}$	LTC_4
7	17	46
9	32	65
1	27	48
5	36	72
15	46	9
11	0	42

Due to their activities described above, the compounds of the formula I are suitable as anti-inflammatory and anti-allergic medicaments for larger mammals, in particular humans, for the treatment of inflammatory and allergic diseases. The orally active compounds of the invention may act in multiple ways, since

they are active against several of the main mediators implicated in inflammatory processes and asthmatic problems. As a result of this activity profile it can be assumed that the compounds of the invention, within the the treatment of allergy-based and non-allergy-based asthma symptoms, alleviate not only the symptomatic complaints associated with asthmatic diseases, but may also reduce the inflammation associated therewith.

The doses to be used may vary between individuals and of course vary depending on the type of condition to be treated, the compounds used and the form of administration. For example, parenteral formulations will generally contain fewer active ingredients than oral preparations. However, medicament forms having an active ingredient content of 10 to 250 mg per single dosage are generally suitable for administration to larger mammals, in particular humans.

As medicaments, the compounds of the formula I may be used with conventional pharmaceutical auxiliaries in galenic formulations, such as for example tablets, capsules, suppositories or solutions. These galenic formulations may be produced by methods known per se using conventional solid excipients, such as for example lactose, starch or talcum, or liquid paraffins, and using conventional pharmaceutical auxiliaries, for example tablet disintegrating agents, solubility promoters or preserving agents.

The following examples should illustrate the invention in more detail, but in no way limit its scope.

Example 1:

2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one.

A) 45.3 g (= 0.23 m) of 6-bromocaproic acid were treated with 63.6 g (= 0.235 m) of phosphorus tribromide with stirring and then 75.1 g (= 0.047 m) of bromine were added, the first half being added dropwise and the remainder more quickly. The mixture was then heated at a temperature of 85-90°C and kept at this temperature for 1 1/2 hours. A further 18.4 g (= 0.115 m) of bromine were added at this temperature and the reaction mixture was kept at a temperature of 85-90°C for a further 18 hours. For working-up the reaction mixture was then cooled to 20°C and added to a mixture of 700 ml of cooled water and 500 ml of cold hexane. The organic phase was separated off and the aqueous phase was washed twice further using 100 ml of hexane each time. The organic phases were combined and dried over sodium sulphate. The solvent was then distilled off. The 2,6-dibromocaproic acid bromide remaining as an oily residue was characterised by IR and NMR spectroscopy and further processed without further purification.

B) 9.25 g (= 0.07 m) of 2-aminothiophenol, 27.9 g of benzyltrimethylammonium chloride and 25 g of sodium hydrogen carbonate were placed in 150 ml of chloroform with stirring. The suspension obtained was cooled to -5°C and a solution of 25.3 g of 2,6-dibromocaproic acid bromide in 70 ml of chloroform was added slowly with stirring to the cooled suspension. The addition took 30 minutes and the temperature varied between -5°C and +5°C. The mixture was maintained in this temperature range for a further hour. The mixture was then heated under reflux for 7 hours. It was then cooled, filtered and the chloroform was distilled off from the filtrate obtained.

The remaining residue was treated with water and toluene. The organic phase was separated off, dried and fractionated by means of column chromatography. The fraction containing 2-(4-bromobutyl)-2H-1,4-benzothiazin-3(4H)-one was separated off. 5.9 g of 2-(4-bromobutyl)-2H-1,4-benzothiazine-3(4H)-one were obtained from this after crystallisation in the presence of diethyl ether as slightly beige-coloured crystals having a melting point of 100°C.

C) A mixture of 3.6 g (= 0.012 m) of 2-(4-bromobutyl)-2H-1,4-benzothiazin-3(4H)-one, 2.12 g (= 0.012 m) of N-(4-methylpyridin-2-yl)-piperazine and 1.83 g (= 0.018 m) of triethylamine in 100 ml of toluene was heated at reflux for 9 hours with stirring, a further 0.46 g of triethylamine being added after 3 hours and again a further 0.9 g of triethylamine being added after 6 hours.

