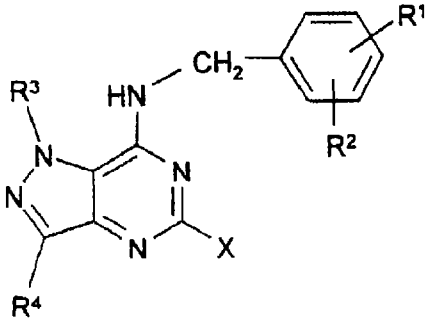
Pyrazolo[4.3-d]pyrimidines

159159

The invention relates to compounds of the formula I



G00002

I

in which

R^1 and R^2	are each, independently of one another, H, A, OH, OA or Hal,
R^1 and R^2	together are alternatively alkylene having 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
R^3 and R^4	are each, independently of one another, are H or A,
X	is R^5, R^6 or R^7 which is monosubstituted by R^8,
R^5	is linear or branched alkylene having 1-10 carbon atoms, in which one or two CH_2 groups may be replaced by -CH=CH- groups, O, S or SO,
R^6	is cycloalkyl or cycloalkylalkylene having 5-12 carbon atoms,
R^7	is phenyl or phenylmethyl,
R^8	is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,
A	is alkyl having from 1 to 6 carbon atoms, and
Hal	is F, Cl, Br or I,

and their physiologically acceptable salts and solvates.

Pyrimidine derivatives are disclosed, for example, in EP 201 188 and WO 93/06104.

The invention had the object of finding novel compounds having valuable properties, in particular those which can be used for the preparation of medicaments.

It has been found that the compounds of the formula I and their salts have very valuable pharmacological properties and are well tolerated. In particular, they exhibit specific inhibition of cGMP phosphodiesterase (PDE V).

Quinazolines having cGMP phosphodiesterase-inhibiting activity are described, for example, in J. Med. Chem. 36, 3765 (1993) and ibid. 37, 2106 (1994).

The biological activity of the compounds of the formula I can be determined by methods as are described, for example, in WO 93/06104. The affinity of the compounds according to the invention for cGMP and cAMP phosphodiesterase is determined by the measurement of their IC_{50} values (concentration of the inhibitor which is needed in order to achieve 50% inhibition of the enzyme activity).
The determinations can be carried out using enzymes isolated by known methods (for example W.J. Thompson et al., Biochem. 1971, 10, 311). The experiments can be carried out using a modified batch method of W.J. Thompson and M.M. Appleman (Biochem. 1979, 18, 5228).

The compounds are therefore suitable for the treatment of disorders of the cardiovascular system, in particular of cardiac insufficiency, and for the treatment and/or therapy of potency disorders (erectile dysfunction).

The use of substituted pyrazolopyrimidinones for the treatment of impotence is described, for example, in WO 94/28902.

The compounds are effective as inhibitors of phenylephrine-induced contractions in corpus cavernosum preparations from rabbits.
This biological activity can be demonstrated, for example, by the method described by F. Holmquist et al. in J. Urol., 150, 1310-1315 (1993).

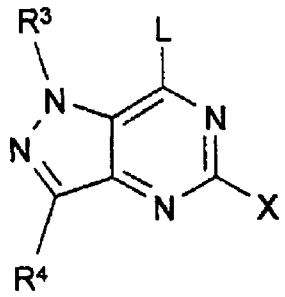
The inhibition of the contraction demonstrates the efficacy of the compounds according to the invention for the therapy and/or treatment of potency disorders.

The compounds of the formula I can be employed as medicament active ingredients in human and veterinary medicine. They can furthermore be employed as intermediates for the preparation of further medicament active ingredients.

The invention accordingly relates to the compounds of the formula I and to a process for the preparation of compounds of the formula I according to Claim 1 and their salts,

characterised in that

a) a compound of the formula II



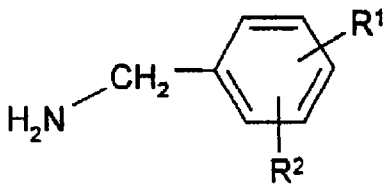
II

in which

R^3, R^4 and X are as defined,

and L is Cl, Br, OH, SCH_3 or a reactive esterified OH group,

is reacted with a compound of the formula III



III

in which

R^1 and R^2 are as defined,

or

b) a radical X in a compound of the formula I is converted into another radical X by, for example, hydrolysing an ester group to a COOH group or converting a COOH group into an amide or into a cyano group

and/or in that a compound of the formula I is converted into one of its salts.

