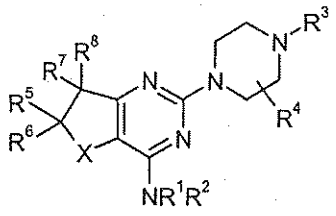
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NOVEL COMPOUNDS FOR THE TREATMENT OF INFLAMMATORY DISEASES

The invention relates to new dihydrothienopyrimidines of formula **1**, and the pharmacologically acceptable salts, pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof,



1

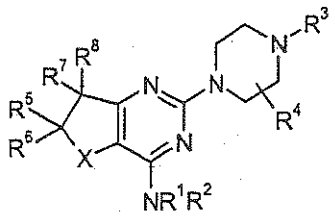
which are suitable for the treatment of respiratory or gastrointestinal complaints or diseases, inflammatory diseases of the joints, skin or eyes, diseases of the peripheral or central nervous system or cancers, as well as pharmaceutical compositions which contain these compounds.

PRIOR ART

US 3,318,881 and BE 663693 disclose the preparation of dihydrothieno[3,2-d]pyrimidines which have cardiovascular and sedative properties.

SUMMARY

In a first aspect, there is provided compounds of formula 1,



1

wherein

X denotes O, S, SO or SO_2;

R^1 denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{6-10}-aryl or C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene;

R^2 denotes H or an optionally mono- or polysubstituted group selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, an optionally mono- or poly-bridged mono- or bicyclic C_{3-10}-cycloalkyl, C_{6-10}-aryl, an aromatic or non-aromatic, heterocyclic C_{3-10} ring, a bicyclic ring and a C_{6-10}-aryl fused to a C_{3-10} heterocycle;

or **NR^1R^2** together denote a heterocyclic ring which is optionally substituted by one or more groups selected from C_{1-4}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, straight-chain or branched C_{1-6}-alkanol and oxo;

R^3 denotes a mono- or polysubstituted group selected from among a heterocyclic C_{6-10} ring, C_{3-7}-cycloalkyl, C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene, a fused, bicyclic ring which may optionally contain 1-4 heteroatoms selected independently of one another from N, O, S,

or **R^3** denotes optionally substituted phenyl;

or R^3 denotes a group $COR^{3.7}$, $COCH_2R^{3.8}$, $CONHR^{3.8}$ or $SO_2R^{3.8}$;

wherein

$R^{3.7}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl or C_{6-10}-aryl;

$R^{3.8}$ denotes C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-7}-cycloalkyl or a group selected from among C_{6-10}-aryl, a heterocyclic C_{3-10} ring and a bicyclic ring, which is optionally substituted by one or more groups selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, halogen, $NR^{3.8.1}R^{3.8.2}$, C_{6-10}-aryl and a heterocyclic C_{3-10} ring ;

wherein

$R^{3.8.1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

$R^{3.8.2}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

R^4 denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, or oxo;

R^5 denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl or C_{2-4}-alkynyl;

R^6 denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl or C_{2-4}-alkynyl;

R^7 denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, C_{6-10}-aryl, or OH;

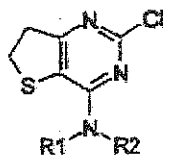
R^8 denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, C_{6-10}-aryl or OH;

or R^7 and R^8 together form oxo;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

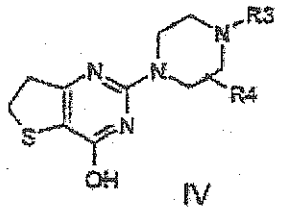
In a second aspect, there is provided intermediate products selected from among:

- compounds according to formula VIII according to preparation method B as illustrated in Scheme 1



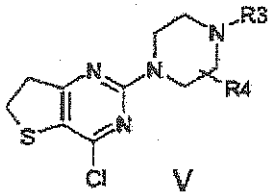
VIII

- compounds according to formula IV and V according to preparation method A as illustrated in Scheme 1



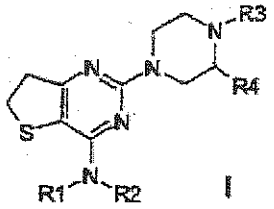
IV

and



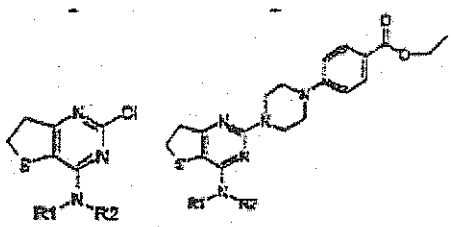
V

- compounds according to formula I as illustrated in Scheme 1

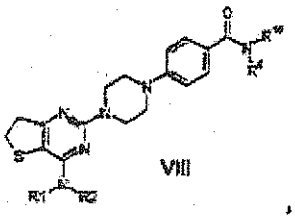


I

- compounds according to formula IV, VI, VII and VIII as illustrated in Scheme 2

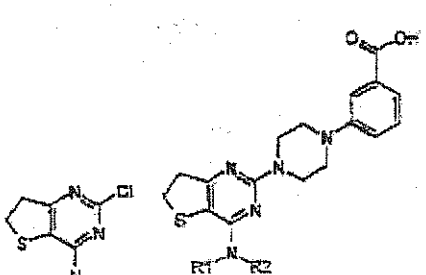


IV , VI , VII and

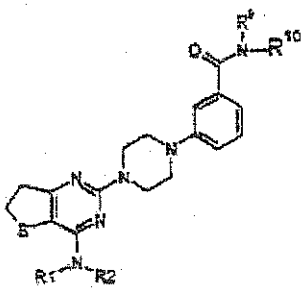


VIII ,

- compounds according to formula V, VII and VIII as illustrated in Scheme 3

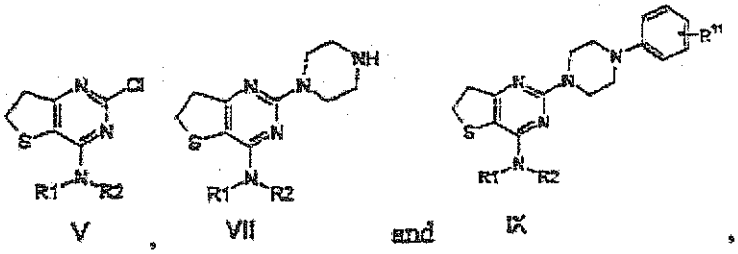


V , VII and



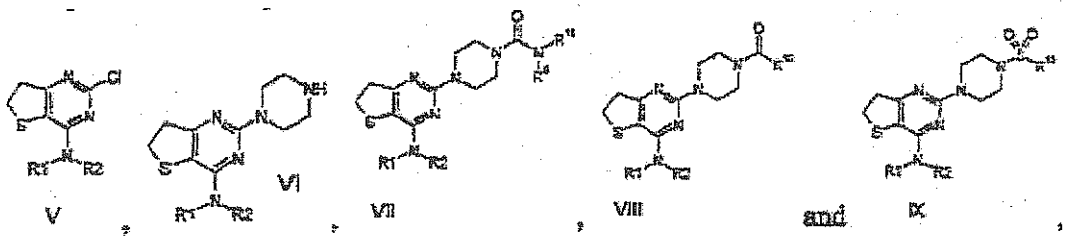
VIII .

- compounds according to formula V, VII and IX as illustrated in Scheme 4



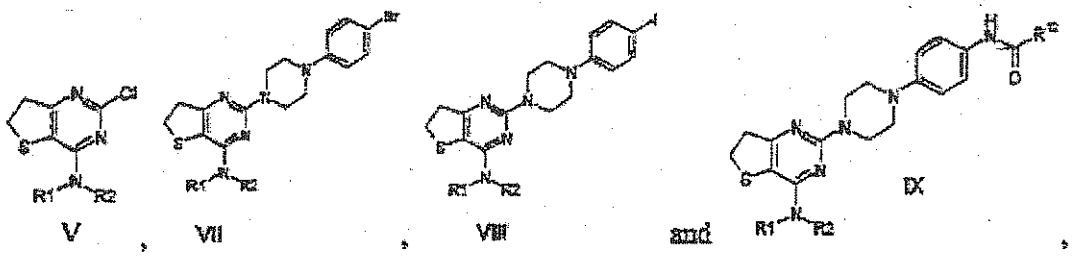
V , VII and IX ,

- compounds according to formula V, VI, VII, VIII and IX as illustrated in Scheme 5



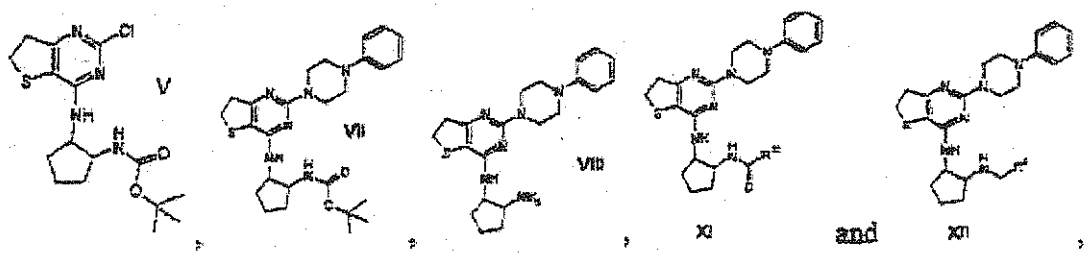
V , VI , VII , VIII and IX ,

- compounds according to formula V, VII, VIII and IX as illustrated in Scheme 6



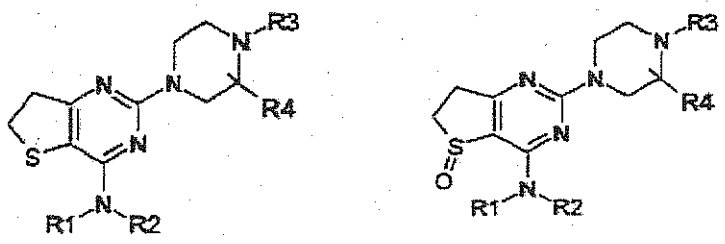
V , VII , VIII and IX ,

- compounds according to formula V, VII, VIII, XI and XII as illustrated in Scheme 7



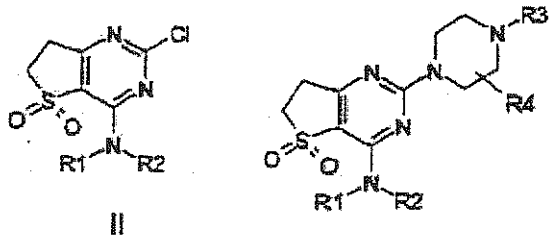
V , VII , VIII , XI and XII ,

- compounds according to formula I and II as illustrated in Scheme 8



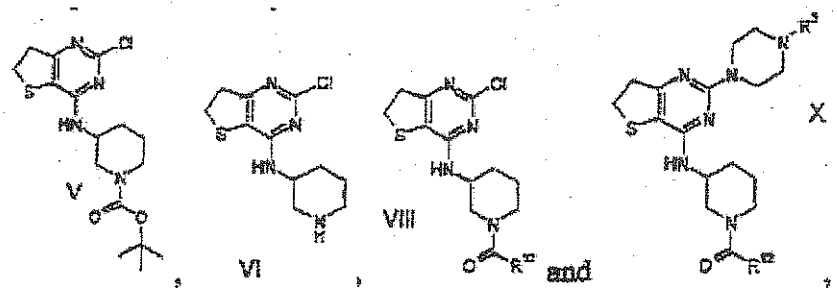
I and II

- compounds according to formula II and III as illustrated in Scheme 9

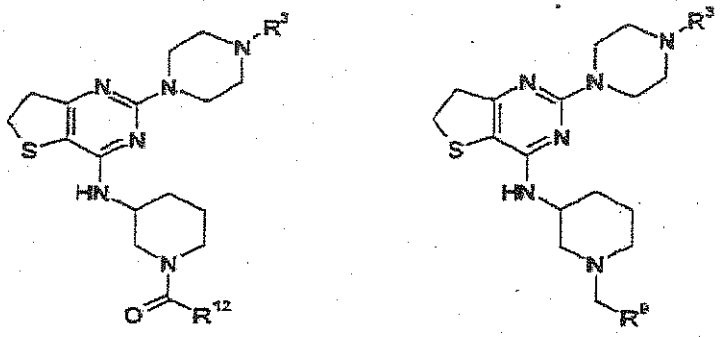


II and III

- compounds according to formula V, VI, VIII and X as illustrated in Scheme 10



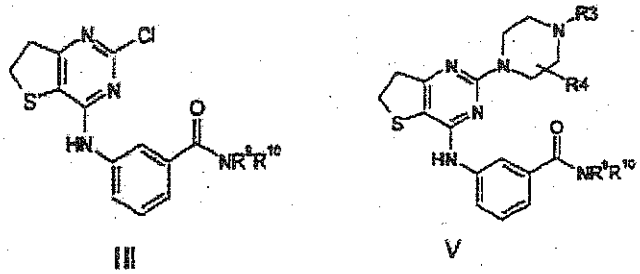
- compounds according to formula III and V as illustrated in Scheme 11



III V

and

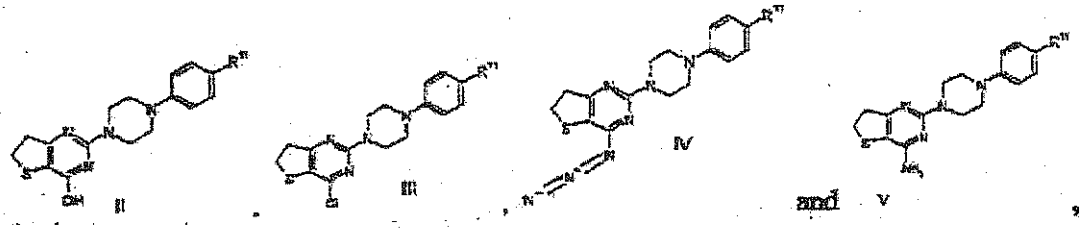
- compounds according to formula III and V as illustrated in Scheme 12



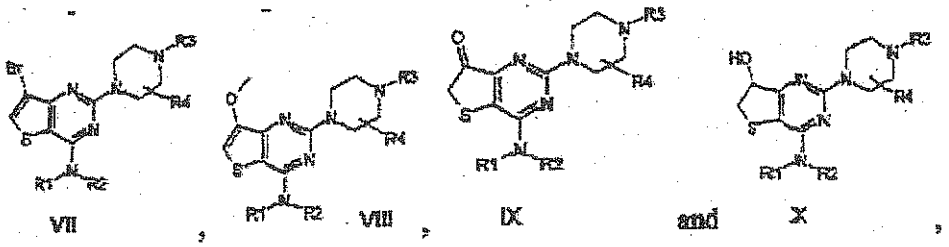
III V

and

- compounds according to formula II, III, IV and V as illustrated in Scheme 13



- compounds according to formula VII, VIII, IX and X as illustrated in Scheme 14,



wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and X have the meanings defined above,

and wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and X have the meanings defined hereinbefore and wherein R^9, R^{10}, R^{11}, R^{12} in each case independently of one another denote a group selected from among H, halogen, C_{1-6}-alkyl, C_{1-6}-haloalkyl, C_{6-10}-aryl, C_{3-7}-cycloalkyl, aromatic or non-aromatic C_{3-10} heterocycle, C_{6-10}-aryl-C_{1-6}-alkylene, C_{3-7}-cycloalkyl- C_{1-6}-alkylene and C_{3-10} heterocycle-C_{1-6}-alkylene, which may optionally be substituted by one or more groups selected from among OH, oxo, C_{1-6}-alkyl, phenyl C_{3-7}-cycloalkyl, C_{3-7} heterocycle and halogen,
and wherein R^{13} is selected from among OH, halogen, O-C_{1-6}-alkyl, C_{1-6}-alkyl, phenyl and C_{3-7}-cycloalkyl and C_{3-7} heterocycle.

In a third aspect, there is provided compounds as defined above as pharmaceutical compositions.

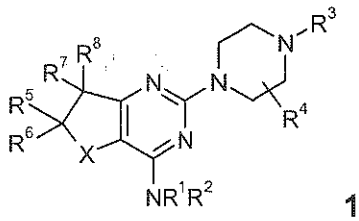
In a fourth aspect, there is provided the use of the compounds as defined above for preparing a medicament for the treatment of a disease selected from among respiratory or gastrointestinal complaints or diseases, inflammatory diseases of the joints, skin or eyes, cancers, and diseases of the peripheral or central nervous system.

In a fifth aspect, there is provided pharmaceutical formulations, characterised in that they contain one or more compounds of formula 1 as defined above.

In a sixth aspect, there is provided pharmaceutical formulation suitable for administration by inhalation, characterised in that it contains a compound of formula 1 as defined above.

DESCRIPTION OF THE INVENTION

Surprisingly it has now been found that dihydrothienopyrimidines of formula **1** are suitable for the treatment of inflammatory diseases. The present invention therefore relates to compounds of formula **1**



1

wherein

X denotes O, S, SO or SO_2;

R^1 denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{6-10}-aryl or C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene;

R^2 denotes H or an optionally mono- or polysubstituted group selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, an optionally mono- or poly-bridged mono- or bicyclic C_{3-10}-cycloalkyl, C_{6-10}-aryl, an aromatic or non-aromatic, heterocyclic C_{3-10} ring, a bicyclic ring and a C_{6-10}-aryl fused to a C_{3-10} heterocycle;

or **NR^1R^2** together denote a heterocyclic ring which is optionally substituted by one or more groups selected from C_{1-4}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, straight-chain or branched C_{1-6}-alkanol and oxo;

R^3 denotes a mono- or polysubstituted group selected from among a heterocyclic C_{6-10} ring, C_{3-7}-cycloalkyl, C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene, a fused, bicyclic ring which may optionally contain 1-4 heteroatoms selected independently of one another from N, O, S,

or **R^3** denotes optionally substituted phenyl;

or **R^3** denotes a group $COR^{3.7}$, $COCH_2R^{3.8}$, $CONHR^{3.8}$ or $SO_2R^{3.8}$;

wherein

$R^{3.7}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl or C_{6-10}-aryl;

$R^{3.8}$ denotes C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-7}-cycloalkyl or a group selected from among C_{6-10}-aryl, a heterocyclic C_{3-10} ring and a bicyclic ring, which is optionally substituted by one or more groups selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, halogen, $NR^{3.8.1}R^{3.8.2}$, C_{6-10}-aryl and a heterocyclic C_{3-10} ring;

wherein

$R^{3.8.1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

$R^{3.8.2}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

R^4 denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, or oxo;

R^5 denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl or C_{2-4}-alkynyl;

R^6 denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl or C_{2-4}-alkynyl;

R^7 denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, C_{6-10}-aryl, or OH;

R^8 denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, C_{6-10}-aryl or OH;

or **R^7** and **R^8** together form oxo;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Preferred compounds of formula 1 above are those wherein

X denotes O, S, SO or SO_2;

R^1 denotes H, C_{1-6}-alkyl, C_{6-10}-aryl, C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene,

R^2 denotes H or C_{1-6}-alkyl, which may optionally be substituted by one or more groups selected from among C_{1-6}-haloalkyl, CN, $OR^{2.1}$, $NR^{2.1}R^{2.2}$, $COOR^{2.1}$,

$CONR^{2.1}R^{2.2}$, C_{3-7}-cycloalkyl optionally substituted by C_{1-4}-alkyl or oxo, an aromatic or non-aromatic heterocycle optionally substituted by C_{1-4}-alkyl, oxo, OH or halogen, C_{6-10}-aryl optionally substituted by C_{1-4}-alkyl or oxo and C_{6-10}-aryl fused to a C_{5-6} heterocycle, while this fused ring system may optionally be substituted by C_{1-4}-alkyl or oxo

wherein

$R^{2.1}$ denotes H or C_{1-6}-alkyl which is optionally substituted by a C_{3-7}-cycloalkyl, C_{3-10} heterocycle or C_{6-10}-aryl, each of which is optionally substituted,

$R^{2.2}$ denotes H or C_{1-6}-alkyl;

or **R^2** denotes a group selected from optionally mono- or poly-bridged C_{3-10}-cycloalkyl or a C_{3-10}-cycloalkyl, which may optionally be fused to a C_{6-10}-aryl ring which is optionally substituted by one or more groups selected from among C_{1-6}-alkyl, OH, $CH_2OR^{2.3}$, $COOR^{2.3}$, $COR^{2.3}$, $CONR^{2.3}R^{2.4}$, O-C_{1-6}-alkyl, O-C_{7-11}-aralkyl, $NR^{2.3}R^{2.4}$ and $NHCOR^{2.5}$,

wherein

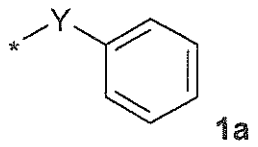
$R^{2.3}$ is H or a heterocycle or a C_{1-6}-alkyl, which may optionally be substituted by a group selected from C_{3-7}-cycloalkyl, C_{3-10} heterocycle and C_{6-10}-aryl, while this group may optionally be substituted in each case by one or more groups selected from among C_{1-6}-alkyl, halogen, OH and O-C_{1-6}-alkyl;

while

$R^{2.4}$ denotes H or C_{1-6}-alkyl;

