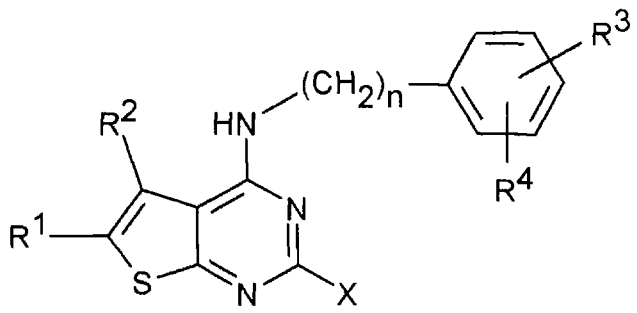
G00002

Pharmaceutical formulation comprising thienopyrimidines and antithrombotics, calcium antagonists, prostaglandins or prostaglandin derivatives (1)

The invention relates to pharmaceutical formulations comprising at least one phosphodiesterase V inhibitor and/or physiologically acceptable salts and/or solvates thereof and at least one antithrombotic.

The invention relates in particular to pharmaceutical formulations comprising at least one compound of the formula I

159159



I

in which

R^1 and R^2	are each, independently of one another, H, A or Hal, where one of the radicals R^1 and R^2 is always ≠ H,
R^1 and R^2	together are alternatively alkylene having 3-5 carbon atoms,
R^3 and R^4	are each, independently of one another, H, A, OH, OA or Hal,
R^3 and R^4	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 or R^6, each of which is monosubstituted by R^7,
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, or is $-C_6H_4-(CH_2)_m-$,
R^6	is cycloalkylalkylene having 6-12 carbon atoms,
R^7	is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,
A	is alkyl having from 1 to 6 carbon atoms.
Hal	is F, Cl, Br or I,

m is 1 or 2, and

n is 0, 1, 2 or 3,

and/or physiologically acceptable salts and/or solvates thereof, and

a) at least one antithrombotic or

b) at least one calcium antagonist or

c) at least one prostaglandin or prostaglandin derivative

The invention furthermore relates to the use of the formulation for the preparation of a medicament for the treatment of angina, high blood pressure, pulmonary hypertension, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale, dextrocardiac insufficiency, atherosclerosis, conditions of reduced patency of heart vessels, peripheral vascular diseases, strokes, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency, liver cirrhosis and for the treatment of female sexual disorders.

Pharmaceutical formulations consisting of other phosphodiesterase V (PDE V) inhibitors together with a second active ingredient are described in WO 00/15639.

The compounds of the formula I are described in WO 99/28325. Pyrimidine derivatives are disclosed, for example, in EP 201 188 and WO 93/06104

The use of other PDE-V inhibitors is described, for example, in WO 94/28902.

Pharmaceutical formulations consisting of other phosphodiesterase V (PDE V) inhibitors together with calcium antagonists (= calcium channel blockers) are described in WO 00/15639.

Pharmaceutical formulations consisting of other phosphodiesterase V (PDE V) inhibitors together with a prostaglandin or prostaglandin derivative are described in WO 00/15639 and WO 0015228

The use of (other) phosphodiesterase IV or V inhibitors in combination with a prostaglandin or prostaglandin derivative for the local treatment of erectile dysfunction is described in WO 9921558

R.T. Schermuly et al. in the *American Journal of Respiratory and Critical Care Medicine*, 160, 1500-6 (1999), describe the therapeutic potential of prostaglandin I_2 (PGI_2) in aerosol form with systemic PDE inhibitors, preferably dual-selective PDE III/IV inhibitors, in low doses for acute and chronic pulmonary hypertension.

In *Pneumologie* (54, Suppl 1, S42, 2000), R. Schermuly et al. describe the influence of PDE-V inhibition on prostacyclin-induced vasorelaxation in experimental pulmonary hypertonia.

The invention had the object of providing novel medicaments in the form of pharmaceutical preparations which have better properties than known medicaments which can be used for the same purpose

This object has been achieved by the discovery of the novel preparation.

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 a 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 described, for example, in WO 93/06104
The affinity of the compounds according to the invention for cGMP and cAMP phosphodiesterase is determined by measuring their IC_{50} values (concentration of the inhibitor needed 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

experiment 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 illnesses of the cardiovascular system, in particular cardiac insufficiency, and for the treatment and/or therapy of impotence (erectile dysfunction).

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

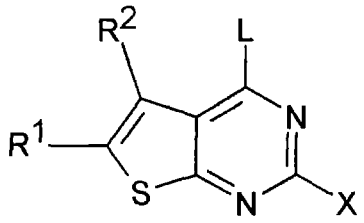
The compounds are effective as inhibitors of phenylephrine-induced contractions in corpus cavernosum preparations of rabbits. This biological action can be demonstrated, for example, by the method described by F. Holmquist et al. in J. Urol., 150, 1310-1315 (1993)
The inhibition of the contraction demonstrates the effectiveness of the compounds according to the invention for the therapy and/or treatment of impotence

The efficacy of the pharmaceutical formulations according to the invention, in particular for the treatment of pulmonary hypertension, can be demonstrated, as described by E Braunwald in Heart Disease 5th edition, WB Saunders Company, 1997, Chapter 6: Cardiac Catheterisation, 177-200

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 compounds of the formula I according to Claim 1 and their salts are prepared by a process which is characterised in that

a) a compound of the formula II

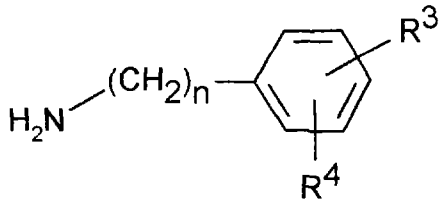


II

in which

R^1, R^2 and X are as defined above,
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 are as defined above,

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 invention also relates to the use of all optically active forms (stereoisomers), the enantiomers, the racemates, the diastereomers, and the hydrates and solvates of the compounds

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 form owing to their mutual attractive force. Solvates are, for example, monohydrates or dihydrates or alkoxides

Above and below, the radicals R^1, R^2, R^3, R^4, R^5, R^6, R^7, X, L and n are as defined under 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 or R^6 radical which is monosubstituted by R^7

R^5 is a linear or branched alkylene radical having 1-10 carbon atoms, preferably 1-8 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-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 carbon atoms, preferably, for example, cyclopentylmethylene, cyclohexylmethylene, cyclohexylethylene, cyclohexylpropylene or cyclohexylbutylene.

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

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

The radicals R^3 and R^4 may be identical or different and are preferably located in the 3- or 4-position of the phenyl ring. They are, for example, in each case independently of one another, H, OH, alkyl, 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 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.

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

The term antithrombotics also covers so-called anticoagulants and blood platelet aggregation inhibitors (thrombocyte aggregation inhibitors).

The invention relates in particular to pharmaceutical formulations comprising an antithrombotic, a calcium antagonist or a prostaglandin or prostaglandin derivative and at least one compound of the formula I in which at least one of the said radicals has one of the preferred meanings indicated above. Some preferred groups of compounds may be expressed by the following sub-formulae Ia to Ie, which conform to the formula I and in which the radicals not designated in greater detail are as defined under the formula I, but in which

in Ia	X	is R^5 or R^6, each of which is substituted by COOH or COOA;
in Ib	R^1 and R^2	are each, independently of one another, 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 carbon atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,
	X	is R^5 or R^6, each of which is substituted by COOH or COOA;

in Ic	R^1 and R^2	are each, independently of one another, 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	are each, independently of one another, H, A, OA or Hal,
	R^3 and R^4	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 or R^6, each of which is substituted by COOH or COOA,
	n	is 1 or 2;
in Id	R^1 and R^2	are each, independently of one another, 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 alternatively alkylene having 3-5 carbon atoms,
	R^3 and R^4	are each, independently of one another, H, A, OA or Hal,
	R^3 and R^4	together are alternatively $-O-CH_2-O-$,
	X	is R^5 which is monosubstituted by R^7,
	R^5	is linear or branched alkylene having 1-10 carbon atoms or $-C_6H_4-CH_2-$,
	R^7	is COOH or COOA,
	A	is alkyl having from 1 to 6 carbon atoms,
	Hal	is F, Cl, Br or I,
	m	is 1, and
	n	is 1 or 2;
in Ie	R^1 and R^2	are each, independently of one another, 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 alternatively alkylene having 3-5 carbon atoms,
	R^3 and R^4	are each, independently of one another, H, A, OH, OA or Hal,
	R^3 and R^4	together are alternatively $-O-CH_2-O-$,
	X	is R^5 which is monosubstituted by R^7,

	R^5	is linear or branched alkylene having 1-10 carbon atoms or $-C_6H_4-CH_2-$,
	R^7	is COOH or COOA,
	A	is alkyl having from 1 to 6 carbon atoms,
5	Hal	is F, Cl, Br or I,
	m	is 1, and
	n	is 1 or 2

The invention preferably relates to a formulation comprising 5-[4-(3-chloro-
10 4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric acid and physiologically acceptable salts and/or solvates thereof and an antithrombotic
Besides the free acid, the ethanolamine salt is preferred.

15 Preferred antithrombotics are vitamin K antagonists, heparin compounds, thrombocyte aggregation inhibitors, enzymes, factor Xa inhibitors, factor VIIa inhibitors and other antithrombotic agents.

Preferred vitamin K antagonists are selected from the group consisting of
20 dicoumarol, phenindione, warfarin, phenprocoumon, acenocoumarol, ethyl biscoumacetate, clorindione, diphenadione and tioclomarol

Preferred heparin compounds are selected from the group consisting of heparin, antithrombin III. dalteparin, enoxaparin, nadroparin, parnaparin,
25 reviparin, danaparoid, tinzaparin and sulodexide.

Preferred thrombocyte aggregation inhibitors are selected from the group consisting of ditazole, cloricromen, picotamide, clopidogrel, ticlopidine, acetylsalicylic acid, dipyridamole, calcium carbassalate, epoprostenol,
30 indobufen, iloprost, abciximab, tirofiban, aloxiprin and intrifiban.

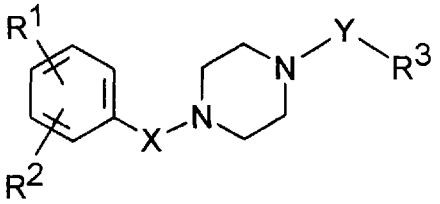
Preferred enzymes are selected from the group consisting of streptokinase, alteplase, anistreplase, urokinase, fibrinolysin, brinase, reteplase and saruplase

35

Preferred antithrombotics are furthermore the blood platelet glycoprotein receptor (IIb/IIIa) antagonists which inhibit blood platelet aggregation Preferred compounds are described, for example, in EP 0 623 615 B1 on page 2 or in EP 0 741 133 A2, page 2, line 2, to page 4, line 56.

Preferred factor Xa and VIIa inhibitors are, for example,

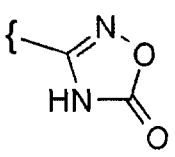
a) the compounds of the formula I



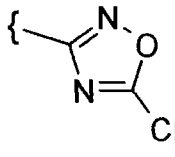
I

in which

R^1 is $-C(=NH)-NH_2$, which may also be monosubstituted by -COA, $-CO-[C(R^6)_2]_n-Ar$, -COOA, -OH or by a conventional amino protecting group, or is



or



,

R^2 is H, A, OR^6, $N(R^6)_2$, NO_2, CN, Hal, NHCOA, NHCOAr, $NHSO_2A$, $NHSO_2Ar$, $COOR^6$, $CON(R^6)_2$, CONHAr, COR^6, COAr, $S(O)_nA$ or $S(O)_nAr$,

R^3 is A, cycloalkyl, $-[C(R^6)_2]_nAr$, $-[C(R^6)_2]_n-O-Ar$, $[C(R^6)_2]_nHet$ or $-C(R^6)_2=C(R^6)_2-Ar$,

R^6 is H, A or benzyl,

X is absent or is -CO-, $-C(R^6)_2-$, $-C(R^6)_2-C(R^6)_2-$, $-C(R^6)_2-CO-$, $-C(R^6)_2-C(R^6)_2-CO-$, $-C(R^6)=C(R^6)-CO-$, NR^6CO-, $-N\{[C(R^6)_2]_n-COOR^6\}-CO-$ or $-C(COOR^6)R^6-C(R^6)_2-CO-$,

Y is $-C(R^6)_2-$, $-SO_2-$, -CO-, -COO- or $-CONR^6-$,

A is alkyl having 1-20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms or by

$-CR^6=CR^6-$ groups and/or 1-7 H atoms may be replaced by F,

Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, Ar', OR^6, $N(R^6)_2$, NO_2, CN, Hal, NHCOA, NHCOAr', $NHSO_2A$, $NHSO_2Ar'$, $COOR^6$, $CON(R^6)_2$, CONHAr', COR^6, COAr', $S(O)_nA$ or $S(O)_nAr$,

Ar' is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR^6, $N(R^6)_2$, NO_2, CN, Hal, NHCOA, $COOR^6$, $CON(R^6)_2$, COR^6 or $S(O)_nA$,

Het is a monocyclic or bicyclic, saturated or unsaturated heterocyclic ring system which contains one, two, three or four identical or different heteroatoms, such as nitrogen, oxygen and sulfur, and is unsubstituted or monosubstituted or polysubstituted by Hal, A, Ar', $COOR^6$, CN, $N(R^6)_2$, NO_2, Ar-CONH-CH_2 and/or carbonyl oxygen,