The term solvates of the compounds of the formula I is taken to mean adductions of inert solvent molecules onto the compounds of the formula I which are formed as a result of their mutual attractive force. Solvates are, for example, mono- or dihydrates or alcoholates.

Above and below, the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, X and L are as defined in the formulae I, II and III, unless expressly stated otherwise.

A is alkyl having 1-6 carbon atoms.
In the above formulae, alkyl is preferably unbranched and has 1, 2, 3, 4, 5 or 6 carbon atoms and is preferably methyl, ethyl or propyl, furthermore preferably isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, but also n-pentyl, neopentyl, isopentyl or hexyl.

X is an R^5, R^6 or R^7 radical which is monosubstituted by R^7.

R^5 is a linear or branched alkylene radical having 1-10 carbon atoms, where the alkylene radical is preferably, for example, methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, pentylene, 1-, 2- or 3-methylbutylene, 1,1-, 1,2- or 2,2-dimethylpropylene, 1-ethyl-propylene, hexylene, 1-, 2-, 3- or 4-methylpentylene, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutylene, 1- or 2-ethylbutylene, 1-ethyl-1-methyl-propylene, 1-ethyl-2-methylpropylene, 1,1,2- or 1,2,2-trimethylpropylene, linear or branched heptylene, octylene, nonylene or decylene. R^5 is furthermore, for example, but-2-enylene or hex-3-enylene.
A CH_2 group in R^5 can preferably be replaced by oxygen.
Very particular preference is given to ethylene, propylene, butylene or

CH_2-O-CH_2.

R^6 is cycloalkylalkylene having 5-12 carbon atoms, preferably, for example, cyclopentylmethylene, cyclohexylmethylene, cyclohexylethylene, cyclohexylpropylene or cyclohexylbutylene.
R^6 is alternatively cycloalkyl, preferably having 5-7 carbon atoms. Cycloalkyl is, for example, cyclopentyl, cyclohexyl or cycloheptyl.

Hal is preferably F, Cl or Br, but also I.

The radicals R^1 and R^2 may be identical or different and are preferably in the 3- or 4-position of the phenyl ring. They are, for example, each, independently of one another, H, alkyl, OH, F, Cl, Br or I or together are alkylene, such as, for example, propylene, butylene or pentylene, furthermore ethyleneoxy, methylenedioxy or ethylenedioxy. They are preferably also each alkoxy, such as, for example, methoxy, ethoxy or propoxy.

The radical R^8 is preferably, for example, COOH, COOA, such as, for example, $COOCH_3$ or $COOC_2H_5$, $CONH_2$, $CON(CH_3)_2$, $CONHCH_3$ or CN, but in particular COOH or COOA.

Throughout the invention, all radicals which occur more than once may be identical or different, i.e. are independent of one another.

Accordingly, the invention relates in particular to the compounds of the formula I in which at least one of the radicals mentioned has one of the preferred meanings indicated above. Some preferred groups of compounds can be expressed by the following sub-formulae Ia to If, which conform to the formula I and in which the radicals not designated in greater detail have the meanings indicated in the formula I, but in which

in Ia	X	is R^5, phenyl or phenylmethyl, each of which is substituted by COOH, COOA, $CONH_2$, $CONA_2$, CONHA or CN;
in Ib	R^1 and R^2	together are alkylene having 3-5 carbon atoms, -O-CH_2-CH_2-, -O-CH_2-O- or -O-CH_2-CH_2-O-,
	X	is R^5, phenyl or phenylmethyl, each of which is substi-

tuted by COOH, COOA, $CONH_2$, $CONA_2$, CONHA or CN;

in Ic
R^1 and R^2 are each, independently of one another, H, A, OH, OA or Hal,
R^1 and R^2 together are alternatively alkylene having 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
X is R^5, phenyl or phenylmethyl, each of which is substituted by COOH, COOA, $CONH_2$, $CONA_2$, CONHA or CN;