$R^{2.5}$ denotes a group selected from among C_{3-7}-cycloalkyl, a heterocyclic C_{3-10} ring and C_{1-6}-alkyl, which may optionally be substituted by OH;

or R^2 denotes a group of formula **1a**,



1a

Y denotes C_{1-6}-alkylene, optionally substituted by one or two $R^{2.7}$ wherein $R^{2.7}$ are in each case selected independently of one another from C_{1-6}-alkyl, COOH, $CONH_2$, $OR^{2.1}$, and $COOR^{2.1}$; or $R^{2.7}$ together with one or two carbon atoms of Y forms a carbocyclic ring with 3 carbon atoms

or **R^2** denotes C_{6-10}-aryl, which may optionally be substituted by one or more groups selected independently of one another from among C_{1-6}-alkyl, C_{1-6}-haloalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$, NHCOMe, $CONR^{2.3}R^{2.4}$, a C_{1-4} alkylene group substituted by $NR^{2.1}R^{2.2}$, or $NR^{2.1}R^{2.2}$,

or **R^2** denotes C_{6-10}-aryl, which may optionally be substituted by one or more groups selected independently of one another from among C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene, C_{3-7}-cycloalkyl, a C_{3-7}-cycloalkyl-C_{1-4}-alkylene, C_{6-10}-aryl, and a heterocyclic C_{3-10} ring, while these groups may each optionally be substituted by one or more groups selected from C_{1-6}-alkyl, C_{1-6}-haloalkyl, $COOR^{2.8}$, CN, halogen, $OR^{2.8}$, $NHCOR^{2.8}$, oxo, a C_{3-10} heterocycle, a C_{3-7}-cycloalkyl-C_{1-4} alkylene, a C_{5-10} heterocycle -C_{1-4}-alkylene and a $NR^{2.1}R^{2.2}$ -C_{1-4} alkylene,

wherein

$R^{2.8}$ denotes H, C_{1-6}-alkyl, C_{6-10}-aryl, a $NR^{2.1}R^{2.2}$-C_{1-4} alkylene group;

$R^{2.10}$ denotes $NHR^{2.10.1}$ or a heterocyclic C_{3-10} ring which may optionally be substituted by C_{1-4}-alkyl;

$R^{2.10.1}$ denotes H, C_{3-7}-cycloalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl,C_{1-6}-alkyl or C_{1-6}-alkyl-O-C_{1-4}-alkyl

or **R^2** denotes C_{6-10}-aryl, to which an aromatic or non-aromatic C_{3-10} heterocycle is fused;

or **R^2** denotes an aromatic or non-aromatic heterocyclic C_{3-10} ring which may optionally be substituted by one or more groups selected from among halogen, OH, oxo, CN, C_{1-6}-alkyl, C_{1-6}-alkanol, C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene, $COR^{2.11}$, C_{3-7}-cycloalkyl-C_{1-4}-alkylene and C_{3-10} heterocycle-C_{1-4}-alkylene;
wherein

$R^{2.11}$ denotes a group selected from among C_{3-10} heterocycle- C_{1-4}-alkylene, C_{3-7}-cycloalkyl and a heterocyclic aromatic or non-aromatic C_{3-10} ring,
which may optionally be substituted by C_{1-6}-alkyl, which may in turn optionally be substituted by OH, CH_2OH, OMe, NH_2, a C_{3-10} heterocycle or NHCOO-^{t}Bu;

or **R^2** denotes a group selected from among C_{2-6}-alkenyl or a bicyclic ring, which may optionally be substituted by methyl;

or **NR^1R^2** denotes a heterocyclic ring which may optionally be substituted by one or more groups selected from among C_{1-4}-alkyl, OH and C_{1-4}-alkanol;

R^3 denotes a group selected from among a heterocyclic C_{3-10} ring, a C_{3-7}-cycloalkyl, a bicyclic, fused aromatic or non-aromatic ring system, which optionally contains 1 to 4 heteroatoms selected from S, N, O, or it denotes C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene and CH_2-benzo[1, 3]dioxolyl, which may optionally be substituted by one or more groups

selected from OH, halogen, C_{1-6}-alkyl, O-C_{1-6}-alkyl, C_{1-6}-haloalkyl and CO-$R^{3.1}$,

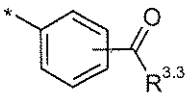
or **R^3** denotes phenyl, which may optionally be substituted by one or more groups selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-4}-haloalkyl, C_{1-6}-alkylene-$NR^{3.1}R^{3.2}$, CN, $COOR^{3.1}$, $CONR^{3.1}R^{3.2}$, $NR^{3.1}R^{3.2}$, $NHCOR^{3.1}$, CF_3, $OR^{3.1}$, halogen, $NHCOR^{3.1}$, NO_2, $SO_2NR^{3.1}R^{3.2}$ and C_{1-6}-alkylene-$NHCOR^{3.1}$;

wherein

$R^{3.1}$ denotes H,C_{1-6}-alkyl; C_{2-6}-alkenyl or C_{2-6}-alkynyl, optionally bridged, mono-or bicyclic C_{3-10} heterocycle or C_{3-10} heterocycle-C_{1-4}-alkylene group;

$R^{3.2}$ denotes H, C_{1-6}-alkyl,, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

or **R^3** denotes a group of formula 1b



1b;

wherein

$R^{3.3}$ denotes a group selected from among a heterocyclic C_{3-10} ring which may optionally be substituted by one or more groups selected from among C_{1-6}-alkyl, oxo, $COR^{3.3.1}$, $COR^{3.3.2}$, C_{1-6}-alkylene-$R^{3.3.2}$, CH_2CO-pyrrolidine and a heterocyclic C_{3-10} ring, wherein a sulphur atom optionally contained in the heterocyclic ring, may optionally be in the form of the oxide or dioxide;

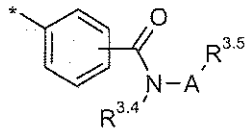
wherein

$R^{3.3.1}$ denotes C_{1-6}-alkyl;

$R^{3.3.2}$ denotes NH_2, $NH(C_{1-6}$-alkyl), $N(C_{1-6}$-alkyl$)_2$;

or $R^{3.3}$ denotes a bicyclic ring or heterocyclic spiro ring;

or R^3 denotes a group of formula **1c**;



1c;

wherein

A may be a bond or C_{1-6}-alkyl, which may optionally be substituted by oxo or NMe_2;

$R^{3.4}$ denotes H or C_{1-6}-alkyl;

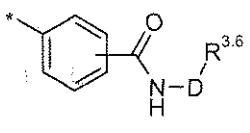
$R^{3.5}$ denotes a group selected from among

C_{1-6}-alkyl, which may optionally be substituted by one or more groups selected from C_{3-7}-cycloalkyl, C_{6-10}-aryl and a C_{3-10} heterocycle, while this group may also optionally be substituted in each case by a group selected from among OH, oxo, C_{1-6}-alkyl, O-C_{1-6}-alkyl and C_{1-6}-haloalkyl,

or a group selected from a heterocyclic C_{3-10} ring and a bicyclic ring, which is optionally substituted by one or more groups selected independently of one another from among oxo, C_{1-6}-alkyl, OH, C_{6-10}-aryl, a heterocyclic C_{3-10} ring, C_{1-6}-alkylene-$R^{3.5.1}$, O-C_{1-6}-alkylene-$R^{3.5.1}$ and NH-C_{1-6}-alkylene-$R^{3.5.1}$,

$R^{3.5.1}$ denotes a group selected from among C_{6-10}-aryl and a heterocyclic C_{3-10} ring which may optionally be substituted by C_{1-6}-alkyl;

or R^3 denotes a group of formula **1d**;



1d;

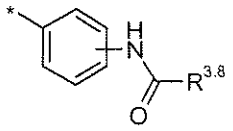
wherein

D denotes C_{2-4}-alkynyl; an optionally bridged, bicyclic C_{3-10}-cycloalkyl group, which may optionally be substituted by one or more groups selected from C_{1-6}-alkyl, halogen, OH, C_{1-6}-haloalkyl and O-C_{1-6}-alkyl,

$R^{3.6}$ denotes pyridinyl;

or **R^3** denotes a group selected from among $COR^{3.7}$, $COCH_2R^{3.8}$, $CONHR^{3.8}$, $SO_2R^{3.8}$ and a heterocyclic group fused to a C_{6-10}-aryl group, which may optionally be substituted by methyl,

or **R^3** denotes a group of formula **1e**;



1e;

$R^{3.7}$ denotes H, C_{1-6}-alkyl, C_{6-10}-aryl;

$R^{3.8}$ denotes a group selected from among C_{1-6}-alkyl, C_{3-7}-cycloalkyl or a group selected from among C_{6-10}-aryl, a heterocyclic C_{3-10} ring and a bicyclic ring, which may optionally be substituted by one or more groups selected from among C_{1-6}-alkyl, halogen, $NR^{3.8.1}R^{3.8.2}$, C_{6-10}-aryl and a heterocyclic C_{3-10} ring;

$R^{3.8.1}$ denotes H or C_{1-6}-alkyl;

$R^{3.8.2}$ denotes H or C_{1-6}-alkyl;

R^4 denotes H, C_{1-4}-alkyl or oxo;

R^5 denotes H or C_{1-4}-alkyl;

R^6 denotes H or C_{1-4}-alkyl;

R^7 denotes H, C_{1-4}-alkyl, C_{6-10}-aryl or OH;

R^8 denotes H, C_{1-4}-alkyl, C_{6-10}-aryl or OH;

or $\mathbf{R^7}$ and $\mathbf{R^8}$ together form oxo;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Preferred compounds of formula 1 above are those wherein

X denotes O, S, SO or SO_2; preferably S, SO or SO_2;

$\mathbf{R^1}$ denotes H, C_{1-4}-alkyl;

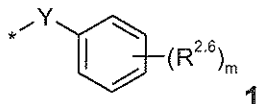
$\mathbf{R^2}$ denotes H or C_{1-6}-alkyl, optionally substituted by a group selected from among C_{1-4}-haloalkyl, CN, $OR^{2.1}$, $NR^{2.1}R^{2.2}$, $COOR^{2.1}$ and $CONR^{2.1}R^{2.2}$ or optionally substituted by a group selected from among C_{3-7}-cycloalkyl, C_{6-10}-aryl and a heterocyclic, aromatic C_{5-10} ring, optionally substituted by methyl or oxo;

$R^{2.1}$ denotes H or C_{1-4}-alkyl;
$R^{2.2}$ denotes H or C_{1-4}-alkyl;

or $\mathbf{R^2}$ denotes C_{3-7}-cycloalkyl, optionally substituted by a group selected from among C_{1-4}-alkyl, $CH_2OR^{2.3}$, $COOR^{2.3}$, $CONR^{2.3}R^{2.4}$, O-benzyl, $NR^{2.3}R^{2.4}$ or $NHCOR^{2.5}$;

$R^{2.3}$ denotes H or C_{1-4}-alkyl;
$R^{2.4}$ denotes H or C_{1-4}-alkyl;
$R^{2.5}$ denotes C_{3-7}-cycloalkyl, a heterocyclic, aromatic C_{5-10} ring or C_{1-6}-alkyl, optionally substituted by OH;

or $\mathbf{R^2}$ denotes a group of formula **1a**,



1a

Y denotes C_{1-4}-alkylene, optionally substituted by one or two $R^{2.7}$

m denotes 0, 1, 2;

$R^{2.7}$ each independently of one another denote C_{1-4}-alkyl, COOH, $CONH_2$; or together with one or two carbon atoms of Y forms a carbocyclic ring with 3 carbon atoms

or **R^2** denotes C_{6-10}-aryl, optionally substituted by one or more groups selected from among C_{1-4}-alkyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$ and NHCOMe

$R^{2.8}$ denotes C_{1-4}-alkyl or C_{6-10}-aryl;

$R^{2.10}$ denotes $NHR^{2.10.1}$ or a heterocyclic non-aromatic C_{3-10} ring, optionally substituted by C_{1-4}-alkyl; preferably a heterocyclic, non-aromatic C_{3-10} ring which may contain one, two or three heteroatoms, selected from among oxygen and nitrogen;

$R^{2.10.1}$ denotes H, cyclopropyl or C_{1-6}-alkyl, optionally substituted by O-C_{1-4}-alkyl;

or **R^2** denotes C_{6-10}-aryl, optionally substituted by a group selected from among phenyl and a heterocyclic C_{3-10} ring, optionally substituted by C_{1-4}-alkyl, $COOR^{2.8}$, CN, halogen, $OR^{2.8}$ and NHCOMe, oxo;

or **R^2** denotes a heterocyclic, non-aromatic C_{5-10} ring, optionally substituted by a group selected from among benzyl, $COR^{2.11}$;

$R^{2.11}$ denotes a group selected from among C_{3-7}-cycloalkyl and a heterocyclic aromatic or non-aromatic C_{5-10} ring, optionally

substituted by one or more C_{1-4}-alkyl, optionally substituted by OH, OMe, NH_2 or NHCOO-^{t}Bu;

or **R^2** denotes a group selected from among C_{2-6}-alkenyl, indanyl, 1,2,3,4-tetrahydro-naphthalyl or 8-methyl-8-aza-bicyclo[3.2.1]octane;

or **NR^1R^2** together denotes a heterocyclic, non-aromatic C_{3-10} ring which is optionally substituted by methyl;

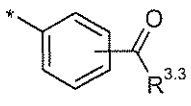
R^3 denotes a group selected from among a heterocyclic, aromatic C_{5-10} ring, C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene and CH_2-benzo[1,3]dioxolyl;

or **R^3** denotes phenyl, optionally substituted by one or more groups selected from among C_{1-4}-alkyl, C_{1-4}-alkylene-$NR^{3.1}R^{3.2}$, CN, $COOR^{3.1}$, $CONR^{3.1}R^{3.2}$, CF_3, $OR^{3.1}$, halogen, $NHCOR^{3.1}$, NO_2, $SO_2NR^{3.1}R^{3.2}$, C_{1-4}-alkylene-$NHCOR^{3.1}$;

$R^{3.1}$ denotes H or C_{1-4}-alkyl;

$R^{3.2}$ denotes H or C_{1-4}-alkyl;

or **R^3** denotes a group of formula **1b**



1b;

wherein

$R^{3.3}$ denotes a group selected from among a heterocyclic, non-aromatic C_{3-10} ring, optionally substituted by one or more groups selected from among C_{1-4}-alkyl, oxo, $COR^{3.3.1}$, $COR^{3.3.2}$, C_{1-4}-alkylene-$R^{3.3.2}$, CH_2CO-pyrrolidine, heterocyclic C_{3-10} ring, wherein a sulphur atom

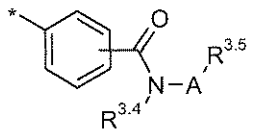
optionally contained in the heterocyclic C_{3-10} ring may optionally be in the form of the oxide or dioxide;

$R^{3.3.1}$ denotes C_{1-4}-alkyl;

$R^{3.3.2}$ denotes NH_2, $NH(C_{1-4}$-alkyl) or $N(C_{1-4}$-alkyl)$_2$;

or $R^{3.3}$ denotes a fused, bicyclic heteroring or heterocyclic spiroring;

or **R^3** denotes a group of formula **1c**;



1c;

wherein

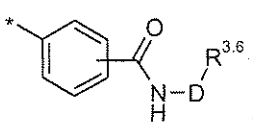
A denotes a bond or C_{1-4}-alkyl, optionally substituted by oxo or NMe_2;

$R^{3.4}$ denotes H or C_{1-4}-alkyl;

$R^{3.5}$ denotes a group selected from among a heterocyclic C_{3-10} ring or a bicyclic ring, optionally substituted by one or more groups selected independently of one another from among oxo, C_{1-4}-alkyl, OH, C_{6-10}-aryl, heterocyclic, aromatic C_{5-10} ring, C_{1-4}-alkylene-$R^{3.5.1}$, O-C_{1-4}-alkylene-$R^{3.5.1}$, NH-C_{1-4}-alkylene-$R^{3.5.1}$;

$R^{3.5.1}$ denotes a group selected from among C_{6-10}-aryl, heterocyclic C_{3-10} ring, optionally substituted by C_{1-4}-alkyl;

or **R^3** denotes a group of formula **1d**;



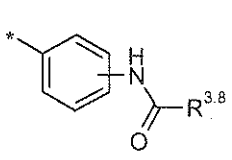
1d;

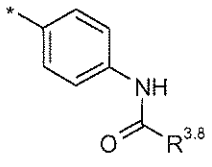
wherein

D denotes C_{2-4}-alkynyl;

$R^{3.6}$ denotes pyridinyl;

or **R^3** denotes a group $COR^{3.7}$, $COCH_2R^{3.8}$, $CONHR^{3.8}$, $SO_2R^{3.8}$ or a group of formula **1e**;





1e; preferably

$R^{3.7}$ denotes H, C_{1-4}-alkyl, C_{6-10}-aryl;

$R^{3.8}$ denotes C_{1-4}-alkyl, C_{3-7}-cycloalkyl or a group selected from among C_{6-10}-aryl, heterocyclic C_{5-10} ring and a bicyclic ring, optionally substituted by one or more groups selected from among C_{1-4}-alkyl, halogen, $NR^{3.8.1}R^{3.8.2}$, C_{6-10}-aryl and heterocyclic, non-aromatic C_{3-10} ring ;

$R^{3.8.1}$ denotes H or C_{1-4}-alkyl;

$R^{3.8.2}$ denotes H or C_{1-4}-alkyl;

R^4 denotes H, methyl or oxo;

R^5 denotes H or methyl;

R^6 denotes H or methyl;

R^7 denotes H, methyl, phenyl or OH;

R^8 denotes H, methyl, phenyl or OH;

or **R^7** and **R^8** together form oxo;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Preferred compounds of formula 1 above are those wherein

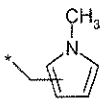
X denotes O, S, SO or SO_2; preferably S, SO or SO_2;

R^1 denotes H, methyl, ethyl or propyl; preferably H and propyl

R^2 denotes H or C_{1-6}-alkyl, which may optionally be substituted by one or more groups selected from among CF_3, CN, OH, NMe_2, OMe, COOH and $CONMe_2$,

or **R^2** denotes C_{1-6}-alkyl, which may optionally be substituted by one or more groups selected from cyclopropyl, cyclopentyl, cyclohexyl, phenyl, pyrrolidinyl, imidazolidinyl, pyrazolyl, imidazolyl and pyridinyl, which may optionally be substituted by methyl or oxo;

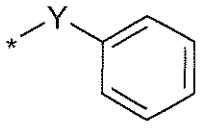
or **R^2** denotes C_{3-7}-cycloalkyl, which may optionally be substituted by a group selected from among methyl, $OR^{2.3}$,$CH_2OR^{2.3}$, COOH, $CONR^{2.3}R^{2.4}$, CONH-^{t}Bu, O-benzyl, $NR^{2.3}R^{2.4}$ and $NHCOR^{2.5}$,
wherein

$R^{2.3}$ denotes H or methyl, or ,

$R^{2.4}$ denotes H or methyl;

$R^{2.5}$ denotes $CH_2C(CH_3)_3$, $CH_2C(CH_3)_2(CH_2OH)$, cyclopentyl, tetrahydrofuranyl, pyrrolyl, pyrazolyl, imidazolyl or isoxazolyl;

or **R^2** denotes a group of formula **1a**,



1a

Y denotes C_{1-4}-alkylene, optionally substituted by one or two $R^{2.7}$

$R^{2.7}$ each independently of one another denote C_{1-4}-alkyl, COOH, $CONH_2$; or $R^{2.7}$ together with one or two carbon atoms of Y forms a carbocyclic ring with 3 carbon atoms

or **R^2** denotes C_{6-10}-aryl, which may optionally be substituted by one or more groups selected independently of one another from among methyl, *tert*-butyl, CN, F, Cl, Br, OH, OMe, OEt, O-phenyl, COOH, COOMe, $COR^{2.10}$, NHCOMe and morpholinyl-C_{1-4}-alkylene,
wherein