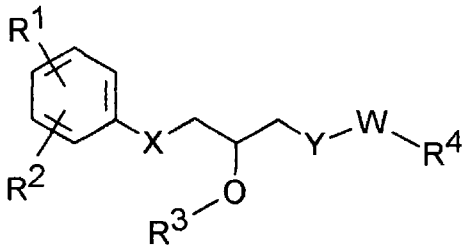
Hal is F, Cl, Br or I,

n is 0, 1 or 2,

and salts thereof,

which are described in WO 9916751,

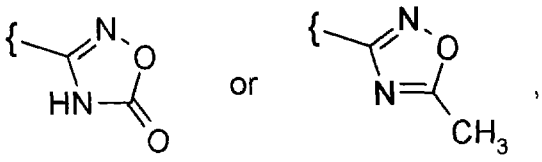
b) the compounds of the formula I

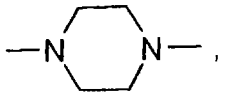
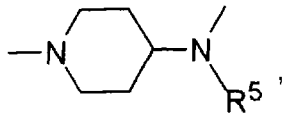
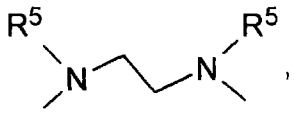


I

in which

R^1 is $-C(=NH)-NH_2$, which may also be monosubstituted by -COA, $-CO-[C(R^5)_2]_m-Ar$, -COOA, -OH or by a conventional amino-protecting group, or is



	R^2	is H, A, OR^5, $N(R^5)_2$, NO_2, CN, Hal, NR^5COA, NHCOAr, $NHSO_2A$, $NHSO_2Ar$, $COOR^5$, $CON(R^5)_2$, CONHAr, COR^5, COAr, $S(O)_nA$ or $S(O)_nAr$,
	R^3	is R^5 or $-[C(R^5)_2]_m-COOR^5$,
	R^3 and X	together are alternatively -CO-N-, with formation of a 5-membered ring, where R^3 is -C=O and X is N,
	R^4	is A, cycloalkyl, $-[C(R^5)_2]_mAr$, $-[C(R^5)_2]_mHet$ or $-CR^5=CR^5-Ar$,
	R^5	is H, A or benzyl,
	X	is O, NR^5 or CH_2,
	Y	is O, NR^5, $N[C(R^5)_2]_m-Ar$, $N[C(R^5)_2]_m-Het$, $N[C(R^5)_2]_m-COOR^5$,    $N[C(R^5)_2]_m-CON(R^5)_2$, $N[C(R^5)_2]_m-CONR^5Ar$ or $N[C(R^5)_2]_m-CONAr_2$,
	W	is a bond, $-SO_2-$, -CO-, -COO- or $-CONR^5-$,
	A	is alkyl having 1-20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms or by $-CR^5=CR^5-$ groups and/or 1-7 H atoms may be replaced by F,
	Ar	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R^1, A, Ar', OR^5, $N(R^5)_2$, NO_2, CN, Hal, NHCOA, NHCOAr', $NHSO_2A$, $NHSO_2Ar'$, $COOR^5$, $CON(R^5)_2$, CONHAr', COR^5, COAr', $S(O)_nA$ or $S(O)_nAr$,
	Ar'	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R^1, A,

OR^5, $N(R^5)_2$, NO_2, CN, Hal, NHCOA, $COOR^5$, $CON(R^5)_2$, COR^5 or $S(O)_nA$,

Het is a monocyclic or bicyclic, saturated or unsaturated heterocyclic ring system which contains one, two, three or four identical or different heteroatoms, such as nitrogen, oxygen and sulfur, and which is unsubstituted or monosubstituted or polysubstituted by Hal, A, Ar', OR^5, $COOR^5$, CN, $N(R^5)_2$, NO_2, NHCOA, NHCOAr' and/or carbonyl oxygen,

Hal is F, Cl, Br or I,

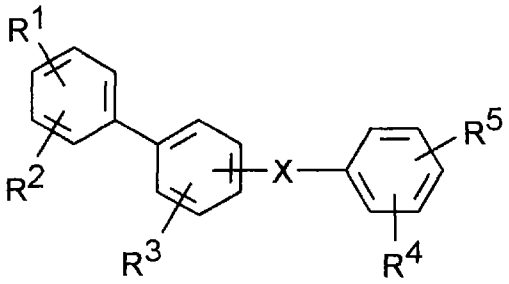
m is 0, 1, 2, 3 or 4,

n is 0, 1 or 2 ,

and salts thereof,

which are described in WO 9931092,

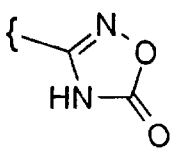
c) the compounds of the formula I



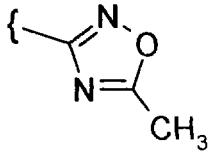
I

in which

R^1 and R^4 are each, independently of one another, -C(=NH)-NH_2, which may also be monosubstituted by -COA, -CO-[$C(R^6)_2$]$_n$-Ar, -COOA, -OH or by a conventional amino-protecting group, or are NH-C(=NH)-NH_2, -CO-N=$C(NH_2)_2$,



or



,

R^2, R^3

and R^5 are each, independently of one another, H, A, OR^6, $N(R^6)_2$, NO_2, CN, Hal, NHCOA, NHCOAr, $NHSO_2A$, $NHSO_2Ar$, $COOR^6$, $CON(R^6)_2$, CONHAr, COR^6, COAr, $S(O)_nA$, $S(O)_nAr$, $-O-[C(R^6)_2]_m-COOR^6$, $-[C(R^6)_2]_p-COOR^6$, $-O-[C(R^6)_2]_m-CON(R^6)_2$, $-[C(R^6)_2]_p-CON(R^6)_2$, $-O-[C(R^6)_2]_m-CONHAr$ or $-[C(R^6)_2]_p-CONHAr$,

X is $-[C(R^6)_2]_n-$, $-CR^6=CR^6-$, $-[C(R^6)_2]_n-O-$, $-O-[C(R^6)_2]_n-$, -COO-, -OOC-, $-CONR^6-$ or $-NR^6CO-$,

R^6 is H, A or benzyl,

A is alkyl having 1-20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms or by $-CR^6=CR^6-$ groups and/or 1-7 H atoms may be replaced by F,

Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, Ar', OR^6, OAr', $N(R^6)_2$, NO_2, CN, Hal, NHCOA, NHCOAr', $NHSO_2A$, $NHSO_2Ar'$, $COOR^6$, $CON(R^6)_2$, CONHAr', COR^6, COAr', $S(O)_nA$ or $S(O)_nAr'$,

Ar' is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR^6, $N(R^6)_2$, NO_2, CN, Hal, NHCOA, $COOR^6$, $CON(R^6)_2$, COR^6 or $S(O)_nA$,

Hal is F, Cl, Br or I,

n is 0, 1 or 2,

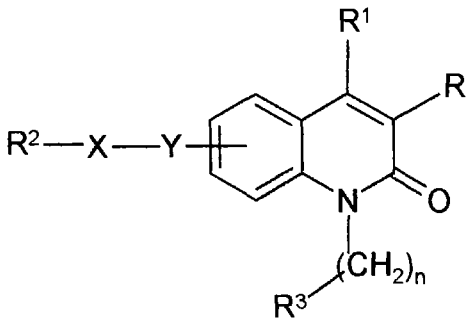
m is 1 or 2,

p is 1 or 2,

and salts thereof,

which are described in WO 9957096,

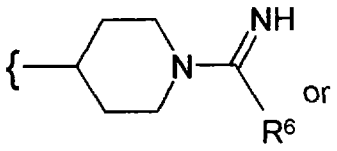
d) the compounds of the formula I

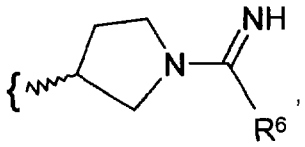


I

in which

R and R^1 are each, independently of one another, H, A, $-(CH_2)_m-R^4$, $-(CH_2)_m-OA$ or $-(CH_2)_m-Ar$,

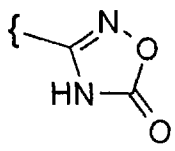
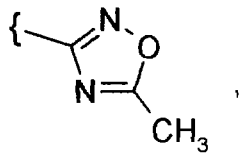
R^2 is Ar,  or



R^3 is Ar,

R^4 is CN, COOH, COOA, $CONH_2$, CONHA, $CONA_2$ or $C(=NH)-NH_2$,

R^5 is $-C(=NH)-NH_2$, $-NH-C(=NH)-NH_2$ or $-C(=O)-N=C(NH_2)_2$, each of which is unsubstituted or monosubstituted by -COA, -COOA, -OH or by a conventional amino-protecting group, or is

 or 

R^6 is H, A or NH_2,

Ar is phenyl, naphthyl or biphenyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, cycloalkyl having 3-6 carbon atoms, OH, OA, Hal, CN, NO_2, CF_3, NH_2, NHA, NA_2, pyrrolidin-1-yl, piperidin-1-yl, benzyloxy, SO_2NH_2, SO_2NHA, SO_2NA_2,

$-(CH_2)_n-NH_2$, $-(CH_2)_n-NHA$, $-(CH_2)_n-NA_2$, $-O-(CH_2)_n-NH_2$, $-O-(CH_2)_n-NHA$, $-O-(CH_2)_n-NA_2$, $-O-(CH_2)_m-O-$ or R^5,

A is alkyl having 1-6 carbon atoms,

X is absent or is alkylene having 1-4 carbon atoms or carbonyl,

Y is absent or is NH, O or S,

Hal is F, Cl, Br or I,

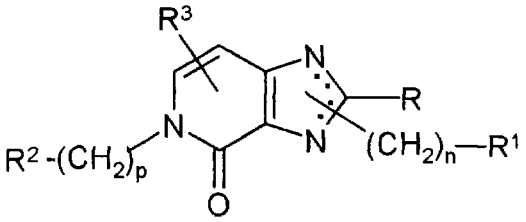
m is 0, 1 or 2,

n is 0, 1, 2 or 3,

and salts thereof,

which are described in WO 0012479,

e) the compounds of the formula I



I

in which

R is H, unbranched or branched alkyl having 1-6 carbon atoms or cycloalkyl having 3-6 carbon atoms,

R^1 is Ar,

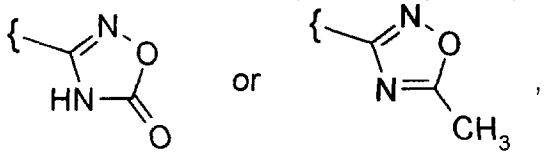
R^2 is Ar',

R^3 is H, R, R^4, Hal, CN, COOH, COOA or $CONH_2$,

Ar and Ar' are each, independently of one another, phenyl, naphthyl or biphenyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R, OH, Hal, CN, NO_2, CF_3, NH_2, NHR, NR_2, pyrrolidin-1-yl, piperidin-1-yl, benzyloxy, SO_2NH_2, SO_2NHR, SO_2NR_2, -CONHR, $-CONR_2$, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NHR$, $-(CH_2)_n-NR_2$, $-O-(CH_2)_n-NH_2$, $-O-(CH_2)_n-NHR$, $-O-(CH_2)_n-NR_2$, R^4 or together by $-O-(CH_2)_m-O-$,

R^4 is $-C(=NH)-NH_2$, $-NH-C(=NH)-NH_2$ or $-C(=O)-N=C(NH_2)_2$, each of which is unsubstituted or

monosubstituted by -COR, -COOR, -OH or by a conventional amino-protecting group, or is



A is alkyl having 1-4 carbon atoms,

Hal is F, Cl, Br or I,

m is 1 or 2,

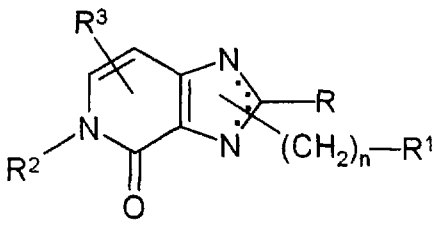
n is 0, 1, 2 or 3,

p is 0 or 1,

and salts thereof,

which are described in WO 0020416,

f) the compounds of the formula I



I

in which

R is H, unbranched or branched alkyl having 1-6 carbon atoms or cycloalkyl having 3-6 carbon atoms,

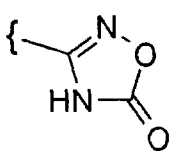
R^1 is Ar,

R^2 is Ar',

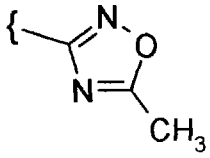
R^3 is H, R, R^4, Hal, CN, COOH, COOA or $CONH_2$,

Ar and Ar' are each, independently of one another, phenyl, naphthyl or biphenyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by R, OH, Hal, CN, NO_2, CF_3, NH_2, NHR, NR_2, pyrrolidin-1-yl, piperidin-1-yl, benzyloxy, SO_2NH_2, SO_2NHR, SO_2NR_2, -CONHR, $-CONR_2$, $-(CH_2)_n-NH_2$, $-(CH_2)_n-NHR$, $-(CH_2)_n-NR_2$, $-O-(CH_2)_n-NH_2$, $-O-(CH_2)_n-NHR$, $-O-(CH_2)_n-NR_2$, R^4 or together by $-O-(CH_2)_m-O-$, or isoquinolinyl which is substituted by NH_2,