in Id
R^1 and R^2 are each, independently of one another, H, A, OH, OA or Hal,
R^1 and R^2 together are alternatively alkylene having 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
X is alkylene having 2-5 carbon atoms, cyclohexyl, phenyl or phenylmethyl, each of which is substituted by R^8,
R^3 is alkyl having 1-6 carbon atoms,
R^4 is alkyl having 1-6 carbon atoms,
R^8 is COOH or COOA,
A is alkyl having from 1 to 6 carbon atoms,
Hal is F, Cl, Br or I;

in Ie
R^1 and R^2 are each, independently of one another, H, A, OH, OA or Hal,
R^1 and R^2 together are alternatively alkylene having 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
R^3 is alkyl having 1-6 carbon atoms,
R^4 is alkyl having 1-6 carbon atoms,
X is $-(CH_2)_{2-5}-R^8$, 4-R^8-cyclohexyl, 4-R^8-phenyl or 4-(R^8-methyl)phenyl;

in If
R^1 and R^2 are each, independently of one another, H, A, OH, OA or Hal,
R^1 and R^2 together are alternatively alkylene having 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
R^3 is alkyl having 1-6 carbon atoms,

	R^4	is alkyl having 1-6 carbon atoms,
	X	is $-(CH_2)_{2-5}-R^8$, in which one CH_2 group may have been replaced by O, or is 4-R^8-cyclohexyl, 4-R^8-phenyl or 4-(R^8-methyl)phenyl,
	R^8	is COOH or COOA.

In addition, the compounds of the formula I and also the starting materials for their preparation are prepared by methods known per se, as described in the literature (for example in the standard works, such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart], to be precise under reaction conditions which are known and suitable for the reactions mentioned. Use can also be made here of variants which are known per se, but are not mentioned here in greater detail.

In the compounds of the formulae II or III, R^1, R^2, R^3, R^4 and X have the meanings indicated, in particular the preferred meanings indicated.

If L is a reactive esterified OH group, this is preferably alkylsulfonyloxy having 1-6 carbon atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 carbon atoms (preferably phenyl- or p-tolylsulfonyloxy, furthermore also 2-naphthalenesulfonyloxy).

The compounds of the formula I can preferably be obtained by reacting compounds of the formula II with compounds of the formula III.
If desired, the starting materials can also be formed in situ by not isolating them from the reaction mixture, but immediately converting them further into the compounds of the formula I.
On the other hand, it is possible to carry out the reaction stepwise.

The starting compounds of the formula II and III are generally known. If they are not known, they can be prepared by methods known per se.
Compounds of the formula II can be prepared by methods known from the literature, for example from 4-amino-3-alkoxycarbonylpyrazoles by cyclisation with nitriles followed by reaction of the cyclisation products with phosphorus oxychloride (analogously to Houben Weyl E9b/2).

In detail, the reaction of the compounds of the formula II with the com-

pounds of the formula III is carried out in the presence or absence of an inert solvent at temperatures between about -20 and about 150°, preferably between 20 and 100°.

The addition of an acid-binding agent, for example an alkali or alkaline-earth metal hydroxide, carbonate or bicarbonate or another salt of a weak acid of the alkali or alkaline-earth metals, preferably of potassium, sodium or calcium, or the addition of an organic base, such as triethylamine, dimethylamine, pyridine or quinoline, or an excess of the amine component, may be favourable.

Suitable inert solvents are, for example, hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether, ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, N-methylpyrrolidone or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the solvents mentioned.

It is furthermore possible to convert a radical X in a compound of the formula I into another radical X, for example by hydrolysing an ester or a cyano group to a COOH group.
Ester groups can be hydrolysed, for example, using NaOH or KOH in water, water/THF or water/dioxane at temperatures between 0 and 100°. Carboxylic acids can be converted into the corresponding carboxylic acid chlorides, for example using thionyl chloride, and these can be converted into carboxamides. Carbonitriles are obtained from these in a known manner by elimination of water.