For working-up the reaction mixture was cooled to 20°C and 200 ml of water were added. The organic phase was separated off and the toluene was distilled off. The remaining residue was dissolved in 50 ml of 20 % strength aqueous hydrochloric acid solution and the solution was washed using toluene. The aqueous phase was made alkaline at pH 9 and then extracted using dichloromethane. The dichloromethane extract was washed, dried over calcium chloride and the dichloromethane was distilled off. The crude title compound remaining as residue was purified by means of column chromatography and then recrystallised from a mixture of toluene/isopropanol 50/50 v/v. 2.4 g of 2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one were obtained as colourless crystals having a melting point of 119°C.

Example 2:

2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-thione.

5.95 g (= 0.015 m) of 2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one (= preparation see Example 1) were dissolved in 60 ml of xylene at a temperature of 60°C. 6.9 g of P_4S_{10} were added to the solution and the reaction mixture was heated at reflux for 1 hour with stirring.

It was cooled for working-up, the precipitate thus formed was separated off and added to a mixture of 160 ml of 2N aqueous sodium hydroxide solution and 200 ml of dichloromethane. Further addition of 50 ml of water and 50 ml of dichloromethane led to a reaction solution with a slight precipitate which was removed by filtration. The organic phase was then separated off, dried and the solvent was distilled off. 5.2 g of residue were obtained and fractionated by means of column chromatography. The title compound was crystallised from the fraction containing the title compound in a mixture of diethyl ether/ethyl acetate 50/50 v/v. 3.1 g of 2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-thione were obtained in the form of beige-coloured crystals having a melting point of 119°C.

Example 3:

4-methyl-2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one.

2 g (= 0.005 m) of 2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one (preparation see Example 1) were dissolved in 20 ml of anhydrous dimethylformamide with stirring. 0.151 g of

sodium hydride were added under a nitrogen atmosphere and the suspension formed was maintained at room temperature for 10 minutes. 0.86 g of methyl iodide was then added in one batch and the reaction mixture was stirred for 2.5 hours at room temperature. For working-up the solvent was distilled off, 100 ml of water were added to the residue and the mixture was extracted using 100 ml of ethyl acetate. The organic phase was concentrated by evaporating the solvent, and the crude title compound remaining as residue was purified by means of column chromatography. The base thus obtained was dissolved in isopropanolic 2.3 N hydrochloric acid. The hydrochloride of the title compound occurring as a white precipitate was filtered off. 0.7 g of 4-methyl-2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one dihydrochloride of empirical formula $C_{23}H_{30}N_4OS$. 2HCl. 2.5 H_2O having a melting point of 163°C were obtained.

Example 4:

4-methyl-2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one.

A) 0.1 mole of 2-aminobenzothiazole and 0.1 mole of methyl iodide were heated under reflux in 50 ml of absolute ethanol for 12-15 hours. The 2-imino-3-methylbenzthiazole hydroiodide precipitated was separated off and dissolved in hot water. The solution was rendered alkaline by adding a saturated aqueous sodium carbonate solution. The 2-imino-3-methylbenzthiazole precipitated was separated off, washed with water and dried under reduced pressure.

B) The product obtained above was heated under reflux for 36 hours in 50 % strength potassium hydroxide solution. For working-up the solution was diluted using

water and set at pH 6 by adding aqueous 5N acetic acid solution. The aqueous solution was then extracted several times using ethyl acetate. The solvent was distilled off from the combined organic phases under reduced pressure. The 2-(methylamino)-thiophenol remaining as residue was used in the subsequent reaction step without further purification.

C) 4.5 g (= 0.032 m) of 2-(methylamino)-thiophenol, 6 g of triethylbenzylammonium chloride and 11.20 g of sodium hydrogen carbonate were added to 120 ml of chloroform. The suspension formed was cooled to 5°C and then a solution of 10.88 g of 2,6-dibromohexanoyl bromide in 20 ml of chloroform was added dropwise slowly so that the temperature did not exceed 5°C. 20 minutes were required for the addition. The reaction mixture was then allowed to rise to room temperature and was then heated under reflux for 4 hours. For working-up the reaction mixture was cooled and filtered. The chloroform phase was washed, dried over sodium sulphate and the solvent was distilled off. The 2-(4-bromobutyl)-4-methyl-2H-1,4-benzothiazin-3(4H)-one formed was obtained from the remaining residue by fractional column chromatography. 2.78 g of white crystals having a melting point of 116°C were obtained.