$R^{2.10}$ denotes NH_2, NHMe, NH-^{i}Pr, NH-cyclopropyl, $NHCH_2CH_2OMe$ or a heterocyclic, non-aromatic C_{3-10} ring, which may contain one, two or three heteroatoms selected from among oxygen and nitrogen; preferably NH_2, NHMe, NH-^{i}Pr, NH-cyclopropyl, $NHCH_2CH_2OMe$, morpholinyl or methyl-piperazinyl;

or **R^2** denotes C_{6-10}-aryl, which may optionally be substituted by a group selected from among phenyl and a heterocyclic C_{3-10} ring, which may optionally be substituted by one or more groups selected from among methyl, *tert*-butyl, COOH, COOMe, CN, F, Cl, Br, OH, OMe, OEt and NHCOMe, oxo; preferably phenyl, imidazolidinyl, optionally substituted by methyl or oxo;

or **R^2** denotes a heterocyclic non-aromatic C_{3-10} ring which may optionally be substituted by a group selected from among benzyl and $COR^{2.11}$;
wherein

$R^{2.11}$ denotes a group selected from among cyclopentyl, tetrahydrofuranyl, furan, pyridyl, pyrrolyl, pyrrazolyl, imidazolyl, which may optionally be substituted by one or two methyl groups, or by one or more groups

selected from among $CH_2C(CH_3)_3$, $C(CH_3)_2(CH_2OH)$, CH_2OMe, $C(CH_3)_2NH_2$ and $C(CH_3)_2NHCOO\text{-}^tBu$;

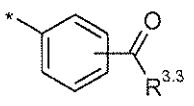
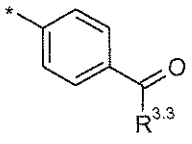
or **R^2** denotes a group selected from among C_{2-6}-alkenyl, indanyl, 1,2,3,4-tetrahydro-naphthalyl and 8-methyl-8-aza-bicyclo[3.2.1]octane;

or **NR^1R^2** denotes a group selected from among pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, which may optionally be substituted by methyl;

R^3 denotes H or a group selected from among pyridinyl, pyrimidinyl, benzyl, and CH_2-benzo[1, 3]dioxolyl;

or **R^3** denotes phenyl, which may optionally be substituted by one, two or three groups selected from among methyl, CH_2NH_2, CN, COOH, $CONH_2$, CF_3, OH, F, Cl, Br, OMe, NHCOMe, $NR^{3.1}COR^{3.2}$, $CONR^{3.1}R^{3.2}$, NO_2, $SONMe_2$ and $CH_2NHCOMe$;
wherein
$R^{3.1}$ denotes H, C_{1-6}-alkyl or an optionally bridged, mono- or bicyclic C_{3-10} heterocycle
$R^{3.2}$ denotes H or C_{1-6}-alkyl;

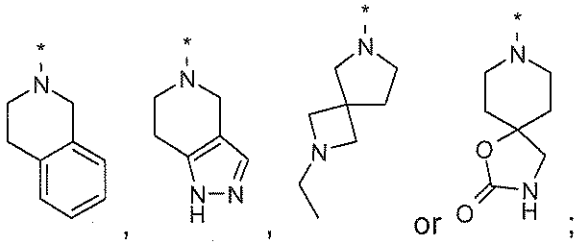
or **R^3** denotes a group of formula **1b**

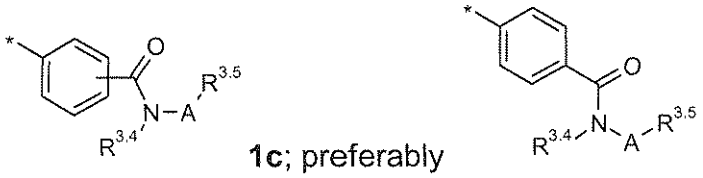
1b; preferably

wherein
$R^{3.3}$ denotes a group selected from among piperidinyl, piperazinyl, azepanyl, which may optionally be substituted by one or more groups selected independently of one another from among methyl, oxo, $COCH_3$, $CONH_2$, CH_2NEt_2, $CH_2CH_2NMe_2$, CH_2CO-pyrrolidine, pyridinyl, isothiazolidinyl-1,1-dioxide and thiazolidinyl-1,1-dioxide;

or $R^{3.3}$ denotes a group of formula



or **R^3** denotes a group of formula **1c**;



1c; preferably

wherein

A denotes a bond or C_{1-4}-alkyl, which may optionally be substituted by oxo or NMe_2,

$R^{3.4}$ denotes H or methyl;

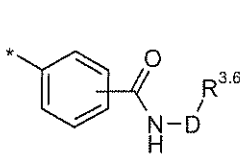
$R^{3.5}$ denotes a group selected from among pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, cyclohexyl, imidazolyl, pyrazolyl, phenyl, pyridinyl, benzimidazolyl, imidazolidin-2-one, pyrrolidin-2-one, pyrrolidin-3-one, tetrahydro-thiophene-1,1-dioxide and 1-aza-bicyclo[2,2,2]octane, which may optionally be substituted by one or more groups selected independently of one another from among methyl, ethyl, OH, phenyl, pyridinyl, pyrazolyl, pyrrolidinyl, $(CH_2)_o$-$R^{3.5.1}$, O-$(CH_2)_o$-$R^{3.5.1}$ and NH-$(CH_2)_o$-$R^{3.5.1}$;

wherein

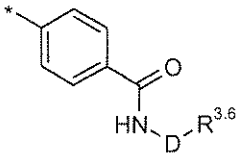
o denotes 0, 1 or 2

$R^{3.5.1}$ denotes a group selected from among phenyl, pyrrolidinyl, piperidinyl and imidazolidin-2-one, which may optionally be substituted by methyl;

or R^3 denotes a group of formula **1d**;



1d; preferably

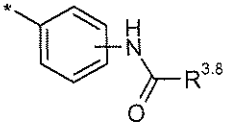


wherein

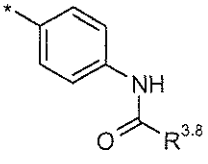
D denotes C_{2-4}-alkynyl;

$R^{3.6}$ denotes pyridinyl;

or R^3 denotes a group $COR^{3.7}$, $COCH_2R^{3.8}$, $CONHR^{3.8}$, $SO_2R^{3.8}$ or a group of formula **1e**;



1e; preferably



wherein

$R^{3.7}$ denotes H, methyl or phenyl;

$R^{3.8}$ denotes a group selected from among *iso*-propyl, cyclopropyl, cyclopentyl, cyclohexyl, pyrrolidinyl, pyrrolidin-2-one, furanyl and azabicyclo[2,2,2]octanyl or a group selected from among piperidinyl, pyrazolyl, imidiazolyl, isoxazolyl, pyridinyl, phenyl, benzyl, which may optionally be substituted by one or more groups selected from among methyl, chlorine, NH_2, NMe_2, phenyl and morpholinyl;

R^4 denotes H, methyl or oxo;

R^5 denotes H or methyl;

R^6 denotes H or methyl;

R^7 denotes H, methyl or OH; preferably H or methyl;

R^8 denotes H, methyl or OH; preferably H or methyl;

or R^7 and R^8 together form oxo;

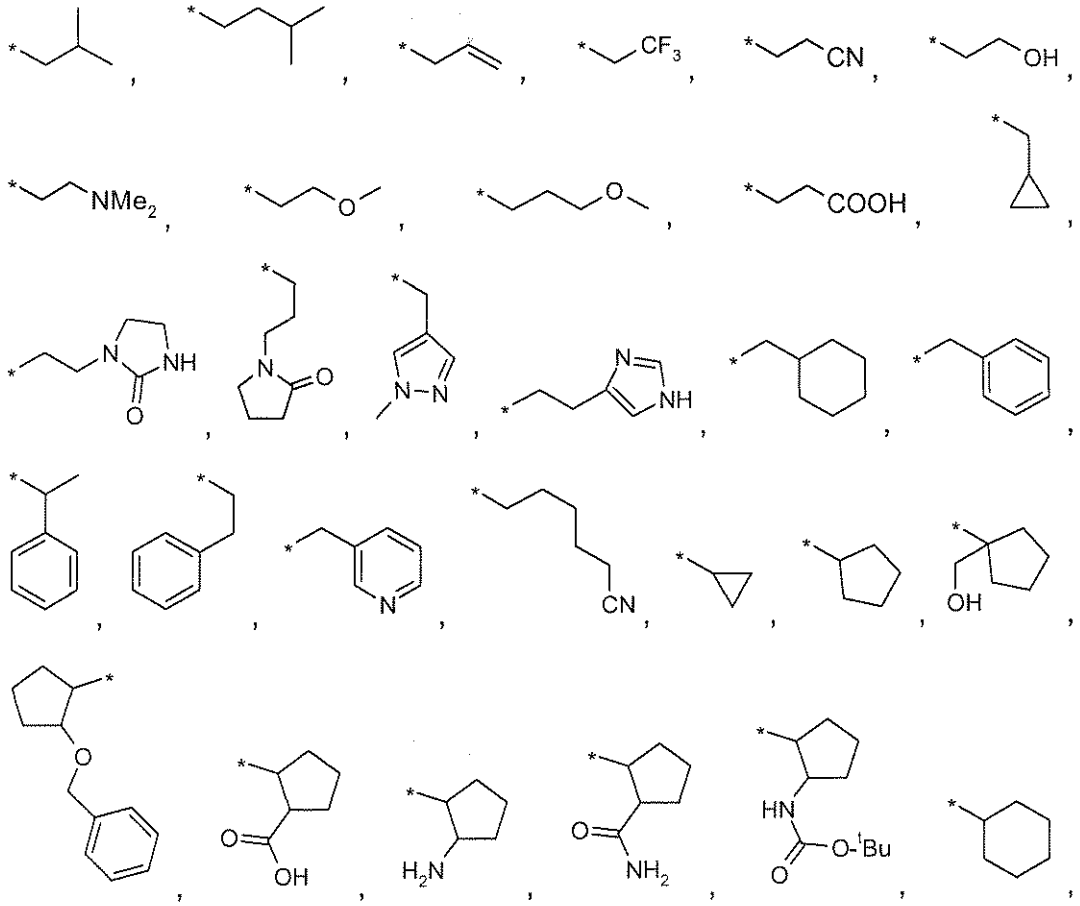
and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

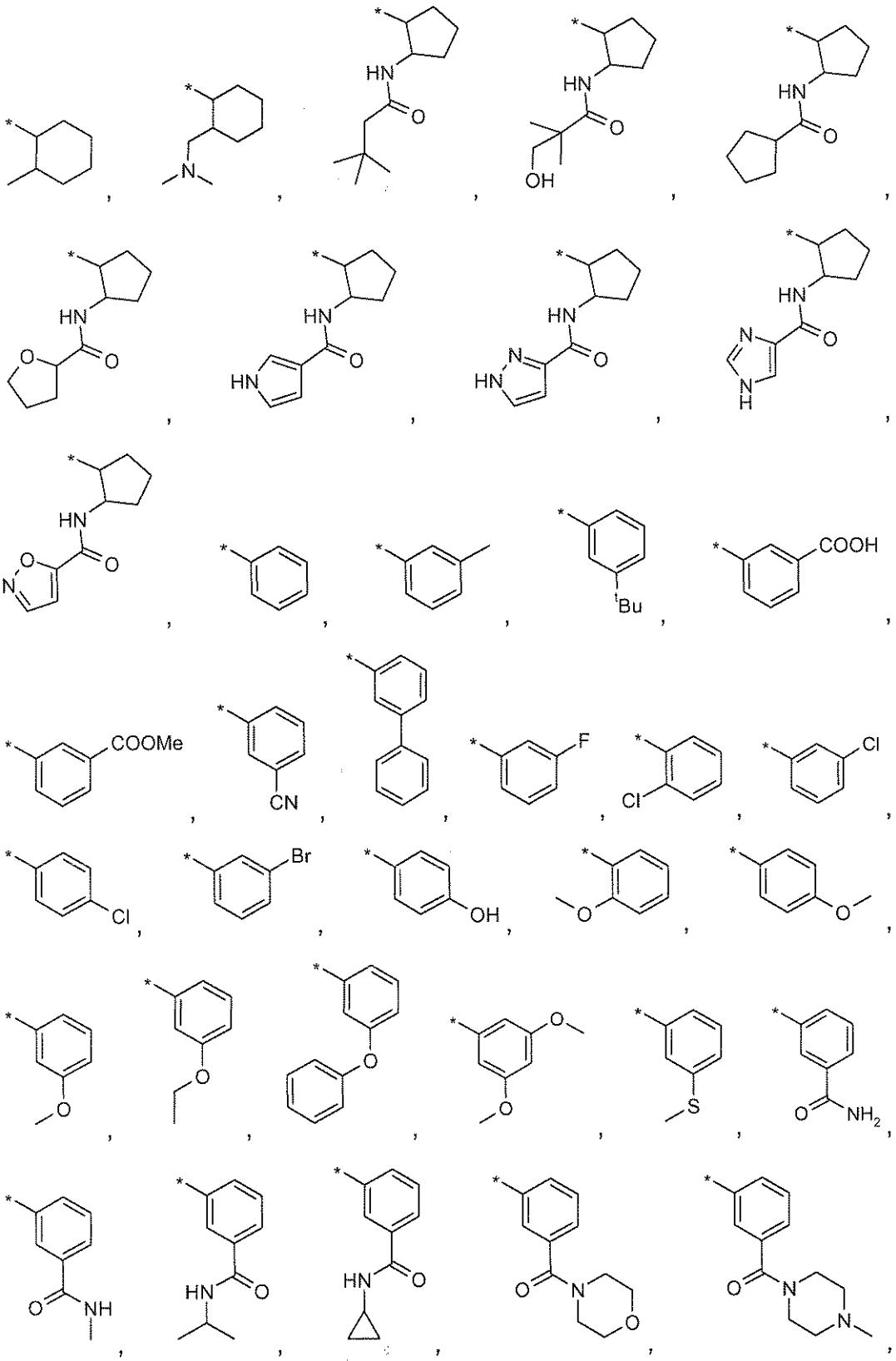
Preferred compounds of formula **1** above are those wherein

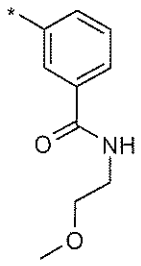
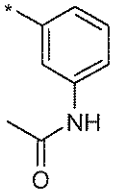
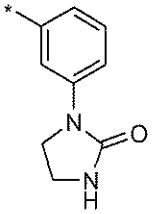
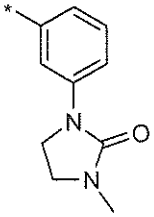
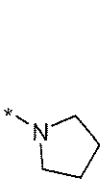
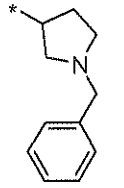
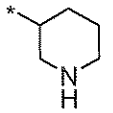
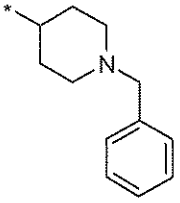
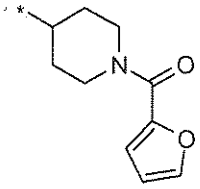
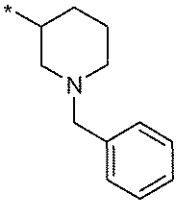
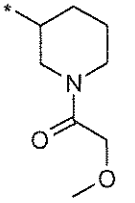
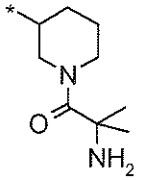
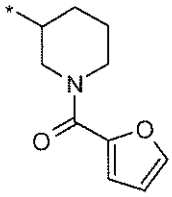
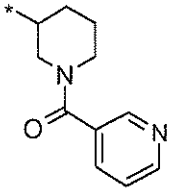
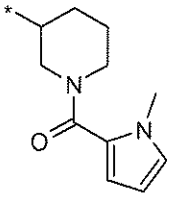
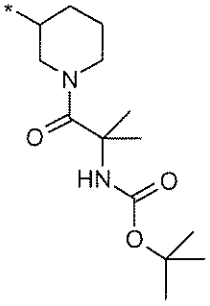
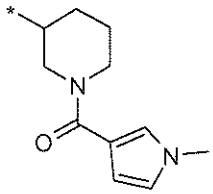
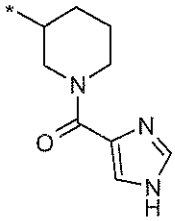
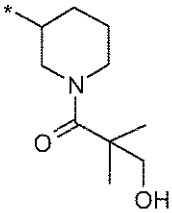
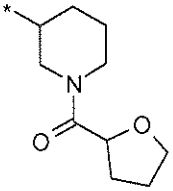
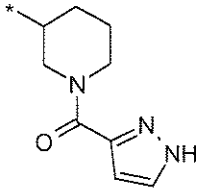
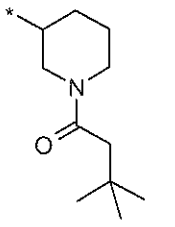
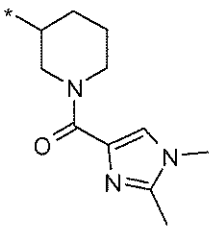
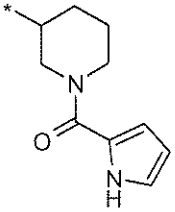
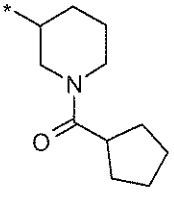
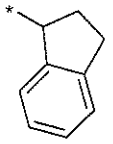
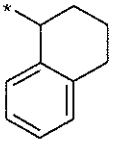
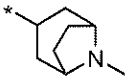
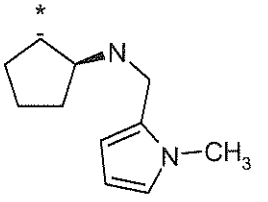
X denotes S, SO or SO_2;

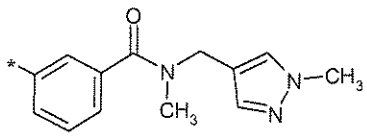
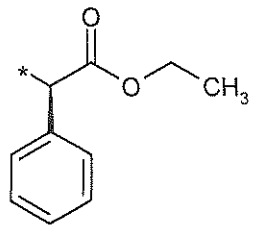
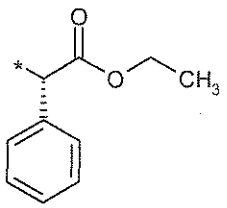
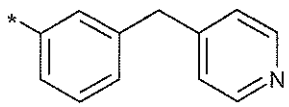
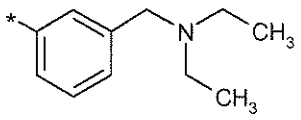
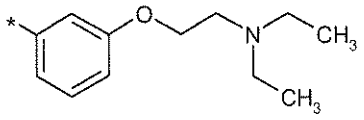
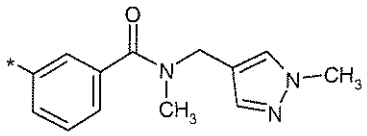
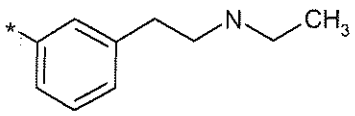
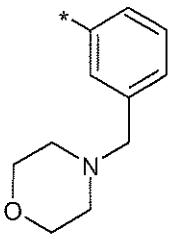
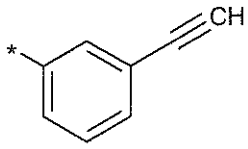
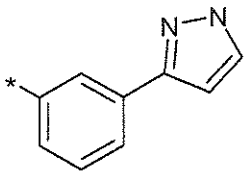
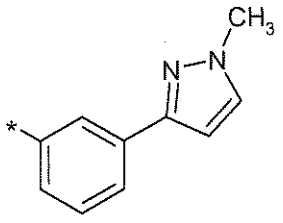
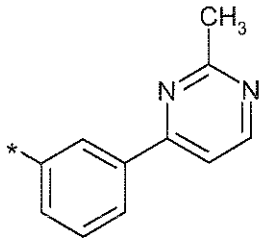
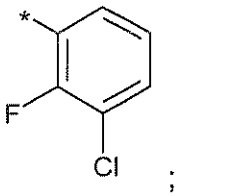
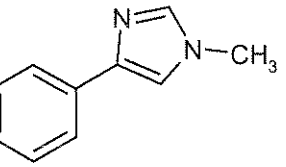
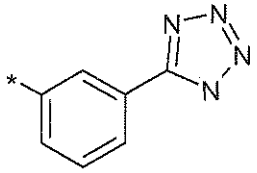
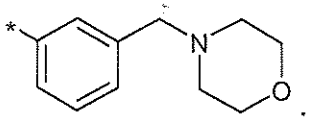
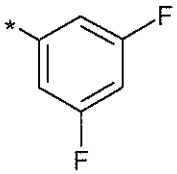
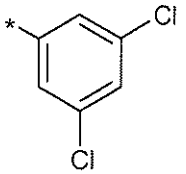
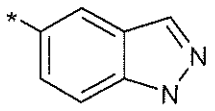
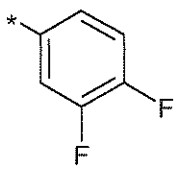
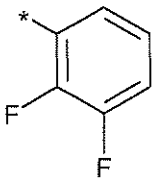
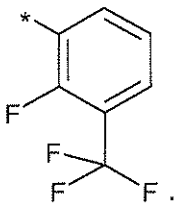
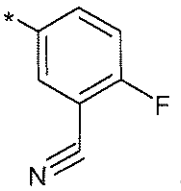
R^1 denotes H, methyl or ethyl;

