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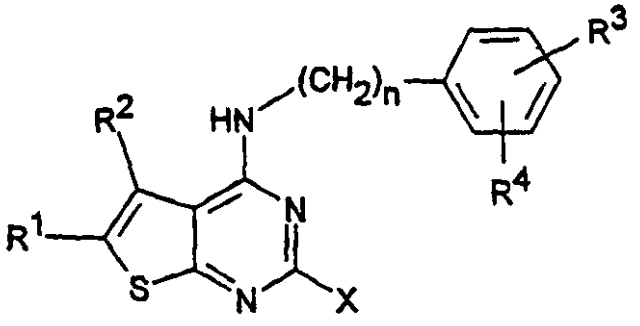
(54) Title: THIENOPYRIMIDINES

(54) Bezeichnung: THIENOPYRIMIDINE

(57) Abstract

The invention relates to thienopyrimidines of formula (I) wherein R^1, R^2, R^3, R^4, X and n have the meanings given in claim 1, and to their physiologically compatible salts. Said thienopyrimidines and their salts display a phosphodiesterase V-inhibition and can be used for treating diseases of the cardiovascular system and for treating and/or as a therapy for disturbances in potency.



(I)

(57) Zusammenfassung

Thienopyrimidine der Formel (I), sowie deren physiologisch unbedenklichen Salze, worin R^1, R^2, R^3, R^4, X und n die in Anspruch 1 angegebenen Bedeutungen haben, zeigen eine Phosphodiesterase V-Hemmung und können zur Behandlung von Erkrankungen des Herz-Kreislaufsystems und zur Behandlung und/oder Therapie von Potenzstörungen eingesetzt werden.

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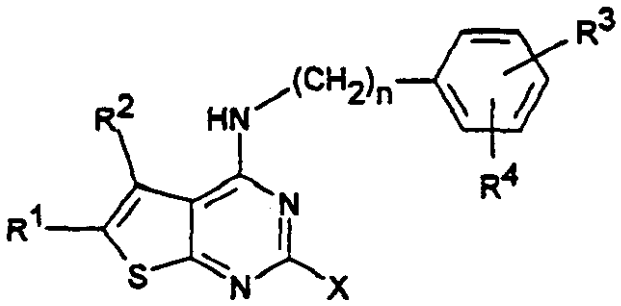
Thienopyrimidines

The invention relates to compounds of the formula I



I

in which

R^1, R^2 in each case independently of one another are H, A or Hal, where one of the radicals R^1 or R^2 is always ≠ H,

R^1 and R^2 together are also alkylene having 3-5 C atoms,

R^3, R^4 in each case independently of one another are H, A, OA or Hal,

R^3 and R^4 together are also alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,

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

R^5 is linear or branched alkylene having 1-10 C atoms, in which one or two CH_2 groups can be replaced by -CH=CH- groups, or
is $-C_6H_4-(CH_2)_m-$,

R^6 is cycloalkylalkylene having 6-12 C atoms,

R^7 is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,

A is alkyl having 1 to 6 C atoms,

Hal is F, Cl, Br or I,

m is 1 or 2,

and

n is 0, 1, 2 or 3,

and their physiologically acceptable salts.

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

The invention is based on the object of finding novel compounds having valuable properties, in particular those which can be used for the production of medicaments.

It has been found that the compounds of the formula I and their salts have very valuable pharmacological properties together with good tolerability.

In particular, they show a 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 such 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 ascertaining their IG_{50} values (concentration of the inhibitor which is needed in order to achieve a 50% inhibition of the enzyme activity).

To carry out the determinations, enzymes isolated by known methods can be used (e.g. W.J. Thompson et al., Biochem. 1971, 10, 311). To carry out the experiments,

a modified "batch" method of W.J. Thompson and M.M. Appleman (Biochem. 1979, 18, 5228) can be used.

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.

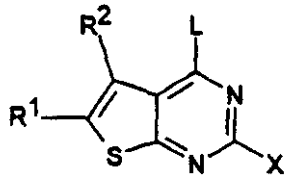
The compounds are effective as inhibitors of phenylephrine-induced contractions in cavernous body preparations of hares. This biological action can be demonstrated, for example, by the method which is described by F. Holmquist et al. in J. Urol., 150, 1310-1315 (1993).

The inhibition of the contraction shows 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 pharmaceutical active compounds in human and veterinary medicine. They can furthermore be employed as intermediates for the production of further pharmaceutical active compounds.

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, characterized in that

a) a compound of the formula II



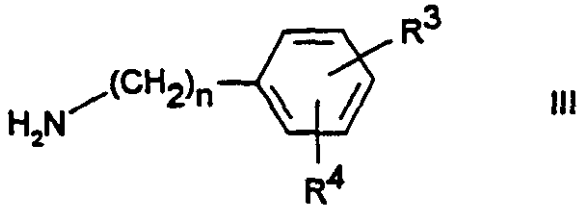
II

in which

R^1, R^2 and X have the meanings indicated,

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^3, R^4 and n have the meanings indicated,

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 by converting a compound of the formula I into one of its salts.

Above and below, the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7, X, L and n have the meanings indicated in the formulae I, II and III, if not expressly stated otherwise.

A is alkyl having 1-6 C atoms.

In the above formulae, alkyl is preferably unbranched and has 1, 2, 3, 4, 5 or 6 C 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 or R^6 radical which is monosubstituted by R^7.

R^5 is a linear or branched alkylene radical having 1-10, preferably 1-8, C atoms, the alkylene

radical preferably being, 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-ethylpropylene, 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-methylpropylene, 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.

R^6 is cycloalkylalkylene having 6-12 C atoms, preferably, for example, cyclopentylmethylene, cyclohexylmethylene, cyclohexylethylene, cyclohexylpropylene or cyclohexylbutylene.

One of the radicals R^1 and R^2 is preferably H, while the other is preferably propyl or butyl, but particularly preferably ethyl or methyl. Furthermore, R^1 and R^2 are also together preferably propylene, butylene or pentylene.

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

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

The radical R^7 is preferably, for example, COOH, $COOCH_3$, $COOC_2H_5$, $CONH_2$, $CON(CH_3)_2$, $CONHCH_3$ or CN.

It applies to the entire invention that all radicals which occur a number of times can be identical or different, i.e. are independent of one another.

Accordingly, the invention relates in particular to those 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 subformulae Ia to Id, which correspond to the formula I and in which the radicals not designated in greater detail have the meaning indicated in the formula I, but in which

in Ia X is R^5 or R^6, which is substituted by COOH or COOA;

in Ib R^1, R^2 in each case independently of one another are H, A or Hal, where at least one of the radicals R^1 and R^2 is always $\neq$ H,

R^3 and R^4 together are alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O$,

X is R^5 or R^6, which is substituted by COOH or COOA;

in Ic R^1, R^2 in each case independently of one another are H, A or Hal, where at least one of the radicals R^1 and R^2 is always $\neq$ H,

R^3, R^4 in each case independently of one another are H, A, OA or Hal,

R^3 and R^4 together are alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O$,

X is R^5 or R^6, which is substituted by COOH or COOA,

n is 1 or 2,

in Id R^1, R^2 in each case independently of one another are H, A or Hal, where one of the radicals R^1 and R^2 is always $\neq$ H,

R^1 and R^2 together are also alkylene having 3-5 C atoms,

R^3, R^4 in each case independently of one another are H, A, OA or Hal,

R^3 and R^4 together are also $-O-CH_2-O-$,
X is R^5 which is monosubstituted by R^7,
R^5 is linear or branched alkylene having 1 to 10 C atoms, or
$-C_6H_4-CH_2-$,
R^7 is COOH or COOA,
A is alkyl having 1 to 6 C atoms,
Hal is F, Cl, Br or I,
m is 1 and
n is 1 or 2.

The compounds of the formula I and also the starting substances for their preparation are otherwise prepared by methods known per se, such as are described in the literature (e.g. in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), namely under reaction conditions which are known and suitable for the reactions mentioned. Use can also be made in this case of variants which are known per se, which are not mentioned here in greater detail.

In the compounds of the formula II or III, R^1, R^2, R^3, R^4, X and n 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 C atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (preferably phenyl- or p-tolylsulfonyloxy, furthermore also 2-naphthalene-sulfonyloxy)).

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 substances can also be formed in situ such that they are not isolated from the reaction mixture, but immediately reacted further to give the compounds of the formula I.

On the other hand, it is possible to carry out the reaction stepwise.

As a rule, the starting compounds of the formulae II and III are known. If they are not known, they can be prepared by methods known per se.

Compounds of the formula II can be obtained, for example, by reaction with $POCl_3$ of compounds which are synthesized from thiophene derivatives and CN-substituted alkylenecarboxylic acid esters (Eur. J. Med. Chem. 23, 453 (1988)).

In detail, the reaction of the compounds of the formula II with the compounds of the formula III is carried out in the presence or absence of an inert solvent at temperatures between approximately -20 and approximately 150°, preferably between 20 and 100°.

The addition of an acid-binding agent, for example of an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or of another salt of a weak acid of the alkali metals 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 of an excess of the amine component, can 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 (methyl glycol or ethyl glycol), 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, in a compound of the formula I, to convert a radical X into another radical X, e.g. 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°C.

Carboxylic acids can be converted into the corresponding carbonyl chlorides, for example, using thionyl chloride and these can be converted into carboxamides. Carbonitriles are obtained from these by elimination of water in a known manner.

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 of the base in an inert solvent such as ethanol and subsequent evaporation. Possible bases for this reaction are those which yield physiologically acceptable salts.

Thus the acid of the formula I can be converted into the corresponding metal salt, in particular alkali metal or alkaline earth metal salt, or into the corresponding ammonium salt using a base (e.g. sodium or potassium hydroxide or carbonate).