R^4 is -C(=NH)-NH_2, -NH-C(=NH)-NH_2 or -C(=O)-N=C(NH_2)$_2$, each of which is unsubstituted or monosubstituted by -COR, -COOR, -OH or by a conventional amino-protecting group, or is



or



A is alkyl having 1-4 carbon atoms,

Hal is F, Cl, Br or I,

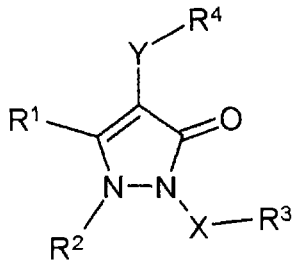
m is 1 or 2,

n is 0 or 1,

and salts and solvates thereof,

which are described in WO 0040583,

g) the compounds of the formula I



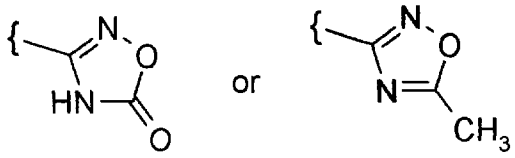
I

in which

R^1 and R^2 are each, independently of one another, H, A, cycloalkyl-[C($R^7R^{7'}$)]$_n$- or Ar-[C($R^7R^{7'}$)]$_n$-,

R^3 and R^4 are each, independently of one another, H, Ar, Het or R^5, where at least one of the two radicals is R^5,

R^5 is phenyl, naphthyl or biphenyl, each of which is substituted by –C(=NH)-NH_2, which may also be monosubstituted by –COA, Ar-[C($R^7R^{7'}$)]$_n$-CO-, COOA, OH or by a conventional amino-protecting group, -NH-C(=NH)-NH_2, -CO-N=C(NH_2)$_2$,



and which may optionally additionally be monosubstituted or disubstituted by A, Ar', Het, OR^6, $NR^6R^{6'}$, NO_2, CN, Hal, NR^6COA, NR^6COAr', NR^6SO_2A, NR^6SO_2Ar', $COOR^6$, $CO\text{-}NR^6R^{6'}$, COR^7, CO-Ar', $SO_2NR^6R^{6'}$, $S(O)_nAr'$ or $S(O)_nA$,

R^6 and $R^{6'}$ are each, independently of one another, H, A, $CR^7R^{7'}$-Ar' or $CR^7R^{7'}$-Het,

R^7 and $R^{7'}$ are each, independently of one another, H or A,

X and Y are each, independently of one another, $(CR^7R^{7'})_n$,

A is alkyl having 1-20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms and/or by –CH=CH- groups and/or in addition 1-7 H atoms may be replaced by F,

Ar is phenyl, naphthyl or biphenyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, Ar', Het, OR^6, $NR^6R^{6'}$, NO_2, CN, Hal, NR^6COA, NR^6COAr', NR^6SO_2A, NR^6SO_2Ar', $COOR^6$, $CO\text{-}NR^6R^{6'}$, CON^6Ar', COR^7, COAr', $SO_2NR^6R^{6'}$, $S(O)_nAr'$ or $S(O)_nA$,

Ar' is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR^7, $NR^7R^{7'}$, NO_2, CN, Hal, NR^7COA, NR^7SO_2A, $COOR^7$, $CO\text{-}NR^7R^{7'}$, COR^7, $SO_2NR^7R^{7'}$ or $S(O)_nA$,

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR^7, $NR^7R^{7'}$, NO_2, CN, Hal, NR^7COA, NR^7SO_2A, $COOR^7$, $CO\text{-}NR^7R^{7'}$, COR^7, $SO_2NR^7R^{7'}$, $S(O)_nA$ and/or carbonyl oxygen,

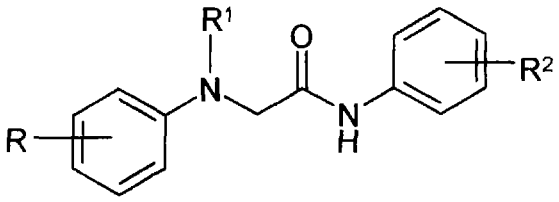
Hal is F, Cl, Br or I,

n is 0, 1 or 2,

and their pharmaceutically tolerated salts and solvates,

which are described in WO 0051989,

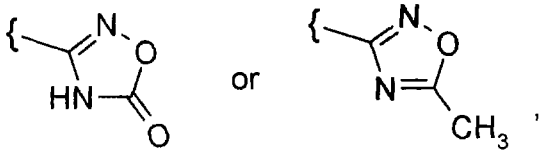
h) compounds of the formula I



I

in which

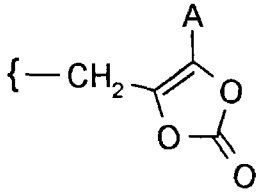
R is -CO-N=C(NH_2)$_2$, -NH-C(=NH)-NH_2 or –C(=NH)-NH_2, which may also be monosubstituted by OH, -OCOOA, -OCOO(CH_2)$_n$NAA', -COO(CH_2)$_n$NAA', -OCOO(CH_2)$_m$-Het, -COO(CH_2)$_m$-Het, -CO-CAA'-R^3, -COO-CAA'-R^3, COOA, COSA, COOAr, COOAr' or by a conventional amino-protecting group, or is



R^1 is unbranched, branched or cyclic alkyl having 1-20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms, or is Ar, Ar' or X,

R^2 is phenyl which is monosubstituted by S(O)$_p$A, S(O)$_p$NHA, CF_3, COOA, CH_2NHA, CN or OA,

R^3 is -C(Hal)$_3$, -O(C=O)A or



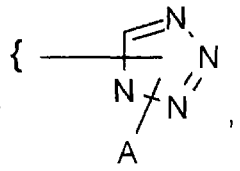
Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OA, NAA', NO_2, CF_3, CN, Hal, NHCOA, COOA, CONAA', S(O)$_p$A or S(O)$_p$NAA',

Ar' is -(CH_2)$_n$-Ar,

A and A' are each, independently of one another, H or unbranched, branched or cyclic alkyl having 1-20 carbon atoms,

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or substituted by A,

X is $-(CH_2)_n-Y$,

Y is COOA or ,

Hal is F, Cl, Br or I,

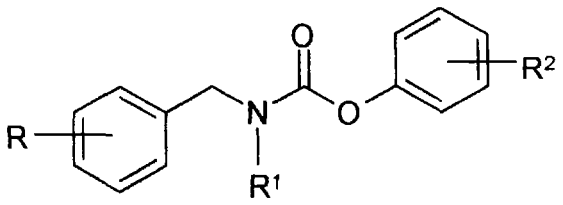
m is 0 or 1,

n is 1, 2, 3, 4, 5 or 6,

p is 0, 1 or 2,

and their pharmaceutically tolerated salts and solvates,

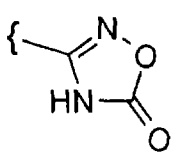
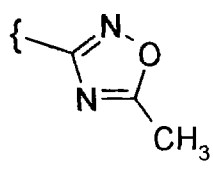
i) compounds of the formula I

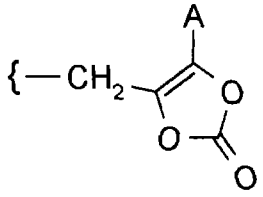
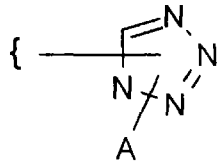


I

in which

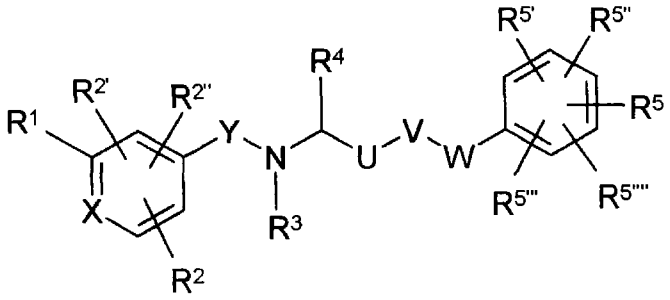
R is $-CO-N=C(NH_2)_2$, $-NH-C(=NH)-NH_2$ or $-C(=NH)-NH_2$, which may also be monosubstituted by OH, -OCOOA, $-OCOO(CH_2)_nNAA'$, $-COO(CH_2)_nNAA'$, $-OCOO(CH_2)_m$-Het, $-COO(CH_2)_m$-Het, $-CO-CAA'-R^3$, $-COO-CAA'-R^3$, COOA, COSA, COOAr, COOAr' or by a conventional amino-protecting group, or is

 or ,

	R^1	is unbranched, branched or cyclic alkyl having 1-20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms, or is Ar, Ar' or X,
	R^2	is phenyl which is monosubstituted by $S(O)_pA$, $S(O)_pNHA$, CF_3, COOA, CH_2NHA, CN or OA,
	R^3	is $-C(Hal)_3$, $-O(C=O)A$ or  ,
	Ar	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OA, NAA', NO_2, CF_3, CN, Hal, NHCOA, COOA, CONAA', $S(O)_pA$ or $S(O)_pNAA'$,
	Ar'	is $-(CH_2)_n$-Ar,
	A and A'	are each, independently of one another, H or unbranched, branched or cyclic alkyl having 1-20 carbon atoms,
	Het	is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or substituted by A,
	X	is $-(CH_2)_n$-Y,
	Y	is COOA or  ,
	Hal	is F, Cl, Br or I,
	m	is 0 or 1,
	n	is 1, 2, 3, 4, 5 or 6,
	p	is 0, 1 or 2,

and their pharmaceutically tolerated salts and solvates,

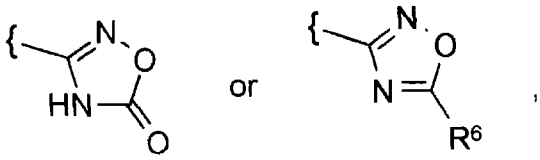
j) compounds of the formula I



I

in which

R^1 is H, Cl, F, OH, OA, O-$(CH_2)_n$-Ar, NH_2, NHCOA, NHCOOA, NH-$(CH_2)_n$-Ar, CN, $CONH_2$, $CSNH_2$, C(=NH)SA, $C(=NH)NH_2$, C(=NH-OH)-NH_2, C(=NH-O-COA)-NH_2, C(=NH-O-COAr)-NH_2, C(=NH-O-COHet)-NH_2, C(=NH)-OA, $C(=NH)NHNH_2$, C(=NH)NHNHA, C(=NH)NH-COOA, C(=NH)NH-COA, C(=NH)NH-COO-$(CH_2)_m$-Ar, C(=NH)NH-COO-$(CH_2)_m$-Het, NH-C(=NH)NH_2, NH-C(=NH)NH-COOA, NHC(=NH)NH-COO-$(CH_2)_m$-Ar,



R^2, $R^{2'}$ and $R^{2''}$ are each, independently of one another, H, A, CF_3, Cl, F, COA, COOH, COOA, $CONH_2$, CONHA, $CONA_2$, CH_2NH_2, CH_2NHCOA, $CH_2NHCOOA$, OH, OA, OCF_3, NO_2, SO_2A, SO_2NH_2 or SO_2NHA,

R^3 and R^4 together are $(CH_2)_p$, $CO(CH_2)_p$, $COO(CH_2)_n$, COOCH(A)-, COOCH(Ar)-, $CONH(CH_2)_n$, $CH_2CH(OR^7)$-$(CH_2)_n$-, CH_2-O-$(CH_2)_n$, CH_2-S-$(CH_2)_n$, CA_2-O-$(CH_2)_n$, CA_2-S-$(CH_2)_n$, CHAr-S-$(CH_2)_n$, $(CH_2)_2NHCH_2$ or $(CH_2)_2$-N(R^8)-CH_2,

R^5, $R^{5'}$, $R^{5''}$, $R^{5'''}$ and $R^{5''''}$ are each, independently of one another, $(CH_2)_n$-COOH, $(CH_2)_n$-COO-$(CH_2)_n$-Ar, Ar, Py or R^2,

R^6 is OH, A or Ar,

	R^7	is H, A, Ar or Het,
	R^8	is H, $(CH_2)_n$-COOH, $(CH_2)_m$-COOA, $(CH_2)_m$-COO-$(CH_2)_n$-Ar, $(CH_2)_m$-COO-$(CH_2)_n$-Het, $(CH_2)_m$-$CONH_2$, $(CH_2)_m$-CONHA, $(CH_2)_m$-$CONA_2$, A, COA, SO_2A or SO_3H,
	R^9	is H, A or benzyl,
	U	is CO or CH_2,
	V	is NH or CO,
	W	is absent or is CO,
	X	is CH or N,
	Y	is absent or is CH_2, CO or SO_2,
	A	is unbranched, branched or cyclic alkyl having 1-20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms, -CH=CH- or -C≡C- and/or 1-7 H atoms may be replaced by F,
	Ar	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, CF_3, Hal, OH, OA, OCF_3, SO_2A, SO_2NH_2, SO_2NHA, SO_2NA_2, NH_2, NHA, NA_2, NHCHO, NHCOA, NHCOOA, NACOOA, $NHSO_2A$, $NHSO_2Ar$, COOH, COOA, COO-$(CH_2)_m$-Ar', COO-$(CH_2)_m$-Het, $CONH_2$, CONHA, $CONA_2$, CONHAr', CHO, COA, COAr', CH_2Ar', $(CH_2)_mNH_2$, $(CH_2)_mNHA$, $(CH_2)_mNA_2$, $(CH_2)_mNHCHO$, $(CH_2)_mNHCOA$, $(CH_2)_mNHCOOA$, $(CH_2)_mNHCOO$-$(CH_2)_mAr'$, $(CH_2)_mNHCOO$-$(CH_2)_mHet$, NO_2, CN, $CSNH_2$, C(=NH)SA, C(=NH)OA, $C(=NH)NH_2$, C(=NH)NHOH, C(=NH)NHCOOA or C(=NH)NHCOOAr',
	Ar'	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR^9, $N(R^9)_2$, NO_2, CN, Hal, NHCOA, $COOR^9$, $CON(R^9)_2$, COR^9 or $S(O)_2A$,
	Het	is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1-4 N, O and/or S atoms, bonded via N or C, which is unsubstituted or monosubstituted, disubstituted, trisubstituted or tetra-substituted by A, CF_3, Hal, OH, OA, OCF_3, SO_2A,