D) The product obtained above was reacted analogously to Example 1 C) with N-(4-methylpyridin-2-yl)-piperazine in toluene with addition of triethylamine. The 4-methyl-2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one obtained was converted to its dihydrochloride of empirical formula $C_{23}H_{30}N_4OS$. 2HCl. 2.5 H_2O having a melting point of 163°C, as described in Example 3.

Example 5:

2-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-2H-1,4-benzothiazin-3(4H)-one.

A) 0.8 ml (= 1 equivalent) of sulphonyl chloride was added dropwise with stirring at room temperature to a suspension of 10.0 mmoles of 2H-1,4-benzothiazin-3(4H)-one in 10 ml of dichloromethane, and the reaction mixture was stirred for a further 5 hours at room temperature. For working-up the mixture was evaporated to dryness under reduced pressure. The 2-chloro-2H-1,4-benzothiazin-3(4H)-one remaining as residue (melting point 189-210°C with decomposition) was further processed in the next step without further purification.

B) 7 g (= 0.035 m) of 2-chloro-2H-1,4-benzothiazin-3(4H)-one, 6.2 g of N-(4-methylpyridin-2-yl)-piperazine and 7 g triethylamine were heated at reflux with stirring for 5 hours in 100 ml of toluene. For working-up the suspension was diluted using 200 ml of toluene, the precipitate was filtered off and dissolved in 20 % strength aqueous hydrochloric acid solution. The solution was rendered alkaline by adding an ammonium hydroxide solution, the precipitate formed was filtered off, washed with water and dried. 2 g of beige-coloured crystalline 2-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-2H-1,4-benzothiazin-3(4H)-one having a melting point of 245°C were obtained.

Example 6:

7-hydroxy-2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one.

360 mg of 7-methoxy-2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one (see Example 19, preparation analogous to Example 1) were added to 5 ml of dichloromethane with exclusion of

moisture. After cooling to -5°C, a solution of 0.73 g of boron tribromide in 1 ml of methylene chloride was added dropwise with stirring. Stirring was then continued for a further 30 minutes at room temperature. For working-up the reaction mixture was added with stirring to a mixture of ice and aqueous sodium hydrogen carbonate solution. 200 ml of chloroform were then added. The organic solution formed was washed using water, dried over sodium sulphate, filtered and concentrated under reduced pressure. The title compound was obtained from the remaining residue by fractional column chromatography. The fractions containing the title compound were concentrated and treated with ether. 30 mg of 7-hydroxy-2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one were obtained as white crystals having a melting point of 212°C.

The compounds of the formula I listed in the following Table I were also obtained by the processes described in the above examples.

Table I

Ex.	R^1	R^2	R^3	X	Y	n	R^4	Salt form	M.p. in °C
7	H	H	H	O	O	4	4-CH_3-pyrid-2-	2·HCl	180 (D)
8	H	H	H	S	O	3	4-CH_3-pyrid-2-	Base	140
9	H	H	H	O	O	3	4-CH_3-pyrid-2-	2·HCl	183
10	H	H	7-CH_3	S	O	3	4-CH_3-pyrid-2-	2·HCl	126
11	H	H	H	S	S	3	4-CH_3-pyrid-2-	Base	134
12	H	H	H	S	O	4	pyrim-2-	Base	140
13	H	H	H	S	O	4	5-CH_3-pyrid-2-	Base	128
14	H	H	H	O	S	3	4-CH_3-pyrid-2-	2·HCl	170
15	H	H	H	S	O	3	5-Cl-pyrid-2-	Base	153
16	H	H	H	S	O	4	6-CH_3O-pyrid-2-	Base	132
17	H	H	H	S	O	4	pyrid-2-	Base	125
18	H	7-F-	H	S	O	4	4-CH_3-pyrid-2-	HCl	162
19	H	7-CH_3O-	H	S	O	4	4-CH_3-pyrid-2-	Base	123
20	H	7-Cl-	H	S	O	4	6-CH_3-pyrid-2-	Base	92
21	H	6-CH_3-	7-CH_3	S	O	4	4-CH_3-pyrid-2-	Base	114
22	H	6-CH_3-	H	O	O	3	4-CH_3-pyrid-2-	Base	115
23	H	6-Cl-	H	O	O	4	4-CH_3-pyrid-2-	Base	116
24	H	6-CH_3-	H	O	O	4	4-CH_3-pyrid-2-	Base	126
25	H	7-HO-	H	S	O	4	4-CH_3-pyrid-2-	Base	126
26	H	H	H	S	O	4	3-CH_3-pyrid-2-	Base	119
27	H	7-Cl	H	S	O	4	4-CH_3-pyrid-2-	Base	152
28	n-C_4H_9	H	H	S	O	4	4-CH_3-pyrid-2-	3·HCl	148