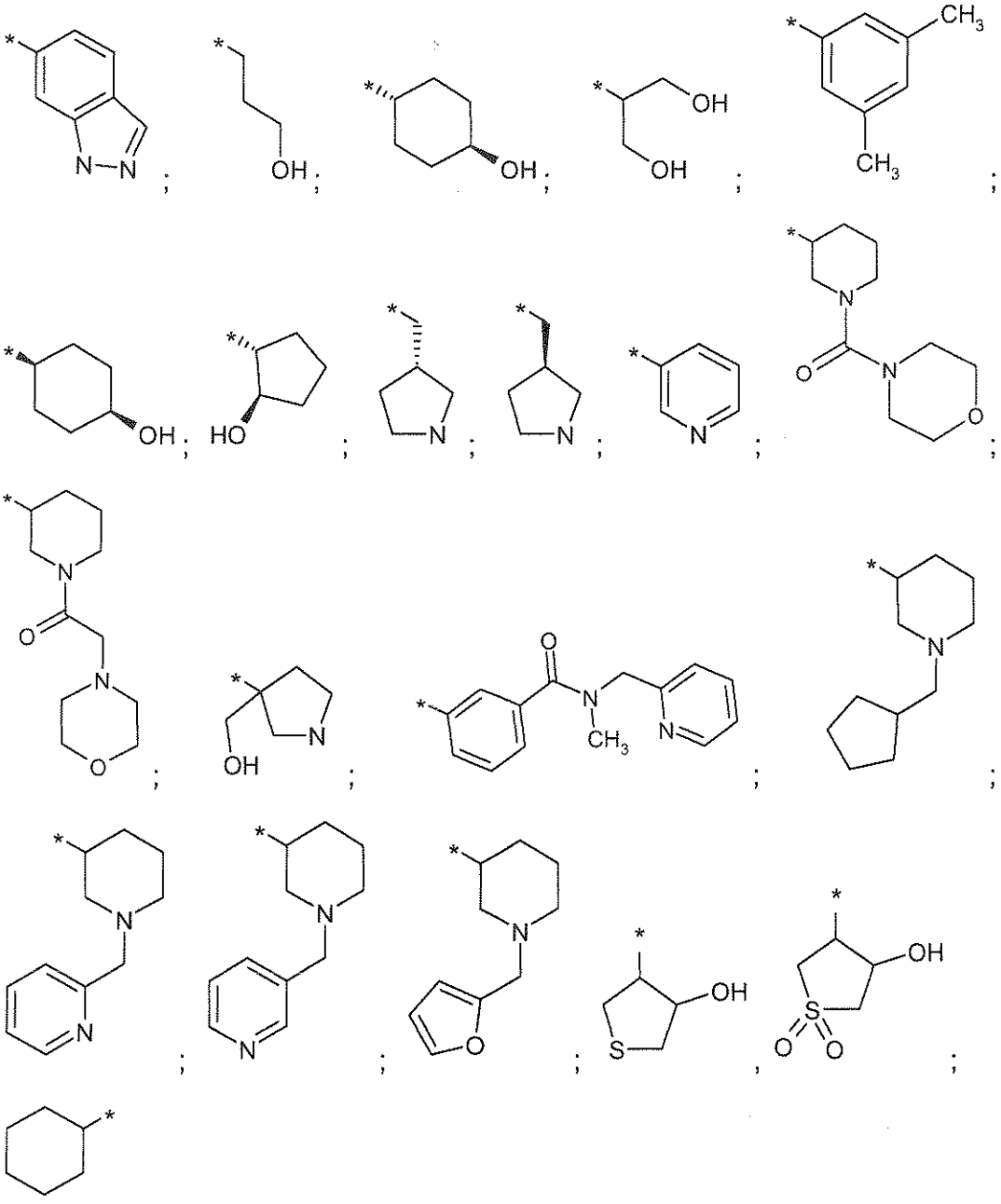
R^2 denotes a group selected from among H, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl,



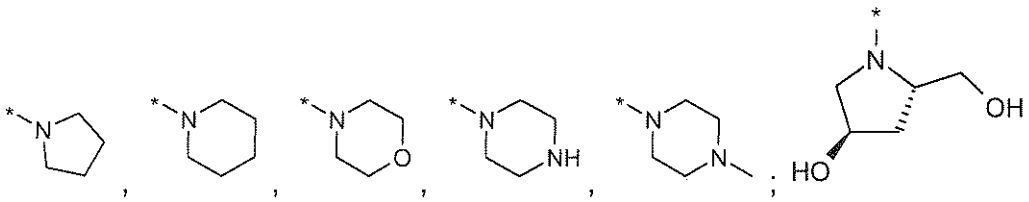



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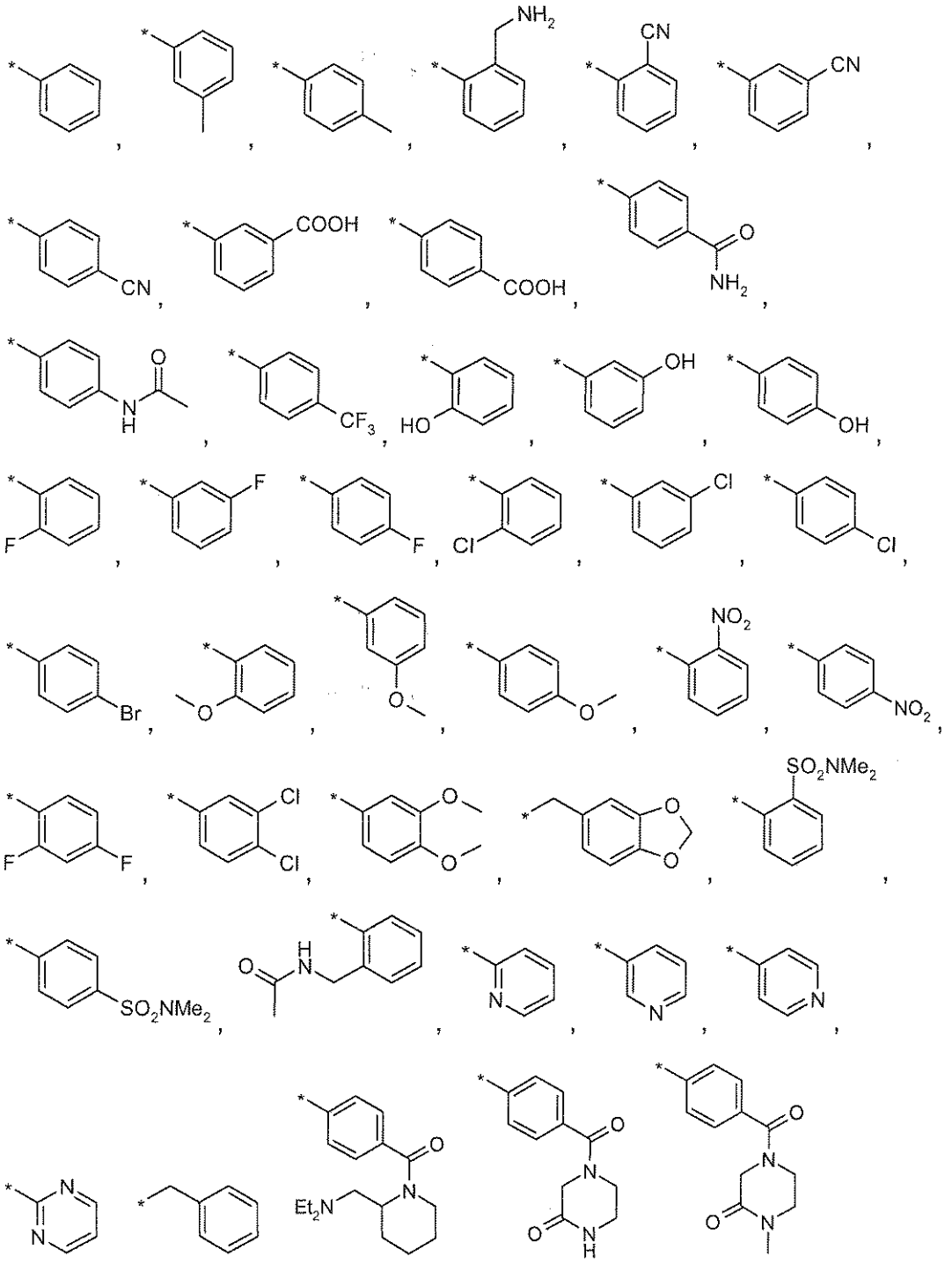

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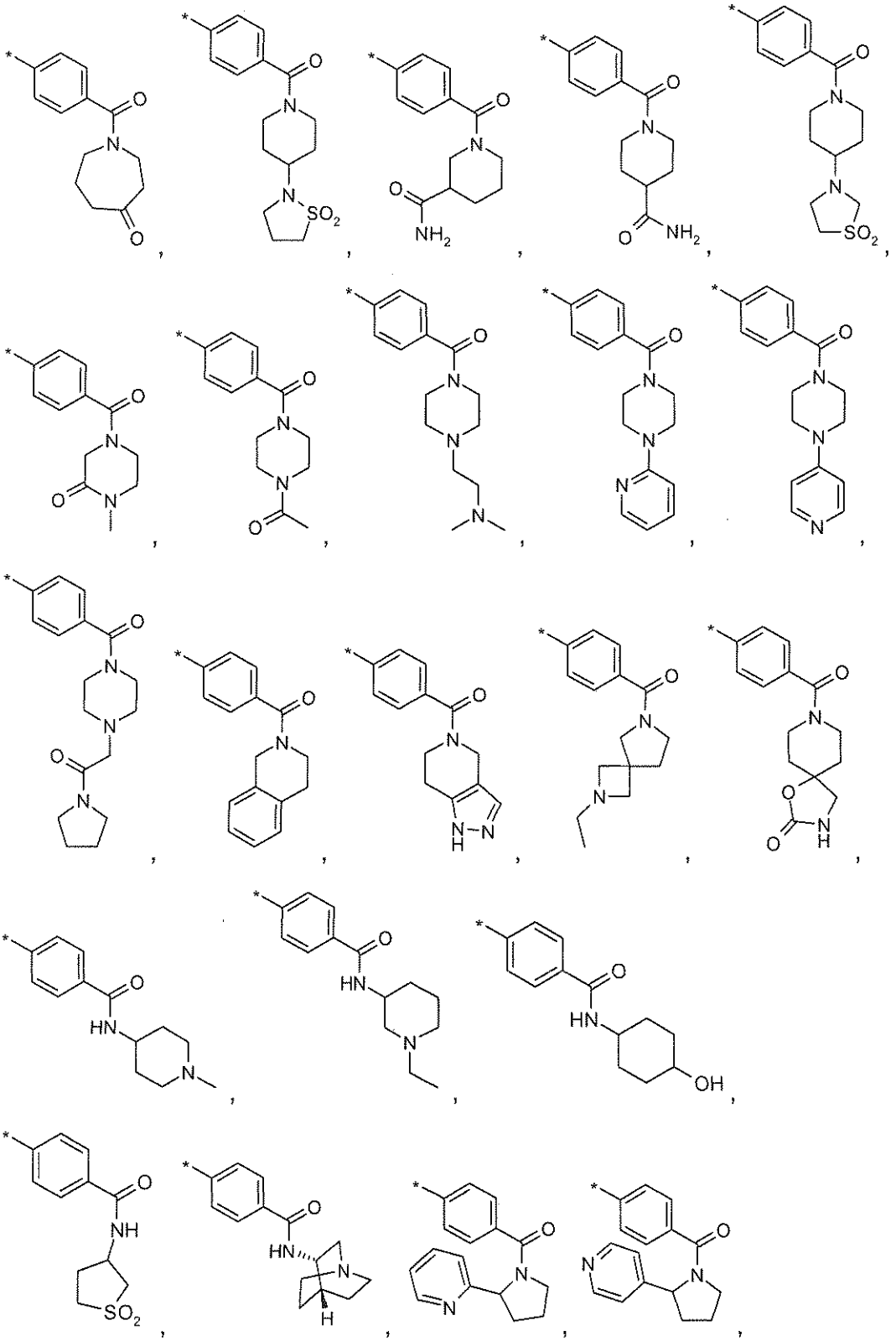


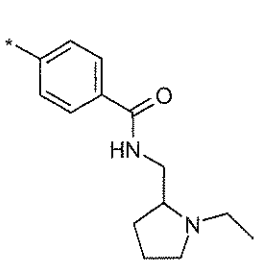
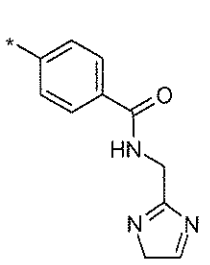
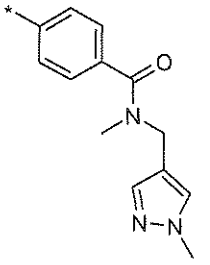
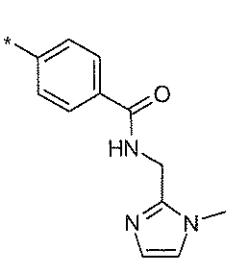
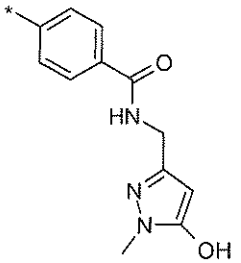
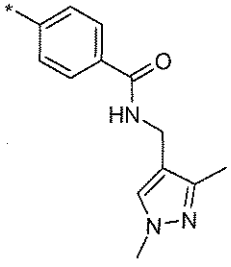
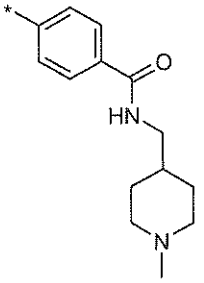
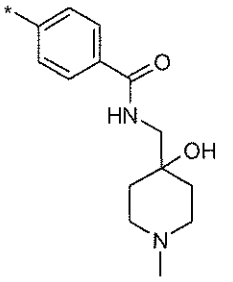
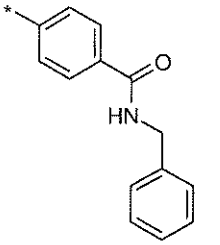
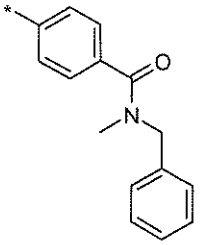
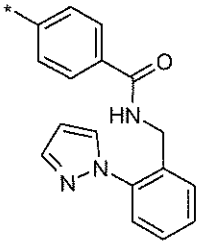
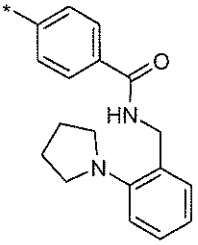
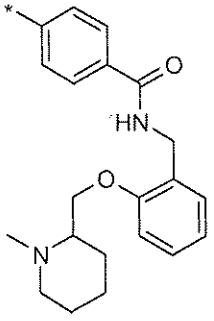
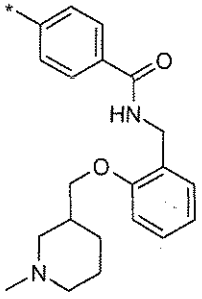
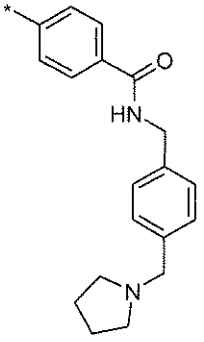
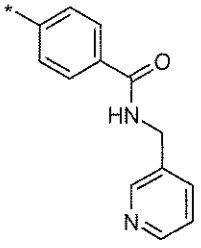
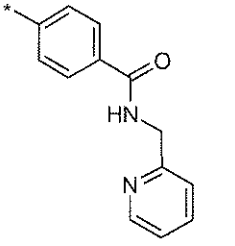
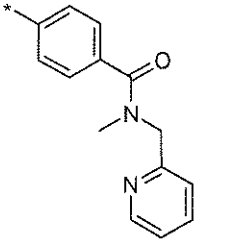
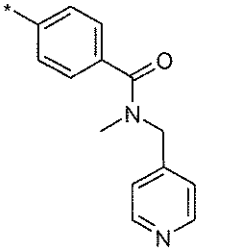
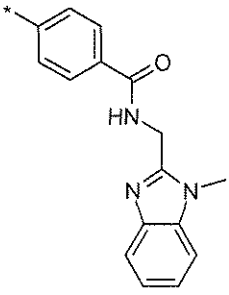
or **NR^1R^2** denotes a group selected from among



R^3 denotes a group selected from among





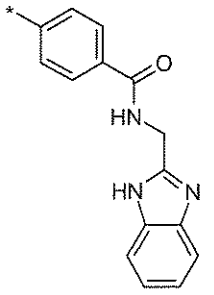
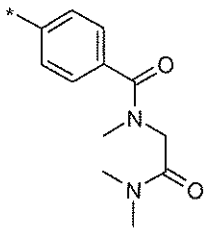
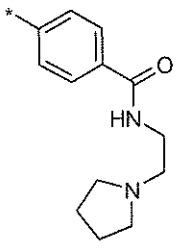
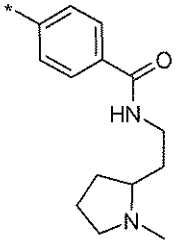
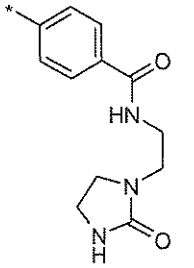
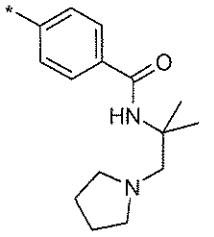
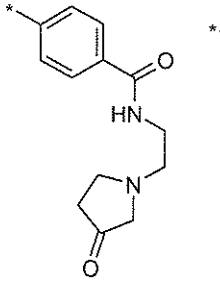
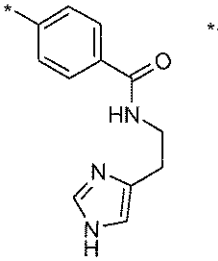
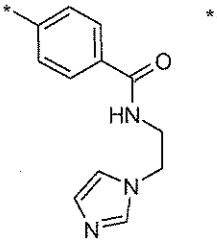
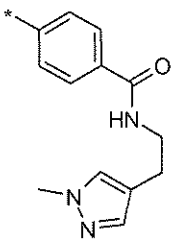
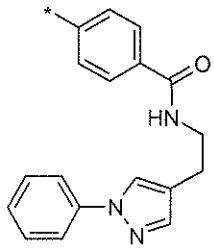
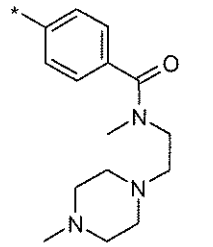
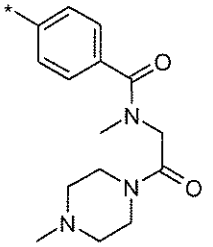
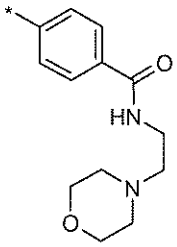
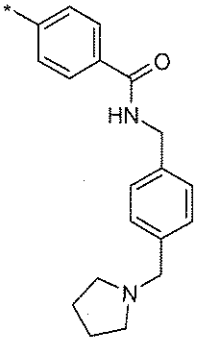
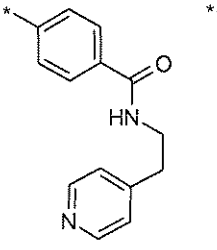
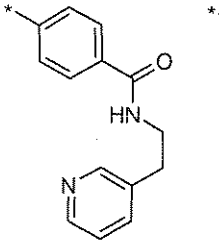
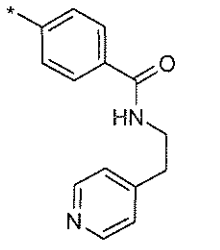
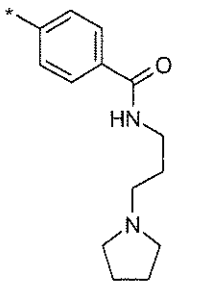
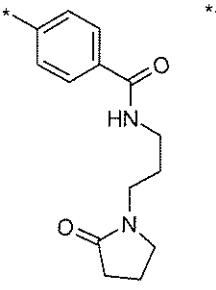
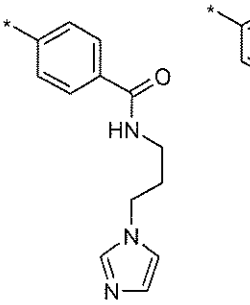
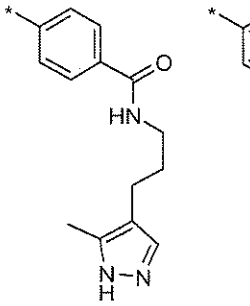
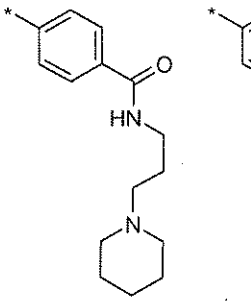
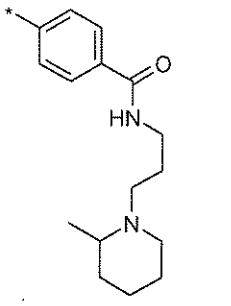