An acid of the formula I can be converted into the associated acid-addition salt using a base, for example by reaction of equivalent amounts of the acid and the base in an inert solvent, such as ethanol, and subsequent evaporation. Particularly suitable bases for this reaction are those which

give physiologically acceptable salts.
Thus the acid of the formula I can be converted into the corresponding metal salts, in particular alkali metal or alkaline-earth metal salts, or into the corresponding ammonium salt using a base (for example sodium hydroxide or carbonate or potassium hydroxide or carbonate).
Particularly suitable for this reaction are also organic bases which give physiologically acceptable salts, such as, for example, ethanolamine.

On the other hand, a base of the formula I can be converted into the associated acid-addition salt using an acid, for example by reaction of equivalent amounts of the base and the acid in an inert solvent, such as ethanol, followed by evaporation. Suitable acids for this reaction are, in particular, those which give physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, or sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic monobasic or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenemono- and -disulfonic acids, and laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used for the isolation and/or purification of the compounds of the formula I.

The invention furthermore relates to the use of the compounds of the formula I and/or their physiologically acceptable salts for the preparation of pharmaceutical preparations, in particular by non-chemical methods. They can be converted here into a suitable dosage form together with at least one solid, liquid and/or semi-liquid excipient or assistant and, if desired, in combination with one or more further active ingredients.

The invention also relates to medicaments of the formula I and their physiologically acceptable salts as phosphodiesterase V inhibitors.

The invention furthermore relates to pharmaceutical preparations compris-

ing at least one compound of the formula I and/or one of its physiologically acceptable salts.

These preparations can be used as medicaments in human or veterinary medicine. Suitable excipients are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc or Vaseline. Suitable for oral administration are, in particular, tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops, suitable for rectal administration are suppositories, suitable for parenteral administration are solutions, preferably oil-based or aqueous solutions, furthermore suspensions, emulsions or implants, and suitable for topical application are ointments, creams or powders. The novel compounds may also be lyophilised and the resultant lyophilisates used, for example, for the preparation of injection preparations. The preparations indicated may have been sterilised and/or comprise assistants, such as lubricants, preservatives, stabilisers and/or wetting agents, emulsifiers, salts for modifying the osmotic pressure, buffer substances, colorants and flavours and/or a plurality of further active ingredients, for example one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts can be used for combatting illnesses in which an increase in the cGMP (cycloguanosine monophosphate) level leads to inhibition or prevention of inflammation and muscle relaxation. The compounds according to the invention can particularly be used in particular in the treatment of illnesses of the cardiovascular system and for the treatment and/or therapy of potency disorders.

In general, the substances according to the invention are preferably administered in doses between about 1 and 500 mg, in particular between 5 and 100 mg, per dosage unit. The daily dose is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on a wide variety of factors, for example on the efficacy of the specific compound employed, on the age, body weight, general state of health, sex, on the diet, on the time and method of administration, on the

excretion rate, medicament combination and severity of the particular disorder to which the therapy applies. Oral administration is preferred.

Above and below, all temperatures are given in °C. In the following examples, "conventional work-up" means that water is added if necessary, the pH is adjusted, if necessary, to between 2 and 10, depending on the constitution of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried over sodium sulfate and evaporated, and the product is purified by chromatography on silica gel and/or by crystallisation.

Mass spectrometry (MS): EI (electron impact ionisation) M^+
FAB (fast atom bombardment) $(M+H)^+$

Example 1

3 g of methyl 3-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]propionate and 1.9 g of 3-chloro-4-methoxybenzylamine ("A") in 50 ml of dimethylformamide (DMF) are stirred for 12 hours at 60° in the presence of potassium carbonate. After filtration, the solvent is removed, and the mixture is subjected to conventional work-up, giving 4.6 g of methyl 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]-pyrimidin-5-yl]propionate as a colourless oil.

Analogous reaction of "A"

with methyl 2-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-acetate gives
methyl 2-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]acetate.

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 3-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-propionate gives
methyl 3-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]propionate.

Analogous reaction of "A"

with methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-butyrate gives

methyl 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyrate.

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-butyrate gives

methyl 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyrate.

Analogous reaction of "A"

with methyl 5-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-valerate gives

methyl 5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]valerate.