Possible bases for this reaction are, in particular, also organic bases which yield 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 of the acid in an inert solvent such as ethanol and subsequent evaporation. Possible acids for this reaction are in particular those which yield physiologically acceptable salts. Thus inorganic acids can be used, e.g. sulfuric acid, nitric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, sulfamic acid, furthermore organic acids, in particular aliphatic, alicyclic,

araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, e.g. 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, laurylsulfuric acid. Salts with physiologically unacceptable acids, e.g. picrates, can be used for the isolation and/or purification of 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 production of pharmaceutical preparations, in particular in a non-chemical way. In this case, they can be brought into a suitable dose form together with at least one solid, liquid and/or semi-liquid excipient or auxiliary and, if appropriate, in combination with one or more further active compounds.

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

These preparations can be used as pharmaceuticals in human or veterinary medicine. Possible excipients are organic or inorganic substances which are suitable for enteral (e.g. oral) or parenteral administration or topical application and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glyceryl triacetates, gelatin, carbohydrates such as lactose or starch, magnesium

stearate, talc, petroleum jelly. Tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops are used, in particular, for oral administration, suppositories are used for rectal administration, solutions, preferably oily or aqueous solutions, furthermore suspensions, emulsions or implants, are used for parenteral administration, and ointments, creams or powders are used for topical application. The novel compounds can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations. The preparations indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants, flavourings and/or one or more further active compounds, e.g. one or more vitamins.

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

In this case, as a rule the substances are preferably administered in doses of between approximately 1 and 500 mg, in particular between 5 and 100 mg, per dose unit. The daily dose is preferably between approximately 0.02 and 10 mg/kg of body weight. The specific dose for each patient depends, however, on all sorts 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 route of administration, and on the excretion rate, pharmaceutical combination and severity of the respective disorder to which the therapy applies. Oral administration is preferred.

Above and below, all temperatures are indicated in °C. In the following examples, "customary working up" means: water is added, if necessary, the mixture is adjusted, if necessary, to pHs of between 2 and 10 depending on the constitution of the final product and extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate and evaporated, and the residue is purified by chromatography on silica gel and/or by crystallization.

Mass spectrometry (MS): EI (electron impact ionization) M^+

FAB (fast atom bombardment) $(M+H)^+$

Example 1

1.9 g of methyl 3-(4-chloro-5,6,7,8-tetrahydro-[1]benzothieno[2,3-d]pyrimidin-2-yl)propionate [obtainable by cyclization of methyl 2-amino-4,5,6,7-tetrahydrobenzothiophene-3-carboxylate with methyl 3-cyanopropionate and subsequent chlorination with phosphorus oxychloride/dimethylamine] and 2.3 g of 3-chloro-4-methoxybenzylamine ("A") in 20 ml of N-methylpyrrolidone are stirred at 110° for 5 hours. The solvent is removed and worked up in the customary manner. 2.6 g of methyl 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno-[2,3-d]pyrimidin-2-yl]propionate are obtained as a colourless oil.

The following are obtained analogously by reaction of "A"

with methyl 3-(4-chloro-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-5,6-dimethylthieno[2,3-d]-pyrimidin-2-yl)propionate

methyl 3-[4-(3-chloro-4-methoxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4,6-dichlorothieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 2-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)acetate

methyl 2-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]acetate.

The following are obtained analogously by reaction of 3,4-methylenedioxybenzylamine

with methyl 3-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]propionate

with methyl 3-(4-chloro-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-5,6-cycloheptenо[1]benzothieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-[4-(3,4-methylenedioxybenzylamino)-5,6-cycloheptenо[1]benzothieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno-[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno-[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]propionate;

with methyl 3-(4,6-dichlorothieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]propionate.

The following are obtained analogously by reaction of "A"

with methyl 4-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 4-(4-chloro-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 4-(4-chloro-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 4-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 4-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3-chloro-4-methoxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 4-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 4-(4,6-chloro-6-chlorothieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]butyrate.

The following are obtained analogously by reaction of 3,4-methylenedioxybenzylamine

with methyl 4-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 4-(4-chloro-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl)butyrate;

methyl 4-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 4-(4-chloro-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 4-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 4-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 4-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]butyrate;

with methyl 4-(4,6-dichlorothieno[2,3-d]pyrimidin-2-yl)butyrate

methyl 4-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]butyrate.

The following are obtained analogously by reaction of "A"

with methyl 5-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno-[2,3-d]pyrimidin-2-yl)valerate
methyl 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4-chloro-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl)valerate
methyl 5-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]valerate

with methyl 5-(4-chloro-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl)valerate
methyl 5-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]valerate

with methyl 5-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)valerate
methyl 5-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4-chloro-5,6-dimethylthieno-[2,3-d]-2-yl)valerate
methyl 5-[4-(3-chloro-4-methoxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)valerate
methyl 5-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4,6-dichlorothieno[2,3-d]pyrimidin-2-yl)valerate

methyl 5-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]valerate.

The following are obtained analogously by reaction of 3,4-methylenedioxybenzylamine

with methyl 5-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)valerate
methyl 5-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4-chloro-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl)valerate
methyl 5-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4-chloro-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl)valerate
methyl 5-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)valerate
methyl 5-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)valerate
methyl 5-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]valerate

with methyl 5-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)valerate
methyl 5-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 5-(4,6-dichlorothieno[2,3-d]pyrimidin-2-yl)valerate

methyl 5-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]valerate.

The following are obtained analogously by reaction of "A"

with methyl 7-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)heptanoate

methyl 7-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl)heptanoate

methyl 7-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl)heptanoate

methyl 7-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)heptanoate

methyl 7-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)heptanoate

methyl 7-[4-(3-chloro-4-methoxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)heptanoate

methyl 7-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-6-chlorothieno[2,3-d]pyrimidin-2-yl)heptanoate
methyl 7-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]heptanoate.

The following are obtained analogously by reaction with 3,4-methylenedioxybenzylamine

with methyl 7-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)heptanoate
methyl 7-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl)heptanoate
methyl 7-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl)heptanoate
methyl 7-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)heptanoate
methyl 7-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]valerate;

with methyl 7-(4-chloro-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl)heptanoate
methyl 7-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)heptanoate

methyl 7-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]heptanoate;

with methyl 7-(4,6-dichlorothieno[2,3-d]pyrimidin-2-yl)heptanoate

methyl 7-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]heptanoate.

The following are obtained analogously by reaction of "A"

with methyl 2-[4-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)cyclohex-1-yl]acetate

methyl 2-{4-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]cyclohex-1-yl}acetate;

with methyl 2-[4-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)cyclohex-1-yl]acetate

methyl 2-{4-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]cyclohex-1-yl}acetate.

The following are obtained analogously by reaction of 3,4-methylenedioxybenzylamine

with methyl 2-[4-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)cyclohex-1-yl]acetate

methyl 2-{4-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]cyclohex-1-yl}acetate.

The following are obtained analogously by reaction of benzylamine

with methyl 3-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)propionate

methyl 3-(4-benzylamino-5,6,7,8-tetrahydro[1]-benzothieno[2,3-d]pyrimidin-2-yl)propionate;

with methyl 4-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)butyrate
methyl 4-(4-benzylamino-5,6,7,8-tetrahydro[1]-benzothieno[2,3-d]pyrimidin-2-yl)butyrate;

with methyl 5-(4-chloro-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)valerate
methyl 5-(4-benzylamino-5,6,7,8-tetrahydro[1]-benzothieno[2,3-d]pyrimidin-2-yl)valerate;

with methyl 4-(4-chloro-6-methylthieno[2,3-d]pyrimidin-2-yl)butyrate
methyl 4-(4-benzylamino-6-methylthieno[2,3-d]pyrimidin-2-yl)butyrate;

with methyl 5-(4-chloro-6-ethylthieno[2,3-d]pyrimidin-2-yl)valerate
methyl 5-(4-benzylamino-6-ethylthieno[2,3-d]pyrimidin-2-yl)valerate.

Example 2

2.2 g of methyl 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]propionate are dissolved in 20 ml of ethylene glycol monomethyl ether and, after addition of 10 ml of 32% NaOH solution, the mixture is stirred at 110° for 5 hours. After addition of 20% HCl, it is extracted with dichloromethane. By addition of petroleum ether, 2.0 g of 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno-[2,3-d]pyrimidin-2-yl]propionic acid, m.p. 229° are obtained.

The deposited crystals are dissolved in 30 ml of isopropanol and treated with 0.5 g of ethanolamine. After crystallization, 1.35 g of 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-

tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]propionic acid, ethanolamine salt, m.p. 135° are obtained.

The carboxylic acids below are obtained analogously from the esters listed under Example 1:

3-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]propionic acid;

3-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]propionic acid;

3-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]propionic acid;

3-[4-(3-chloro-4-methoxybenzylamino)-5,6-methylthieno[2,3-d]pyrimidin-2-yl]propionic acid;

3-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]propionic acid;

3-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]propionic acid;

2-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]acetic acid, ethanolamine salt, m.p. 126°;

3-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]propionic acid;

3-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]propionic acid;

3-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]propionic acid;

3-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]propionic acid;

3-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]propionic acid;

3-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]propionic acid;

3-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]propionic acid;

4-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]butyric acid;

4-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]butyric acid;

4-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]butyric acid;

4-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p. 142°;

4-[4-(3-chloro-4-methoxybenzylamino)-5,6-methylthieno[2,3-d]pyrimidin-2-yl]butyric acid;

4-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p. 170°;

4-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]butyric acid;

4-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p. 114°;

4-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]butyric acid;

4-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]butyric acid;

4-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p. 170°;

4-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]butyric acid;

4-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]butyric acid;

4-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]butyric acid;

5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]valeric acid, m.p. 165°; ethanolamine salt, m.p. 112°;

5-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]valeric acid;

5-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]valeric acid;

5-[4-(3-chloro4-methoxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 156°;

5-[4-(3-chloro-4-methoxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]valeric acid;

5-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 156°;

5-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]valeric acid;

5-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]valeric acid;

5-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]valeric acid;

5-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]valeric acid;

5-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 167°;

5-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]valeric acid;

5-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]valeric acid;

5-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]valeric acid;

7-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid, ethanolamine salt, m.p. 130°;

7-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid

7-[4-(3-chloro-4-methoxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

7-[4-(3-chloro-4-methoxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

7-[4-(3-chloro-4-methoxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

7-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

7-[4-(3-chloro-4-methoxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

7-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid, ethanolamine salt, m.p. 137°;

7-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclopenteno[1]benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

7-[4-(3,4-methylenedioxybenzylamino)-5,6-cyclohepteno[1]benzothieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

7-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

7-[4-(3,4-methylenedioxybenzylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

7-[4-(3,4-methylenedioxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]valeric acid;

7-[4-(3,4-methylenedioxybenzylamino)-6-chlorothieno[2,3-d]pyrimidin-2-yl]heptanoic acid;

2-{4-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl}acetic acid;

2-{4-[4-(3-chloro-4-methoxybenzylamino)-6-ethylthieno[2,3-d]pyrimidin-2-yl]cyclohexyl}acetic acid;

2-{4-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]cyclohexyl}acetic acid;

3-(4-benzylamino-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]propionic acid, ethanolamine salt, m.p. 126°;

4-(4-benzylamino-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p. 133°;

4-(4-benzylamino-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p. 133°;

5-(4-benzylamino-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 135°;

4-[4-benzylamino-6-methylthieno[2,3-d]pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p. 165°;

5-[4-benzylamino-6-ethylthieno[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 162°.