SO_2-$(CH_2)_m$-Ar, SO_2NH_2, SO_2NHA, SO_2NA_2, NH_2, NHA, NA_2, NHCHO, NHCOA, NHCOOA, NACOOA, $NHSO_2A$, $NHSO_2Ar$, COOH, COOA, COO-$(CH_2)_m$-Ar', $CONH_2$, CONHA, COA, COAr', CH_2NH_2, CH_2NHA, CH_2NHCHO, CH_2NHCOA, $CH_2NHCOOA$, NO_2, CN, $CSNH_2$, C(=NH)SA, C(=NH)OA, $C(=NH)NH_2$, C(=NH)NHOH, C(=NH)NHCOOA, C(=NH)COOAr' and/or carbonyl oxygen,

Py is 2-, 3- or 4-pyridyl, each of which is unsubstituted or monosubstituted or polysubstituted by A, Hal, CN, $CONH_2$, CONHA, COOH, COOA, CH_2NH_2, CH_2NHA, CH_2NHCHO, CH_2NHCOA, $CH_2NHCOOA$, CH_2OH, CH_2OA, CH_2OAr, CH_2OCOA, NO_2, NH_2, NHA or NA_2,

Hal is F, Cl, Br or I,

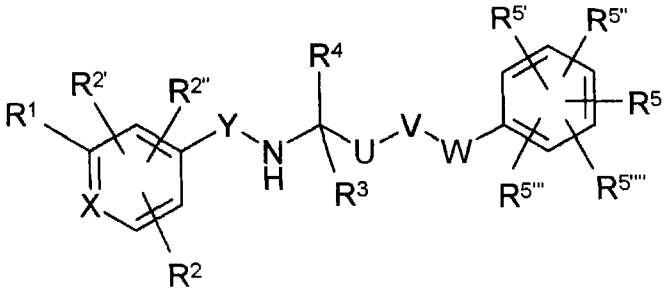
n is 1 or 2,

m is 0, 1 or 2,

p is 2, 3 or 4,

and their pharmaceutically tolerated salts and solvates,

k) compounds of the formula I

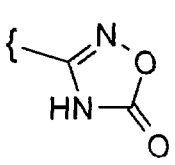
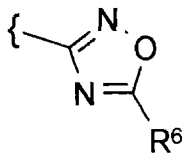


I

in which

R^1 is H, Cl, F, OH, OA, O-$(CH_2)_n$-Ar, NH_2, NHCOA, NHCOOA, NH-$(CH_2)_n$-Ar, CN, $CONH_2$, $CSNH_2$, C(=NH)SA, $C(=NH)NH_2$, C(=NH-OH)-NH_2, C(=NH-O-COA)-NH_2, C(=NH-O-COAr)-NH_2, C(=NH-O-COHet)-NH_2, C(=NH)-OA, $C(=NH)NHNH_2$, C(=NH)NHNHA, C(=NH)NH-COOA, C(=NH)NH-COA, C(=NH)NH-COO-$(CH_2)_m$-Ar,

$C(=NH)NH\text{-}COO\text{-}(CH_2)_m\text{-}Het$, $NH\text{-}C(=NH)NH_2$, $NH\text{-}C(=NH)NH\text{-}COOA$, $NHC(=NH)NH\text{-}COO\text{-}(CH_2)_m\text{-}Ar$,

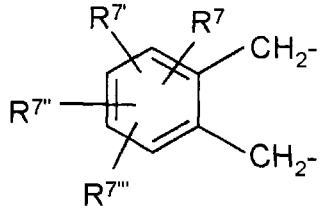

or

,

R^2, $R^{2'}$ and $R^{2''}$ are each, independently of one another, H, A, CF_3, Cl, F, COA, COOH, COOA, $CONH_2$, CONHA, $CONA_2$, CH_2NH_2, CH_2NHCOA, $CH_2NHCOOA$, OH, OA, OCF_3, NO_2, SO_2A, SO_2NH_2, SO_2NHA or SO_2NA_2,

R^3 is A, $(CH_2)_n$-Ar or $(CH_2)_n$-Het,

R^4 is A,

R^3 and R^4 together are alternatively $(CH_2)_p$, $(CH_2)_n\text{-}N(R^8)\text{-}(CH_2)_2$, $(CH_2)_2\text{-}CH(NH_2)\text{-}(CH_2)_2$-, $(CH_2)_2\text{-}CH(NH\text{-}COOA)\text{-}(CH_2)_2$-, $(CH_2)_2\text{-}CH(NH\text{-}CH_2\text{-}COOA)\text{-}(CH_2)_2$-, $(CH_2)_2\text{-}CH[NH\text{-}CH(A)\text{-}COOA]\text{-}(CH_2)_2$-, $(CH_2)_2\text{-}O\text{-}(CH_2)_2$, $(CH_2)_2\text{-}S(O)_m\text{-}(CH_2)_2$ or


,

R^5, $R^{5'}$, $R^{5''}$, $R^{5'''}$ and $R^{5''''}$ are each, independently of one another, $(CH_2)_n$-COOH, $(CH_2)_n$-COOA, $(CH_2)_n\text{-}COO\text{-}(CH_2)_m$-Ar, $(CH_2)_n\text{-}COO\text{-}(CH_2)_m$-Het, Ar, Py or R^2,

R^6 is OH, A or Ar,

R^7, $R^{7'}$, $R^{7''}$ and $R^{7'''}$ are each, independently of one another, H, Hal, OH, OA, COOH, COOA, $COO(CH_2)_mAr$, $CONH_2$, CONHA or $CONA_2$,

R^8 is H, A, COA, COOA, $(CH_2)_n$-COOH, $(CH_2)_m$-COOA, $COO\text{-}(CH_2)_m$-Ar, $COO\text{-}(CH_2)_m$-Het,

		$(CH_2)_n$-COO-$(CH_2)_m$-Ar, $(CH_2)_n$-COO-$(CH_2)_m$-Het, $(CH_2)_m$-$CONH_2$, $(CH_2)_m$-CONHA, $(CH_2)_m$-$CONA_2$, SO_2A or SO_3H,
	R^9	is H, A or benzyl,
	U	is CO or CH_2,
	V	is NH or CO,
	W	is absent or is CO,
	X	is CH or N,
	Y	is absent or is CH_2, CO or SO_2,
	A	is unbranched, branched or cyclic alkyl having 1-20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms, -CH=CH- or -C≡C- and/or 1-7 H atoms may be replaced by F,
	Ar	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, CF_3, Hal, OH, OA, OCF_3, SO_2A, SO_2NH_2, SO_2NHA, SO_2NA_2, NH_2, NHA, NA_2, NHCHO, NHCOA, NHCOOA, NACOOA, $NHSO_2A$, $NHSO_2Ar$, COOH, COOA, COO-$(CH_2)_m$-Ar', COO-$(CH_2)_m$-Het, $CONH_2$, CONHA, $CONA_2$, CONHAr', CHO, COA, COAr', CH_2Ar', $(CH_2)_mNH_2$, $(CH_2)_m$NHA, $(CH_2)_mNA_2$, $(CH_2)_m$NHCHO, $(CH_2)_m$NHCOA, $(CH_2)_m$NHCOOA, $(CH_2)_m$NHCOO-$(CH_2)_m$Ar', $(CH_2)_m$NHCOO-$(CH_2)_m$Het, NO_2, CN, $CSNH_2$, C(=NH)SA, C(=NH)OA, $C(=NH)NH_2$, C(=NH)NHOH, C(=NH)NHCOOA or C(=NH)NHCOOAr',
	Ar'	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR^9, $N(R^9)_2$, NO_2, CN, Hal, NHCOA, $COOR^9$, $CON(R^9)_2$, COR^9 or $S(O)_2A$,
	Het	is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having 1-4 N, O and/or S atoms, bonded via N or C, which is unsubstituted or monosubstituted, disubstituted, trisubstituted or tetra-substituted by A, CF_3, Hal, OH, OA, OCF_3, SO_2A, SO_2-$(CH_2)_m$-Ar, SO_2NH_2, SO_2NHA, SO_2NA_2, NH_2, NHA, NA_2, NHCHO, NHCOA, NHCOOA, NACOOA, $NHSO_2A$,

$NHSO_2Ar$, COOH, COOA, $COO-(CH_2)_m-Ar'$, $CONH_2$, CONHA, COA, COAr', CH_2NH_2, CH_2NHA, CH_2NHCHO, CH_2NHCOA, $CH_2NHCOOA$, NO_2, CN, $CSNH_2$, C(=NH)SA, C(=NH)OA, $C(=NH)NH_2$, C(=NH)NHOH, C(=NH)NHCOOA, C(=NH)COOAr' and/or carbonyl oxygen,

Py is 2-, 3- or 4-pyridyl, each of which is unsubstituted or monosubstituted or polysubstituted by A, Hal, CN, $CONH_2$, CONHA, COOH, COOA, CH_2NH_2, CH_2NHA, CH_2NHCHO, CH_2NHCOA, $CH_2NHCOOA$, CH_2OH, CH_2OA, CH_2OAr, CH_2OCOA, NO_2, NH_2, NHA or NA_2,

Hal is F, Cl, Br or I,

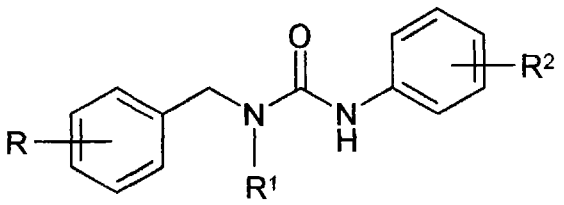
n is 1 or 2,

m is 0, 1 or 2,

p is 2, 3, 4 or 5,

and their pharmaceutically tolerated salts and solvates,

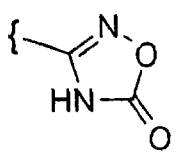
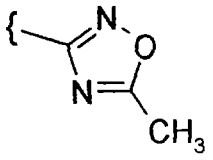
I) compounds of the formula I



I

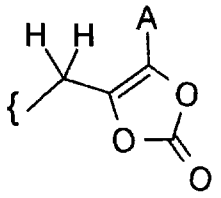
in which

R is CN, CH_2NH_2, $-NH-C(=NH)-NH_2$, $-CO-N=C(NH_2)_2$, $-C(=NH)-NH_2$, which may also be monosubstituted by Ar', OH, O-COA, O-COAr, OCOOA, $OCOO(CH_2)_nN(A)_2$, $-COO(CH_2)_nNA_2$, $OCOO(CH_2)_mHet$, $COO-(CH_2)_m-Het$, $CO-C(A)_2-R^3$, COOA, COSA, COSAr, COOAr, COOAr', COA, COAr, COAr' or by a conventional amino-protecting group, or is

 or ,

R^1 is R^4, Ar, Ar' or X,

R^2 is phenyl which monosubstituted by SA, SOA, SO_2A, SONHA, SO_2NHA, CF_3,COOA, CH_2NHA, CN or OA,

R^3 is $CHal_3$, OCOA or ,

R^4 is alkyl having 1-20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms and/or by –CH=CH- groups and/or in addition 1-7 H atoms may be replaced by F,

A is H or alkyl having 1-20 carbon atoms,

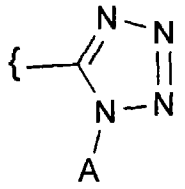
A' is alkyl having 1-10 carbon atoms,

Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A', OH, OA', NH_2, NHA', NA'_2, NO_2, CF_3, CN, Hal, NHCOA, COOA, $CONH_2$, CONHA', $CONA'_2$, SA, SOA, SO_2A, SO_2NH_2, SO_2NHA' or $SO_2NA'_2$,

Ar' is $(CH_2)_n$-Ar,

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, which may be unsubstituted or mono-substituted, disubstituted or trisubstituted by A', OA', NH_2, NHA', NA'_2, NO_2, CN, Hal, NHCOA', $NHSO_2A'$, COOA, $CONH_2$, CONHA', $CONA'_2$, COA, SO_2NH_2, SA', SOA', SO_2A' and/or carbonyl oxygen,

X is $(CH_2)_nY$,

Y is COOA or ,

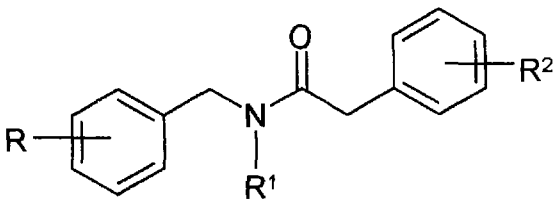
Hal is F, Cl, Br or I,

n is 1, 2, 3, 4, 5 or 6,

m is 0 or 1,

and their pharmaceutically tolerated salts and solvates,

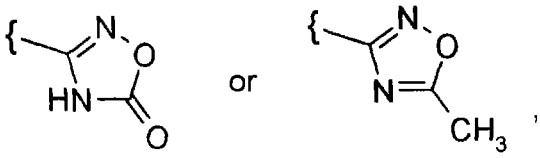
m) compounds of the formula I



I

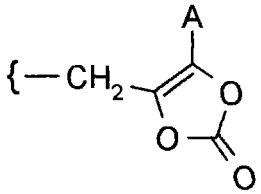
in which

R is CH_2NH_2, -CO-N=C(NH_2)$_2$, -NH-C(=NH)-NH_2 or -C(=NH)-NH_2, which may also be monosubstituted by OH, -OCOOA, -OCOO(CH_2)$_n$NAA', -COO(CH_2)$_n$NAA', -OCOO(CH_2)$_m$-Het, -COO(CH_2)$_m$-Het, -CO-CAA'-R^3, -COO-CAA'-R^3, COOA, COSA, COOAr, COOAr' or by a conventional amino-protecting group, or is