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 5-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-valerate gives

methyl 5-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]valerate.

Analogous reaction of "A"

with methyl 7-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-heptanoate gives

methyl 7-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]heptanoate.

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 7-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-

heptanoate gives
methyl 7-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]heptanoate.

Analogous reaction of "A"

with methyl 2-[4-(7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl)cyclohex-1-yl]acetate gives
methyl 2-{4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetate.

Analogous reaction of 3,4-methylenedioxybenzylamine

with methyl 2-[4-(7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohex-1-yl]acetate gives
methyl 2-{4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetate.

Analogous reaction of benzylamine

with methyl 3-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-propionate gives
methyl 3-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]-pyrimidin-5-yl]propionate;

with methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-butyrate gives
methyl 4-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]-pyrimidin-5-yl]butyrate;

with methyl 5-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-valerate gives
methyl 5-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]-pyrimidin-5-yl]valerate.

Analogous reaction of "A"

with methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-

cyclohexanecarboxylate gives
methyl 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohexanecarboxylate

and reaction of 3,4-methylenedioxybenzylamine gives
methyl 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohexanecarboxylate.

Example 2

4.3 g of methyl 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]propionate are dissolved in 30 ml of tetrahydrofuran (THF) and, after addition of 10 ml of 10% NaOH, stirred at 60° for 8 hours. After addition of 10% HCl, the deposited crystals are separated off and recrystallised from methanol, giving 3.7 g of 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]-propionic acid, m.p. 178°.

Evaporation with the equivalent amount of methanolic potassium hydroxide solution gives the potassium salt of the acid as an amorphous powder.

Analogous reaction of the esters mentioned in Example 1 gives the compounds

2-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]acetic acid,

3-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]propionic acid,

4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyric acid, m.p. 152°;

4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyric acid, m.p. 172°;

5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]valeric acid, m.p. 159°;

5-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]valeric acid, ethanolamine salt, m.p. 160°;

7-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]heptanoic acid,

7-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]heptanoic acid,

2-{4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

2-{4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

3-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]propionic acid,

4-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyric acid,

5-[7-benzylamino-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]valeric acid, m.p. 185°;

4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid,

4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid.

Analogous reactions give the compounds

5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-isopropyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]valeric acid, cyclohexylamine salt, m.p. 148°;

4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-ethyl-1*H*-

pyrazolo[4.3-d]pyrimidin-5-yl]butyric acid, m.p. 176°;

4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-ethyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyric acid, m.p. 187°;

4-[7-(3-chloro-4-methoxybenzylamino)-1-ethyl-3-methyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyric acid, m.p. 206°;

4-[7-(3,4-methylenedioxybenzylamino)-1-ethyl-3-methyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyric acid, m.p. 177°;

4-[7-benzylamino-1-methyl-3-ethyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyric acid, m.p. 208°;

4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-methyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyric acid, m.p. 250°;

4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-methyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyric acid, m.p. 225°;

4-[7-benzylamino-1-methyl-3-methyl-1*H*-pyrazolo[4.3-d]-pyrimidin-5-yl]butyric acid, m.p. 201°;

5-[7-(4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]valeric acid, m.p. 160°;

5-[7-(3-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]valeric acid, m.p. 141°;

5-[7-(4-chlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]valeric acid, m.p. 148°;

5-[7-(3-chlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]valeric acid, m.p. 151°.

Example 3

A mixture of 1.8 g of methyl 4-[7-chloro-1-methyl-3-propyl-1*H*-pyrazolo-

[4.3-d]pyrimidin-5-yl]phenylcarboxylate ("B") and 1.5 g of 3-chloro-4-methoxybenzylamine in 20 ml of N-methylpyrrolidone is heated at 110° for 4 hours. After cooling, the mixture is subjected to conventional work-up, giving 2.2 g of methyl 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]benzoate.

Analogously to Example 2, 1.2 g of the ester give 1.0 g of 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]benzoic acid, ethanolamine salt, m.p. 139°.

Analogously to Example 1, "B" and 3,4-methylenedioxybenzylamine give methyl 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]benzoate and ester hydrolysis thereof gives 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]benzoic acid.