pyrid-2- = pyridin-2-yl, pyrim-2- = pyrimidin-2-yl,

Base = free base, HCl = hydrochloride,

D = decomposition

Example I:

Tablets containing 2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one.

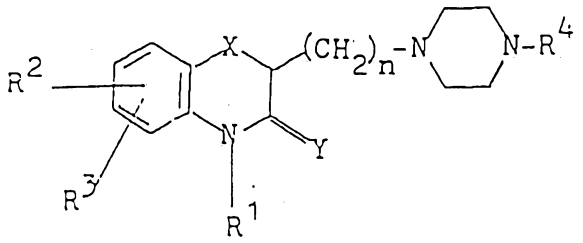
Tablets are produced with the following composition per tablet:

2-{4-[4-(4-methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one	20 mg
Corn starch	60 mg
Lactose	135 mg
Gelatine (as 10 % strength solution)	6 mg

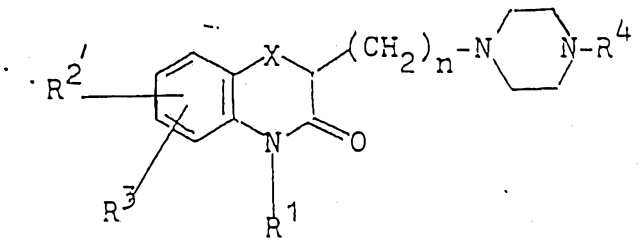
The active ingredient, the corn starch and the lactose were mixed with the 10 % strength gelatine solution. The paste was comminuted and the resulting granules were placed on a suitable plate and dried at 45°C. The dried granules were passed through a comminuting machine and mixed with the following further auxiliaries in a mixer:

Talcum	5 mg
Magnesium stearate	5 mg
Corn starch	9 mg

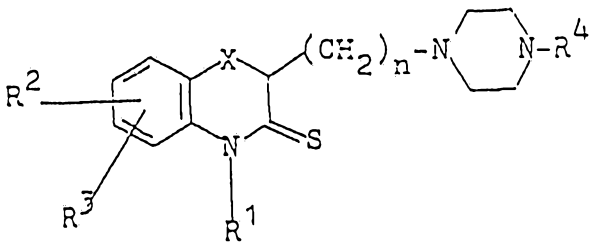
and then pressed to form tablets of 240 mg.



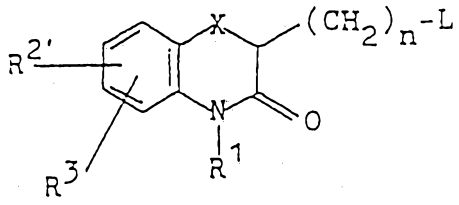
I



Ia



Ib



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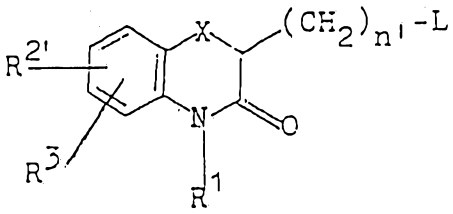

