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HETEROCYCLIC COMPOUNDS

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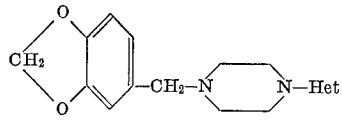
ABSTRACT OF THE DISCLOSURE

1-(3',4'-methylenedioxybenzyl)-piperazines substituted in 4-position by (1) pyrimidin-4-yl, pyrazinyl, s-triazinyl, or quinazolinyl unsubstituted or substituted by one or two alkyl, alkoxy or amino groups, or (2) pyrimidin-2-yl monosubstituted by halogen, carboxy, carbalkoxy, or caralkoxymethoxy, or disubstituted by alkoxy and carboxy or carbalkoxy.

These compounds possess bronchodilating and peripheral vasodilating properties.

The present invention provides new heterocyclic compounds of the general formula



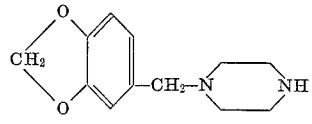
(I)

in which "Het" represents a pyrimidinyl radical attached in the 4- position, or a prazinyl, s-triazinyl, or quinazolinyl radical which may be unsubstituted or substituted by one two lower alkyl radicals containing 1 to 4 carbon atoms, by lower alkoxy radicals containing 1 to 4 carbon atoms, or by an amino group, or a pyrimidinyl radical attached in the 2-position which is mono-substituted by a halogen atom or by a carboxy, carbalkoxy or carbalkoxymethoxy group, or disubstituted by an alkoxy radical and a carboxy or carbalkoxy radical, wherein the alkoxy have from 1 to 4 carbon atoms inclusive.

The new compounds of this invention are obtained by condensing a halogenated derivative of the general formula

Het—Z (II)

where Z represents a chlorine or bromine atom and "Het" has the meaning given above with 1-(3',4'-methylenedioxybenzyl)-piperazine of the formula



(III)

The condensation is carried out in a polar solvent such, for example, as a high-boiling alcohol, for example butanol or pentanol, or in an aromatic amide such, for example, as dimehtylformamide, in a non-polar solvent such, for example, as an aromatic hydrocarbon, for example benzene, toluene or xylene. The condensation is advantageously carried out at a temperature ranging from 80 to 140° C. in the presence of an acceptor for the hydrohalic acid formed during the reaction. The latter may be an alkali or alkaline earth metal salt of carbonic acid such, for example, as the bicarbonate or carbonate of sodium or potassium, or calcium carbonate, or a tertiary organic base, for example, dimethylaniline, pyridine or

triethylamine. If desired, these salts or tertiary bases may be replaced by an excess of the monosubstituted piperazine.

The new heterocyclic compounds obtained in this manner are weak bases and can be converted into acid addition salts which are likewise included in this invention. These acid addition salts are obtained by reacting the new derivatives with acids in suitable solvents, for example in water or water-miscible alcohols. As acids capable of forming such acid addition salts there may be mentioned mineral acids such, for example, as hydrochloric, hydrobromic, methanesulphonic, sulphuric and phosphoric acids, and organic acids such as acetic, propionic, maleic, fumaric, tartaric, citric, oxalic, benzoic acid and the like.

If desired or required, the new compounds may be purified by physical operations such as distillation, crystallization or chromatography, or by chemical operations such as decomposition of the acid addition salts by reaction with alkaline agents.

The compounds of the invention possess interesting pharmacological and therapeutic properties and may be used especially as peripheral vasodilators and bronchodilators.

The acute toxicity was determined in mice and it was found that the DL_{50} varies from 50 to 1500 mg./kg. I.P. and from 1200 to >3000 mg./kg. P.O. according to the compound tested.

An intravenous perfusion of the new compounds at a level of 5 mg./kg. in the rabbit increases the blood flow of the paw from 20 to 225%, demonstrating an important vasodilator activity.

The bronchodilator activity was demonstrated by the method of Konzett and Rossler [Arch. Exptl. Pathol. U. Pharmak. 195, 71 (1940)]. It was found that the new compounds inhibit the bronchospasm in the guinea-pig provoked by histamine, serotonine or acetylcholine. The doses from 1 to 5 mg./kg. administered intravenously inhibit these spasms from 30 to 100%.