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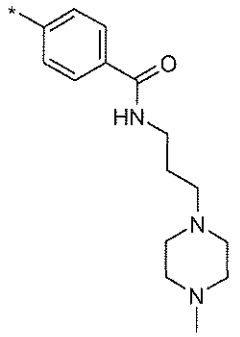
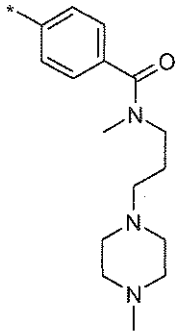
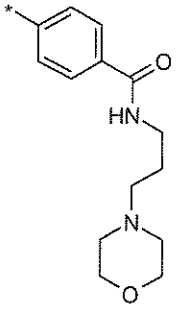
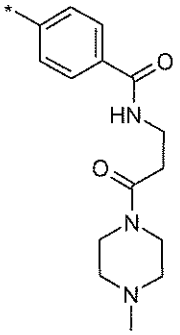
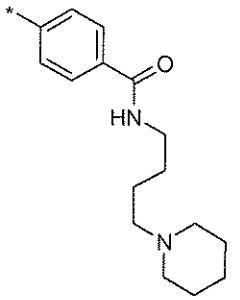
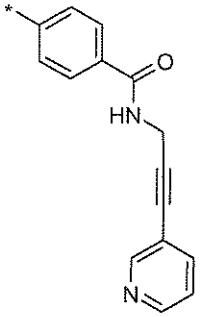
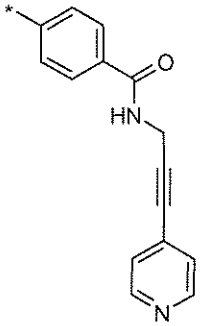
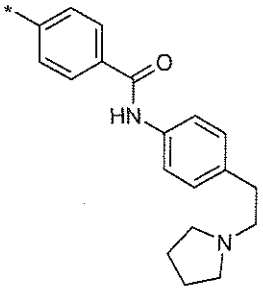
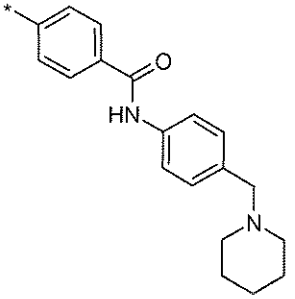
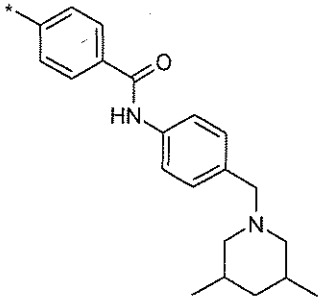
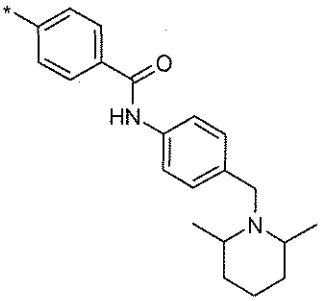
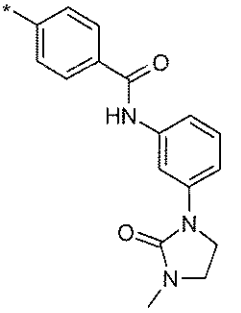
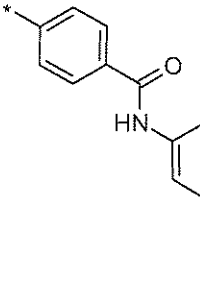
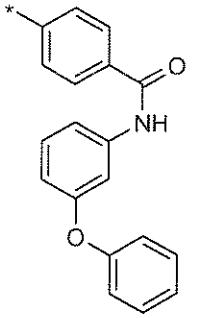
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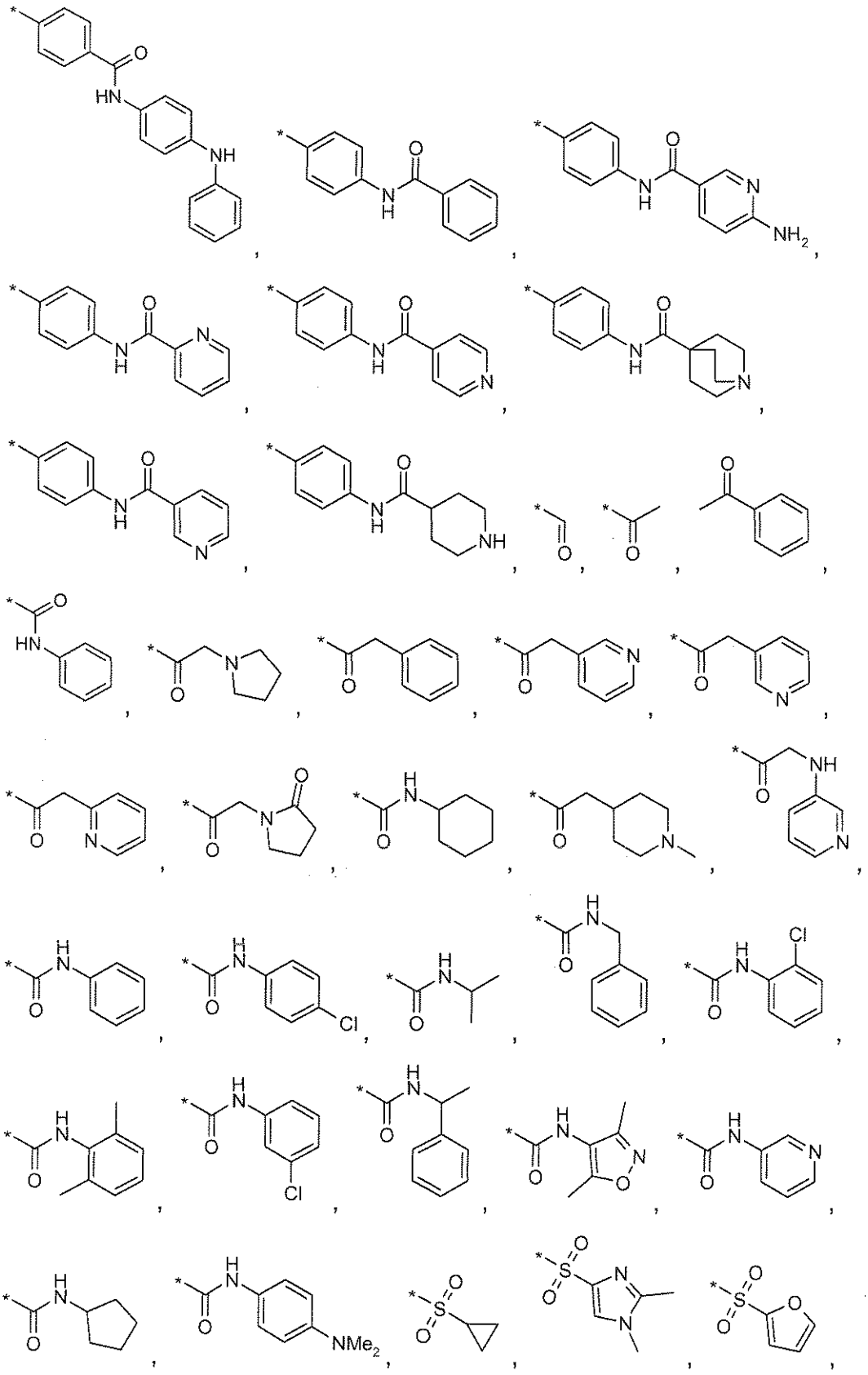
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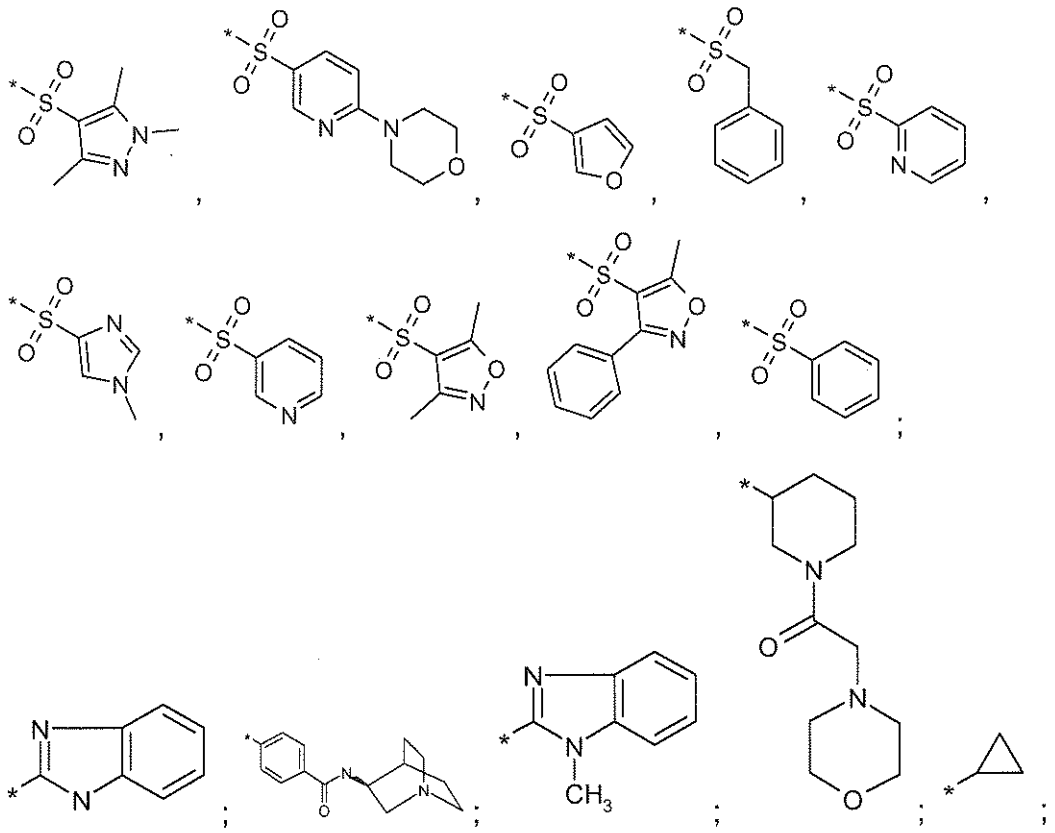
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R^4 denotes H, methyl or oxo;

R^5 denotes H or methyl;

R^6 denotes H or methyl;

R^7 denotes H or methyl;

R^8 denotes H or methyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and

R^1 denotes H;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and

X denotes SO;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein R^1, R^2, R^3, R^4 and X are as hereinbefore defined and

R^5, R^6, R^7 and R^8 denote H;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein R^1, R^2, R^3, R^5, R^6, R^7 and R^8 and X are as hereinbefore defined and

R^4 denotes H;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8 and X are as hereinbefore defined and

wherein

$\mathbf{R^2}$ denotes C_{6-10}-aryl, which may optionally be substituted by one or more groups selected independently of one another from among C_{1-6}-alkyl, C_{1-4}-haloalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$, $NR^{2.8}R^{2.9}$, $NHCOR^{2.8}$, $SR^{2.8}$, $SOR^{2.8}$, $SO_2R^{2.8}$ and $SO_2NR^{2.8}R^{2.9}$

or $\mathbf{R^2}$ denotes C_{6-10}-aryl, which may optionally be substituted by one or more groups selected from among C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene, C_{6-10}-aryl and a heterocyclic C_{3-10} ring, which may optionally be substituted by a group selected from among C_{1-6}-alkyl, C_{1-6}-haloalkyl, $COOR^{2.8}$, CN, halogen, $OR^{2.8}$, $NHCOR^{2.8}$, oxo, a C_{3-7}-cycloalkyl-C_{1-4} alkylene, a heterocycle-C_{1-4} alkylene and a $NR^{2.1}R^{2.2}$-C_{1-4} -alkylene,

wherein

$R^{2.8}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, a $NR^{2.1}R^{2.2}$-C_{1-4}-alkylene or C_{6-10}-aryl;

$R^{2.9}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

$R^{2.10}$ denotes $NHR^{2.10.1}$,C_{1-6}-alkylene-O-C_{1-4}-alkyl, or a heterocyclic C_{3-10} ring which may optionally be substituted by C_{1-4}-alkyl;

$R^{2.10.1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl or C_{3-7}-cycloalkyl;

or $\mathbf{R^2}$ denotes C_{6-10}-aryl, to which an aromatic or non-aromatic C_{3-10} heterocycle is fused;

or $\mathbf{R^2}$ denotes C_{6-10}-aryl, which may optionally be substituted by a group selected from among C_{6-10}-aryl and a heterocyclic C_{3-10} ring, which is optionally substituted by one or more groups selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-4}-haloalkyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$ $NR^{2.8}R^{2.9}$, $NHCOR^{2.8}$, $SR^{2.8}$, $SOR^{2.8}$, $SO_2R^{2.8}$, $SO_2NR^{2.8}R^{2.9}$ and oxo;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and

R^2 denotes C_{6-10}-aryl, optionally substituted by one or more groups selected independently of one another from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-4}-haloalkyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$ $NR^{2.8}R^{2.9}$, $NHCOR^{2.8}$, $SR^{2.8}$, $SOR^{2.8}$, $SO_2R^{2.8}$ and $SO_2NR^{2.8}R^{2.9}$

$R^{2.8}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl or C_{6-10}-aryl;

$R^{2.9}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

$R^{2.10}$ denotes $NHR^{2.10.1}$ C_{1-6}-alkylene-O-C_{1-4}-alkyl, or a heterocyclic C_{3-10} ring, optionally substituted by C_{1-4}-alkyl;

$R^{2.10.1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl or C_{3-7}-cycloalkyl;

or **R^2** denotes C_{6-10}-aryl, optionally substituted by a group selected from among C_{6-10}-aryl and a heterocyclic C_{3-10} ring, optionally substituted by C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-4}-haloalkyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$ $NR^{2.8}R^{2.9}$, $NHCOR^{2.8}$, $SR^{2.8}$, $SOR^{2.8}$, $SO_2R^{2.8}$, $SO_2NR^{2.8}R^{2.9}$ and oxo;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and

$\mathbf{R^2}$ denotes C_{6-10}-aryl, which may optionally be substituted by one or more groups selected from among C_{1-4}-alkyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$ and NHCOMe

wherein

$R^{2.8}$ denotes C_{1-4}-alkyl or C_{6-10}-aryl;

$R^{2.10}$ denotes $NHR^{2.10.1}$, morpholinyl, methyl-piperazinyl;

$R^{2.10.1}$ denotes H, cyclopropyl or C_{1-4}-alkyl, which may optionally be substituted by one or more groups selected from O-C_{1-4}-alkyl, OH or C_{6-10}-aryl;

or $\mathbf{R^2}$ denotes C_{6-10}-aryl, which may optionally be substituted by a group selected from among phenyl and a heterocyclic C_{3-10} ring, which may optionally be substituted by C_{1-4}-alkyl, $COOR^{2.8}$, CN, halogen, $OR^{2.8}$, NHCOMe and oxo;

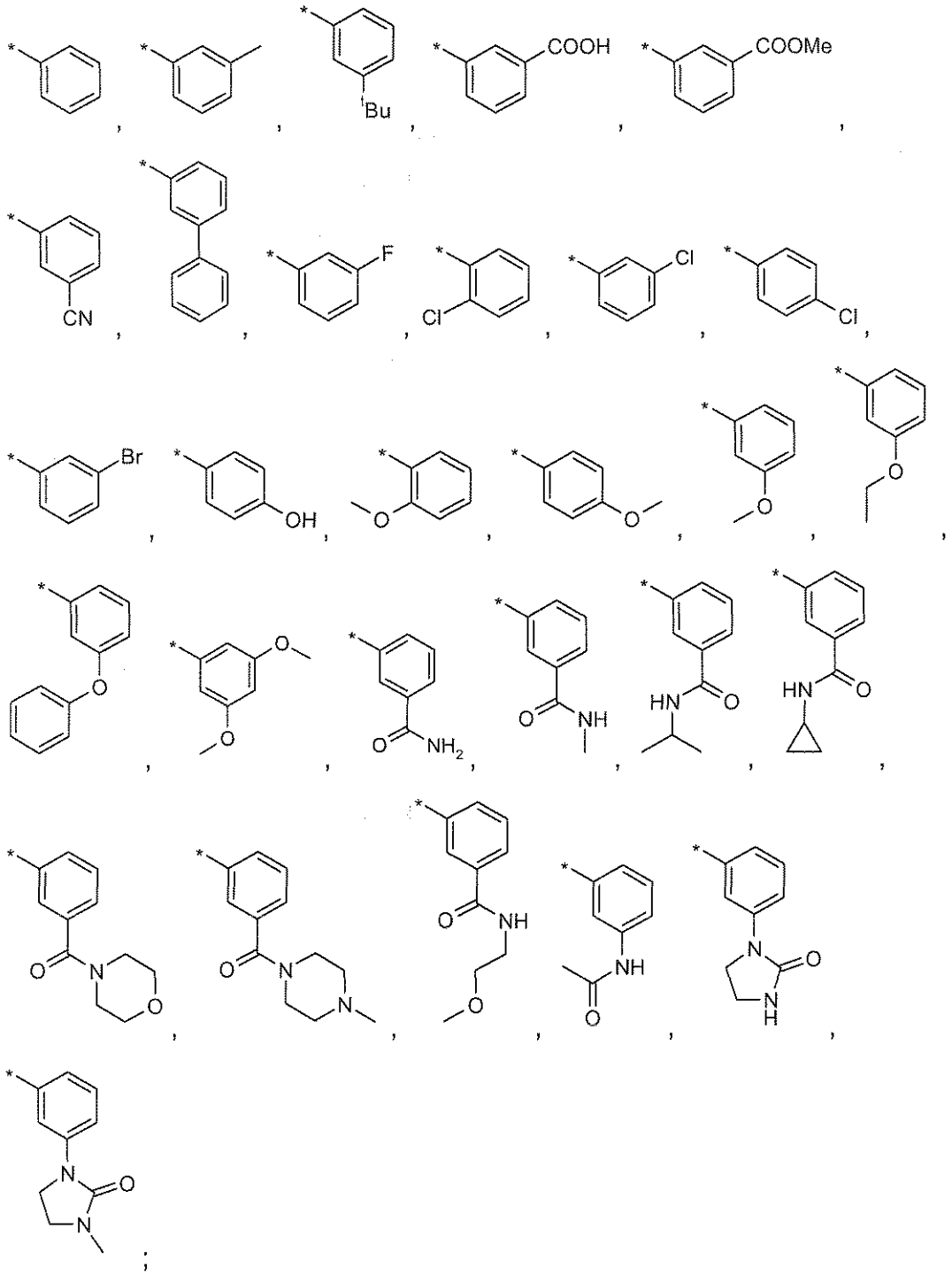
and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and wherein

$\mathbf{R^2}$ denotes C_{6-10}-aryl, optionally substituted by one or more groups selected independently of one another from among methyl, *tert*-butyl, CN, F, Cl, Br, OH, OMe, OEt, O-phenyl, COOH, COOMe, $COR^{2.10}$ and NHCOMe

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and $\mathbf{R^2}$ denotes



and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and

R^2 denotes H;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula 1, wherein X, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and wherein