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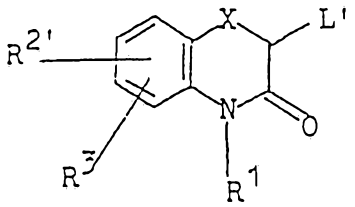

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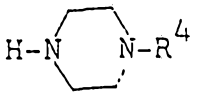

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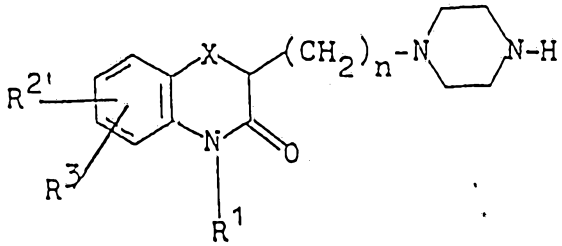
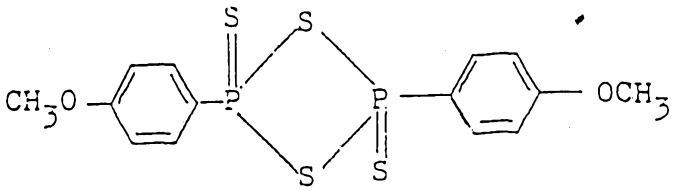


IV

R^4-L' V



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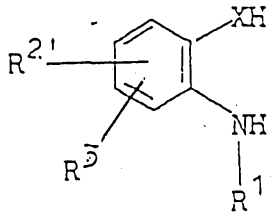

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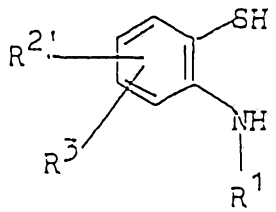

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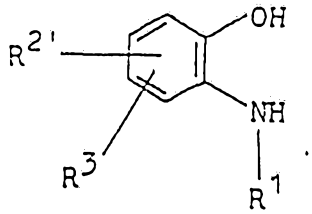

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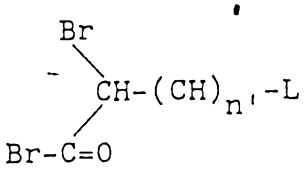

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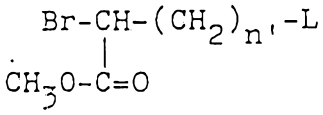

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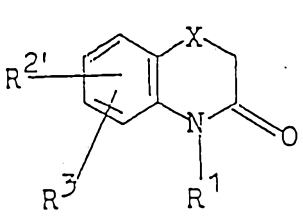

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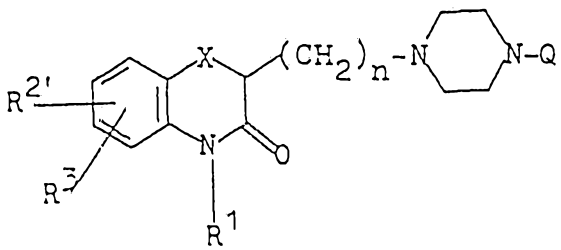

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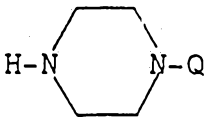

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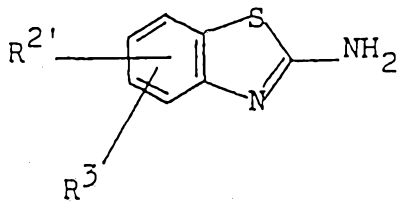

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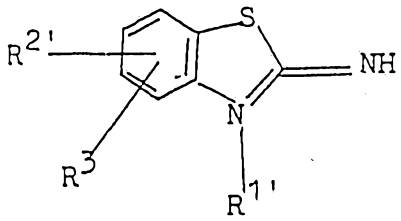
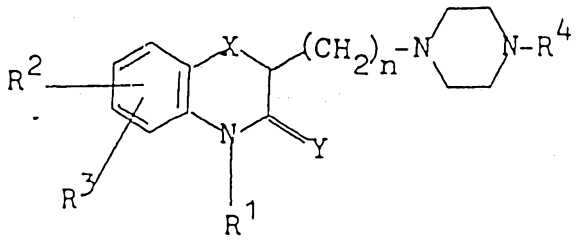