R^1 is unbranched, branched or cyclic alkyl having 1-20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms, or is Ar, Ar' or X,

R^2 is phenyl which is monosubstituted by S(O)$_p$A, S(O)$_p$NHA, CF_3, COOA, CH_2NHA, CN or OA,

R^3 is -C(Hal)$_3$, -O(C=O)A or ,

Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A,

OA, NAA', NO_2, CF_3, CN, Hal, NHCOA, COOA, CONAA', $S(O)_pA$ or $S(O)_pNAA'$,

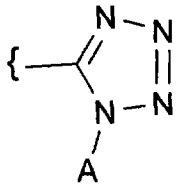
Ar' is $-(CH_2)_n$-Ar,

A is H or unbranched, branched or cyclic alkyl having 1-20 carbon atoms,

A' is unbranched, branched or cyclic alkyl having 1-10 carbon atoms,

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or substituted by A,

X is $-(CH_2)_n$-Y,

Y is COOA or ,

Hal is F, Cl, Br or I,

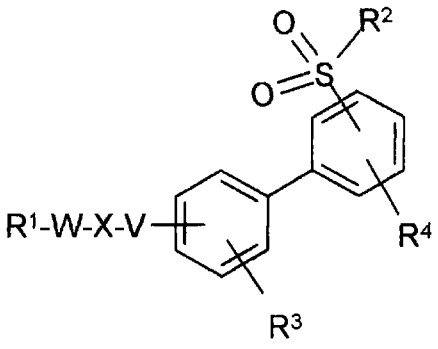
m is 0 or 1,

n is 1, 2, 3, 4, 5 or 6,

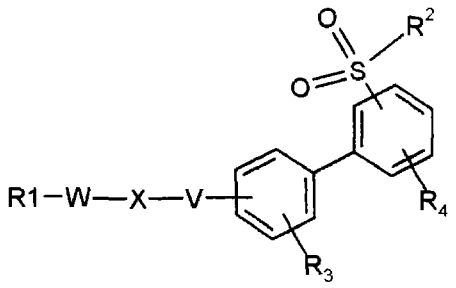
p is 0, 1 or 2,

and their pharmaceutically tolerated salts and solvates,

n) compounds of the formula I



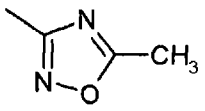
I



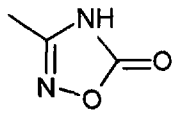
I

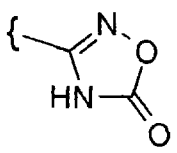
in which:

R^1 is phenyl or naphthyl, each of which is substituted by $-C(=NH)NH_2$, which may also be monosubstituted by -COA, $-CO-[C(R^6)_2-Ar'$, -COOA, -OH or by a conventional amino-protecting group, $-NHC(=NH)-NH_2$,

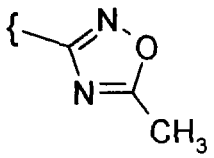


or





or



,

and which may optionally be substituted by -A, $-OR^5$, $-N(R^5)_2$, $-NO_2$, -CN, -Hal, $-NR^5COA$, $-NR^5COAr'$, $-NR^5SO_2A$, $-NR^5SO_2Ar'$, $-COOR^5$, $-CON(R^5)_2$, $-CONR^5Ar'$, $-COR^6$, -COAr' or $S(O)_nA$;

R^2 is $-N(R^5)_2$, $-NR^5COA$, $-NR^5COAr$ or $-NR^5COOR^5$;

R^3 and R^4, independently of one another, are -H, -A, $-OR^5$, $-N(R^5)_2$, $-NO_2$, -CN, -Hal, $-NR^5COA$, $-NR^5COAr'$, $-NR^5SO_2A$, $-NR^5SO_2Ar'$, $-COOR^5$, $-CON(R^5)_2$, $-CONR^5Ar'$, $-COR^6$, -COAr', -S(O)Ar' or $S(O)_nA$;

R^5- R^6 and R^7, is H, -A, $-C(R^6R^7)Ar'$ or $-C(R^6R^7)Het$;

independently of one another, are -H, -A or $-(CH_2)_l-Ar'$;

R^8 is H or A;

X is -O-, $-NR^5-$, $-CONR^5-$, $-N(SO_2Ar)-$ or $-N(SO_2Het)-$;

W is $-(CR^6R^7)_n-$, $-OCR^6R^7-$, 1,3-phenylene, 1,3-phenylene-$-C(R^6)_2-$, 1,4-phenylene or 1,4-phenylene-$C(R^6)_2-$;

V is $-(C(R^6)_2)_m-$,

A is alkyl having from 1 to 20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms or by -CH=CH- groups and in addition by from 1 to 7 H atoms may be replaced by F;

Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by -A, -Ar', -Het, $-OR^5$, $-N(R^5)_2$, $-NO_2$, -CN, -Hal, $-NR^5COA$, $-NR^5COAr$, $-NR^5SO_2A$, $-NR^5SO_2Ar'$, $-COOR^5$, $-CON(R^5)_2$, $-CONR^5Ar'$, $-COR^6$, -COAr' or $-S(O)_nA$,

Ar' is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by -A, $-OR^6$, $-N(R^6)_2$, $-NO_2$, -CN, -Hal, $-NR^6COA$, $-NR^6SO_2A$, $-COOR^6$, $-CON(R^6)_2$, $-COR^6$, $-SO_2NR^6$ or $-S(O)_nA$,

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by -A, $-OR^6$, $-N(R^6)_2$, $-NO_2$, -CN, -Hal, $-NR^6COA$, $-NR^6SO_2A$, $-COOR^6$, $-CON(R^6)_2$, $-COR^6$, $-SO_2NR6$, $-S(O)_nA$ and/or carbonyl oxygen;

Hal is -F, -Cl, -Br or -I;

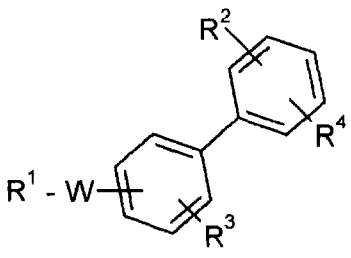
l is 0, 1, 2, 3, 4 or 5;

m is 0 or 1,

n is 0, 1 or 2;

and their pharmaceutically tolerated salts and solvates,

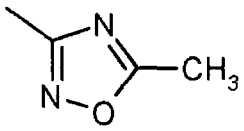
o) compounds of the formula I



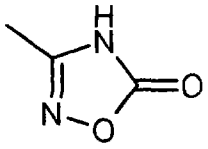
I

in which

R^1 is phenyl or naphthyl, each of which is substituted by $-C(=NH)NH_2$, which may also be monosubstituted by -COA, $-CO-[C(R^7)_2]_n-Ar'$, -COOA, -OH or by a conventional amino-protecting group, $-NHC(=NH)-NH_2$, $-CON=C(NH_2)_2$,



or



and which may optionally be substituted by -A, $-OR^5$, $-N(R^5)_2$, $-NO_2$, -CN, -Hal, $-NR^5COA$, $-NR^5COAr'$, $-NR^5SO_2A$, $-NR^5SO_2Ar'$, $-COOR^5$, $-CON(R^5)_2$, $-COR^7$, -COAr' or $S(O)_nA$;

R^2 is $-S(O)_nA$, $-CF_3$, $-COOR^7$ or -OA;

R^3 and R^4, independently of one another, are -H, -A, $-OR^5$, $-N(R^5)_2$, $-NO_2$, -CN, -Hal, $-NR^5COA$, $-NR^5COAr'$, $-NR^5SO_2A$, $-NR^5SO_2Ar'$, $-COOR^5$, $-CON(R^5)_2$, $-CONR^5Ar'$, $-COR^7$, -COAr' or $-S(O)_nA$;

R^5 and R^6, independently of one another, are -H, -A, $-[C(R^7R^8)]_nAr'$ or $-[C(R^7R^8)]_nHet$;

R^7 and R^8, independently of one another, are -H or -A;

W is $-[C(R^5R^6)]_mCONR^5[C(R^5R^6)]_l-$ or $-OC(R^5R^6)CONR^5[C(R^5R^6)]_l-$;

A is alkyl having from 1 to 20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms or by -CH=CH- groups and in addition from 1 to 7 H atoms may be replaced by -F;

Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by -A, -Ar', -Het, $-OR^5$, $-N(R^5)_2$, $-NO_2$, -CN, -Hal, $-NR^5COA$, $-NR^5COAr$, $-NR^5SO_2A$, $-NR^5SO_2Ar'$, $-COOR^5$, $-CON(R^5)_2$, $-CONR^5Ar'$, $-COR^7$, -COAr', $-SO_2NR^5$, $-S(O)_nAr'$ or $-S(O)_nA$,

Ar' is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by -A, -OR^7, -$N(R^7)_2$, -NO_2, -CN, -Hal, -NR^7COA, -NR^7SO_2A, -$COOR^7$, -$CON(R^7)_2$, -COR^7, -SO_2NR^7 or -$S(O)_nA$;

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by -A, -OR^7, -$N(R^7)_2$, -NO_2, -CN, -Hal, -NR^7COA, -NR^7SO_2A, -$COOR^7$, -$CON(R^7)_2$, -COR^7, -SO_2NR^7, -$S(O)_nA$ and/or carbonyl oxygen;

Hal is -F, -Cl, -Br or -I;

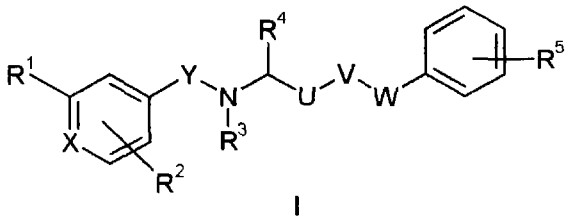
l is 0 or 1,

m is 1 or 2;

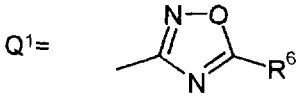
n is 0, 1 or 2;

and their pharmaceutically tolerated salts and solvates,

p) compounds of the formula I



I



in which

R^1 is H, Cl, F, OH, OA, O-$(CH_2)_n$-Ar, NH_2, NHCOA, NHCOOA, NH-$(CH_2)_n$-Ar, CN, $CONH_2$, $CSNH_2$, C[NH]SA, C[NH]NH_2, C[NH]NHA, C[NH]NOH, C[NH]NOA, C[NH]NOCOA, C[NH]NOCOAr, C[NH]OA, C[NH]$NHNH_2$, C[NH]NHNHA, C[NH]NHCOOA, C[NH]NHCOA C[NH]NHCOO-$(CH_2)_m$-Ar, C[NH]NHCOO-$(CH_2)_m$-Het, NHC[NH]NH_2, NHC[NH]NHCOOA, NHC[NH]NHCOO-$(CH_2)_m$-Ar or Q1,

R^2 is H or one or more A, CF_3, Br, Cl, F, COA, COOH, COOA, $CONH_2$, CONHA, $CONA_2$, CH_2NH_2, CH_2NHCOA,

$CH_2NHCOOA$, $NHSO_2A$, OH, OA, OCF_3, NO_2, SO_2A, SO_2NH_2 or SO_2NHA,

R^3 is H, COH, COA, $COCF_3$, COOA or SO_2A

R^4 is H, A, $-(CH_2)_n$-Ar, $-(CH_2)_n$-Het, $-(CH_2)_m$-$COOR^7$, $-(CH_2)_m$-$CONHR^7$, $-(CH_2)_n$ $-S(O)_mA$, $-(CH_2)_o$-NH_2, $-(CH_2)_o$-NHCOOA, $-(CH_2)_o$-NHCOA, $-(CH_2)_o$-NHAr, $-(CH_2)_o$-$NHC[NH]NH_2$, $-(CH_2)_o$-(C[A]OH)-A, $-(CH_2)_o$-OH, $-(CH_2)_o$-OA, $-(CH_2)_o$-OAr, $-(CH_2)_o$-OHet, $-(CH_2)_o$-OCOOA, $-(CH_2)_o$-OCOA, $-(CH_2)_o$-OCOAr, Ar or Het,

R^5 is $-(CH_2)_n$-COOH, $-(CH_2)_n$-COOA, $-(CH_2)_n$-$COO(CH_2)_n$Ar, Ar, Py or R^2,

R^6 is OH, A or Ar,

R^7 is H, A, Ar or Het,

U is CO or CH_2,

V is NH, CO or O,

W is a bond or CO,

X is CH or N,

Y is a bond or CH_2, CO or SO_2,

n is 1 or 2,

m is 0, 1 or 2,

o is 1, 2, 3, 4 or 5,

p is 2, 3 or 4,

A is alkyl having 1 - 20 carbon atoms (linear, branched or cyclic), in which one or two CH_2 groups may be replaced by O or S atoms or by -CH=CH- or -C≡C- groups and in addition 1 – 7 H atoms may be replaced by F,

Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, CF_3, Hal, OA, OCF_3, SO_2A, SO_2NH_2, SO_2NHA, SO_2NA_2, NH_2, NHA, NA_2, NHCHO, NHCOA, NHCOOA, NACOOA, $NHSO_2A$, $NHSO_2Ar$, COOH, COOA, $COO-(CH_2)_m$-Ar, $COO-(CH_2)_m$-Het $CONH_2$, CONHA, $CONA_2$, CONHAr, COA, COAr, CH_2Ar, $-(CH_2)_m$-NH_2, $-(CH_2)_m$-NHA, $-(CH_2)_m$-NA_2, $-(CH_2)_m$-NHCHO, $-(CH_2)_m$-NHCOA, $-(CH_2)_m$-NHCOOA $-(CH_2)_m$-$NHCOO-(CH_2)_m$Ar,