Example 3

1 equivalent of 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro [1]benzothieno-[2,3-d]pyrimidine-2-yl]propionic acid and 1.2 equivalents of thionyl chloride are stirred in dichloromethane for 2 hours. The solvent is removed and 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidine-2-yl]propionyl chloride is obtained.

This is transferred to aqueous ammonia, the mixture is stirred for one hour and, after customary working up, 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidine-2-yl]propionamide is obtained.

Example 4

1 equivalent of DMF and 1 equivalent of oxalyl chloride are dissolved in acetonitrile at 0°. 1 equivalent of 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidine-2-yl]propionamide is then added. The mixture is stirred for one hour. After customary working up, 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]-benzothieno[2,3-d]pyrimidine-2-yl]propionitrile is obtained.

Example 5

The compounds below are obtained analogously to Examples 1 and 2

6-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]hexanoic acid, m.p. 165°;

2-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]propionic acid, ethanolamine salt, m.p. 150°;

4-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]-2,2-dimethylbutyric acid, ethanolamine salt, m.p. 130°;

4-[4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]-2,2-dimethylbutyric acid, ethanolamine salt, m.p. 126°;

5-[4-(3-chloro-4-hydroxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]valeric acid, m.p. 179°;

5-[4-(3,4-dichlorobenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 136°;

5-[4-(3-chloro-4-isopropyloxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]valeric acid, ethanolamine salt, m.p. 118°;

2-[4-(4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)phenyl]acetic acid, ethanolamine salt, m.p. 119°;

2-[4-(4-(3,4-methylenedioxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl)phenyl]acetic acid, m.p. 214.

The following examples relate to pharmaceutical preparations:

Example A: Injection vials

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogenphosphate is adjusted to pH 6.5 with 2 N hydrochloric acid in 3 l of double-distilled water, sterile filled, dispensed into injection vials, lyophilized under sterile conditions and aseptically sealed. Each injection vial contains 5 mg of active compound.

Example B: Suppositories

A mixture of 20 g of active compound of the formula I is fused 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 compound.

Example C: Solution

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

Example D: Ointment

500 mg of an active compound of the formula I are mixed with 99.5 g of petroleum jelly under aseptic conditions.

Example E: Tablets

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

Example F: Coated tablets

Analogously to Example E, tablets are pressed, which are then coated in a customary manner with a coating of sucrose, potato starch, talc, tragacanth and colourant.

Example G; Capsules

2 kg of active compound of the formula I are dispensed into hard gelatin capsules in a customary manner, such that each capsule contains 20 mg of the active compound.

Example H: Ampoules

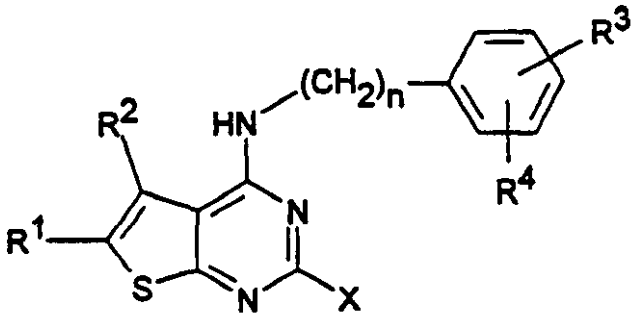
A solution of 1 kg of active compound of the formula I in 60 l of double-distilled water is sterile-filtered, dispensed into ampoules, lyophilized under sterile conditions and aseptically sealed. Each ampoule contains 10 mg of active compound.

Example I: Inhalation spray

14 g of active compound of the formula I are dissolved in 10 l of isotonic NaCl solution and the solution is dispensed into commercially available spray containers having a pump mechanism. The solution can be sprayed into the mouth or the nose. One burst of spray (approximately 0.1 ml) corresponds to a dose of approximately 0.14 mg.

Patent Claims

1. Compounds of the formula I



I

in which

R^1, R^2 in each case independently of one another are H, A or Hal, where one of the radicals R^1 or R^2 is always ≠ H,

R^1 and R^2 together are also alkylene having 3-5 C atoms,

R^3, R^4 in each case independently of one another are H, A, OA or Hal,

R^3 and R^4 together are also alkylene having 3-5 C atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,

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

R^5 is linear or branched alkylene having 1-10 C atoms, in which one or two CH_2 groups can be replaced by -CH=CH- groups, or is $-C_6H_4-(CH_2)m-$,

R^6 is cycloalkylalkylene having 6-12 C atoms,

R^7 is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,

A is alkyl having 1 to 6 C atoms,

(h) 4-[4-(3,4-Methylendioxy-benzylamino)-6-methyl-thieno-[2,3-d]-pyrimidin-2-yl]-buttersäure;

(i) 2-{4-[4-(3-Chlor-4-methoxy-benzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]-cyclohexyl-1-yl}-essigsäure;

(k) 5-[4-(3,4-Methylendioxy-benzylamino)-6-methyl-thieno-[2,3-d]-pyrimidin-2-yl]-valeriansäure;

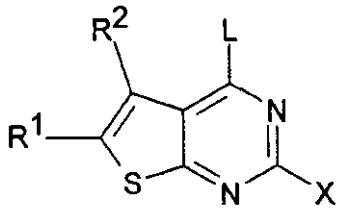
sowie deren physiologisch unbedenklichen Salze.

3. Verfahren zur Herstellung

von Verbindungen der Formel I nach Anspruch 1 sowie deren Salzen,

dadurch gekennzeichnet, daß man

a) eine Verbindung der Formel II



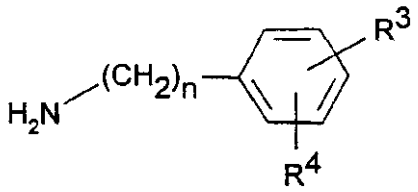
II

worin

R^1, R^2 und X die angegebenen Bedeutungen haben,

und L Cl, Br, OH, SCH_3 oder eine reaktionsfähige veresterte OH-Gruppe bedeutet,

mit einer Verbindung der Formel III



III

worin

R^3, R^4 und n die angegebenen Bedeutungen haben,

umsetzt,

oder

b) in einer Verbindung der Formel I einen Rest X in einen anderen Rest X umwandelt, indem man z.B. eine Estergruppe zu einer COOH-Gruppe hydrolysiert oder eine COOH-Gruppe in ein Amid oder in eine Cyangruppe umwandelt

und/oder daß man eine Verbindung der Formel I in eines ihrer Salze überführt.

4. Verfahren zur Herstellung pharmazeutischer Zubereitungen, dadurch gekennzeichnet, daß man eine Verbindung der Formel I nach Anspruch 1 und/oder eines ihrer physiologischen unbedenklichen Salze zusammen mit mindestens einem festen, flüssigen oder halbflüssigen Träger- oder Hilfsstoff in eine geeignete Dosierungsform bringt.

5. Pharmazeutische Zubereitung, gekennzeichnet durch einen Gehalt an mindestens einer Verbindung der Formel I nach Anspruch 1 und/oder einem ihrer physiologisch unbedenklichen Salze.

6. Verbindungen der Formel I nach Anspruch 1 und ihre physiologisch unbedenklichen Salze zur Bekämpfung von Krankheiten des Herz-Kreislaufsystems und zur Behandlung und/oder Therapie von Potenzstörungen.

7. Arzneimittel der Formel I nach Anspruch 1 und ihre physiologisch unbedenklichen Salze als Phosphodiesterase V-Hemmer.

8. Verwendung von Verbindungen der Formel I nach Anspruch 1 und/oder ihre physiologisch unbedenklichen Salze zur Herstellung eines Arzneimittels.

9. Verwendung von Verbindungen der Formel I nach Anspruch 1 und/oder ihrer physiologisch unbedenklichen Salze bei der Bekämpfung von Krankheiten.