These properties enable the use of the new compounds in therapy, and especially in the treatment of peripheral circulatory disorders such, for example, as arteritis or phlebitis, chronic or acute respiratory insufficiency, and particularly bronchial asthma.

The doses used may vary from 10 to 200 mg., and the dosage regimen may be 2 to 4 times per day.

The compounds can be administered per oral, rectal or parenteral route, and the active principle may be mixed or associated with the usual pharmaceutical carriers such as: distilled water, starch, talc, lactose, ethyl cellulose, cocoa butter, according to the desired pharmaceutical form, which can be: tablet, dragée, capsule suppository, injectable or drinkable solution.

The pharmaceutical preparations containing a compound of the general Formula I, or one of its salts in admixture or conjunction with a pharmaceutically suitable carrier are also a part of this invention.

The following examples illustrate the manufacture of the new compounds. The melting points were determined on a Kofler heater under a microscope, unless otherwise indicated.

EXAMPLE 1

1-(5'-chloro-pyrimidin-2'-yl)-4-(3'',4''-methylendioxybenzyl)-piperazine

28 grams of potassium carbonate are added to a solution of 21 g. of 1-(3',4'-methylenedioxybenzyl)-piperazine and 14.9 g. of 2,5-dichloropyrimidine in 150 cc. of dimethylformamide (DMF) and the mixture is heated for 8 hours at 130° C. After this time the salt formed is filtered off, the DMF is distilled off under reduced pres-

sure and the hot residue is poured into 100 cc. of boiling water. The whole is vigorously agitated while being cooled, whereupon the oil crystallizes; it is suctioned off and recrystallized from ethanol, to yield 25 g. of cream colored crystals melting at 99–101° C.

The following derivatives may be prepared as described above, using the appropriate starting materials:

(a) 1-(4'-carbethoxy-methoxy-pyrimidin - 2' - yl) - 4-(3'',4'' - methylenedioxybenzyl)-piperazine, starting from 2-chloro-4-carbethoxy-methoxy-pyrimidine. Its dihydrochloride melts at 195–200° C.

In the same manner other 4' - carbalkoxy-methoxy-pyrimidin-2'-yl compounds are prepared, starting only from the appropriate starting material, wherein alkoxy has 1 to 4 carbon atoms inclusive, for example, the corresponding carbomethoxy, carbopropoxy, carboisopropoxy and carbobutoxy compounds.

(b) 1-(5'-carbethoxy-pyrimidin-2'-yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine, starting from 2 - chloro-5-carbethoxy-pyrimidine. The free base melts at 104° C.

In the same manner other 5'-carbalkoxy-pyrimidin-2'-yl compounds are prepared, starting only from the appropriate starting material, wherein alkoxy has 1 to 4 carbon atoms inclusive, for example, the corresponding carbomethoxy, carbopropoxy, carboisopropoxy and carbobutoxy compounds.

(c) 1 - (4' - ethoxy-5'-carbethoxy-pyrimidin-2'-yl)-4-(3'',4''-methylenedioxybenzyl)piperazine, starting from 2-chloro-4-ethoxy-5-carbethoxy-pyrimidine. Its hydrochloride melts at 260° C.

In the same manner other 4'-alkoxy-5'-carbethoxy-pyrimidin-2'-yl compounds are prepared starting only from the appropriate starting material, wherein alkoxy has 1 to 4 carbon atoms inclusive, for example the corresponding methoxy, propoxy, isopropoxy and butoxy compounds.

(d) 1-(4'-ethoxy-5'-carboxy-pyrimidin-2'-yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine, starting from 2-chloro-4-ethoxy-5-carboxy-pyrimidine. Its hydrochloride melts at 196–200° C.

In the same manner other 4'-alkoxy-5'-carboxy-pyrimidin-2'-yl compounds are prepared, starting only from the appropriate starting material, wherein alkoxy has 1 to 4 carbon atoms inclusive, for example, the corresponding methoxy, propoxy, isopropoxy and butoxy compounds.

(e) 1-(5'-carboxy - pyrimidin - 2'-yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine, starting from 2-chloro-5-carboxy-pyrimidine. The free base melts at 234° C.