XIV

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

~~Patent Claims~~

1. A compound of the general formula I:



wherein
X denotes oxygen or sulphur,
Y denotes oxygen or sulphur,
R^1 denotes hydrogen or lower alkyl,
R^2 denotes hydrogen, lower alkyl, halogen, lower alkoxy, hydroxy, nitro or trifluoromethyl, and
R^3 denotes hydrogen, lower alkyl, halogen or lower alkoxy, or
R^2 and R^3 are bonded to neighbouring carbon atoms and together denote an alkylenedioxy group having 1-2 carbon atoms,
n is a whole number from 0 to 4, and
R^4 is a 6-membered unsaturated heterocycle containing 1 or 2 nitrogen atoms not directly bonded to the piperazine ring, which heterocycle may optionally be substituted by 1-2 substituents, bonded to carbon atoms, from the group of lower alkyl, lower alkoxy and halogen,
and physiologically acceptable acid addition salts thereof.

2. A compound according to Claim 1, wherein Y denotes oxygen.

3. A compound according to Claim 1 or Claim 2, wherein n is 3 or 4.

4. A compound according to any preceding claim, wherein R^4 is an optionally substituted pyridyl radical.

5. A compound according to Claim 4, wherein R^4 is a 4-lower-alkylpyrid-2-yl radical.

6. A compound according to any preceding claim, wherein R^1 denotes hydrogen.

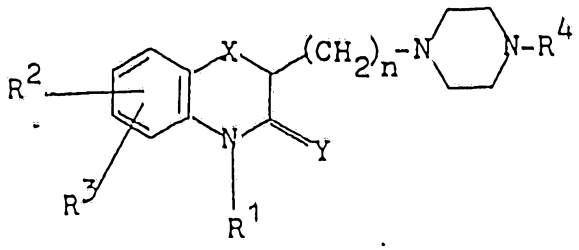
7. A compound according to any preceding claim, wherein R^2 denotes hydrogen or lower alkyl and R^3 denotes hydrogen.

8. A compound according to Claim 1, wherein X denotes oxygen or sulphur and Y denotes oxygen, R^1 denotes hydrogen, R^2 denotes hydrogen or lower alkyl, R^3 denotes hydrogen, n is 3 or 4 and R^4 is a pyridyl radical substituted optionally by lower alkyl.

9. 2-{4-[4-(4-Methylpyridin-2-yl)-piperazin-1-yl]-butyl}-2H-1,4-benzothiazin-3(4H)-one, or a physiologically acceptable acid addition salt thereof.

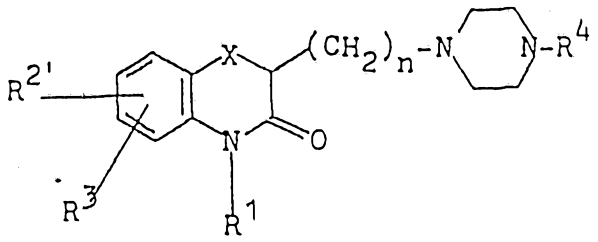
10. A pharmaceutical composition comprising a compound according to any preceding claim, and a pharmaceutically acceptable carrier, diluent and/or excipient.