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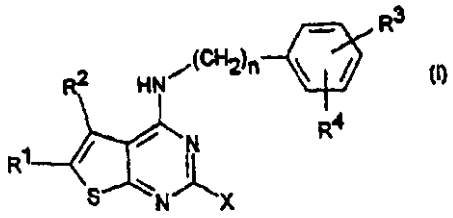
[54]发明名称 噻吩并嘧啶类

[57]摘要

本发明涉及式I的噻吩并嘧啶类及其生理上可接受的盐,其中R^1,R^2,R^3,R^4,X和n定义如权利要求1。所述噻吩并嘧啶类及其盐显示抑制磷酸二酯酶-V并可以被用于治疗心血管系统疾病和治疗和/或治愈性交障碍。



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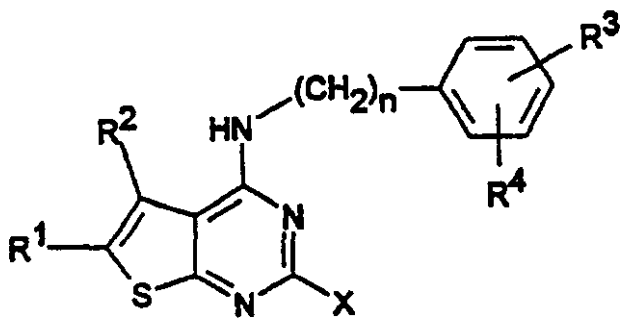
权　利　要　求　书

1. 式 I 化合物及其生理上可接受的盐



I

其中

R^1，R^2在每种情况下彼此独立地是 H，A 或 Hal，其中基团 R^1或 R^2之一总不为 H，

R^1和 R^2还一起是具有 3－5 个 C 原子的亚烷基，

R^3，R^4在每种情况下彼此独立地是 H，A，OA 或 Hal，

R^3和 R^4还一起是具有 3－5 个 C 原子的亚烷基，$-O-CH_2-CH_2-$，$-O-CH_2-O-$或$-O-CH_2-CH_2-O-$，

X 是 R^5或 R^6，其被 R^7单取代，

R^5是具有 1－10 个 C 原子的直链或支链亚烷基，其中一个或两个 CH_2基团可以被-CH=CH-基团取代，或者是$-C_6H_4-(CH_2)_m-$，

R^6是具有 6－12C 原子的环烷基亚烷基，

R^7是 COOH，COOA，CONH2，CONHA，$CON(A)_2$或 CN，

A 是具有 1－6 个 C 原子的烷基，

Hal 是 F，Cl，Br，或 I，

m 是 1 或 2，及

n 是 0，1，2 或 3.

2. 根据权利要求 1 的式 I 化合物及其生理上可接受的盐

(a) 3－[4－（3－氯－4－甲氧基苄氨基）－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基]丙酸；

(b) 4－[4－（3，4－亚甲基二氧基苄氨基）－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基]丁酸；

(c) 7－[4－（3，4－亚甲基二氧基苄氨基）－5，6，7，8－四

氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]庚酸;

(d) 7-[4-(3-氯-4-甲氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]庚酸;

(e) 5-[4-(3-氯-4-甲氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]戊酸;

(f) 5-[4-(3-氯-4-甲氧基苄氨基)-6-甲基噻吩并[2,3-d]嘧啶-2-基]戊酸;

(g) 4-[4-(3-氯-4-甲氧基苄氨基)-6-甲基噻吩并[2,3-d]嘧啶-2-基]丁酸;

(h) 4-[4-(3,4-亚甲基二氧基苄氨基)-6-甲基噻吩并[2,3-d]嘧啶-2-基]丁酸;

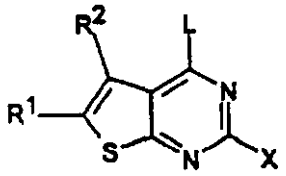
(i) 2-{4-[4-(3-氯-4-甲氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]环己-1-基}乙酸;

(k) 5-[4-(3,4-亚甲基二氧基苄氨基)-6-甲基噻吩并[2,3-d]嘧啶-2-基]戊酸.

3. 制备根据权利要求1的式I化合物及其盐的方法,

其特征在于

a) 式II化合物

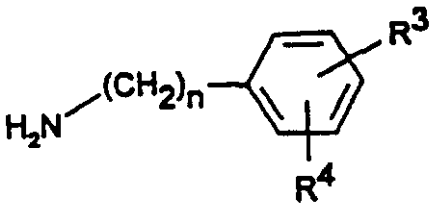


II

其中 R^1, R^2 和 X 如上定义,

及 L 是 Cl, Br, OH, SCH_3 或活性酯化的 OH 基团,

与式III化合物反应



III

其中 R^3，R^4和 n 定义如上，或

b）在式 I 化合物中的基团 X 被转化为另一个基团 X，例如，通过水解酯基为 COOH 基团或将 COOH 基团转化为酰胺或氰基和/或将式 I 化合物转化为其一种盐。

4. 制备药物制剂的方法，其特征在于将根据权利要求 1 的式 I 化合物和/或其一种生理上可接受的盐与至少一种固体、液体或半固体赋形剂或佐剂制成适当的剂型。

5. 药物制剂，其特征在于其至少含有一种根据权利要求 1 的式 I 化合物和/或其一种生理上可接受的盐。

6. 根据权利要求 1 的式 I 化合物及其生理上可接受的盐用于控制心血管系统疾病和治疗和/或治愈性交障碍。

7. 根据权利要求 1 的式 I 化合物及其生理上可接受的盐用作磷酸二酯酶抑制剂的药物。

8. 根据权利要求 1 的式 I 化合物和/或其生理上可接受的盐在制备药物中的用途。

9. 根据权利要求 1 的式 I 化合物和/或其生理上可接受的盐在控制疾病中的用途。

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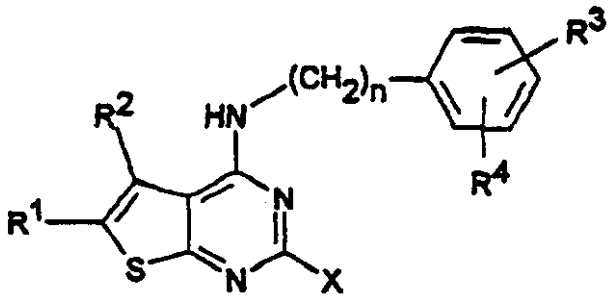
说　明　书

噻吩并嘧啶类

本发明涉及式 I 化合物及其生理上可接受的盐



I

其中

R^1，R^2在每种情况下彼此独立地是 H，A 或 Hal，其中基团 R^1或 R^2之一总不为 H，

R^1和 R^2还一起是具有 3－5 个 C 原子的亚烷基，

R^3，R^4在每种情况下彼此独立地是 H，A，OA 或 Hal，

R^3和 R^4还一起是具有 3－5 个 C 原子的亚烷基，$-O-CH_2-CH_2-$，$-O-CH_2-O-$或$-O-CH_2-CH_2-O-$，

X 是 R^5或 R^6，其被 R^7单取代，

R^5是具有 1－10 个 C 原子的直链或支链亚烷基，其中一个或两个 CH_2基团可以被-CH=CH-基团取代，或者是$-C_6H_4-(CH_2)_m-$，

R^6是具有 6－12C 原子的环烷基亚烷基，

R^7是 COOH，COOA，$CONH_2$，CONHA，$CON(A)_2$或 CN，

A 是具有 1－6 个 C 原子的烷基，

Hal 是 F，Cl，Br，或 I，

m 是 1 或 2，及

n 是 0，1，2 或 3.

嘧啶衍生物已经被公开，例如在 EP 201188 或 WO93/06104 中.

本发明基于发现具有有价值的性质的新化合物为目的，特别是可以被用于生产药物的新化合物为目的.

已经发现式 I 化合物及其盐具有非常有价值的药理学性质，同时

具有良好的耐受性.

特别地，它们显示对 cGMP 磷酸二酯酶（PDE V）的特殊抑制.

已经公开喹唑啉类具有 cGMP 磷酸二酯酶抑制活性，例如在《药物化学》(J. Med. Chem.)，36，3765（1993）及出处同上，37，2106（1994）中描述的.

式 I 化合物的生物活性可以通过如在 WO93/06104 中描述的方法测定.本发明化合物对 cGMP 和 cAMP 磷酸二酯酶的亲和力通过测定其 IG_{50} 值（为了得到 50% 抑制酶活性需要的抑制剂的浓度）来确定.

为了进行这种测定，可以使用已知方法(例如 W.J. Thompson 等人,Biochem. 1971,10,311)分离的酶. 为了进行这种实验，可以使用 W.J. Thomson 和 M.M. Appleman(Biochem. 1979, 18, 5228)改进的“分批”方法.

因此，本发明化合物适于治疗心血管系统疾病，特别是心机能不全，及治疗性交疾病（勃起机能障碍）.

取代的吡唑并嘧啶酮类用于治疗阳痿的用途已经公开，例如在 WO94/28902 中.

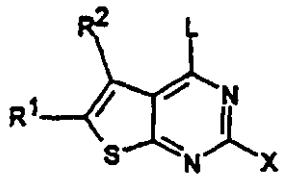
本发明化合物作为野兔海绵体标本的苯福林诱发的收缩的抑制剂是有效的. 这种生物作用可以被证明，例如，通过 F. Holmquist 等人在 J. Urol.，150，1310－1315（1993）中描述的方法证明.

抑制收缩说明本发明化合物用于治愈(therapy)和/或治疗(treatment)性交疾病是有效的.

式 I 化合物可以药物活性化合物在人和兽医药物中被使用. 它们还可以作为生产进一步的药物活性化合物的中间体被使用.

因此，本发明涉及根据权利要求 1 的式 I 化合物及制备式 I 化合物及其盐的方法，其特征在于

a) 式 II 化合物

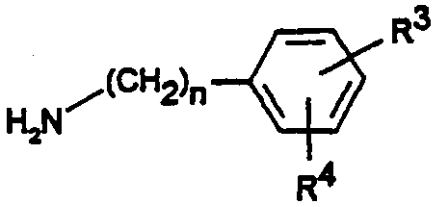


II

其中 R^1，R^2 和 X 如上定义，

及 L 是 Cl，Br，OH，SCH_3 或活性酯化的 OH 基团，

与式 III 化合物反应



III

其中 R^3，R^4 和 n 定义如上，或

b）在式 I 化合物中的基团 X 被转化为另一个基团 X，例如，通过水解酯基为 COOH 基团或将 COOH 基团转化为酰胺或氰基

和/或将式 I 化合物转化为其一种盐。

上文和下文中，如果没有特别指出，基团 R^1，R^2，R^3，R^4，R^5，R^6，R^7，X，L 和 n 定义如在式 I，II 和 III 中所述。

A 是具有 1－6 个 C 原子的烷基。

在上述式中，烷基优选是直链并具有 1，2，3，4，5 或 6 个 C 原子的烷基，其优选甲基，乙基或丙基，进一步优选异丙基，丁基，异丁基，仲丁基或叔丁基，但是还优选正戊基，新戊基，异戊基或己基。

X 是被 R^7 单取代的 R^5 或 R^6 基团。

R^5 是直链或支链具有 1－10 个，优选 1－8 个 C 原子的亚烷基，亚烷基优选，例如亚甲基，亚乙基，亚丙基，亚异丙基，亚丁基，亚异丁基，亚仲丁基，亚戊基，1－，2－或 3－甲基亚丁基，1，1－，1，2－或 2，2－二甲基亚丙基，1－乙基亚丙基，亚己基，1－，2－，3－，或 4－甲基亚戊基，1，1－，1，2－，1，3－，2，2－，2，3－或 3，3－二甲基亚丁基，1－或 2－乙基亚丁基，1－乙基－1－甲基亚丙基，1－乙基－2－甲基亚丙基，1，1，2－或 1，2，2－三甲基亚丙基，直链或支链亚庚基，亚辛基，亚壬基或亚癸基。R^5 还是，例如亚丁－2－烯基或亚己－3－烯基。

R^6 是具有 6－12 个 C 原子的环烷基亚烷基，其优选，例如环戊基亚甲基，环己基亚甲基，环己基亚乙基，环己基亚丙基或环己基亚丁基。

基团 R^1 和 R^2 之一优选 H，另一个优选丙基或丁基，但是特别优选

乙基或甲基. R^1和R^2还一起优选亚丙基，亚丁基或亚戊基.