R^2 denotes a group selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl; preferably C_{1-6}-alkyl; particularly preferably propyl, which may optionally be substituted by a group selected from among C_{1-6}-haloalkyl, CN, $OR^{2.1}$, $NR^{2.1}R^{2.2}$, $COOR^{2.1}$, $NHCOR^{2.1}$, $SR^{2.1}$, $SOR^{2.1}$, $SO_2R^{2.1}$, and $CONR^{2.1}R^{2.2}$, preferably by a group selected from among C_{1-4}-haloalkyl, CN, $OR^{2.1}$, $NR^{2.1}R^{2.2}$, $COOR^{2.}$ and $CONR^{2.1}R^{2.2}$ or which may optionally be substituted by a group selected from among C_{3-7}-cycloalkyl, C_{6-10}-aryl and a heterocyclic, aromatic C_{3-10} ring, which may in turn optionally be substituted by C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl or oxo; preferably by methyl or oxo; wherein

$R^{2.1}$ denotes H or is selected from among C_{1-4}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl, preferably H or C_{1-4}-alkyl;

$R^{2.2}$ denotes H or is selected from among C_{1-4}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl, preferably H or C_{1-4}-alkyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and

R^2 denotes a group selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl; preferably C_{1-6}-alkyl; particularly preferably propyl, optionally substituted by a group selected from among C_{1-6}-haloalkyl, CN, $OR^{2.1}$, $NR^{2.1}R^{2.2}$, $NHCOR^{2.1}$, $SR^{2.1}$, $SOR^{2.1}$, $SO_2R^{2.1}$, $SO_2NR^{2.1}R^{2.2}$, $COOR^{2.1}$ and $CONR^{2.1}R^{2.2}$ or optionally substituted by a group selected from among C_{3-7}-cycloalkyl, C_{6-10}-aryl and a heterocyclic C_{3-10} ring, optionally substituted by C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl or oxo;

$R^{2.1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;
$R^{2.2}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and

R^2 denotes C_{1-6}-alkyl, which may optionally be substituted by a group selected from among C_{1-4}-haloalkyl, CN, $OR^{2.1}$, $NR^{2.1}R^{2.2}$, $COOR^{2.1}$ and $CONR^{2.1}R^{2.2}$ or which may optionally be substituted by a group selected from among C_{3-7}-cycloalkyl, C_{6-10}-aryl and a heterocyclic, aromatic C_{3-10} ring, which may in turn optionally be substituted by methyl or oxo;
wherein
$R^{2.1}$ denotes H or C_{1-4}-alkyl;
$R^{2.2}$ denotes H or C_{1-4}-alkyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

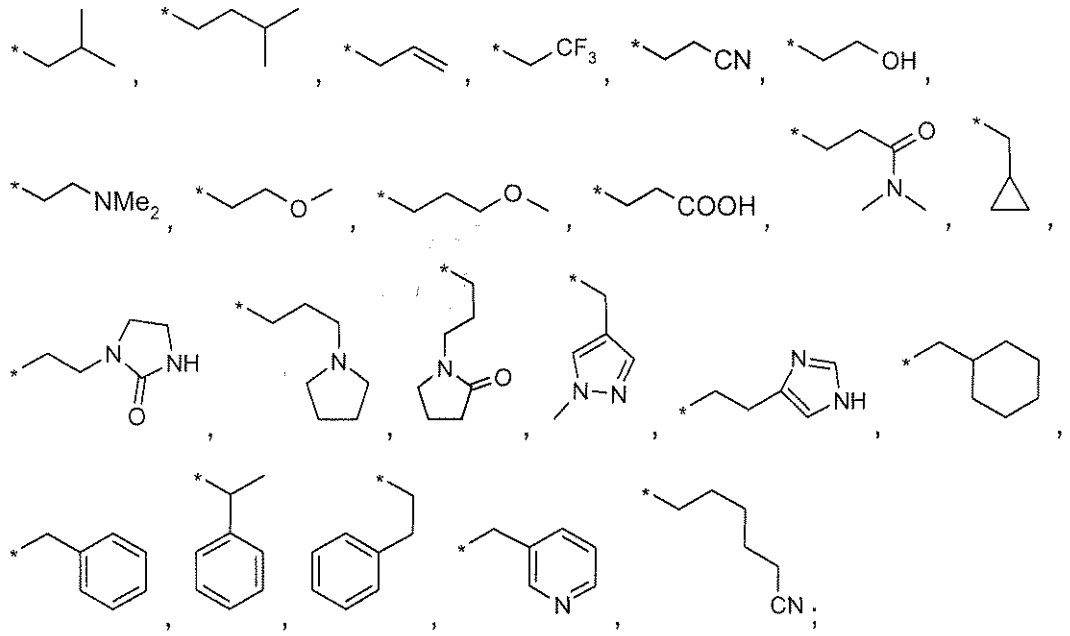
Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and

R^2 denotes C_{1-6}-alkyl; preferably propyl; particularly preferably *n*-propyl, optionally substituted by a group selected from among CF_3, CN, OH, NMe_2, OMe, COOH and $CONMe_2$ or optionally substituted by a group selected from among cyclopropyl, cyclopentyl, cyclohexyl, phenyl, pyrrolidinyl, imidazolidinyl, pyrazolyl, imidazolyl and pyridinyl, optionally substituted by methyl or oxo;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and wherein

R^2 denotes a group selected from among ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl,



and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^3, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and wherein

R^2 denotes C_{6-10}-aryl, which may optionally be substituted in the *meta* position by one or more groups selected independently of one another from among C_{1-4}-alkyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$ and NHCOMe wherein

$R^{2.8}$ denotes C_{1-4}-alkyl or C_{6-10}-aryl;

$R^{2.10}$ denotes $NHR^{2.10.1}$, morpholinyl, methyl-piperazinyl;

$R^{2.10.1}$ denotes H, cyclopropyl or C_{1-4}-alkyl, wherein the C_{1-4}-alkyl may optionally be substituted by one or more groups selected from among O-C_{1-4}-alkyl, OH and C_{6-10}-aryl;

or **R^2** denotes $NH(R^{2.10.1})$, cyclohexyl

or **NR^1R^2** denotes a heterocyclic C_{5-6} ring selected from among pyrrolidine and piperazine, which may optionally be substituted by one or more groups selected from among C_{1-4}-alkyl, OH and C_{1-4}-alkanol

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and wherein

R^3 denotes phenyl, which may optionally be substituted by one or more groups selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-4}-haloalkyl, C_{1-6}-alkylene-$NR^{3.1}R^{3.2}$, CN, halogen, $OR^{3.1}$, $COOR^{3.1}$, $CONR^{3.1}R^{3.2}$, $NR^{3.1}R^{3.2}$, $NHCOR^{3.1}$, NO_2, $SR^{3.1}$, $SOR^{3.1}$, $SO_2R^{3.1}$, $SO_2NR^{3.1}R^{3.2}$ and C_{1-6}-alkylene-$NHCOR^{3.1}$;
wherein
$R^{3.1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;
$R^{3.2}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and wherein

R^3 denotes phenyl, which may optionally be substituted in the *para* position by a group selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-4}-haloalkyl, C_{1-6}-alkylene-$NR^{3.1}R^{3.2}$, CN, halogen, $OR^{3.1}$, $COOR^{3.1}$, $CONR^{3.1}R^{3.2}$, $NR^{3.1}R^{3.2}$, $NHCOR^{3.1}$, NO_2, $SR^{3.1}$, $SOR^{3.1}$, $SO_2R^{3.1}$, $SO_2NR^{3.1}R^{3.2}$ and C_{1-6}-alkylene-$NHCOR^{3.1}$,
wherein
$R^{3.1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;
$R^{3.2}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and

R^3 denotes phenyl, which may optionally be substituted by one or more groups selected from among C_{1-4}-alkyl, C_{1-4}-alkylene-$NR^{3.1}R^{3.2}$, CN, $COOR^{3.1}$, $CONR^{3.1}R^{3.2}$, CF_3, $OR^{3.1}$, halogen, $NHCOR^{3.1}$, NO_2, $SO_2NR^{3.1}R^{3.2}$ and C_{1-4}-alkylene-$NHCOR^{3.1}$;

wherein

$R^{3.1}$ denotes H or C_{1-4}-alkyl;

$R^{3.2}$ denotes H or C_{1-4}-alkyl;

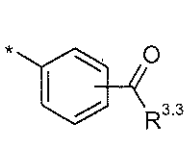
and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and

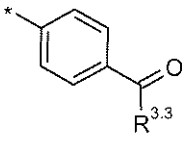
R^3 denotes phenyl, which may optionally be substituted by one, two or three groups selected from among methyl, CH_2NH_2, CN, COOH, $CONH_2$, CF_3, OH, F, Cl, Br, OMe, NHCOMe, NO_2, $SONMe_2$ and $CH_2NHCOMe$;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and **R^3** denotes a group of formula **1b**



1b; preferably



wherein

$R^{3.3}$ denotes a heterocyclic C_{3-10} ring which may optionally be substituted by one or more groups selected from among C_{1-6}-alkyl, oxo, $COR^{3.3.1}$, $COR^{3.3.2}$, C_{1-6}-alkylene-$R^{3.3.2}$, CH_2CO-pyrrolidine and a heterocyclic C_{3-10} ring,

wherein a sulphur atom optionally contained in the heterocyclic C_{3-10} ring may optionally also be present as the oxide or dioxide;

wherein

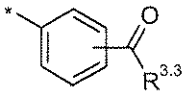
$R^{3.3.1}$ denotes C_{1-6}-alkyl;

$R^{3.3.2}$ denotes NH_2, $NH(C_{1-6}$-alkyl) or $N(C_{1-6}$-alkyl)$_2$;

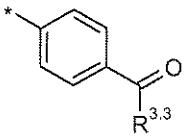
or $R^{3.3}$ denotes a bicyclic ring or a heterocyclic spiro ring;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and wherein $\mathbf{R^3}$ denotes a group of formula **1b**



1b; preferably

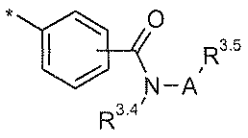


wherein

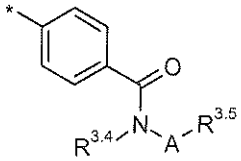
$R^{3.3}$ denotes a group selected from among piperidinyl, piperazinyl and azepanyl, which may optionally be substituted by one or more groups selected from among methyl, oxo, $COCH_3$, $CONH_2$, CH_2NEt_2, $CH_2CH_2NMe_2$, CH_2CO-pyrrolidine, pyridinyl, isothiazolidinyl-1,1-dioxide and thiazolidinyl-1,1-dioxide;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and wherein $\mathbf{R^3}$ denotes a group of formula **1c**;



1c; preferably



wherein

A denotes a bond or C_{1-6}-alkyl, which may optionally be substituted by oxo or NMe_2;

$R^{3.4}$ denotes H or C_{1-6}-alkyl;

$R^{3.5}$ denotes a group selected from among

C_{1-6}-alkyl, which may optionally be substituted by a group selected from among C_{3-7}-cycloalkyl, C_{6-10}-aryl and a C_{5-10} heterocycle, which may also optionally be substituted in each case by one or more groups selected from among halogen, OH, oxo, C_{1-6}-alkyl, O-C_{1-6}-alkyl, C_{1-6}-haloalkyl, a heterocyclic C_{3-10} ring and a bicyclic ring, while these groups may each optionally be substituted by one or more groups selected from among oxo, C_{1-6}-alkyl, OH, C_{6-10}-aryl, a heterocyclic ring, C_{1-6}-alkylene-$R^{3.5.1}$, O-C_{1-6}-alkylene-$R^{3.5.1}$ and NH-C_{1-6}-alkylene-$R^{3.5.1}$,

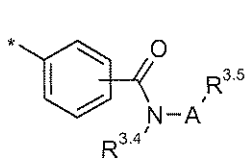
or $R^{3.5}$ denotes a group selected from among heterocyclic or bicyclic ring, optionally substituted by one or more groups selected independently of one another from among oxo, C_{1-6}-alkyl, OH, aryl, a heterocyclic ring, C_{1-6}-alkylene-$R^{3.5.1}$, O-C_{1-6}-alkylene-$R^{3.5.1}$, NH-C_{1-6}-alkylene-$R^{3.5.1}$;

wherein

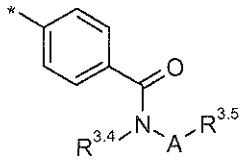
$R^{3.5.1}$ denotes a group selected from among C_{6-10}-aryl and heterocyclic C_{3-10} ring which may optionally be substituted by C_{1-6}-alkyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and wherein $\mathbf{R^3}$ denotes a group of formula **1c**;



1c; preferably



wherein

A denotes a bond or C_{1-4}-alkyl, optionally substituted by oxo or NMe_2;

$R^{3.4}$ denotes H or methyl;

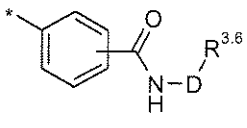
$R^{3.5}$ denotes a group selected from among pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, cyclohexyl, imidazolyl, pyrazolyl, phenyl, pyridinyl, benzimidazolyl, imidazolidin-2-one, pyrrolidin-2-one, pyrrolidin-3-one, 1-aza-bicyclo[2,2,2]octane, optionally substituted by one or more groups selected independently of one another from among methyl, ethyl, OH, phenyl, pyridinyl, pyrazolyl, pyrrolidinyl, $(CH_2)_o$-$R^{3.5.1}$, O-$(CH_2)_o$-$R^{3.5.1}$, NH-$(CH_2)_o$-$R^{3.5.1}$;

o denotes 0, 1 or 2

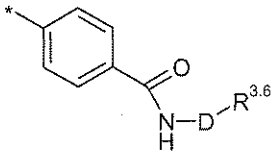
$R^{3.5.1}$ denotes a group selected from among phenyl, pyrrolidinyl, piperidinyl and imidazolidin-2-one, optionally substituted by methyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and wherein $\mathbf{R^3}$ denotes a group of formula **1d**;



1d; preferably



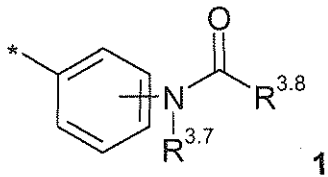
wherein

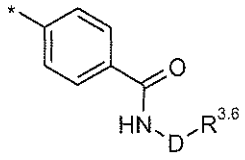
D denotes C_{2-4}-alkynyl;

$R^{3.6}$ denotes pyridinyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Particularly preferred are the above compounds of formula **1**, wherein X, R^1, R^2, R^4, R^5, R^6, R^7 and R^8 are as hereinbefore defined and wherein R^3 denotes a group of formula **1e**;





1e; preferably

wherein

$R^{3.7}$ denotes H, halogen, C_{1-6}-alkyl, C_{2-6}-alkenyl;C_{2-6}-alkynyl or C_{1-6}-haloalkyl;

$R^{3.8}$ denotes H, OH, halogen or a group selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl;C_{2-6}-alkynyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, C_{6-10}-aryl, a heterocyclic C_{3-10} ring and a bicyclic ring which is optionally substituted by one or more groups selected from among halogen, C_{1-6}-alkyl, OH, C_{1-6}-haloalkyl and O-C_{1-6}-alkyl,

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

The present invention also relates to the following -intermediate products for synthesising the compounds according to the invention:

- compounds according to formula VIII according to preparation method B in Scheme 1

- compounds according to formula IV and V according to preparation method A in Scheme 1
- compounds according to formula I in Scheme 1
- compounds according to formula IV, VI, VII and VIII in Scheme 2
- compounds according to formula V, VII and VIII in Scheme 3
- compounds according to formula V, VII and IX in Scheme 4
- compounds according to formula V, VI, VII, VIII and IX in Scheme 5
- compounds according to formula V, VII, VIII and IX in Scheme 6
- compounds according to formula V, VII, VIII, XI and XII in Scheme 7
- compounds according to formula I and II in Scheme 8
- compounds according to formula II and III in Scheme 9
- compounds according to formula V, VI, VIII and X in Scheme 10
- compounds according to formula III and V in Scheme 11
- compounds according to formula III and V in Scheme 12
- compounds according to formula II, III, IV and V in Scheme 13
- compounds according to formula IV, V, VII, VIII, IX and X in Scheme 14,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and X have the meanings defined hereinbefore and wherein R^9, R^{10}, R^{11}, R^{12} in each case independently of one another denote a group selected from among H, halogen, C_{1-6}-alkyl, C_{1-6}-haloalkyl, C_{6-10}-aryl, C_{3-7}-cycloalkyl, aromatic or non-aromatic C_{3-10} heterocycle, C_{6-10}-aryl-C_{1-6}-alkylene, C_{3-7}-cycloalkyl- C_{1-6}-alkylene and C_{3-10} heterocycle-C_{1-6}-alkylene, which may optionally be substituted by one or more groups selected from among OH, oxo, C_{1-6}-alkyl, phenyl C_{3-7}-cycloalkyl, C_{3-7} heterocycle and halogen, and wherein R^{13} is selected from among OH, halogen, O-C_{1-6}-alkyl, C_{1-6}-alkyl, phenyl and C_{3-7}-cycloalkyl and C_{3-7} heterocycle.

Preferred objects of the present invention are the following intermediate products for synthesising the compounds according to the invention:

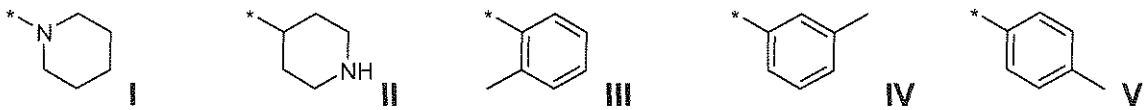
- compounds according to formula I in Scheme 1
- compounds according to formula VI, VII and VIII in Scheme 2

- compounds according to formula VII and VIII in Scheme 3
- compounds according to formula VII and IX in Scheme 4
- compounds according to formula VI, VII, VIII and IX in Scheme 5
- compounds according to formula VII, VIII and IX in Scheme 6
- compounds according to formula VII, VIII, XI and XII in Scheme 7
- compounds according to formula I and II in Scheme 8
- compounds according to formula II and III in Scheme 9
- compounds according to formula X in Scheme 10
- compounds according to formula III and V in Scheme 11
- compounds according to formula III and V in Scheme 12
- compounds according to formula II, III, IV and V in Scheme 13
- compounds according to formula VII, VIII, IX and X in Scheme 14

TERMS AND DEFINITIONS USED

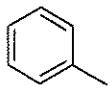
Unless otherwise stated, all the substituents are independent of one another. If for example there are a plurality of C_{1-6}-alkyl groups as substituents in one group, in the case of three substituents C_{1-6}-alkyl, one may represent methyl, one *n*-propyl and one *tert*-butyl.

Within the scope of this application, in the definition of possible substituents, these may also be represented in the form of a structural formula. An asterisk (*) in the structural formula of the substituent is to be understood as being the linking point to the rest of the molecule. Moreover, the atom of the substituent which follows the linking point is referred to as the atom in position number 1. Thus for example the groups N-piperidinyl (**I**), 4-piperidinyl (**II**), 2-tolyl (**III**), 3-tolyl (**IV**) and 4-tolyl (**V**) are shown as follows:



I **II** **III** **IV** **V**

If there is no asterisk (*) in the structural formula of the substituent, each hydrogen atom may be removed from the substitutent and the valency thus freed may act as a binding site to the rest of a molecule. Thus for example **VI** may represent 2-tolyl, 3-tolyl, 4-tolyl and benzyl.



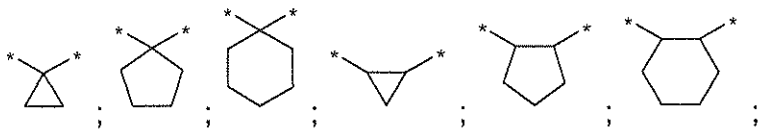
VI

By the term "C_{1-6}-alkyl" (including those which are part of other groups) are meant branched and unbranched alkyl groups with 1 to 6 carbon atoms and by the term "C_{1-4}-alkyl" are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms. Alkyl groups with 1 to 4 carbon atoms are preferred. Examples include: methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl or hexyl. The following abbreviations may optionally also be used for the above-mentioned groups: Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, etc.. Unless stated otherwise, the definitions propyl, butyl, pentyl and hexyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes *n*-propyl and *iso*-propyl, butyl includes *iso*-butyl, *sec*-butyl and *tert*-butyl etc.

By the term "C_{1-6}-alkylene" (including those which are part of other groups) are meant branched and unbranched alkylene groups with 1 to 6 carbon atoms and by the term "C_{1-4}-alkylene" are meant branched and unbranched alkylene groups with 1 to 4 carbon atoms. Preferred are alkylene groups with 1 to 4 carbon atoms. Examples include: methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene, pentylene, 1,1-dimethylpropylene, 2,2-dimethylpropylene, 1,2-dimethylpropylene, 1,3-dimethylpropylene or hexylene. Unless stated otherwise, the definitions propylene, butylene, pentylene and hexylene include all the possible isomeric forms of the

groups in question with the same number of carbons. Thus, for example, propyl also includes 1-methylethylene and butylene includes 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene.