$-(CH_2)_m$-NHCOO-$(CH_2)_m$-Het, $-(CH_2)_m$-Hal, $-(CH_2)_m$-Het, NO_2, CN, $CSNH_2$, C[NH]SA, C[NH]OA, $C[NH]NH_2$, C[NH]NHOH, C[NH]NHCOOA or C[NH]NHCOOAr,

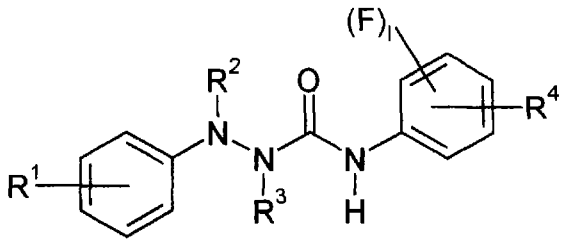
Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or monosubstituted, disubstituted, trisubstituted or tetrasubstituted by A, CF_3, Hal, OH, OA, SO_2A, SO_2-$(CH_2)_m$-Ar, SO_2NH_2, SO_2NHA, SO_2NA_2, NH_2, NHA, NA_2, NHCHO, NHCOA, NHCOOA, $NHSO_2A$, $NHSO_2Ar$, COOH, COOA, COO-$[CH_2]_m$-Ar, $CONH_2$, CONHA, COA, COAr, CH_2NH_2, CH_2NHA, CH_2NHCHO, CH_2NHCOA, $CH_2NHCOOA$, NO_2, CN, $CSNH_2$, C[NH]SA, C[NH]OA, $C[NH]NH_2$, C[NH]NHOH, C[NH]NHCOOA, C[NH]NHCOOAr and/or carbonyl oxygen,

Py is 2-, 3- and/or 4-pyridyl, unsubstituted or monosubstituted or polysubstituted by A, Hal, CN, $CONH_2$, CONHA, COOH, COOA, CH_2NH_2, CH_2NHA, CH_2NHCHO, CH_2NHCOA, $CH_2NHCOOA$, CH_2OH, CH_2OA, CH_2OAr, CH_2OCOA, NO_2, NH_2, NHA or NA_2,

Hal is F, Cl, Br or I,

and their pharmaceutically tolerated salts and solvates,

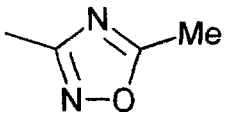
q) *compounds of the formula I*



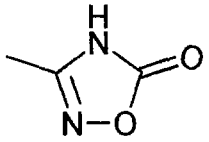
in which

R^1 is $-(CH_2)_n-NH_2$, $-CON=C(NH_2)_2$, $-NHC(=NH)-NH_2$ or $-C(=NH)-NH_2$, which may also be monosubstituted by -OH, -OCOOA, $-OCOO(CH_2)_nN(A)_2$, $-OCOO(CH_2)_m$-Het,

-CO-C(A)$_2$-R^5, -COOA, -COSA, -COOAr, -COOAr' or



or

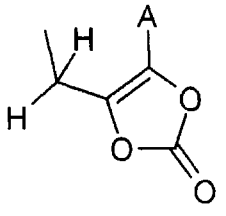


by

R^2 is H or COOA,

R^3 is unbranched, branched or cyclic alkyl having 1-20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms, or is Ar, Ar', X or Hal,

R^4 is phenyl which is monosubstituted by $S(O)_kA$, $S(O)_kNHA$, CF_3, COOA, CH_2NHA, CN or OA,



R^5 is -CHal$_3$, -O(C=O)A or ,

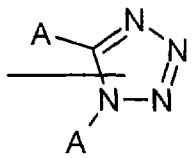
Ar is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OH, OA, NH_2, NHA, NA_2, NO_2, CF_3, CN, Hal, NHCOA, COOA, $CONH_2$, CONHA, $CONA_2$, $S(O)_nA$, $S(O)_nNH_2$, $S(O)_nNHA$ or $S(O)_nNA_2$,

Ar' is $-(CH_2)_n$-Ar,

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or substituted by A,

A is H or unbranched, branched or cyclic alkyl having 1-20 carbon atoms,

X is $-(CH_2)_n$-Y,



Y is COOA, ,

Hal is F, Cl, Br or I,

n is 1, 2, 3, 4, 5 or 6,

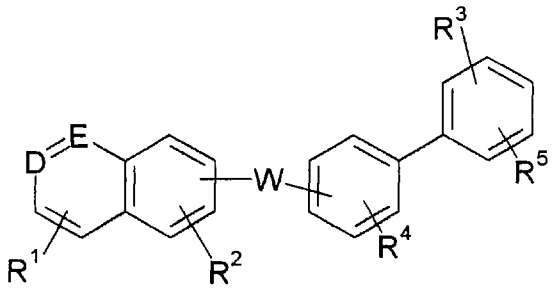
m is 0 or 1,

k is 0, 1 or 2,

l is 0, 1, 2, 3 or 4,

and their pharmaceutically tolerated salts and solvates,

r) compounds of the formula I



I

in which

-D=E-	is $-N=C(NH_2)-$ or $-C(NH_2)=N-$,
R^1 and R^2,	independently of one another, are H, A, OR^6, $N(R^6)_2$, NO_2, CN, Hal, NR^6COA, NR^6COAr', NR^6SO_2A, NR^6SO_2Ar', $COOR^6$, $CON(R^6)_2$, $CONR^6Ar'$, COR^7, $COAr'$ or $S(O)_nA$,
R^3	is $SO_2(NR^6)_2$, $S(O)_nA$, CF_3, $COOR^6$, OA or CN,
R^4 and R^5,	independently of one another, are H, A, OR^6, $N(R^6)_2$, NO_2, CN, Hal, NR^6COA, NR^6COAr', NR^6SO_2A, NR^6SO_2Ar', $COOR^6$, $CON(R^6)_2$, $CONR^6Ar'$, COR^7, $COAr'$ or $S(O)_nA$,
R^6	is H, A, $[C(R^7)_2]_nAr'$ or $[C(R^7)_2]_nHet$,
R^7	is H or A,
W	is $CONR^6C(R^6)_2CONR^6[C(R^6)_2]_l-$, $-NR^6C(R^6)_2CONR^6[C(R^6)_2]_l-$, $-[C(R^6)_2]_mCONR^6[C(R^6)_2]_l-$ or $-OC(R^6)_2CONR^6[C(R^6)_2]_l-$,
A	is alkyl having 1 - 20 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms or by -CH=CH- groups and in addition 1 – 7 H atoms may be replaced by F,
Ar	is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by

A, Ar', Het, OR^6, $N(R^6)_2$, NO_2, CN, Hal, NR^6COA, NR^6COAr', NR^6SO_2A, NR^6SO_2Ar', $COOR^6$, $CON(R^6)_2$, $CONR^6Ar'$, COR^7, $COAr'$, SO_2NR^6, $S(O)_nAr'$ or $S(O)_nA$,

Ar' is phenyl or naphthyl, each of which is unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR^7, $N(R^7)_2$, NO_2, CN, Hal, NR^7COA, NR^7SO_2A, $COOR^7$, $CON(R^7)_2$, COR^7, SO_2NR^7 or $S(O)_nA$,

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, bonded via N or C, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by A, OR^7, $N(R^7)_2$, NO_2, CN, Hal, NR^7COA, NR^7SO_2A, $COOR^7$, $CON(R^7)_2$, COR^7, SO_2NR^7, $S(O)_nA$ and/or carbonyl oxygen,

Hal is F, Cl, Br or I,

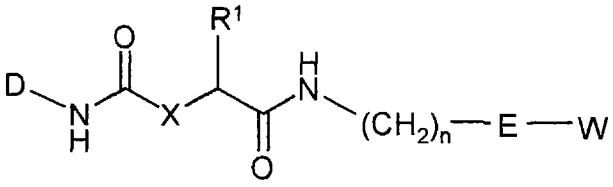
n is 0, 1 or 2,

m is 1 or 2,

l is 0 or 1,

and their pharmaceutically tolerated salts and solvates,

s) compounds of the formula I



I

in which

D is phenyl or pyridyl, each of which is unsubstituted or monosubstituted or polysubstituted by Hal, A, OR^2, $N(R^2)_2$, NO_2, CN, $COOR^2$ or $CON(R^2)_2$,

R^1 is H, Ar, Het, cycloalkyl or A, which may be substituted by OR^2, SR^2, $N(R^2)_2$, Ar, Het, cycloalkyl, CN, $COOR^2$ or $CON(R^2)_2$,

R^2 is H or A,

E is phenylene, which may be monosubstituted or polysubstituted by Hal, A, OR^2, $N(R^2)_2$, NO_2, CN, $COOR^2$ or $CON(R^2)_2$,
or is piperidine-1,4-diyl,

W is Ar, Het or $N(R^2)_2$
and, if E = piperidine-1,4-diyl, is alternatively R^2 or cycloalkyl,

X is NH or O,

A is unbranched or branched alkyl having 1-10 carbon atoms, in which one or two CH_2 groups may be replaced by O or S atoms and/or by –CH=CH- groups and/or in addition 1-7 H atoms may be replaced by F,

Ar is phenyl which is unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, OR^2, $N(R^2)_2$, NO_2, CN, $COOR^2$, $CON(R^2)_2$, NR^2COA, NR^2SO_2A, COR^2, SO_2NR^2, SO_3H or $S(O)_mA$,

Het is a monocyclic or bicyclic, saturated, unsaturated or aromatic heterocyclic radical having from 1 to 4 N, O and/or S atoms, which may be unsubstituted or monosubstituted, disubstituted or trisubstituted by Hal, A, OR^2, $N(R^2)_2$, NO_2, CN, $COOR^2$, $CON(R^2)_2$, NR^2COA, NR^2SO_2A, COR^2, SO_2NR^2, SO_3H or $S(O)_mA$ and/or carbonyl oxygen,

Hal is F, Cl, Br or I,

n is 0 or 1,

m is 0, 1 or 2,

and their pharmaceutically tolerated salts and solvates.

Other preferred factor Xa inhibitors are, for example, the compounds described in the following documents:

a) in WO 97/30971, page 4, line 5, to page 13, line 19;
b) in EP 0 921 116 A1, page 2, line 1, to line 51;
c) in EP 0 540 051 B1, page 2, line 41, to page 3, line 14;
d) in EP 0 798 295 A1, page 69, line 10, to page 71, page 53;

Other preferred compounds are selected from the group consisting of defibrotide, desirudin and lepirudin.

The invention preferably relates to a formulation comprising 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric acid and physiologically acceptable salts and/or solvates thereof and at least one calcium antagonist.
Besides the free acid, the ethanolamine salt is preferred.

Preference is given to calcium antagonists selected from the group consisting of selective and non-selective calcium antagonists.

Preference is given to selective calcium antagonists selected from the group consisting of dihydropyridine derivatives, phenylalkylamine derivatives, benzothiazepine derivatives and other selective calcium antagonists.

Dihydropyridine derivatives are preferably selected from the group consisting of amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, lacidipine, nilvadipine, manidipine, barnidipine and lercanidipine.

The phenylalkylamine derivatives are preferably selected from the group consisting of verapamil and gallopamil.

The benzothiazepine derivatives are preferably diltiazem.

The other selective calcium antagonists are preferably mibefradil.

The non-selective calcium antagonists are preferably selected from the group consisting of fendiline, bepridil, lidoflazine and perhexiline.

The invention preferably relates to a formulation comprising 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric acid and physiologically acceptable salts and/or solvates thereof and at least one prostaglandin or prostaglandin derivative.
Besides the free acid, the ethanolamine salt is preferred.

Preference is given to prostaglandins or prostaglandin derivatives selected from the group consisting of PGE_0, PGA_1, PGB_1, $PGF_{1\alpha}$, PGA_2, PGB_2, 19-hydroxy-PGA_1, 19-hydroxy-PGB_1, 19-hydroxy-PGA_2, 19-hydroxy-PGB_2, PGE_3, $PGF_{3\alpha}$, alprostadil (PGE_1), dinoprost (PGF_2), dinoprostone (PGE_2), epoprostenol sodium (PGI_2; prostacyclin sodium), gemeprost, iloprost, latanoprost, misoprostol, sulprostone, carboprost thromethamin, dinoprost thromethamin, lipoprost, metenoprost and tiaprost

Particular preference is given to prostaglandins or prostaglandin derivatives selected from the group consisting of alprostadil (PGE_1), dinoprost (PGF_2), dinoprostone (PGE_2), epoprostenol sodium (PGI_2; prostacyclin sodium), gemeprost, iloprost, latanoprost, misoprostol, sulprostone, carboprost thromethamin, dinoprost thromethamin, lipoprost, metenoprost and tiaprost

Particular preference is given to PGE_1 or prostacyclin, especially preferably prostacyclin.

The compounds of the formula I and also the starting materials for their preparation are, in addition, 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 said reactions. 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 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 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 instead 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 formulae 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 obtained, for example, from compounds which are built up from thiophene derivatives and CN-substituted alkylenecarboxylic acid esters (Eur. J. Med. Chem. 23, 453 (1988)), by reaction with $POCl_3$.

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 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 of an excess of the amine component, may be favourable.

Examples of suitable inert solvents are hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, tetrachloromethane, 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 or 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 said solvents.

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 give a COOH group
Ester groups can be saponified, 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. Elimination of water therefrom in a known manner gives carbonitriles

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, followed by evaporation Suitable bases for this reaction are, in particular, those which give 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 (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate). Also suitable for this reaction are, in particular, organic bases which give physiologically acceptable salts, such as, for example, ethanolamine.