Hal 优选 F，Cl 或 Br，但也包括 I.

R^3和R^4可以相同或不同并且优选在苯环的 3- 或 4- 位. 它们是，例如，在每一种情况它们彼此独立地是 H，烷基，F，Cl，Br 或 I 或一起是亚烷基，例如，亚丙基，亚丁基或亚戊基，还有亚乙氧基，亚甲基二氧基或亚乙基二氧基. 在每种情况它们还优选是烷氧基，例如甲氧基，乙氧基或丙氧基.

基团 R^7优选，例如 COOH，$COOCH_3$，$COOC_2H_5$，$CONH_2$，$CON(CH_3)_2$，$CONHCH_3$或 CN.

出现多次的所有基团中可以相同或不同，即彼此相互独立，这将适用整个发明.

因此，本发明特别涉及其中至少上述基团之一具有上述优选含义之一的那些式 I 化合物. 一些组优选的化合物可以由下列子通式 Ia 至 Id 表示，其相应式 I，并且其中没有特别详细指定的基团具有式 I 中的含义，但是其中

在 Ia 中，X 是被 COOH 或 COOA 取代 R^5或 R^6;

在 Ib 中，在每一种情况中 R^1，R^2相互独立地是 H，A 或 Hal，其中至少基团 R^1和 R^2之一总不为 H，

R^3和 R^4一起是具有 3- 5 个 C 原子的亚烷基，$-O-CH_2-CH_2-$，$-O-CH_2-O-$或$-O-CH_2-CH_2-O$，

X 是被 COOH 或 COOA 取代的 R^5或 R^6;

在 Ic 中，R^1，R^2在每一种情况中相互独立地是 H，A 或 Hal，其中至少基团 R^1和 R^2之一总不为 H，

R^3，R^4在每一种情况中相互独立地是 H，A，OA 或 Hal，

R^3和 R^4一起是具有 3- 5 个 C 原子的亚烷基，$-O-CH_2-CH_2-$，$-O-CH_2-O-$或$-O-CH_2-CH_2-O$，

X 是被 COOH 或 COOA 取代的 R^5或 R^6;

n 是 1 或 2，

在 Id 中，R^1，R^2在每一种情况中相互独立地是 H，A 或 Hal，其中基团 R^1和 R^2之一总不为 H，

R^1和 R^2一起还是具有 3- 5 个 C 原子的亚烷基，

R^3，R^4在每一种情况中相互独立地是 H，A，OA 或 Hal，

R^3和R^4一起还是-O-CH_2-O-，

X是被R^7单取代的R^5；

R^5是直链或支链具有1-10个C原子的亚烷基，或-C_6H_4-CH_2-

R^7是COOH或COOA，

A是具有1-6个C原子的烷基，

Hal是F，Cl，Br或I，

m是1，及

n是1或2.

式I化合物及制备它们的起始原料是通过本身已知方法制备的，如在文献中描述的方法（例如在标准著作中如Houben-Weyl,Methoden Der Organischen Chemie[Methods of Organic Chemistry]，Georg-Thieme-Verlag，Stuttgart），即在已知的及适用上述反应的反应条件下．在这种情况下，同样可以使用本身已知的变体，这里不详细说明．

在式II或III化合物中，R^1，R^2，R^3，R^4，X和n定义如上，特别是所述优选定义．

如果L是活性酯化OH基团，其优选具有1-6个C原子的烷基磺酰氧基（优选甲基磺酰氧基）或具有6-10个碳原子的芳基磺酰氧基（优选苯基或对甲苯磺酰氧基，还优选2-萘磺酰氧基）．

式I化合物优选通过式II化合物与式III化合物反应获得．

如果需要，起始原料还可以就地制备以便它们不从反应混合物中被分离，但是应立即反应以进一步得到式I化合物．

另一方面，可以进行分步反应．

通常，起始化合物式II和III是已知的．如果它们是未知的，可以通过本身已知的方法制备它们．

式II化合物可以被获得，例如通过从噻吩衍生物合成的化合物$POCl_3$与CN-取代的亚烷基羧酸酯反应获得（Eur. J. Med. Chem. 23, 453(1988)）．

详细地，式II化合物与式III化合物的反应在有或没有惰性溶剂的存在下在温度约-20℃至约150℃之间，优选20至100℃之间进行．

加入酸结合剂，例如碱金属或碱土金属氢氧化物、碳酸盐或碳酸

氢盐或碱金属或碱土金属优选钾、钠或钙的弱酸的另一种盐，或者加入有机碱如三乙胺，二甲胺，吡啶或喹啉或过量的胺成分可能是有利的.

适当的惰性溶剂是，例如烃类如己烷，石油醚，苯，甲苯或二甲苯；氯代烃类如三氯乙烯，1，2－二氯乙烷，四氯化碳，氯仿和二氯甲烷；醇类如甲醇，乙醇，异丙醇，正丙醇，正丁醇或叔丁醇；醚类如乙醚，二异丙醚，四氢呋喃（THF）或二噁烷，二醇醚类如乙二醇单甲基或单乙基醚(甲基甘醇或乙基甘醇)，乙二醇二甲醚（二甘醇二甲醚）；酮类如丙酮或丁酮；酰胺类如乙酰胺，二甲基乙酰胺，N－甲基吡咯烷酮或二甲基甲酰胺（DMF）；腈类如乙腈；亚砜类如二甲亚砜（DMSO）；硝基化合物如硝基甲烷或硝基苯；酯类如乙酸乙酯或上述溶剂的混合物.

还可以将式 I 化合物中的基团 X 转化为另一个基团 X，例如通过将酯或氰基水解为 COOH 基团.

酯基可以被水解，例如用 NaOH 或 KOH 的水、水－THF 或水－二噁烷在温度 0 至 100℃之间水解.

羧酸可以被转化为相应的酰氯，例如用亚硫酰氯及将它们转化为甲酰胺. 用已知方法通过从上述化合物中消去水可以获得甲腈.

用碱可以将式 I 化合物的酸转化为相关酸的加成盐，例如通过等当量的酸和碱在惰性溶剂如乙醇中反应然后接着蒸发得到. 用于该反应可能的碱是那些产生生理上可接受的盐的碱.

因此，式 I 的酸可以被转化为相应的金属盐，特别是碱金属或碱土金属盐，或用碱（例如氢氧化钠或钾或碳酸钠或钾）转化为相应的铵盐.

用于该反应可能的碱特别是产生生理上可接受盐的有机碱，如乙醇胺.

另一方面，用酸可以将式 I 的碱转化为相关酸加成盐，例如通过等当量碱和酸在惰性溶剂如乙醇中反应接着蒸发得到. 用于该反应的可能的酸特别是那些产生生理上可接受的盐的酸. 因此可以使用无机酸，例如硫酸，硝酸，氢卤酸如盐酸或氢溴酸，磷酸如正磷酸，氨基磺酸，还包括有机酸，特别是脂肪族、脂环族、芳香脂肪族、芳香族或杂环单－或多碱价羧酸、磺酸或硫酸，例如甲酸，乙酸，丙酸，新

戊酸，二乙基乙酸，丙二酸，琥珀酸，庚二酸，富马酸，马来酸，乳酸，酒石酸，苹果酸，柠檬酸，葡萄糖酸，抗坏血酸，烟酸，异烟酸，甲－或乙磺酸，乙二磺酸，2－羟基乙磺酸，苯磺酸，对苯磺酸，萘单或双磺酸，月桂基硫酸。可以使用与生理上不接受的酸形成的盐，例如苦味酸盐来分离和/或纯化式 I 化合物。

本发明进一步涉及式 I 化合物和/或其生理上可接受的盐在制备药物制剂中的用途，特别是以非化学方式。为此，可以将它们与至少一种固体、液体和/或半固体赋形剂或辅剂及如果需要，再加入一种或多种活性化合物一起制成剂型。

本发明还涉及式 I 化合物及其生理上可接受的盐作为磷酸二酯酶 V 抑制剂的药物。

本发明进一步涉及含有至少一种式 I 化合物和/或一种其生理上可接受的盐的药物制剂。

这些制剂可以被用作人或兽医用药物。可能的赋形剂是适于肠内（例如口服）或非肠道给药或局部使用并且不与新化合物反应的有机或无机物质，例如水，植物油，苄基醇，亚烷基二醇类，聚乙二醇，三乙酸甘油酯，明胶，碳水化合物类如乳糖或淀粉，硬脂酸镁，滑石，凡士林。可以使用片剂，丸剂，包衣片剂，胶囊剂，粉剂，颗粒剂，糖浆，汁剂或滴剂，特别是用于口服，栓剂可以用于直肠给药，溶液，优选油性或水性溶液，及混悬剂，乳剂或植入剂可以用于非肠道给药，软膏，乳膏或粉剂可以用于局部给药。还可以将新化合物冻干并且使用获得的冻干剂，例如用于制备注射制剂。所述制剂可以被灭菌和/或可以含有辅剂如润滑剂，防腐剂，稳定剂和/或湿润剂，乳化剂，影响渗透压的盐，缓冲物质，着色剂，矫味剂和/或一种或多种其它活性化合物，例如一种或多种维生素。