If the carbon chain is substituted by a group which together with one or two carbon atoms of the alkylene chain forms a carbocyclic ring with 3, 5 or 6 carbon atoms, the following examples of rings are also included:



By the term "C_{2-6}-alkenyl" (including those which are part of other groups) are meant branched and unbranched alkenyl groups with 2 to 6 carbon atoms and by the term "C_{2-4}-alkenyl" are meant branched and unbranched alkenyl groups with 2 to 4 carbon atoms, provided that they have at least one double bond. Alkenyl groups with 2 to 4 carbon atoms are preferred. Examples include: ethenyl or vinyl, propenyl, butenyl, pentenyl or hexenyl. Unless stated otherwise, the definitions propenyl, butenyl, pentenyl and hexenyl include all the possible isomeric forms of the groups in question. Thus, for example, propenyl includes 1-propenyl and 2-propenyl, butenyl includes 1-, 2- and 3-butenyl, 1-methyl-1-propenyl, 1-methyl-2-propenyl etc.

By the term "C_{2-6}-alkenylene" (including those which are part of other groups) are meant branched and unbranched alkenylene groups with 2 to 6 carbon atoms and by the term "C_{2-4}-alkenylene" are meant branched and unbranched alkylene groups with 2 to 4 carbon atoms. Preferred are alkenylene groups with 2 to 4 carbon atoms. Examples include: ethenylene, propenylene, 1-methylethenylene, butenylene, 1-methylpropenylene, 1,1-dimethylethenylene, 1,2-dimethylethenylene, pentenylene, 1,1-dimethylpropenylene, 2,2-dimethylpropenylene, 1,2-dimethylpropenylene, 1,3-dimethylpropenylene or

hexenylene. Unless stated otherwise, the definitions propenylene, butenylene, pentenylene and hexenylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus, for example, propenyl also includes 1-methylethenylene and butenylene includes 1-methylpropenylene, 1,1-dimethylethenylene, 1, 2-dimethylethenylene.

By the term "C_{2-6}-alkynyl" (including those which are part of other groups) are meant branched and unbranched alkynyl groups with 2 to 6 carbon atoms and by the term "C_{2-4}-alkynyl" are meant branched and unbranched alkynyl groups with 2 to 4 carbon atoms, provided that they have at least one triple bond. Alkynyl groups with 2 to 4 carbon atoms are preferred. Examples include: ethynyl, propynyl, butynyl, pentynyl, or hexynyl. Unless stated otherwise, the definitions propynyl, butynyl, pentynyl and hexynyl include all the possible isomeric forms of the groups in question. Thus for example propynyl includes 1-propynyl and 2-propynyl, butynyl includes 1, 2- and 3-butynyl, 1-methyl-1-propynyl, 1-methyl-2-propynyl etc.

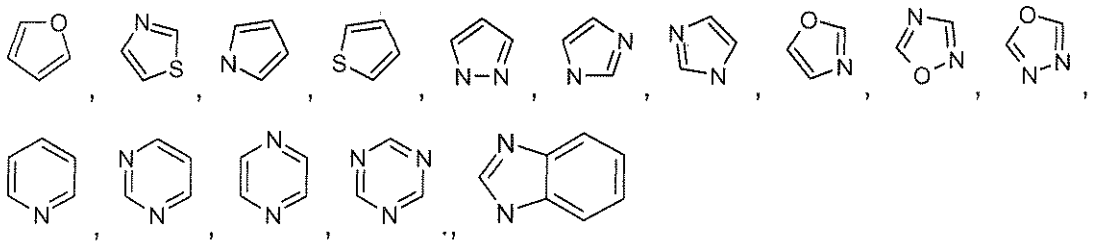
By the term "C_{2-6}-alkynylene" (including those which are part of other groups) are meant branched and unbranched alkynylene groups with 2 to 6 carbon atoms and by the term "C_{2-4}-alkynylene" are meant branched and unbranched alkylene groups with 2 to 4 carbon atoms. Preferred are alkynylene groups with 2 to 4 carbon atoms. Examples include: ethynylene, propynylene, 1-methylethynylene, butynylene, 1-methylpropynylene, 1,1-dimethylethynylene, 1,2-dimethylethynylene, pentynylene, 1,1-dimethylpropynylene, 2,2-dimethylpropynylene, 1,2-dimethylpropynylene, 1,3-dimethylpropynylene or hexynylene. Unless stated otherwise, the definitions propynylene, butynylene, pentynylene and hexynylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus for example propynyl also includes 1-methylethynylene and butynylene includes 1-methylpropynylene, 1,1-dimethylethynylene, 1, 2-dimethylethynylene.

By the term "aryl" (including those which are part of other groups) are meant aromatic ring systems with 6 or 10 carbon atoms. Examples include: phenyl or naphthyl, the preferred aryl group being phenyl. Unless otherwise stated, the aromatic groups may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

By the term "aryl-C_{1-6}-alkylene" (including those which are part of other groups) are meant branched and unbranched alkylene groups with 1 to 6 carbon atoms, which are substituted by an aromatic ring system with 6 or 10 carbon atoms. Examples include: benzyl, 1- or 2-phenylethyl or 1- or 2-naphthylethyl. Unless otherwise stated, the aromatic groups may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

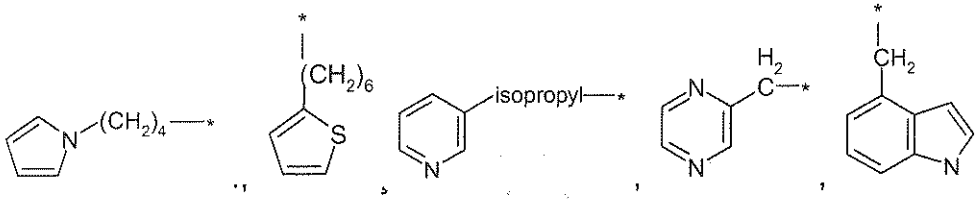
By the term "heteroaryl-C_{1-6}-alkylene" (including those which are part of other groups) are meant - even though they are already included under "aryl-C_{1-6}-alkylene" - branched and unbranched alkylene groups with 1 to 6 carbon atoms, which are substituted by a heteroaryl.

A heteroaryl of this kind includes five- or six-membered heterocyclic aromatic groups or 5-10-membered, bicyclic heteroaryl rings which may contain one, two or three heteroatoms selected from among oxygen, sulphur and nitrogen, and contain so many conjugated double bonds that an aromatic system is formed. The following are examples of five- or six-membered heterocyclic aromatic groups:



Unless otherwise stated, these heteroaryls may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

The following are examples of heteroaryl-C_{1-6}-alkylenes:

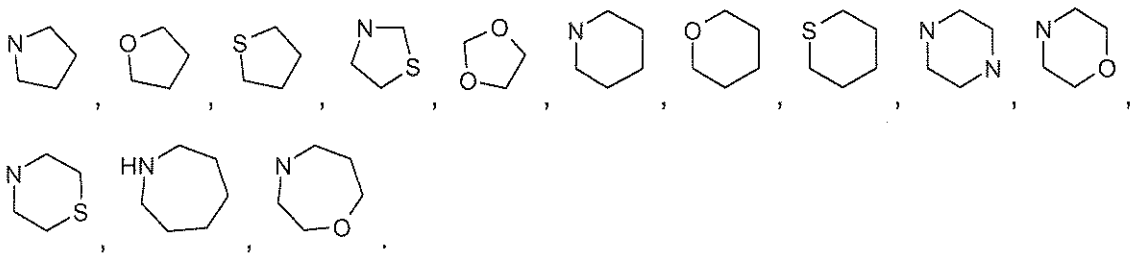


By the term "C_{1-6}-haloalkyl" (including those which are part of other groups) are meant branched and unbranched alkyl groups with 1 to 6 carbon atoms, which are substituted by one or more halogen atoms. By the term "C_{1-4}-alkyl" are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms, which are substituted by one or more halogen atoms. Alkyl groups with 1 to 4 carbon atoms are preferred. Examples include: CF_3, CHF_2, CH_2F, CH_2CF_3.

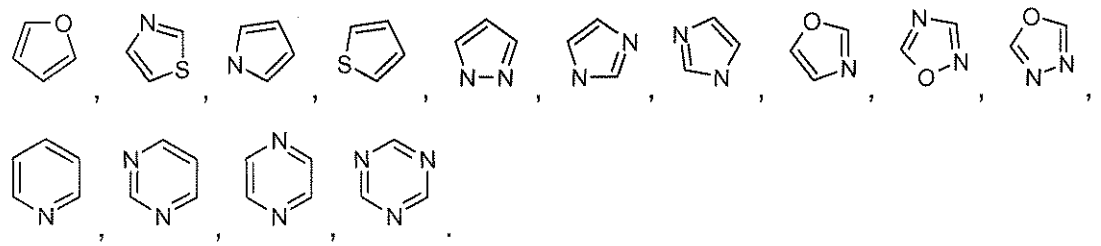
By the term "C_{3-7}-cycloalkyl" (including those which are part of other groups) are meant cyclic alkyl groups with 3 to 7 carbon atoms. Examples include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Unless otherwise statedd, the cyclic alkyl groups may be substituted by one or more groups selected from among methyl, ethyl, *iso*-propyl, *tert*-butyl, hydroxy, fluorine, chlorine, bromine and iodine.

By the term "heterocyclic rings" or also "heterocycles" are meant five-, six- or seven-membered, saturated or unsaturated heterocyclic rings which may contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen, while the ring may be linked to the molecule through a carbon atom or through a nitrogen atom, if there is one. Although included by the term

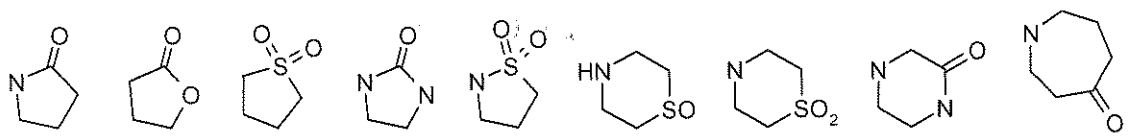
"heterocyclic rings" or "heterocycles", the term "heterocyclic non-aromatic rings" refers to five-, six- or seven-membered unsaturated rings. Examples include:



Although included by the term "heterocyclic rings" or "heterocycles", the term "heterocyclic aromatic rings" or "heteroaryl" refers to five- or six-membered heterocyclic aromatic groups or 5-10-membered, bicyclic heteroaryl rings which may contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen, and contain so many conjugated double bonds that an aromatic system is formed. Examples of five- or six-membered heterocyclic aromatic groups include:

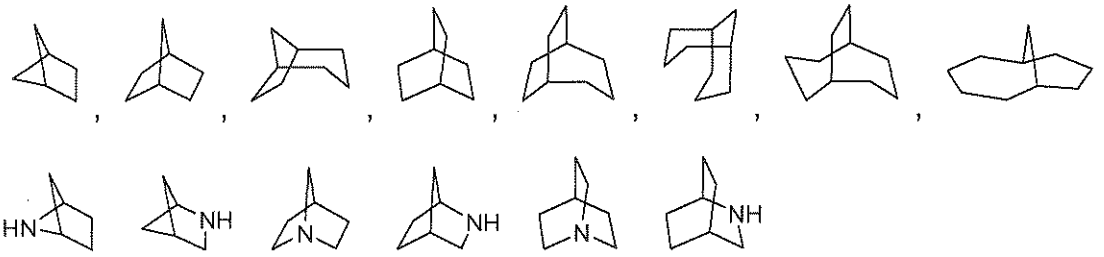


Unless otherwise mentioned, a heterocyclic ring (or "heterocycle") may be provided with a keto group. Examples include.

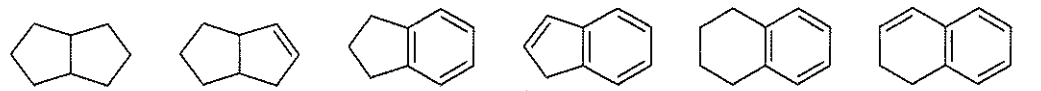


By the term "bicyclic rings" are meant eight-, nine- or ten-membered bicyclic rings which may optionally contain one or more heteroatoms, selected from among oxygen, sulphur and nitrogen. The ring may be linked to the molecule through a

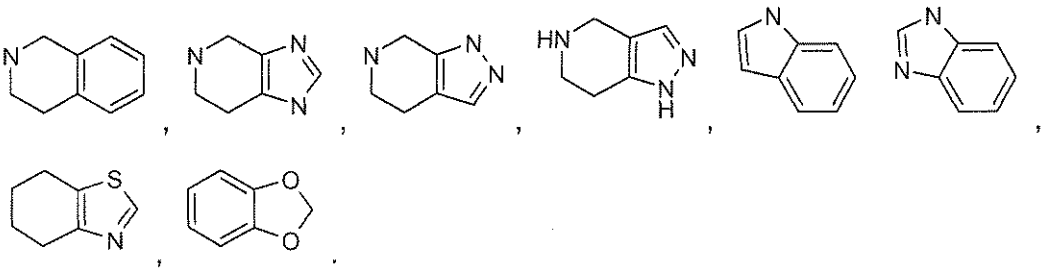
carbon atom of the ring or through a nitrogen atom of the ring, if there is one. Examples include



Although included by the term "bicyclic rings", the term "fused bicyclic rings" denotes bicyclic rings wherein the bridge separating the rings denotes a direct single bond. The following are examples of a fused, bicyclic ring:

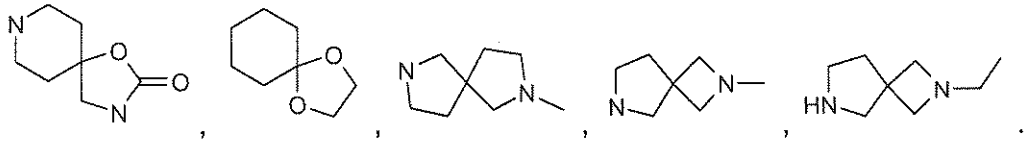


Although included by the term "bicyclic rings", the term "fused bicyclic heterorings" denotes bicyclic 5-10 membered heterorings which contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen and wherein the bridge separating the rings denotes a direct single bond. Examples include pyrrolizine, indole, indolizine, isoindole, indazole, purine, quinoline, isoquinoline, benzimidazole, benzofuran, benzopyran, benzothiazole, benzothiazole, benzoisothiazole, pyridopyrimidine, pteridine, pyrimidopyrimidine,



By the term "heterocyclic spirorings" (spiro) are meant 5-10 membered, spirocyclic rings which may optionally contain one, two or three heteroatoms, selected from among oxygen, sulphur and nitrogen, while the ring may be linked to the molecule

through a carbon atom or through a nitrogen atom, if there is one. Unless otherwise mentioned, a spirocyclic ring may be provided with an oxo, methyl or ethyl group. Examples include:



"Halogen" within the scope of the present invention denotes fluorine, chlorine, bromine or iodine. Unless stated to the contrary, fluorine, chlorine and bromine are regarded as preferred halogens.

Compounds of general formula **1** may have acid groups, mainly carboxyl groups, and/or basic groups such as e.g. amino functions. Compounds of general formula **1** may therefore be present as internal salts, as salts with pharmaceutically useable inorganic acids such as for example hydrochloric acid, sulphuric acid, phosphoric acid, sulphonic acid or organic acids (such as for example maleic acid, fumaric acid, citric acid, tartaric acid or acetic acid) or as salts with pharmaceutically useable bases such as alkali or alkaline earth metal hydroxides or carbonates, zinc or ammonium hydroxides or organic amines such as e.g. diethylamine, triethylamine or triethanolamine, *inter alia*.

As mentioned hereinbefore, the compounds of formula **1** may be converted into the salts thereof, particularly for pharmaceutical use, into the physiologically and pharmacologically acceptable salts thereof. These salts may on the one hand be in the form of the physiologically and pharmacologically acceptable acid addition salts of the compounds of formula **1** with inorganic or organic acids. On the other hand, if R is hydrogen, the compound of formula **1** may also be converted by reaction with inorganic bases into physiologically and pharmacologically acceptable salts with alkali or alkaline earth metal cations as counter ion. The acid addition salts may be prepared for example using hydrochloric acid, hydrobromic

acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid. It is also possible to use mixtures of the above-mentioned acids. The alkali and alkaline earth metal salts of the compound of formula I are preferably prepared using the alkali and alkaline earth metal hydroxides and hydrides thereof, of which the hydroxides and hydrides of the alkaline earth metals, particularly of sodium and potassium, are preferred and sodium and potassium hydroxide are particularly preferred.

If desired, the compounds of general formula (1) may be converted into the salts thereof, particularly, for pharmaceutical use, into the pharmacologically acceptable acid addition salts with an inorganic or organic acid. Suitable acids include for example succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid or citric acid. It is also possible to use mixtures of the above-mentioned acids.

The invention relates to the compounds in question, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in the form of the tautomers as well as in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids - such as for example acid addition salts with hydrohalic acids - for example hydrochloric or hydrobromic acid or organic acids – such as for example oxalic, fumaric, diglycolic or methanesulphonic acid.

The compounds according to the invention may optionally occur as racemates, but they may also be obtained as pure enantiomers, i.e. in the (*R*) or (*S*) form. Preferred compounds are those which occur as racemates or as the (*S*) form.

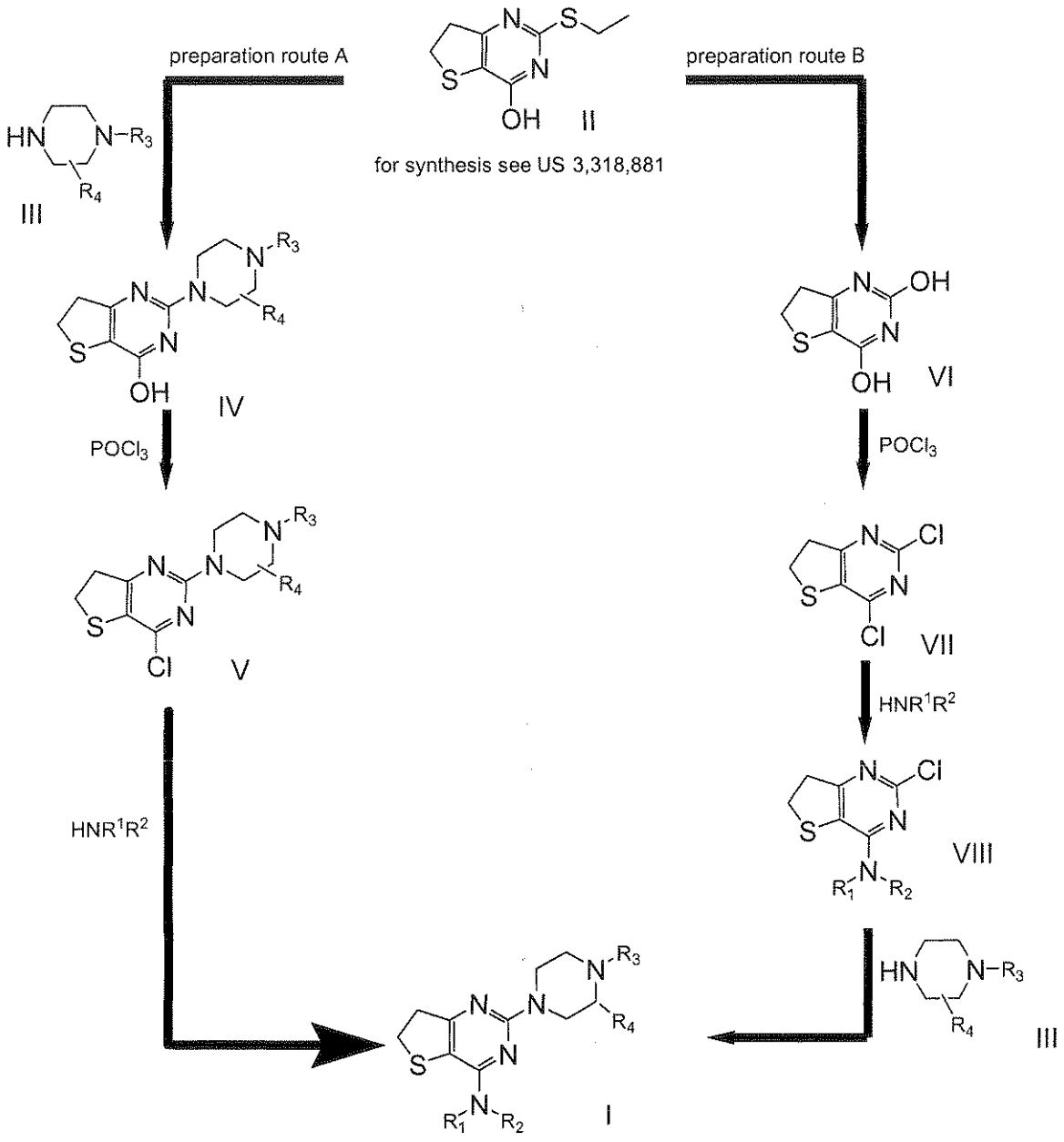
The invention relates to the compounds in question, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates, in

the form of the tautomers as well as in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids - such as for example acid addition salts with hydrohalic acids - for example hydrochloric or hydrobromic acid or organic acids – such as for example oxalic, fumaric, diglycolic or methanesulphonic acid.