Analogous reactions give the compound

4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]phenylacetic acid, glucamine salt, m.p. 114°

and

4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]phenylacetic acid.

Example 4

1 equivalent of 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]propionic acid and 1.2 equivalents of thionyl chloride are stirred in dichloromethane for 2 hours. The solvent is removed, giving 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]propionyl chloride. The product is transferred into aqueous ammonia and stirred for one hour, giving, after conventional work-up, 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]propionamide.

Example 5

1 equivalent of DMF and 1 equivalent of oxalyl chloride are dissolved in acetonitrile at 0°. 1 equivalent of 3-[7-(3-chloro-4-methoxybenzylamino)-

1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]propionamide is then added. The mixture is stirred for one hour. Conventional work-up gives 3-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]propionitrile is obtained.

Example 6

Analogously to Examples 1, 2 and 3, reaction of the corresponding chloro-pyrimidine derivatives with 3,4-ethylenedioxybenzylamine gives the following carboxylic acids

4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]butyric acid,

3-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]propionic acid,

5-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]valeric acid,

7-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]heptanoic acid,

2-{4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid,

4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]benzoic acid,

4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]benzoic acid,

4-[7-(3,4-ethylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]phenylacetic acid.

Analogous reaction with 3,4-dichlorobenzylamine gives the following compounds

4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]butyric acid, m.p. 209°,

3-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]propionic acid,

5-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]valeric acid,

7-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]heptanoic acid,

2-{4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid,

4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]benzoic acid,

4-[7-(3,4-dichlorobenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]phenylacetic acid.

Analogous reaction with 3-chloro-4-ethoxybenzylamine gives the following the compounds

4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]butyric acid,

3-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]propionic acid,

5-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]valeric acid,

7-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]heptanoic acid,

2-{4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid,

4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]benzoic acid,

4-[7-(3-chloro-4-ethoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo-[4.3-d]pyrimidin-5-yl]phenylacetic acid.

Analogous reaction with 3-chloro-4-isopropoxybenzylamine gives the following compounds

4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyric acid,

3-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]propionic acid,

5-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]valeric acid,

7-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]heptanoic acid,

2-{4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohexyl-1-yl}acetic acid,

4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]cyclohexanecarboxylic acid,

4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-

pyrazolo[4.3-d]pyrimidin-5-yl]benzoic acid,

4-[7-(3-chloro-4-isopropoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]phenylacetic acid.

Example 7

Reaction analogously to Examples 1 and 2 gives the compound

[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]-pyrimidin-5-ylmethoxy]acetic acid, ethanolamine salt, m.p. 138°.

The examples below relate to pharmaceutical preparations:

Example A: Injection vials

A solution of 100 g of an active ingredient of the formula I and 5 g of disodium hydrogenphosphate in 3 l of bidistilled water is adjusted to pH 6.5 using 2N hydrochloric acid, sterile filtered, transferred into injection vials, lyophilised under sterile conditions and sealed under sterile conditions. Each injection vial contains 5 mg of active ingredient.

Example B: Suppositories

A mixture of 20 g of an active ingredient of the formula I is melted with 100 g of soya lecithin and 1400 g of cocoa butter, poured into moulds and allowed to cool. Each suppository contains 20 mg of active ingredient.

Example C: Solution

A solution is prepared from 1 g of an active ingredient of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2\ H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12\ H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of bidistilled water. The pH is adjusted to 6.8, and the solution is made up to 1 l and sterilised by irradiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active ingredient of the formula I are mixed with 99.5 g of Vaseline under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active ingredient of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed to give tablets in a conventional manner in such a way that each tablet contains 10 mg of active ingredient.

Example F: Coated tablets

Tablets are pressed analogously to Example E and subsequently coated in a conventional manner with a coating of sucrose, potato starch, talc, tragacanth and dye.

Example G: Capsules

2 kg of active ingredient of the formula I are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of the active ingredient.