可以使用式 I 化合物及其生理上可接受的盐控制其中 cGMP（环鸟苷单磷酸酯）的增加的疾病，从而导致抑制或预防炎症和肌肉松弛。本发明化合物特别被用于治疗心血管系统疾病和治疗(treatment)和/或治愈(therapy)性交障碍。

在这种情况下，一般优选以每剂量单位约 1 至 500mg，特别是 5 至 100mg 的剂量给药。日剂量优选每 kg 体重约 0.02 至 10mg。然而，对于每个患者特定的剂量取决于所有不同因素，例如取决于使用的特

定化合物的效力、年龄、体重、健康状况、性别、饮食、给药时间和途径，排出率，药物联用和治疗的每种病的严重程度。口服给药是优选的。

上文和下文中，所有温度为℃，在下列实施例中，“常规处理”指：加入水，如果需要，根据最终产物的构成将混合物调节至 pH 值 2 至 10 并用乙酸乙酯或二氯甲烷萃取，分离有机相，用硫酸钠干燥并蒸发，并且将剩余物通过硅胶柱色谱和/或结晶纯化。

质谱(MS):EI(电子轰击离子化)M^+

FAB（快速原子轰击）$(M+H)^+$

实施例 1

将 1.9g 3-（4-氯-5，6，7，8-四氢-[1]苯并噻吩并[2,3-d]嘧啶-2-基）丙酸甲酯[通过 2-氨基-4，5-6，7-四氢苯并噻吩-3-羧酸甲酯与 3-氯基丙酸甲酯环化加之用磷酰氯/二甲胺氯化可以获得]和 2.3g3-氯-4-甲氧基苄胺(“A”)的 20mlN-甲基吡咯烷酮在 110℃搅拌 5 小时。除去溶剂并用常规方式处理。得到 2.6g 3-[4-（3-氯-4-甲氧基苄氨基）-5，6，7，8-四氢-[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酸甲酯，为无色油。

通过类似方式使“A”与下述相应物质反应，得到下列化合物:

用 3-（4-氯-5，6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基）丙酸甲酯

得到 3-[4-（3-氯-4-甲氧基苄氨基）-5，6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酸甲酯;

用 3-（4-氯-5，6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基）丙酸甲酯

得到 3-[4-（3-氯-4-甲氧基苄氨基）-5，6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酸甲酯;

用 3-（4-氯-6-甲基噻吩并[2,3-d]嘧啶-2-基）丙酸甲酯

得到 3-[4-（3-氯-4-甲氧基苄氨基）-6-甲基噻吩并[2,3-d]嘧啶-2-基]丙酸甲酯;

用 3-（4-氯-5，6-二甲基噻吩并[2,3-d]嘧啶-2-基）丙酸甲酯

得到 3-[4-（3-氯-4-甲氧基苄氨基）-5，6-二甲基噻吩

并[2,3-d]嘧啶-2-基]丙酸甲酯;

用3-(4-氯-6-乙基噻吩并[2,3-d]嘧啶-2-基)丙酸甲酯

得到3-[4-(3-氯-4-甲氧基苄氨基)-6-乙基噻吩并[2,3-d]嘧啶-2-基]丙酸甲酯;

用3-(4,6-二氯噻吩并[2,3-d]嘧啶-2-基)丙酸甲酯

得到3-[4-(3-氯-4-甲氧基苄氨基)-6-氯噻吩并[2,3-d]嘧啶-2-基]丙酸甲酯;

用2-(4-氯-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)乙酸甲酯

得到2-[4-(3-氯-4-甲氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]乙酸甲酯.

通过3,4-亚甲基二氧基苄胺与下述相应物质反应类似地得到下列化合物:

用3-(4-氯-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)丙酸甲酯

得到3-[4-(3,4-亚甲基二氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酸甲酯;

用3-(4-氯-5,6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基)丙酸甲酯

得到3-[4-(3,4-亚甲基二氧基苄氨基)-5,6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酸甲酯;

用3-(4-氯-5,6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基)丙酸甲酯

得到3-[4-(3,4-亚甲基二氧基苄氨基)-5,6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酸甲酯;

用3-(4-氯-6-甲基噻吩并[2,3-d]嘧啶-2-基)丙酸甲酯

得到3-[4-(3,4-亚甲基二氧基苄氨基)-6-甲基噻吩并[2,3-d]嘧啶-2-基]丙酸甲酯;

用3-(4-氯-5,6-二甲基噻吩并[2,3-d]嘧啶-2-基)丙酸甲酯

得到3-[4-(3,4-亚甲基二氧基苄氨基)-5,6-二甲基噻吩并[2,3-d]嘧啶-2-基]丙酸甲酯;

用 3-（4-氯-6-乙基嘧吩并[2,3-d]嘧啶-2-基）丙酸甲酯得到 3-[4-（3，4-亚甲基二氧基苄氨基）-6-乙基嘧吩并[2,3-d]嘧啶-2-基]丙酸甲酯；

用 3-（4，6-二氯嘧吩并[2,3-d]嘧啶-2-基）丙酸甲酯得到 3-[4-（3，4-亚甲基二氧基苄氨基）-6-氯嘧吩并[2,3-d]嘧啶-2-基]丙酸甲酯.

通过类似地用下述相应物质与“A”反应的方式得到下列化合物：

用 4-（4-氯-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基）丁酸甲酯得到 4-[4-（3-氯-4-甲氧基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]丁酸甲酯；

用 4-（4-氯-5，6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基）丁酸甲酯得到 4-[4-（3-氯-4-甲氧基苄氨基）-5，6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]丁酸甲酯；

用 4-（4-氯-5，6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基）丁酸甲酯得到 4-[4-（3-氯-4-甲氧基苄氨基）-5，6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]丁酸甲酯；

用 4-（4-氯-6-甲基噻吩并[2,3-d]嘧啶-2-基）丁酸甲酯得到 4-[4-（3-氯-4-甲氧基苄氨基）-6-甲基噻吩并[2,3-d]嘧啶-2-基]丁酸甲酯；

用 4-（4-氯-5，6-二甲基噻吩并[2,3-d]嘧啶-2-基）丁酸甲酯得到 4-[4-（3-氯-4-甲氧基苄氨基）-5，6-二甲基噻吩并[2,3-d]嘧啶-2-基]丁酸甲酯；

用 4-（4-氯-6-乙基噻吩并[2,3-d]嘧啶-2-基）丁酸甲酯得到 4-[4-（3-氯-4-甲氧基苄氨基）-6-乙基噻吩并[2,3-d]嘧啶-2-基]丁酸甲酯；

用 4-（4，6-二氯噻吩并[2,3-d]嘧啶-2-基）丁酸甲酯得到 4-[4-(3-氯-4-甲氧基苄氨基)-6-氯噻吩并[2,3-d]嘧啶-2-基]丁酸甲酯.

通过3，4－亚甲基二氧基苄胺反应，类似地得到下列化合物：

用 4－（4－氯－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基）丁酸甲酯

得到 4－[4－（3，4－亚甲基二氧基苄氨基）－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基]丁酸甲酯；

用 4－（4－氯－5，6－环戊烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基）丁酸甲酯

得到 4－[4－（3，4－亚甲基二氧基苄氨基）－5，6－环戊烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基]丁酸甲酯；

用 4－（4－氯－5，6－环庚烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基）丁酸甲酯

得到 4－[4－（3，4－亚甲基二氧基苄氨基）－5，6－环庚烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基]丁酸甲酯；

用 4－（4－氯－6－甲基噻吩并[2,3-d]嘧啶－2－基）丁酸甲酯

得到 4－[4－（3，4－亚甲基二氧基苄氨基）－6－甲基噻吩并[2,3-d]嘧啶－2－基]丁酸甲酯；

用 4－（4－氯－5，6－二甲基噻吩并[2,3-d]嘧啶－2－基）丁酸甲酯

得到 4－[4－（3，4－亚甲基二氧基苄氨基）－5，6－二甲基噻吩并[2,3-d]嘧啶－2－基]丁酸甲酯；

用 4－（4－氯－6－乙基噻吩并[2,3-d]嘧啶－2－基）丁酸甲酯

得到 4－[4－（3，4－亚甲基二氧基苄氨基）－6－乙基噻吩并[2,3-d]嘧啶－2－基]丁酸甲酯；

用 4－（4，6－二氯噻吩并[2,3-d]嘧啶－2－基）丁酸甲酯

得到 4－[4－（3，4－亚甲基二氧基苄氨基）－6－氯噻吩并[2,3-d]嘧啶－2－基]丁酸甲酯.

通过类似的方式反应“A”和下述相应化合物得到下列化合物：

用 5－（4－氯－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基）戊酸甲酯

得到 5－[4－（3－氯－4－甲氧基苄氨基）－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基]戊酸甲酯；

用 5－（4－氯－5，6－环戊烯并[1]苯并噻吩并[2,3-d]嘧啶－2

-基）戊酸甲酯

得到 5-[4-（3-氯-4-甲氧基苄氨基）-5，6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯；

用 5-（4-氯-5，6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基）戊酸甲酯

得到 5-[4-（3-氯-4-甲氧基苄氨基）-5，6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯；

用 5-（4-氯-6-甲基噻吩并[2,3-d]嘧啶-2-基）戊酸甲酯

得到 5-[4-（3-氯-4-甲氧基苄氨基）-6-甲基噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯；

用 5-（4-氯-5，6-二甲基噻吩并[2,3-d]嘧啶-2-基）戊酸甲酯

得到 5-[4-（3-氯-4-甲氧基苄氨基）-5，6-二甲基噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯；

用 5-（4-氯-6-乙基噻吩并[2,3-d]嘧啶-2-基）戊酸甲酯

得到 5-[4-（3-氯-4-甲氧基苄氨基）-6-乙基噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯；

用 5-（4，6-二氯噻吩并[2,3-d]嘧啶-2-基）戊酸甲酯

得到5-[4-(3-氯-4-甲氧基苄氨基)-6-氯噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯.