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, followed by evaporation. Suitable bases for this reaction are, in particular, those which give 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 (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate)

Also suitable for this reaction are, in particular, 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 acids. 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, or 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 pharmaceutical formulations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts and at least one antithrombotic, a calcium antagonist or at least one prostaglandin or prostaglandin derivative, and comprising one or more excipients and/or assistants.
The pharmaceutical preparations are prepared, in particular, by non-chemical methods The active ingredients are converted into a suitable dosage form here together with at least one solid, liquid and/or semi-liquid excipient or assistant.

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 administra-

tion and do no 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 stearates, 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 be 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. They can furthermore be administered as nasal sprays.

In general, the substances are preferably administered in doses of 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 illness to which the therapy applies. Oral administration is preferred.

The invention therefore also relates to the use of the pharmaceutical preparations described for the preparation of a medicament for the treatment of angina, high blood pressure, pulmonary hypertension, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale, dextrocardiac insufficiency, atherosclerosis, conditions of reduced patency of heart vessels, peripheral vascular diseases, strokes, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency, liver cirrhosis and for the treatment of female sexual disorders.

The invention relates in particular to the use of the formulations according to the invention for the preparation of a medicament for the treatment of pulmonary hypertension, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale and/or dextrocardiac insufficiency.

The constituents of the novel pharmaceutical preparation are preferably administered in combination. However, they can also be administered individually at the same time or successively.

The invention also relates to a set (kit) consisting of separate packs of

(a) an effective amount of 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt,

and

(b) an effective amount of an antithrombotic.

The set comprises suitable containers, such as boxes, individual bottles, bags or ampoules. The set may, for example, comprise separate ampoules each containing an effective amount of 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt, and of the antithrombotic in dissolved or lyophilised form

The invention also relates to a set (kit) consisting of separate packs of

(a) an effective amount of 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt,

and

(b) an effective amount of a calcium antagonist.

The set comprises suitable containers, such as boxes, individual bottles, bags or ampoules. The set may, for example, comprise separate ampoules each containing an effective amount of 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric

acid, ethanolamine salt, and of the calcium antagonist in dissolved or lyophilised form

The invention also relates to a set (kit) consisting of separate packs of

(a) an effective amount of 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt,

and

(b) an effective amount of a prostaglandin or prostaglandin derivative.

The set comprises suitable containers, such as boxes, individual bottles, bags or ampoules The set may, for example, comprise separate ampoules each containing an effective amount of 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt, and of the prostaglandin or prostaglandin derivative in dissolved or lyophilised form

The invention furthermore relates to the use of 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]-valeric acid, ethanolamine salt, for the preparation of a medicament for the treatment of pulmonary hypertension, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale and/or dextrocardiac insufficiency.

The invention furthermore relates to the use of a pharmaceutical preparation comprising at least one phosphodiesterase V inhibitor and at least one prostaglandin or prostaglandin derivative for the preparation of a medicament for the oral treatment of pulmonary hypertension, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale and/or dextrocardiac insufficiency.

Above and below, all temperatures are given in °C. In the following examples, "conventional work-up" means that water is added if necessary, a pH of between 2 and 10, depending on the constitution of the final product, is established if necessary, 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

1.9 g of methyl 3-(4-chloro-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl)propionate [obtainable by cyclisation of methyl 2-amino-4,5,6,7-tetrahydrobenzothiophene-3-carboxylate using methyl 3-cyano-propionate followed by chlorination using 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 the mixture is subjected to conventional work-up, giving 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 as a colourless oil.

Analogous reaction of "A"

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

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

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 gives

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

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

methyl 3-[4-(3-chloro-4-methoxybenzylamino)-6-chloroothieno-[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 gives

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

Analogous reaction of 3,4-methylenedioxybenzylamine

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

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 gives

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 gives

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 gives

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 gives

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 gives

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

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

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

Analogous reaction of "A"

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

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 gives

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 gives

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

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

Analogous reaction of 3,4-methylenedioxybenzylamine

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

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

with methyl 4-(4,6-dichloroothieno-[2,3-d]-pyrimidin-2-yl)butyrate gives
methyl 4-[4-(3,4-methylenedioxybenzylamino)-6-chloroothieno-[2,3-d]-pyrimidin-2-yl]butyrate

Analogous reaction of "A"

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

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

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 gives

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

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

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

Analogous reaction of 3,4-methylenedioxybenzylamine

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

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 gives

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 gives

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 gives

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 gives

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 gives

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

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

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

Analogous reaction of "A"

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

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 gives

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 gives

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 gives

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 gives

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 gives

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

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

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

Analogous reaction of 3,4-methylenedioxybenzylamine

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

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 gives

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-cycloheptено-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl)heptanoate gives

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

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

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 gives

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 gives

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

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

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

Analogous reaction of "A"

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

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

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

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

analogous reaction of 3,4-methylenedioxybenzylamine

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

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

Analogous reaction of benzylamine

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

with methyl 5-(4-chloro-6-ethylthieno-[2,3-d]-pyrimidin-2-yl)valerate gives
methyl 5-[4benzylamino-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 is dissolved in 20 ml of ethylene glycol monomethyl ether, 10 ml of 32% NaOH are added, and the mixture is stirred at 110° for 5 hours. After 20% HCl has been added, the mixture is extracted with dichloromethane. Addition of petroleum ether gives 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°.
The precipitated crystals are dissolved in 30 ml of isopropanol, and 0.5 g of ethanolamine is added. Crystallisation gives 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°.

Analogous reaction of the esters listed under Example 1 gives the following carboxylic acids:

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]-benzo-thieno-[2,3-d]-pyrimidin-2-yl]butyric acid, ethanolamine salt, m.p 114°,

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

4-[4-(3,4-methylenedioxybenzylamino)-5,6-cycloheptено-[1]-benzo-thieno-[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]-benzo-thieno-[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]-benzo-thieno-[2,3-d]-pyrimidin-2-yl]valeric acid;

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

5-[4-(3-chloro-4-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]-benzo-thieno-[2,3-d]-pyrimidin-2-yl]valeric acid,

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

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

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

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

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

5-[4benzylamino-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]-pyrimidin-2-yl]propionic acid and 1.2 equivalents of thionyl chloride are stirred in dichloromethane for 2 hours. The solvent is removed, giving 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]propionyl chloride.
The product is transferred into aqueous ammonia, and the mixture is stirred for one hour and subjected to conventional work-up, giving 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]propionamide

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]-pyrimidin-2-yl]propionamide is then added. The mixture is stirred for a further one hour. Conventional work-up gives 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]propionitrile.

Example 5

The following compounds 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]-benzo-thieno-[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]-benzo-thieno-[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]-benzo-thieno-[2,3-d]-pyrimidin-2-yl)phenyl]acetic acid, m.p. 214.

The examples below relate to pharmaceutical preparations:

Example A: Injection vials

A solution of 100 g of an active ingredient of the formula I, 100g of the antithrombotic 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 each active ingredient.

Example B: Suppositories

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

Example C: Solution

A solution is prepared from 1 g of an active ingredient of the formula I, 1 g of an antithrombotic, 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 and 500 mg of an antithrombotic are mixed with 99.5 g of Vaseline under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of an active ingredient of the formula I, 1 kg of an antithrombotic, 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 each 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 an active ingredient of the formula I and 2 kg of an antithrombotic are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of each active ingredient.

Example H: Ampoules

A solution of 1 kg of an active ingredient of the formula I and 1 kg of an antithrombotic 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 each active ingredient

Example I: Inhalation spray

14 g of an active ingredient of the formula I and 14 g of an antithrombotic 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 of each active ingredient.

Example A': Injection vials

A solution of 100 g of an active ingredient of the formula I, 100g of the calcium antagonist 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 each active ingredient.

Example B': Suppositories

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

Example C': Solution

A solution is prepared from 1 g of an active ingredient of the formula I, 1 g of a calcium antagonist, 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 and 500 mg of a calcium antagonist are mixed with 99.5 g of Vaseline under aseptic conditions

Example E': Tablets

A mixture of 1 kg of an active ingredient of the formula I, 1 kg of a calcium antagonist, 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 each 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 an active ingredient of the formula I and 2 kg of a calcium antagonist are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of each active ingredient.

Example H': Ampoules

A solution of 1 kg of an active ingredient of the formula I and 1 kg of a calcium antagonist 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 each active ingredient.

Example I': Inhalation spray

14 g of an active ingredient of the formula I and 14 g of a calcium antagonist 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 of each active ingredient.

Example A": Injection vials

A solution of 100 g of an active ingredient of the formula I, 100g of the prostaglandin or prostaglandin derivative 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 each active ingredient.

Example B": Suppositories

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

Example C": Solution

A solution is prepared from 1 g of an active ingredient of the formula I, 1 g of a prostaglandin or prostaglandin derivative, 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 and 500 mg of a prostaglandin or prostaglandin derivative are mixed with 99.5 g of Vaseline under aseptic conditions

Example E": Tablets

A mixture of 1 kg of an active ingredient of the formula I, 1 kg of a prostaglandin or prostaglandin derivative, 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 each 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 an active ingredient of the formula I and 2 kg of a prostaglandin or prostaglandin derivative are introduced into hard gelatine capsules in a conventional manner in such a way that each capsule contains 20 mg of each active ingredient.

Example H": Ampoules

A solution of 1 kg of an active ingredient of the formula I and 1 kg of a prostaglandin or prostaglandin derivative 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 each active ingredient.

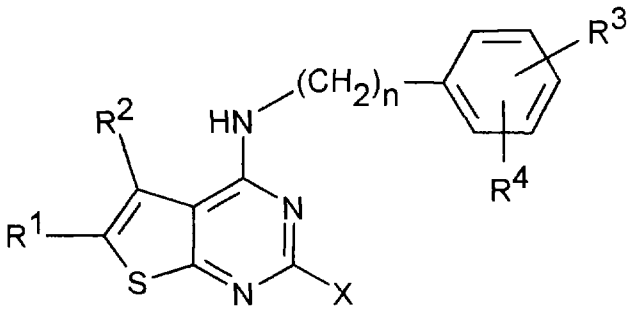
Example I": Inhalation spray

14 g of an active ingredient of the formula I and 14 g of a prostaglandin or prostaglandin derivative 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 of each active ingredient.

Patent Claims

1. Pharmaceutical formulation comprising at least one phosphodiesterase V inhibitor and/or physiologically acceptable salts and/or solvates thereof and at least one antithrombotic.

2 Pharmaceutical formulation comprising at least one compound of the formula I



I

in which

R^1 and R^2	are each, independently of one another, H, A or Hal, where one of the radicals R^1 and R^2 is always ≠ H.
R^1 and R^2	together are alternatively alkylene having 3-5 carbon atoms,
R^3 and R^4	are each, independently of one another, H, A, OH, OA or Hal,
R^3 and R^4	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 or R^6, each of which is monosubstituted by R^7,
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, or is -C_6H_4-$(CH_2)_m$-,
R^6	is cycloalkylalkylene having 6-12 carbon atoms,
R^7	is COOH, COOA, $CONH_2$, CONHA, $CON(A)_2$ or CN,
A	is alkyl having from 1 to 6 carbon atoms,
Hal	is F, Cl, Br or I,
m	is 1 or 2, and
n	is 0, 1, 2 or 3,

and/or physiologically acceptable salts and/or solvates thereof and

a) at least one antithrombotic or

b) at least one calcium antagonist or

c) at least one prostaglandin or prostaglandin derivative.

3. Pharmaceutical formulation according to Claim 2, comprising at least one compound of the formula I according to Claim 2 in which

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

and/or physiologically acceptable salts and/or solvates thereof and at least one antithrombotic.

4. Pharmaceutical formulation according to Claim 2, comprising at least one compound of the formula I according to Claim 2 in which

R^1 and R^2 are each, independently of one another, 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 carbon 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;

and/or physiologically acceptable salts and/or solvates thereof and at least one antithrombotic

5. Pharmaceutical formulation according to Claim 2, comprising at least one compound of the formula I according to Claim 2 in which

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

R^3 and R^4 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 or R^6, each of which is substituted by COOH or COOA,

n is 1 or 2;

and/or physiologically acceptable salts and/or solvates thereof and at least one antithrombotic.

6. Pharmaceutical formulation according to Claim 2, comprising at least one compound of the formula I according to Claim 2 in which

R^1 and R^2	are each, independently of one another, H, A or Hal, where one of the radicals R^1 and R^2 is always ≠ H,
R^1 and R^2	together are alternatively alkylene having 3-5 carbon atoms,
R^3 and R^4	are each, independently of one another, H, A, OA or Hal,
R^3 and R^4	together are alternatively -O-CH_2-O-,
X	is R^5 which is monosubstituted by R^7,
R^5	is linear or branched alkylene having 1-10 carbon atoms or -C_6H_4-CH_2-,
R^7	is COOH or COOA,
A	is alkyl having from 1 to 6 carbon atoms,
Hal	is F, Cl, Br or I,
m	is 1, and
n	is 1 or 2;

and/or physiologically acceptable salts and/or solvates thereof and at least one antithrombotic.

7. Pharmaceutical formulation according to Claim 2, comprising at least one compound of the formula I according to Claim 2 in which

R^1 and R^2	are each, independently of one another, H, A or Hal, where one of the radicals R^1 and R^2 is always ≠ H,
R^1 and R^2	together are alternatively alkylene having 3-5 carbon atoms,
R^3 and R^4	are each, independently of one another, H, A, OH, OA or Hal,
R^3 and R^4	together are alternatively -O-CH_2-O-,
X	is R^5 which is monosubstituted by R^7,
R^5	is linear or branched alkylene having 1-10 carbon atoms or -C_6H_4-CH_2-,
R^7	is COOH or COOA,
A	is alkyl having from 1 to 6 carbon atoms,
Hal	is F, Cl, Br or I,

m is 1, and

n is 1 or 2;

and/or physiologically acceptable salts and/or solvates thereof and at least one antithrombotic.