11. A process for the preparation of a compound of the general formula I:

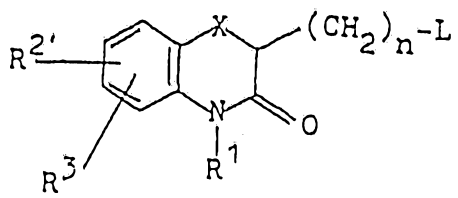


wherein
X denotes oxygen or sulphur,
Y denotes oxygen or sulphur,
R^1 denotes hydrogen or lower alkyl,
R^2 denotes hydrogen, lower alkyl, halogen, lower alkoxy, hydroxy, nitro or trifluoromethyl, and
R^3 denotes hydrogen, lower alkyl, halogen or lower alkoxy, or
R^2 and R^3 are bonded to neighbouring carbon atoms and together denote an alkylenedioxy group having 1-2 carbon atoms,
n is a whole number from 0 to 4, and
R^4 is a 6-membered unsaturated heterocycle containing 1 or 2 nitrogen atoms not directly bonded to the piperazine ring, which heterocycle may optionally be substituted by 1-2 substituents, bonded to carbon atoms, from the group of lower alkyl, lower alkoxy and halogen, and acid addition salts thereof, wherein:

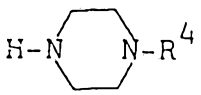
a) to prepare compounds of the general formula Ia:



wherein X, R^1, R^2, R^3, n and R^4 have the above meaning, compounds of the general formula II :

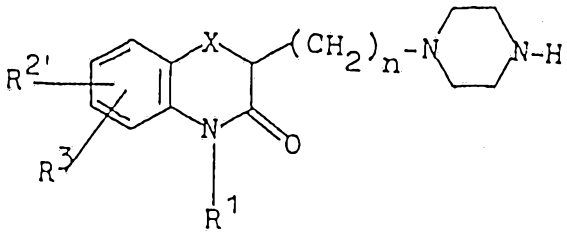


wherein X, R^1, R^3 and n have the above meaning, and $R^{2'}$ has the meaning given for R^2, but wherein a hydroxy group is protected by a subsequently splittable protective group, and L is an aminolytically splittable radical, in particular halogen, are reacted with piperazine derivatives of the general formula III :



wherein R^4 has the above meaning, or

b) compounds of the general formula IV :

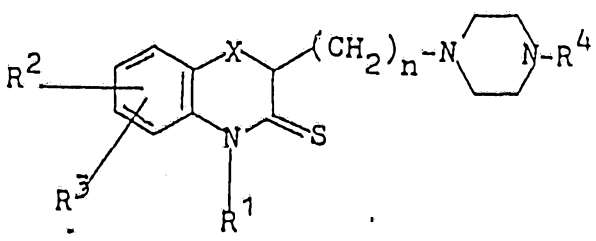


wherein X, R^1, $R^{2'}$, R^3 and n have the above meaning, are reacted with compounds of the general formula V :

$$R^4\text{-}L'$$

wherein R^4 has the above meaning and L' denotes halogen, and then any hydroxy protective group is split off again, or

c) compounds of the general formula Ia are converted to compounds of the general formula Ib



wherein X, R^1, R^2, R^3, n and R^4 have the above meaning, and

optionally compounds of the general formula I obtained where R^1 denotes hydrogen, are alkylated to form compounds of the general formula I, wherein R^1 denotes lower alkyl; and/or in compounds of the general formula I obtained, wherein R^2 denotes methoxy, the methoxy group is split to form the hydroxy group, and optionally free compounds of the formula I are converted into their acid addition salts or the acid addition salts are converted into the free compounds of the formula I.

DATED this 16th day of September, 1993.

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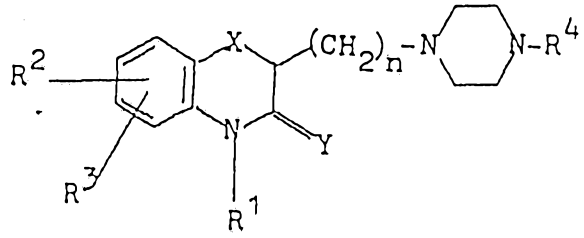
AUSTRALIA

Abstract

There are disclosed novel pharmacologically active compounds of the general formula I



which are optionally substituted in the benzene ring and wherein
X denotes oxygen or sulphur,
Y denotes oxygen or sulphur,
R^1 denotes hydrogen or lower alkyl,
n is a whole number from 0 to 4, and
R^4 is an optionally substituted 6-membered unsaturated heterocycle containing 1 or 2 nitrogen atoms not directly bonded to the piperazine ring,
and physiologically acceptable acid addition salts thereof, are described.