通过 3，4-亚甲基二氧基苄胺与下述相应物质反应类似地得到下列化合物：

用 5-（4-氯-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基）戊酸甲酯

得到 5-[4-（3，4-亚甲基二氧基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯；

用 5-（4-氯-5，6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基）戊酸甲酯

得到 5-[4-（3，4-亚甲基二氧基苄氨基）-5，6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯；

用 5-（4-氯-5，6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基）戊酸甲酯

得到 5-[4-（3，4-亚甲基二氧基苄氨基）-5，6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯;

用 5-（4-氯-6-甲基噻吩并[2,3-d]嘧啶-2-基）戊酸甲酯得到 5-[4-（3，4-亚甲基二氧基苄氨基）-6-甲基噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯;

用 5-（4-氯-5，6-二甲基噻吩并[2,3-d]嘧啶-2-基）戊酸甲酯

得到 5-[4-（3，4-亚甲基二氧基苄氨基）-5，6-二甲基噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯;

用 5-（4-氯-6-乙基噻吩并[2,3-d]嘧啶-2-基）戊酸甲酯得到 5-[4-（3，4-亚甲基二氧基苄氨基）-6-乙基噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯;

用 5-（4，6-二氯噻吩并[2,3-d]嘧啶-2-基）戊酸甲酯得到 5-[4-（3，4-亚甲基二氧基苄氨基）-6-氯噻吩并[2,3-d]嘧啶-2-基]戊酸甲酯.

通过反应“A”与下述相应化合物的方式类似得到下列化合物:

用 7-（4-氯-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基）庚酸甲酯

得到 7-[4-（3-氯-4-甲氧基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]庚酸甲酯;

用 7-（4-氯-5，6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基）庚酸甲酯

得到 7-[4-（3-氯-4-甲氧基苄氨基）-5，6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]庚酸甲酯;

用 7-（4-氯-5，6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基）庚酸甲酯

得到 7-[4-（3-氯-4-甲氧基苄氨基）-5，6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]庚酸甲酯;

用 7-（4-氯-6-甲基噻吩并[2,3-d]嘧啶-2-基）庚酸甲酯得到 7-[4-（3-氯-4-甲氧基苄氨基）-6-甲基噻吩并[2,3-d]嘧啶-2-基]庚酸甲酯;

用 7-（4-氯-5，6-二甲基噻吩并[2,3-d]嘧啶-2-基）庚

酸甲酯

得到 7－[4－（3－氯－4－甲氧基苄氨基）－5，6－二甲基噻吩并[2,3-d]嘧啶－2－基]庚酸甲酯;

用 7－（4－氯－6－乙基噻吩并[2,3-d]嘧啶－2－基）庚酸甲酯得到 7－[4－（3－氯－4－甲氧基苄氨基）－6－乙基噻吩并[2,3-d]嘧啶－2－基]庚酸甲酯;

用 7－（4，6－二氯噻吩并[2,3-d]嘧啶－2－基）庚酸甲酯得到7－[4－(3－氯－4－甲氧基苄氨基)－6－氯噻吩并[2,3-d]嘧啶－2－基]庚酸甲酯.

通过 3，4－亚甲基二氧基苄胺与下述相应物质反应，类似地得到下列化合物:

用 7－（4－氯－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基）庚酸甲酯

得到 7－[4－（3，4－亚甲基二氧基苄氨基）－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基]戊酸甲酯;

用 7－（4－氯－5，6－环戊烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基）庚酸甲酯

得到 7－[4－（3，4－亚甲基二氧基苄氨基）－5，6－环戊烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基]庚酸甲酯;

用 7－（4－氯－5，6－环庚烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基）庚酸甲酯

得到 7－[4－（3，4－亚甲基二氧基苄氨基）－5，6－环庚烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基]庚酸甲酯;

用 7－（4－氯－6－甲基噻吩并[2,3-d]嘧啶－2－基）庚酸甲酯得到 7－[4－（3，4－亚甲基二氧基苄氨基）－6－甲基噻吩并[2,3-d]嘧啶－2－基]戊酸甲酯;

用 7－（4－氯－5，6－二甲基噻吩并[2,3-d]嘧啶－2－基）庚酸甲酯

得到 7－[4－（3，4－亚甲基二氧基苄氨基）－5，6－二甲基噻吩并[2,3-d]嘧啶－2－基]庚酸甲酯;

用 7－（4－氯－6－乙基噻吩并[2,3-d]嘧啶－2－基）庚酸甲酯

得到 7－[4－（3，4－亚甲基二氧基苄氨基）－6－乙基噻吩并

[2,3-d]嘧啶-2-基]庚酸甲酯;

用 7-(4,6-二氯噻吩并[2,3-d]嘧啶-2-基)庚酸甲酯

得到 7-[4-(3,4-亚甲基二氧基苄氨基)-6-氯噻吩并[2,3-d]嘧啶-2-基]庚酸甲酯.

通过反应"A"与下述相应化合物的方式类似得到下列化合物:

用 2-[4-(4-氯-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)环己烷-1-基]乙酸甲酯

得到 2-{4-[4-(3-氯-4-甲氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]环己烷-1-基}乙酸甲酯;

用 2-[4-(4-氯-6-乙基噻吩并[2,3-d]嘧啶-2-基)环己烷-1-基]乙酸甲酯

得到 2-{4-[4-(3-氯-4-甲氧基苄氨基)-6-乙基噻吩并[2,3-d]嘧啶-2-基]环己烷-1-基}乙酸甲酯.

通过 3,4-亚甲基二氧基苄胺与下述相应化合物反应,类似地得到下列化合物:

用 2-[4-(4-氯-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)环己-1-基]乙酸甲酯

得到 2-{4-[4-(3,4-亚甲基二氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]环己-1-基}乙酸甲酯.

通过苄胺与下述相应化合物的反应类似地得到下列化合物:

用 3-(4-氯-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)丙酸甲酯

得到 3-(4-苄氨基-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)丙酸甲酯;

用 4-(4-氯-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)丁酸甲酯

得到 4-(4-苄氨基-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)丁酸甲酯;

用 5-(4-氯-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)戊酸甲酯

得到 5－（4－苄氧基－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基）戊酸甲酯；

用 4－（4－氯－6－甲基噻吩并[2,3-d]嘧啶－2－基）丁酸甲酯得到 4－（4－苄氧基－6－甲基噻吩并[2,3-d]嘧啶－2－基）丁酸甲酯；

用 5－（4－氯－6－乙基噻吩并[2,3-d]嘧啶－2－基）戊酸甲酯得到 5－（4－苄氧基－6－乙基噻吩并[2,3-d]嘧啶－2－基）戊酸甲酯。

实施例 2

将 2.2g 3－[4－（3－氯－4－甲氧基苄氨基）－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基]丙酸甲酯溶解在 20ml 乙二醇单甲基醚中，加入 10ml 32% NaOH 溶液后，将混合物在 110℃搅拌 5 小时．加入 20% HCl 后，用二氯甲烷萃取．通过加入石油醚得到 2.0g 3－[4－（3－氯－4－甲氧基苄氨基）－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基]丙酸，m.p. 229℃．

将沉淀的结晶溶解在 30ml 异丙醇中并用 0.5g 乙醇胺处理．结晶后，得到 1.35 克 3－[4－（3－氯－4－甲氧基苄氨基）－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基]丙酸，乙醇胺盐，m.p. 135℃．

从实施例 1 所列的酯类类似地得到下列羧酸：

3－[4－（3－氯－4－甲氧基苄氨基）－5，6－环戊烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基]丙酸；

3－[4－（3－氯－4－甲氧基苄氨基）－5，6－环庚烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基]丙酸；

3－[4－（3－氯－4－甲氧基苄氨基）－6－甲基噻吩并[2,3-d]嘧啶－2－基]丙酸；

3－[4－(3－氯－4－甲氧基苄氨基)－5,6－甲基噻吩并[2,3-d]嘧啶－2－基]丙酸；

3－[4－（3－氯－4－甲氧基苄氨基）－6－乙基噻吩并[2,3-d]嘧啶－2－基]丙酸；

3－[4－（3－氯－4－甲氧基苄氨基）－6－氯噻吩并[2,3-d]嘧啶－2－基]丙酸；

2-[4-(3-氯-4-甲氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]乙酸,乙醇胺盐,m.p. 126℃;

3-[4-(3,4-亚甲基二氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酸;

3-[4-(3,4-亚甲基二氧基苄氨基)-5,6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酸;

3-[4-(3,4-亚甲基二氧基苄氨基)-5,6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酸;

3-[4-(3,4-亚甲基二氧基苄氨基)-6-甲基噻吩并[2,3-d]嘧啶-2-基]丙酸;

3-[4-(3,4-亚甲基二氧基苄氨基)-5,6-二甲基噻吩并[2,3-d]嘧啶-2-基]丙酸;

3-[4-(3,4-亚甲基二氧基苄氨基)-6-乙基噻吩并[2,3-d]嘧啶-2-基]丙酸;

3-[4-(3,4-亚甲基二氧基苄氨基)-6-氯噻吩并[2,3-d]嘧啶-2-基]丙酸;

4-[4-(3-氯-4-甲氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]丁酸;

4-[4-(3-氯-4-甲氧基苄氨基)-5,6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]丁酸;

4-[4-(3-氯-4-甲氧基苄氨基)-5,6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]丁酸;

4-[4-(3-氯-4-甲氧基苄氨基)-6-甲基噻吩并[2,3-d]嘧啶-2-基]丁酸,乙醇胺盐,m.p. 142℃;

4-[4-(3-氯-4-甲氧基苄氨基)-5,6-甲基噻吩并[2,3-d]嘧啶-2-基]丁酸;

4-[4-(3-氯-4-甲氧基苄氨基)-6-乙基噻吩并[2,3-d]嘧啶-2-基]丁酸,乙醇胺盐,m.p. 170℃;

4-[4-(3-氯-4-甲氧基苄氨基)-6-氯噻吩并[2,3-d]嘧啶-2-基]丁酸;