EXAMPLE 2

1-(pyrimidin-4'-yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine

This compound is obtained by working according to the method given in Example 1 in toluene under reflux in the presence of potassium carbonate and starting from 4-chloropyrimidine. The corresponding dihydrochloride melts at 192–198° C. with decomposition.

In the same manner as described in this example the following compound was obtained:

1-(2' - amino - pyrimidin-4'-yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine, starting from 2-amino-4-chloropyrimidine. The free base melts at 171° C.

EXAMPLE 3

1-(4',6'-dimethoxy-s-triazin-2'-yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine

This compound is obtained by working according to the method given in Example 1 in benzene under reflux in the presence of potassium carbonate and starting from 2-chloro-4,6-dimethoxy-s-triazine. The free base melts on a Kofler heater at 102° C. The corresponding hydrochloride melts at 250° C. with decomposition.

The following compounds were obtained as described in this example:

(a) 1-(6'-methoxy - s - triazin-2'-yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine, starting from 2-chloro-6-methoxy-s-triazine. The hydrochloride melts at 230° C. with decomposition.

(b) 1-(s-triazin - 2' - yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine, starting from 2-chloro-s-triazine. The dihydrochloride melts at 207–211° C.

(c) 1-(4'-amino - s - triazin-2'-yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine, starting from 2-chloro-4-amino-s-triazine. The free base melts at 185–190° C. (capillary).

(d) 1-(4',6'-diamino - s - triazin-2'-yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine, starting from 2-chloro-4,6-diamino-s-triazine. The free base melts at 199–203° C. (capillary).

EXAMPLE 4

1-(quinazolin-4'-yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine

This compound is obtained by working according to the method given in Example 1 in dimethylformamide in the presence of potassium carbonate and starting from 4-chloroquinazoline. The corresponding dihydrochloride melts as 230–233° C.

The following compounds were obtained as described in this example:

(a) 1-(quinazolin - 2' - yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine, starting from 2-chloro quinazoline. The free base melts at 141° C.

(b) 1-(2'-methyl-quinazolin - 4' - yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine, starting from 2-methyl-4-chloro-quinazoline. The dihydrochloride melts at 210–218° C.

EXAMPLE 5

1-(pyrazin-3'-yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine

This compound is obtained by working according to the method given in Example 1 in dimethylformamide in the presence of potassium carbonate and starting from 3-chloropyrazine. The dihydrochloride melts at 228–234° C. (capillary).

The following compounds were also obtained by the method described in this example:

(a) 1-(2',5'-dimethyl-pyrazin - 3' - yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine, starting from 2,5-dimethyl-3-chloro-pyrazine. The dihydrochloride melts at 273–275° C.

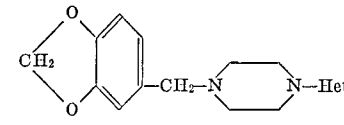
(b) 1-(5'-methyl-pyrazin - 3' - yl)-4-(3'',4'', methylenedioxybenzyl)-piperazine, starting from 3-chloro-5-methyl-pyrazine. The dihydrochloride melts at 254–255° C.

(c) 1-(2'-amino-pyrazin - 3' - yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine, starting from 2-amino-3-chloropyrazine. The dihydrochloride melts at 225–228° C.

Various modifications and equivalents will be apparent to one skilled in the art and may be made in the compounds, compositions, and methods of the present invention without departing from the spirit or scope thereof, and it is therefore to be understood that the invention is to be limited only by the scope of the appended claims.

What we claim is:

1. A compound selected from the group consisting of (A) heterocyclic compounds of the Formula I



(I)

wherein Het is selected from the group consisting of: quinazolinyl optionally substituted by a substituent selected from the group consisting of lower-alkyl of up

to 4 carbon atoms inclusive, lower-alkoxy of up to 4 carbon atoms inclusive and amino, and physiologically acceptable addition salts thereof with organic and mineral acids.

2. 1-(quinazolin - 4' - yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine.

3. 1-(quinazoline - 2' - yl)-4-(3'',4''-methylenedioxybenzyl)-piperazine.

4. 1-(2'-methyl-quinazolin-4'-yl) - 4 - (3'',4''-methylenedioxybenzyl)-piperazine.

References Cited

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