Example H: Ampoules

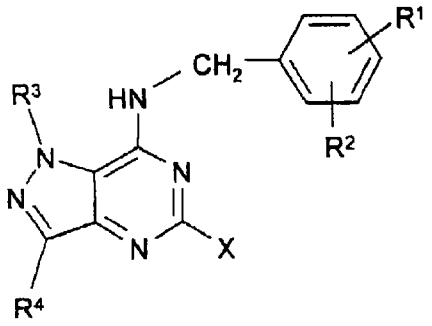
A solution of 1 kg of active ingredient of the formula I in 60 l of bidistilled water is sterile filtered, transferred into ampoules, lyophilised under sterile conditions and sealed under sterile conditions. Each ampoule contains 10 mg of active ingredient.

Example I: Inhalation spray

14 g of active ingredient of the formula I are dissolved in 10 l of isotonic NaCl solution, and the solution is transferred into commercially available spray containers with a pump mechanism. The solution can be sprayed into the mouth or nose. One spray shot (about 0.1 ml) corresponds to a dose of about 0.14 mg.

Patent claims

1. Compounds of the formula I



I

in which

R^1 and R^2 are each, independently of one another, H, A, OH, OA or Hal,

R^1 and R^2 together are alternatively alkylene having 3-5 carbon atoms, $-O-CH_2-CH_2-$, $-CH_2-O-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,

R^3 and R^4 are each, independently of one another, are H or A,

X is R^5, R^6 or R^7 which is monosubstituted by R^8,

R^5 is linear or branched alkylene having 1-10 carbon atoms, in which one or two CH_2 groups may be replaced by -CH=CH- groups, O, S or SO,

R^6 is cycloalkyl or cycloalkylalkylene having 5-12 carbon atoms,

R^7 is phenyl or phenylmethyl,

R^8 is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,

A is alkyl having from 1 to 6 carbon atoms, and

Hal is F, Cl, Br or I,

and their physiologically acceptable salts and solvates.

2. Compounds of the formula I according to Claim 1

(a) 5-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]pentanoic acid;

(b) 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]benzoic acid;

(c) 4-[7-(3,4-methylenedioxybenzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]pyrimidin-5-yl]butyric acid;

(d) 5-[7-(benzylamino)-1-methyl-3-propyl-1*H*-pyrazolo[4.3-d]-pyrimidin-5-yl]pentanoic acid;

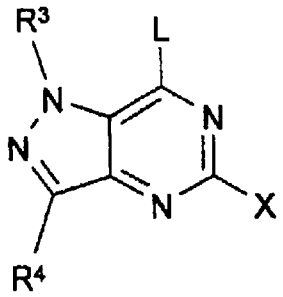
and their physiologically acceptable salts and solvates.

3. Process for the preparation

of compounds of the formula I according to Claim 1 and their salts,

characterised in that

a) a compound of the formula II



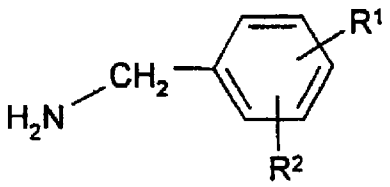
II

in which

R^3, R^4 and X are as defined in Claim 1,

and L is Cl, Br, OH, SCH_3 or a reactive esterified OH group,

is reacted with a compound of the formula III



III

in which

R^1 and R^2 are as defined,

or

b) a radical X in a compound of the formula I is converted into another radical X by, for example, hydrolysing an ester group to a COOH group or converting a COOH group into an amide or into a cyano group

and/or in that a compound of the formula I is converted into one of its salts.

4. Process for the preparation of pharmaceutical preparations, characterised in that a compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts and solvates is converted into a suitable dosage form together with at least one solid, liquid or semi-liquid excipient or assistant.

5. Pharmaceutical preparation, characterised by a content of at least one compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts and solvates.

6. Compounds of the formula I according to Claim 1 and their physiologically acceptable salts and solvates for combating disorders of the cardiovascular system and for the treatment and/or therapy of potency disorders.

7. Medicaments of the formula I according to Claim 1 and their physiologically acceptable salts and solvates as phosphodiesterase V

inhibitors.

8. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts and solvates for the preparation of a medicament.

9. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts and solvates for the preparation of a medicament for combating disorders of the cardiovascular system and for the treatment and/or therapy of potency disorders.