4-[4-(3,4-亚甲基二氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]丁酸,乙醇胺盐,m.p. 114℃;

4－[4－（3，4－亚甲基二氧基苄氨基）－5，6－环戊烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基]丁酸;

4－[4－（3，4－亚甲基二氧基苄氨基）－5，6－环庚烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基]丁酸;

4－[4－（3，4－亚甲基二氧基苄氨基）－6－甲基噻吩并[2,3-d]嘧啶－2－基]丁酸，乙醇胺盐，m.p. 170℃;

4－[4－（3，4－亚甲基二氧基苄氨基）－5，6－二甲基噻吩并[2,3-d]嘧啶－2－基]丁酸;

4－[4－（3，4－亚甲基二氧基苄氨基）－6－乙基噻吩并[2,3-d]嘧啶－2－基]丁酸;

4－[4－（3，4－亚甲基二氧基苄氨基）－6－氯噻吩并[2,3-d]嘧啶－2－基]丁酸;

5－[4－（3－氯－4－甲氧基苄氨基）－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基]戊酸，m.p. 165℃；乙醇胺盐，m.p. 112℃;

5－[4－（3－氯－4－甲氧基苄氨基）－5，6－环戊烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基]戊酸;

5－[4－（3－氯－4－甲氧基苄氨基）－5，6－环庚烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基]戊酸;

5－[4－（3－氯－4－甲氧基苄氨基）－6－甲基噻吩并[2,3-d]嘧啶－2－基]戊酸，乙醇胺盐，m.p. 156℃;

5－[4－（3－氯－4－甲氧基苄氨基）－5，6－二甲基噻吩并[2,3-d]嘧啶－2－基]戊酸;

5－[4－（3－氯－4－甲氧基苄氨基）－6－乙基噻吩并[2,3-d]嘧啶－2－基]戊酸，乙醇胺盐，m.p. 156℃;

5－[4－（3－氯－4－甲氧基苄氨基）－6－氯噻吩并[2,3-d]嘧啶－2－基]戊酸.

5－[4－（3，4－亚甲基二氧基苄氨基）－5，6，7，8－四氢[1]苯并噻吩并[2,3-d]嘧啶－2－基]戊酸;

5－[4－（3，4－亚甲基二氧基苄氨基）－5，6－环戊烯并[1]苯并噻吩并[2,3-d]嘧啶－2－基]戊酸;

5－[4－（3，4－亚甲基二氧基苄氨基）－5，6－环庚烯并[1]

苯并噻吩并[2,3-d]嘧啶-2-基]戊酸;

5-[4-(3,4-亚甲基二氧基苄氨基)-6-甲基噻吩并[2,3-d]嘧啶-2-基]戊酸,乙醇胺盐,m.p. 167℃;

5-[4-(3,4-亚甲基二氧基苄氨基)-5,6-二甲基噻吩并[2,3-d]嘧啶-2-基]戊酸;

5-[4-(3,4-亚甲基二氧基苄氨基)-6-乙基噻吩并[2,3-d]嘧啶-2-基]戊酸;

5-[4-(3,4-亚甲基二氧基苄氨基)-6-氯噻吩并[2,3-d]嘧啶-2-基]戊酸;

7-[4-(3-氯-4-甲氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]庚酸,乙醇胺盐,m.p. 130℃;

7-[4-(3-氯-4-甲氧基苄氨基)-5,6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]庚酸;

7-[4-(3-氯-4-甲氧基苄氨基)-5,6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]庚酸;

7-[4-(3-氯-4-甲氧基苄氨基)-6-甲基噻吩并[2,3-d]嘧啶-2-基]庚酸;

7-[4-(3-氯-4-甲氧基苄氨基)-5,6-二甲基噻吩并[2,3-d]嘧啶-2-基]庚酸;

7-[4-(3-氯-4-甲氧基苄氨基)-6-乙基噻吩并[2,3-d]嘧啶-2-基]庚酸;

7-[4-(3-氯-4-甲氧基苄氨基)-6-氯噻吩并[2,3-d]嘧啶-2-基]庚酸;

7-[4-(3,4-亚甲基二氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]庚酸,乙醇胺盐,m.p. 137℃;

7-[4-(3,4-亚甲基二氧基苄氨基)-5,6-环戊烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]庚酸;

7-[4-(3,4-亚甲基二氧基苄氨基)-5,6-环庚烯并[1]苯并噻吩并[2,3-d]嘧啶-2-基]庚酸;

7-[4-(3,4-亚甲基二氧基苄氨基)-6-甲基噻吩并[2,3-d]嘧啶-2-基]庚酸;

7-[4-(3,4-亚甲基二氧基苄氨基)-5,6-二甲基噻吩并

[2,3-d]嘧啶-2-基]庚酸;

7-[4-(3,4-亚甲基二氧基苄氨基)-6-乙基噻吩并[2,3-d]嘧啶-2-基]庚酸;

7-[4-(3,4-亚甲基二氧基苄氨基)-6-氯噻吩并[2,3-d]嘧啶-2-基]庚酸;

2-{4-[4-(3-氯-4-甲氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]环己基}乙酸;

2-{4-[4-(3-氯-4-甲氧基苄氨基)-6-乙基噻吩并[2,3-d]嘧啶-2-基]环己基}乙酸;

2-{4-[4-(3,4-亚甲基二氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]环己基}乙酸;

3-(4-苄氨基-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)丙酸,乙醇胺盐,m.p. 126℃;

4-(4-苄氨基-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)丁酸,乙醇胺盐,m.p. 133℃;

5-(4-苄氨基-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)戊酸,乙醇胺盐,m.p. 135℃;

4-[4-苄氨基-6-甲基噻吩并[2,3-d]嘧啶-2-基]丁酸,乙醇胺盐,m.p. 165℃;

5-[4-苄氨基-6-乙基噻吩并[2,3-d]嘧啶-2-基]戊酸,乙醇胺盐,m.p. 162℃.

实施例3

将1当量3-[4-(3-氯-4-甲氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酸和1.2当量亚硫酰氯在二氯甲烷中搅拌2小时.除去溶剂得到3-[4-(3-氯-4-甲氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酰氯.

将上述物质转移至氨水中,将该混合物搅拌1小时,常规处理后得到3-[4-(3-氯-4-甲氧基苄氨基)-5,6,7,8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酰胺.

实施例4

在0℃将1当量DMF和1当量草酰氯溶解在乙腈中.然后加入1

当量 3-[4-（3-氯-4-甲氧基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酰胺．将混合物搅拌 1 小时．常规处理后，得到 3-[4-（3-氯-4-甲氧基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙腈．

实施例 5

类似实施例 1 和 2 的方式得到下列化合物:

6-[4-（3-氯-4-甲氧基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]己酸，m.p. 165℃;

2-[4-（3-氯-4-甲氧基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]丙酸，乙醇胺盐，m.p. 150℃;

4-[4-（3-氯-4-甲氧基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]-2，2-二甲基丁酸，乙醇胺盐，m.p. 130℃;

4-[4-（3，4-亚甲基二氧基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]-2，2-二甲基丁酸，乙醇胺盐，m.p. 126℃;

5-[4-（3-氯-4-羟基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]戊酸，m.p. 179℃;

5-[4-（3，4-二氯苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]戊酸，乙醇胺盐，m.p. 136℃;

5-[4-（3-氯-4-异丙氧基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基]戊酸，乙醇胺盐，m.p. 118℃;

2-[4-（4-（3-氯-4-甲氧基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基)苯基]乙酸，乙醇胺盐，m.p. 119℃;

2-[4-（4-（3，4-亚甲基二氧基苄氨基）-5，6，7，8-四氢[1]苯并噻吩并[2,3-d]嘧啶-2-基）苯基]乙酸，m.p. 214℃.

下列实施例涉及药物制剂:

实施例 A: 注射小瓶

将 100g 式 I 活性化合物和 5g 磷酸氢二钠溶液用 2 N 盐酸的 3 L 双蒸馏水调节 pH 至 6.5，无菌填充、混合至注射瓶中，无菌条件下冷冻干燥并无菌密封．每个注射瓶中含有 5mg 活性化合物．

实施例 B: 栓剂

将 20g 式 I 活性化合物的混合物与 100g 大豆卵磷脂及 1400g 可可脂熔合，倒入铸模中并使其冷却．每个栓剂中含有 20mg 活性化合物。

实施例 C: 溶液剂

从 1g 式 I 活性化合物，9.38g $NaH_2PO_4.2H_2O$，28.48g $Na_2HPO_4.12H_2O$，和 0.1g 氯化苯甲烃铵溶液的 940 ml 双蒸馏水制备溶液．调节混合物 pH 至 6.8，补足至 1L 并照射灭菌．该溶液可以用于眼滴剂．

实施例 D: 软膏

将 500mg 式 I 活性化合物与 99.5g 凡士林在无菌条件下混合．

实施例 E: 片剂

将 1kg 式 I 活性化合物，4kg 乳糖，1.2kg 马铃薯淀粉，0.2kg 滑石和 0.1kg 硬脂酸镁用常规方法压制成片剂，以便每片中含有 10mg 活性化合物．

实施例 F: 糖衣片剂

类似实施例 E 压制片剂，然后以常规方法用包衣剂蔗糖、马铃薯淀粉、滑石．黄蓍胶和着色剂进行包衣．

实施例 G: 胶囊剂

将 2kg 式 I 活性化合物以常规方法装入硬明胶胶囊中，以便每个胶囊中含有 20mg 活性化合物．

实施例 H: 安瓿

将 1kg 式 I 活性化合物的 60 L 双蒸馏水溶液无菌过滤，装入安瓿中，无菌条件下冷冻干燥并无菌密封．每个安瓿含有 10mg 活性化合物．

实施例 I: 吸入喷雾剂

将 14g 式 I 活性化合物溶解在 10 L 等渗氯化钠溶液中并将溶液装入具有唧筒结构的商用喷雾容器中．该溶液可以被喷雾至嘴或鼻中。每次喷雾（约 0.1 ml）相当于剂量约 0.14mg.