8. Pharmaceutical formulation according to Claim 2, comprising at least one compound of the formula I according to Claim 2 selected from the group consisting of

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

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

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

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

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

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

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

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

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

(k) 5-[4-(3,4-methylenedioxybenzylamino)-6-methylthieno-[2,3-d]-pyrimidin-2-yl]valeric acid.

9 Pharmaceutical formulation according to Claim 8, comprising at least 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt, and at least one antithrombotic

10. Pharmaceutical formulation according to Claims 1 to 9, in which the antithrombotic is selected from the group consisting of vitamin K

antagonists, heparin compounds, thrombocyte aggregation inhibitors, enzymes, factor Xa inhibitors, factor VIIa inhibitors and other anti-thrombotic agents.

11. Pharmaceutical formulation according to Claim 10, where the vitamin K antagonists are selected from the group consisting of dicoumarol, phenindione, warfarin, phenprocoumon, acenocoumarol, ethyl biscoumacetate, clorindione, diphenadione and tioclomarol.

12 Pharmaceutical formulation according to Claim 10, where the heparin compounds are selected from the group consisting of heparin, antithrombin III, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, danaparoid, tinzaparin and sulodexide.

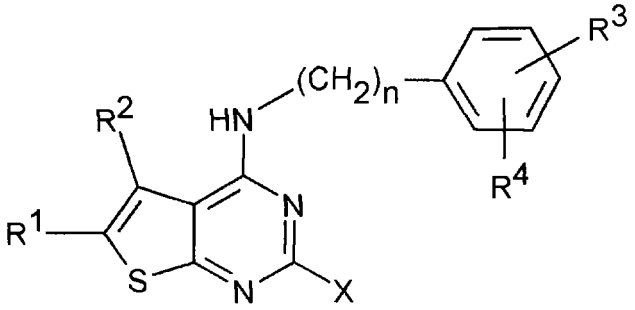
13. Pharmaceutical formulation according to Claim 10, where the thrombocyte aggregation inhibitors are selected from the group consisting of ditazole, cloricromen, picotamide, clopidogrel, ticlopidine, acetylsalicylic acid, dipyridamole, calcium carbassalate, epoprostenol, indobufen, iloprost, abciximab, tirofiban, aloxiprin and intrifiban.

14 Pharmaceutical formulation according to Claim 10, where the enzymes are selected from the group consisting of streptokinase, alteplase, anistreplase, urokinase, fibrinolysin, brinase, reteplase and saruplase.

15. Pharmaceutical formulation according to Claim 10, where other antithrombotic agents are selected from the group consisting of defibrotide, desirudin and lepirudin.

16. Pharmaceutical formulation according to Claims 1-9, where the antithrombotic is selected from the group consisting of blood platelet glycoprotein receptor (IIb/IIIa) antagonists.

17. Pharmaceutical formulation according to Claim 2, comprising at least one compound of the formula I



I

in which

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

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

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

R^3 and R^4 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 or R^6, each of which is monosubstituted by R^7,

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, or is $-C_6H_4-(CH_2)_m-$,

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

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

A is alkyl having from 1 to 6 carbon atoms,

Hal is F, Cl, Br or I,

m is 1 or 2, and

n is 0, 1, 2 or 3,

and/or physiologically acceptable salts and/or solvates thereof and at least one calcium antagonist.

18. Pharmaceutical formulation according to Claim 17, comprising at least one compound of the formula I according to Claim 17 in which

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

and/or physiologically acceptable salts and/or solvates thereof and at least one calcium antagonist.

19 Pharmaceutical formulation according to Claim 17, comprising at least one compound of the formula I according to Claim 17 in which

R^1 and R^2 are each, independently of one another, 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 carbon 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;

and/or physiologically acceptable salts and/or solvates thereof and at least one calcium antagonist.

20. Pharmaceutical formulation according to Claim 17, comprising at least one compound of the formula I according to Claim 17 in which

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

R^3 and R^4 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 or R^6, each of which is substituted by COOH or COOA,

n is 1 or 2;

and/or physiologically acceptable salts and/or solvates thereof and at least one calcium antagonist.

21 Pharmaceutical formulation according to Claim 17, comprising at least one compound of the formula I according to Claim 17 in which

R^1 and R^2 are each, independently of one another, 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 alternatively alkylene having 3-5 carbon atoms,

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

R^3 and R^4 together are alternatively $-O-CH_2-O-$,

X is R^5 which is monosubstituted by R^7,
R^5 is linear or branched alkylene having 1-10 carbon atoms or $-C_6H_4-CH_2-$,
R^7 is COOH or COOA,
A is alkyl having from 1 to 6 carbon atoms,
Hal is F, Cl, Br or I,
m is 1, and
n is 1 or 2;
and/or physiologically acceptable salts and/or solvates thereof and at least one calcium antagonist.

22. Pharmaceutical formulation according to Claim 17, comprising at least one compound of the formula I according to Claim 17 in which
R^1 and R^2 are each, independently of one another, 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 alternatively alkylene having 3-5 carbon atoms,
R^3 and R^4 are each, independently of one another, H, A, OH, OA or Hal,
R^3 and R^4 together are alternatively $-O-CH_2-O-$,
X is R^5 which is monosubstituted by R^7,
R^5 is linear or branched alkylene having 1-10 carbon atoms or $-C_6H_4-CH_2-$,
R^7 is COOH or COOA,
A is alkyl having from 1 to 6 carbon atoms,
Hal is F, Cl, Br or I,
m is 1, and
n is 1 or 2;
and/or physiologically acceptable salts and/or solvates thereof and at least one calcium antagonist.

23 Pharmaceutical formulation according to Claim 17, comprising at least one compound of the formula I according to Claim 17 selected from the group consisting of
(a) 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]propionic acid;

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

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

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

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

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

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

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

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

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

and/or physiologically acceptable salts and/or solvates thereof and at least one calcium antagonist

24. Pharmaceutical formulation according to Claim 23, comprising at least 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt, and at least one calcium antagonist.

25. Pharmaceutical formulation according to Claims 2 and 17 to 24, in which the calcium antagonist is selected from the group consisting of selective and non-selective calcium antagonists.

26. Pharmaceutical formulation according to Claim 25, in which the selective calcium antagonists are selected from the group consisting of dihydropyridine derivatives, phenylalkylamine derivatives, benzothiazepine derivatives and other selective calcium antagonists.

27 Pharmaceutical formulation according to Claim 26, in which the dihydropyridine derivatives are selected from the group consisting of amlodipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, lacidipine, nilvadipine, manidipine, barnidipine and lercanidipine.

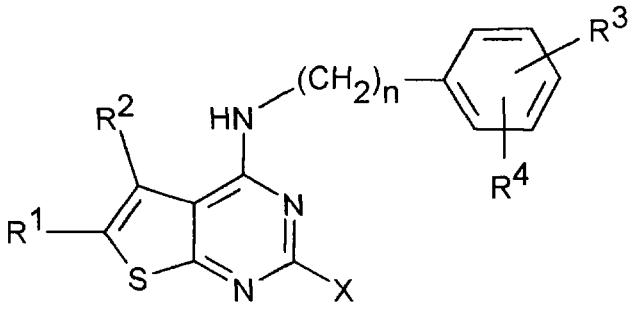
28. Pharmaceutical formulation according to Claim 26, in which the phenylalkylamine derivatives are selected from the group consisting of verapamil and gallopamil

29. Pharmaceutical formulation according to Claim 26, in which the benzothiazepine derivative is diltiazem.

30 Pharmaceutical formulation according to Claim 26, in which the other selective calcium antagonist is mibefradil

31 Pharmaceutical formulation according to Claim 25, in which the non-selective calcium antagonists are selected from the group consisting of fendiline, bepridil, lidoflazine and perhexiline.

32. Pharmaceutical formulation according to Claim 2, comprising at least one compound of the formula I



I

in which

R^1 and R^2 are each, independently of one another, 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 alternatively alkylene having 3-5 carbon atoms,

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

R^3 and R^4 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 or R^6, each of which is monosubstituted by R^7,

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, or is $-C_6H_4-(CH_2)_m-$,

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

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

A is alkyl having from 1 to 6 carbon atoms,

Hal is F, Cl, Br or I,

m is 1 or 2, and

n is 0, 1, 2 or 3,

and/or physiologically acceptable salts and/or solvates thereof and at least one prostaglandin or prostaglandin derivative

33 Pharmaceutical formulation according to Claim 32, comprising at least one compound of the formula I according to Claim 32 in which

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

and/or physiologically acceptable salts and/or solvates thereof and at least one prostaglandin or prostaglandin derivative.

34. Pharmaceutical formulation according to Claim 32, comprising at least one compound of the formula I according to Claim 32 in which

R^1 and R^2 are each, independently of one another, 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 carbon atoms, $-O-CH_2-CH_2-$, $-O-CH_2-O-$ or $-O-CH_2-CH_2-O-$,

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

and/or physiologically acceptable salts and/or solvates thereof and at least one prostaglandin or prostaglandin derivative.

35. Pharmaceutical formulation according to Claim 32, comprising at least one compound of the formula I according to Claim 32 in which

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

R^3 and R^4 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 or R^6, each of which is substituted by COOH or COOA,

n is 1 or 2;

and/or physiologically acceptable salts and/or solvates thereof and at least one prostaglandin or prostaglandin derivative

36. Pharmaceutical formulation according to Claim 32, comprising at least one compound of the formula I according to Claim 32 in which

R^1 and R^2 are each, independently of one another, 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 alternatively alkylene having 3-5 carbon atoms,

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

R^3 and R^4 together are alternatively $-O-CH_2-O-$,

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

R^5 is linear or branched alkylene having 1-10 carbon atoms or $-C_6H_4-CH_2-$,

R^7 is COOH or COOA,

A is alkyl having from 1 to 6 carbon atoms,

Hal is F, Cl, Br or I,

m is 1, and

n is 1 or 2;

and/or physiologically acceptable salts and/or solvates thereof and at least one prostaglandin or prostaglandin derivative.

37 Pharmaceutical formulation according to Claim 32, comprising at least one compound of the formula I according to Claim 32 in which

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

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

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

R^3 and R^4 together are alternatively -O-CH_2-O-,

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

R^5 is linear or branched alkylene having 1-10 carbon atoms or -C_6H_4-CH_2-,

R^7 is COOH or COOA,

A is alkyl having from 1 to 6 carbon atoms,

Hal is F, Cl, Br or I,

m is 1, and

n is 1 or 2;

and/or physiologically acceptable salts and/or solvates thereof and at least one prostaglandin or prostaglandin derivative.

38. Pharmaceutical formulation according to Claim 32, comprising at least one compound of the formula I according to Claim 32 selected from the group consisting of

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

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

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

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

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

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

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

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

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

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

and/or physiologically acceptable salts and/or solvates thereof and at least one prostaglandin or prostaglandin derivative

39. Pharmaceutical formulation according to Claim 38, comprising at least 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt, and at least one prostaglandin or prostaglandin derivative.

40 Pharmaceutical formulation according to Claims 2 and 32 to 39, in which the prostaglandin or prostaglandin derivative is selected from the group consisting of alprostadil (PGE_1), dinoprost (PGF_2), dinoprostone (PGE_2), epoprostenol sodium (PGI_2; prostacyclin sodium), gemeprost, iloprost, latanoprost, misoprostol, sulprostone, carboprost, thromethamin, dinoprost thromethamin, lipoprost, metenoprost and tiaprost

41 Pharmaceutical formulation according to Claim 40, in which the prostaglandin is PGE_1 or prostacyclin.

42. Pharmaceutical formulation according to Claim 40, in which the prostaglandin is prostacyclin

43 Pharmaceutical formation according to one of the preceding claims, comprising one or more excipients and/or assistants

44. Use of a pharmaceutical preparation according to one of Claims 1 to 43 for the preparation of a medicament for the treatment of angina, high blood pressure, pulmonary hypertension, congestive heart

failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale, dextrocardiac insufficiency, atherosclerosis, conditions of reduced patency of heart vessels, peripheral vascular diseases, strokes, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, glaucoma, irritable bowel syndrome, tumours, renal insufficiency, liver cirrhosis and for the treatment of female sexual disorders.

45 Use according to Claim 44 for the preparation of a medicament for the treatment of pulmonary hypertension, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale and/or dextrocardiac insufficiency

46. Set (kit) consisting of separate packs of
(a) an effective amount of 5-[4-(3-chloro-4-methoxybenzyl-amino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]-valeric acid, ethanolamine salt,
and
(b) an effective amount of an antithrombotic.

47. Use of 5-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]valeric acid, ethanolamine salt, for the preparation of a medicament for the treatment of pulmonary hypertension, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale and/or dextrocardiac insufficiency.

48 Set (kit) consisting of separate packs of
(a) an effective amount of 5-[4-(3-chloro-4-methoxybenzyl-amino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]-valeric acid, ethanolamine salt,
and
(b) an effective amount of a calcium antagonist

49. Set (kit) consisting of separate packs of

(a) an effective amount of 5-[4-(3-chloro-4-methoxybenzyl-amino)-5,6,7,8-tetrahydro-[1]-benzothieno-[2,3-d]-pyrimidin-2-yl]-valeric acid, ethanolamine salt,
and

(b) an effective amount of a prostaglandin or prostaglandin derivative.

50. Use of a pharmaceutical preparation comprising at least one phosphodiesterase V inhibitor and at least one prostaglandin or prostaglandin derivative for the preparation of a medicament for oral treatment of pulmonary hypertension, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cor pulmonale and/or dextrocardiac insufficiency.