Methods of synthesis:

EXAMPLES

Scheme 1:



SYNTHESIS OF [2-(4-PHENYL-PIPERAZIN-1-YL)-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDINE-4-YL]-PROPYL-AMINE BY SYNTHESIS METHOD A (I) (SCHEME 1)

2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ol (IV): 6.4 g (39 mmol) N-phenylpiperazine (III) are placed in 2.2 ml glacial acetic acid, heated to 125°C, then 3.2 g (15 mmol) 2-ethylsulphanyl-6,7-dihydro-thieno[3,2-d] pyrimidin-4-ol (II) are added, and the mixture is heated to 175°C. After 1.5 hours the resulting solid is stirred with water, suction filtered, washed with ethanol and dried. 4.3 g product (91%) are obtained as a powder.

4-chloro-2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidine (V): 4.3 g (13.7 mmol) 2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ol (IV) and 25 ml phosphorus oxychloride are combined and stirred for 5 hours at 120°C. Excess phosphorus oxychloride is concentrated by evaporation, the residue is combined with ice water and dichloromethane. The organic phase is separated off and evaporated to dryness. The residue is triturated with water, suction filtered and dried. 5.6 g of the product (100%) are obtained as a powder.

[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidine-4-yl]-propyl-amine (I) (Example 27): 0.83 g (2.5 mmol) 4-chloro-2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidine (V) are combined with 8.3 ml n-propylamine, reacted for 0.2 hours at 130°C in the microwave. Then the reaction mixture is added to water and extracted with dichloromethane. The organic phase is concentrated by evaporation, the residue is crystallised. The aqueous phase is extracted with ethyl acetate, the organic phase evaporated to dryness. The solids are combined and stirred with methanol. 0.68 g of the product (76%) are obtained as a powder.

SYNTHESIS OF [2-(4-PHENYL-PIPERAZIN-1-YL)-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDINE-4-YL]-PROPYL-AMINE BY SYNTHESIS METHOD B (SCHEME 1)

6,7-dihydro-thieno[3,2-d]pyrimidine-2,4-diol (VI): 3.5 g (16.33 mmol) 2-ethylsulphanyl-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ol (II) are placed in 70 ml 1N hydrochloric acid, reacted for 0.75 hours at 150°C in the microwave (14 x 0.250 g in 5 ml hydrochloric acid in each case). Then the reaction mixture is left to stand for 7 hours at ambient temperature. It is suction filtered, washed with water and dried. 2.6 g of the product VI (95%) are obtained as a powder.

2.4-dichloro-thieno[3,2-d]pyrimidine (VII): 2.4 g (14.1 mmol) 6,7-dihydro-thieno[3,2-d]pyrimidine-2,4-diol (VI) are suspended in 14 ml phosphorus oxychloride, combined with 4.5 ml (28.2 mmol) diethylaniline and stirred for 22 hours at 80°C. After cooling to ambient temperature the reaction mixture is added to ice water, the precipitate formed is suction filtered and washed with water. The precipitate is dissolved in dichloromethane, any water present is separated off using a phase separator. The organic phase is evaporated to dryness. 2.5 g of the product VII (85%) are obtained.

(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (VIII): 10.4 g (50.2 mmol) 2,4-dichloro-thieno[3,2-d]pyrimidine (VII), 8.2 ml (100 mmol) N-propylamine and 17.5 ml (100 mmol) N-ethyldiisopropylamine are placed in 100 ml of tetrahydrofuran and stirred for 20 hours at ambient temperature. The suspension is filtered, the filtrate is concentrated by evaporation. The residue is combined with 100 ml of water and treated in the ultrasound bath. Solid substance is suction filtered, dried and stirred with 50 ml petroleum ether. 10.0 g of the product VIII (86%) are obtained as a powder.

[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl]-propyl-amine (Example 27) (I) **:** 9.7 g (42.3 mmol) 2-chloro-6,7-dihydro-thieno[3,2-

d]pyrimidin-4-yl)-propyl-amine (VIII) and 25.7 ml (169.2 mmol) 1-phenylpiperazine (III) are placed in 200 ml dioxane (carried out in 10 batches), then reacted for 1 hour at 160°C in the microwave. The reaction mixture is concentrated by evaporation, the residue is combined with 250 ml of water. Then the mixture is suction filtered, washed with water and dried. The residue is stirred with acetonitrile, then recrystallised from isopropanol. 8.3 g of the product (I) (55%) are obtained as a powder (m.p 121°C). ^{1}H NMR (400 MHz, DMSO): 7.22 (2H, t); 6.97 (2H, d); 6.79 (1H, t); 6.43 (2H, t); 3.81-3.69 (4H, m); 3.37-3.19 (4H, m); 3.19-3.09 (4H, m); 2.99 (2H, t); 1.62-1.47 (2H, m); 0.87 (3H, t).

The following Examples are prepared by synthesis method A (Scheme 1) as described above (in each case only the last step of the synthesis is described, namely the reaction of V with an amine to form product I):

cyclohexyl-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl]-amine (Example 16) (I) : 0.300 g (0.90 mmol) 4-chloro-2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidine (V) are placed in 4 ml cyclohexylamine, then reacted for 0.1 hours at 130°C in the microwave. Then the reaction mixture is concentrated by evaporation, the residue is stirred with water and suction filtered. 0.120 g of product I (34%) are obtained as a powder.
^{1}H NMR (400 MHz, DMSO): 7.22 (2H, t); 6.97 (2H, d); 6.79 (1H, t); 6.08 (1H, d); 3.93-3.81 (1H, m); 3.80-3.69 (4H, m); 3.22 (2H, t); 3.18-3.11 (4H, m); 2.98 (2H, t); 1.92-1.79 (2H, m); 1.79-1.66 (2H, m); 1.66-1.55 (1H, m); 1.37-1.21 (4H, m); 1.18-1.04 (1H, m).

(3-chloro-phenyl)-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl]-amine (Example 10) (I) : 0.320 g (0.96 mmol) 4-chloro-2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidine (V) 1.0 ml (9.5 mmol) 3-chloro-phenylamine and 0.33 ml (1.92 mmol) diisopropylethylamine are combined and the mixture is reacted for 0.5 hours at 130°C in the microwave. Then the reaction mixture is combined with ethyl acetate and acidically extracted. The

organic phase is dried and evaporated to dryness. The residue is combined with acetonitrile, water and trifluoroacetic acid. The phase containing the product I is purified by chromatography through an RP column by HPLC (column: Microsorb, RP-C18, 300Å, 10µm, 21.4*250 mm, eluant: acetonitrile + 0.1 % formic acid (A), water + 0.13% formic acid (B))

gradient: minutes	% eluant A	% eluant B
0	10	90
4.9	10	90
27	100	0
32	100	0
32.5	10	90
37.5	10	90

Corresponding fractions are combined and freeze-dried. 0.101 g of the product are obtained as a powder.

^{1}H NMR (400 MHz, DMSO): 8.63 (1H, s); 7.87 (1H, t); 7.60 (1H, dd); 7.31 (1H, t); 7.26-7.20 (2H, m); 7.05-7.01 (1H, m); 6.99 (2H, d); 7.80 (1H; t); 3.81-3.76 (4H, m); 3.22-3.15 (4H, m); 3.10 (2H, t).

(3-methoxy-phenyl)-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl]-amine (Example 11) (I) : 0.320 g (0.96 mmol) 4-chloro-2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidine (V), 1.5 ml (13.1 mmol) 3-methoxy-phenylamine and 0.33 ml (1.92 mmol) diisopropylethylamine are combined, and reacted for 0.5 hours at 130°C in the microwave. Then the reaction mixture is purified by chromatography using HPLC through an RP column (column: Microsorb, RP-C18, 300Å, 10µm, 21.4*250 mm, eluant: acetonitrile + 0.1 % formic acid (A), water + 0.13% formic acid (B))

gradient: minutes	% eluant A	% eluant B
0	10	90
4.9	10	90
27	100	0
32	100	0
32.5	10	90
37.5	10	90

0.095 g of the product (23%) are obtained as a powder (m.p 133-135°C).
^{1}H NMR (400 MHz, DMSO): 8.37 (1H, s); 7.36 (1H, t); 7.26-7.14 (4H, m); 6.98 (2H, d); 6.80 (1H, t); 6.57 (1H, dd); 3.82-3.76 (4H, m); 3.75 (3H, s); 3.32-3.24 (2H, m); 3.21-3.15 (4H, m); 3.09 (2H, t).

phenyl-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl]-amine (Example 18) (I) : 0.300 g (0.90 mmol) 4-chloro-2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidine (V) and 3 ml phenylamine are combined, then reacted for 0.3 hours at 130°C in the microwave. Then the reaction mixture is combined with water and extracted with ethyl acetate. The organic phase is dried and evaporated to dryness. The residue is triturated with diethyl ether and suction filtered. 0.18 g of product I (51%) are obtained (m.p 174-175°C).
^{1}H-NMR (400 MHz, DMSO): 8.59 (1H, s); 7.63 (2H, d); 7.31 (2H, t); 7.22 (2H, t); 7.03 (1H, t); 6.99 (2H, d); 6.80 (1H, t); 3.83-3.73 (4H, m); 3.31 (2H, t); 3.23 (4H, m); 3.12 (2H, t).

The following Examples are prepared by synthesis method B (Scheme 1) as described above (in each case only the last step of the synthesis is described (reaction of VIII with III to obtain product I)::

{2-[4-(4-chloro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine (I) (Example 37): 0.250 g (1.1 mmol) 2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-propylamine (VIII), 0.700 g (3.6 mmol) 1-(4-

chlorophenyl)-piperazine (III) and 0.400 ml (2.3 mmol) diisopropylethylamine are placed in 4 ml dioxane, then reacted for 1.5 hours at 160°C in the microwave. The reaction mixture is combined with water while cooling with ice and treated in the ultrasound bath. The precipitate formed is suction filtered, washed with water and petroleum ether and dried. 0.300 g of product I (72%) are obtained as a powder.
^{1}H NMR (400 MHz, DMSO): 7.24 (2H, d); 6.98 (2H, d); 6.42 (1H, t); 3.79-3.70 (4H, m); 3.23 (2H, t); 3.19-3.11 (4H, m); 2.98 (2H, t); 1.61-1.47 (2H, m); 0.87 (4, 3H).

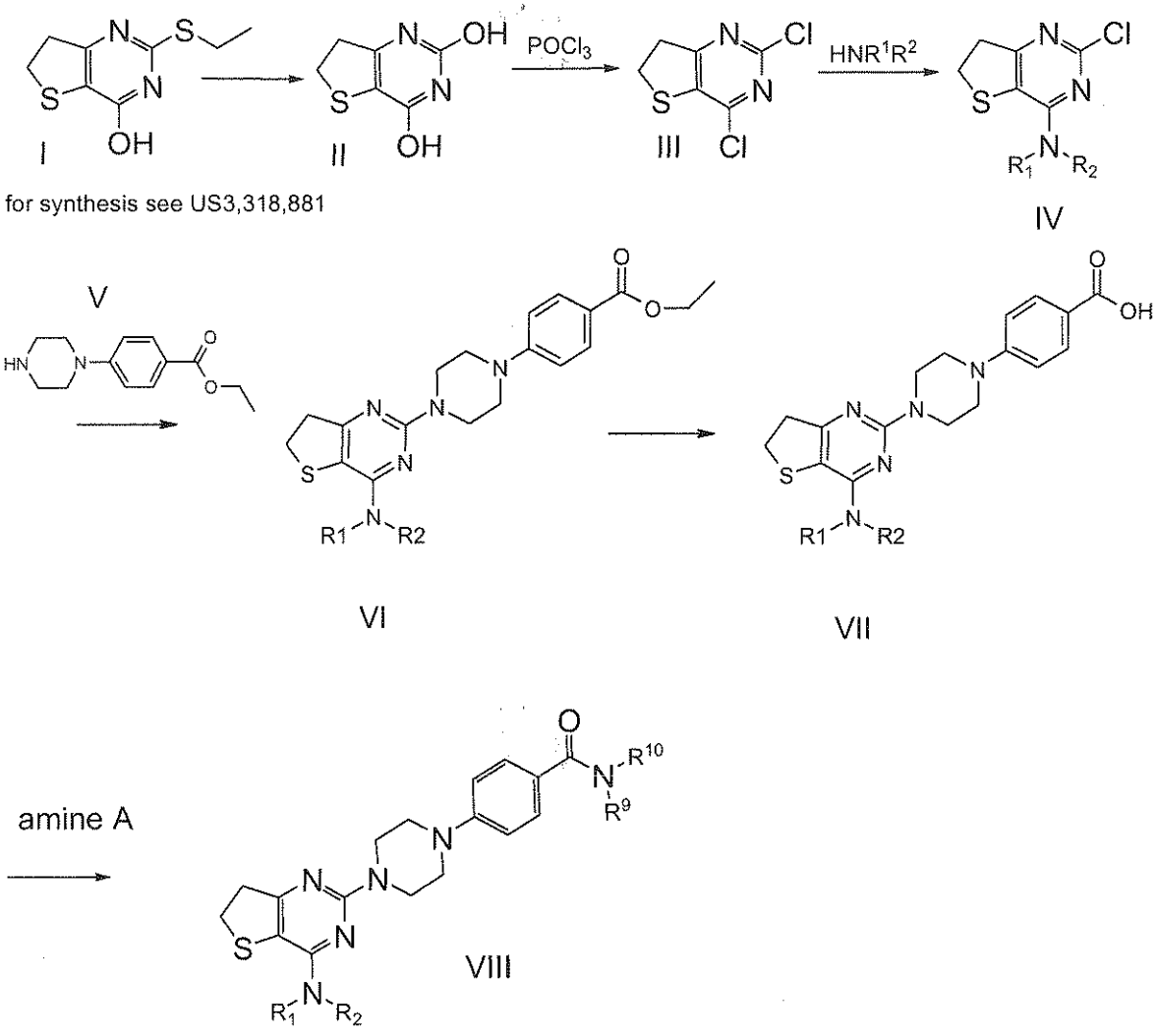
{2-[4-(4-hydroxy-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine (I) (Example 39) : 0.400 g (1.7 mmol) 2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-propylamine (VIII), 1.55 g (8.7 mmol) 1-(4-hydroxyphenyl)-piperazine (III) and 0.610 ml (3.5 mmol) diisopropylethylamine are placed in 4 ml of dimethylformamide, reacted for 2 hours at 160°C in the microwave. Then the reaction mixture is combined with water and extracted with dichloromethane. The organic phase is dried and evaporated to dryness. The residue is purified by chromatography through a 10 g silica gel cartridge with petroleum ether/ethyl acetate 1:1. 0.370 g of product I (57%) are obtained as a powder.
^{1}H NMR (400 MHz, DMSO): 8.80 (1H, s); 6.82 (2H, d); 6.66 (2H, d); 6.39 (1H, t); 3.76-3.69 (4H, m); 3.23 (2H, t); 3.02-2.92 (6H, m); 1.60-1.48 (2H, m); 0.86 (3H, t).

((*1R.2R*)-2-benzyloxy-cyclopentyl)-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl]-amine (chiral) (Example 112) (I) : 0.450 g (1.2 mmol) ((*1R.2R*)-2-benzyloxy-cyclopentyl)-(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-amine (chiral) (VIII) and 0.760 ml (5.0 mmol) 1-phenyl-piperazine (III) are placed in 5 ml dioxane, then reacted for 1 hour at 160°C in the microwave. The reaction mixture is concentrated by evaporation, the residue is combined with water and extracted with dichloromethane. The organic phase is separated off using a phase separator and evaporated to dryness. The crude product I is purified by chromatography through a 100g silica gel cartridge with a solvent

mixture of petroleum ether/ethyl acetate 8/2. 0.540 g of the product (89%) are obtained (m.p 100-105°C).

^{1}H NMR (400 MHz, DMSO): 7.36-7.18 (7H, m); 6.91 (2H, d); 6.79 (1H, t); 6.39 (1H, d); 4.59-4.40 (3H, m); 3.95-3.89 (1H, m); 3.79-3.69 (4H, m); 3.23 (2H, t); 3.11-3.03 (4H, m); 2.99 (2H, t); 2.11-2.00 (1H, m); 1.93-1.79 (1H, m); 1.77-1.50 (4H, m).

Scheme 2:



SYNTHESIS OF 4-[4-(4-CYCLOHEXYLAMINO-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-2-YL)-PIPERAZIN-1-YL]-BENZOIC ACID (ACCORDING TO SCHEME 2)

ethyl 4-[4-(4-cyclohexylamino-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-benzoate (VI): 2.1 g (7.8 mmol) (2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-cyclohexyl-amine (IV), 3.1 g (13.2 mmol) ethyl 4-piperazin-1-yl-benzoate (V) and 2.9 ml (16.5 mmol) diisopropylethylamine are placed in 20 ml dioxane, then the mixture is reacted for 4 hours at 160°C in the microwave. The precipitated substance is suction filtered, the mother liquor is concentrated by evaporation. The residue is extracted with water and ethyl acetate, the combined organic phases are dried and evaporated to dryness. The crude product VI is crystallised from petroleum ether/ethyl acetate 9:1.
2.3 g of the product (62%) are obtained.

4-[4-(4-cyclohexylamino-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-benzoic acid (VII) (Example 106): 2.3 g (4.8 mmol) ethyl 4-[4-(4-cyclohexylamino-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-benzoate (VI) and 26 ml (26 mmol) sodium hydroxide are placed in 15 ml of tetrahydrofuran and 15 ml of methanol, and refluxed for 2 hours with stirring. Then the reaction mixture is concentrated by evaporation, the residue is acidified with 2N hydrochloric acid. The precipitate formed is suction filtered, washed with water and dried. 2.1 g of the product VII (100%) are obtained as a powder.

Standard method for synthesising amides: A solution of 0.01 mmol of the acid (VII) in 500 µl dimethylformamide is combined with 1.388 µl (0.01 mmol) triethylamine and 3.21 mg (0.01 mmol) O-(1H-benzotriazol-1-yl)-N,N,N´,N´-tetramethyluronium tetrafluoroborate [TBTU] and shaken for 15 min. at ambient temperature. To this reaction mixture is added a solution of 0.01 mmol of the amine (amine A) in 500 µl dimethylformamide and the mixture is shaken for 12 h at ambient temperature. Then the reaction mixture is evaporated to dryness and purified by preparative HPLC (this yields product VIII).

The following Examples may be prepared analogously to the method of synthesis set out above (according to Scheme 2) (in each case only the reactions of the acids VII with the amines A to yield product VIII are described):

4-[4-(4-propylamino-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-N-(4-pyrrolidin-1-ylmethyl-benzyl)-benzamide (VIII) (Example 90): 0.350 g (0.9 mmol) 4-[4-(4-propylamino-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-benzoic acid (VII) are placed in 8 ml dimethylsulphoxide, 0.15 ml (0.9 mmol) diisopropylethylamine and 0.340 g (0.9 mmol) O-(7-azabenzotriazol-1-yl-)-N,N,N´,N´-tetramethyluronium-hexafluoro-phosphat (HATU) are added. The mixture is stirred for 0.1 hours at ambient temperature, then 0.170 g (0.9 mmol) 4-pyrrolidin-1-ylmethyl-benzylamine (amine A) are added and a further 0.9 mmol diisopropylethylamine are added. The reaction mixture is stirred for 3 hours at ambient temperature, then suction filtered through Alox and washed with dimethylsulphoxide. The mother liquor is concentrated by evaporation, the residue is cooled in the ice bath and combined with water. Any precipitate formed is suction filtered and dried. Then it is treated with approx. 50 ml petroleum ether in the ultrasound bath, and the precipitate is then suction filtered. 0.374 g of product VIII (75%) are obtained (m.p 157-158°C).

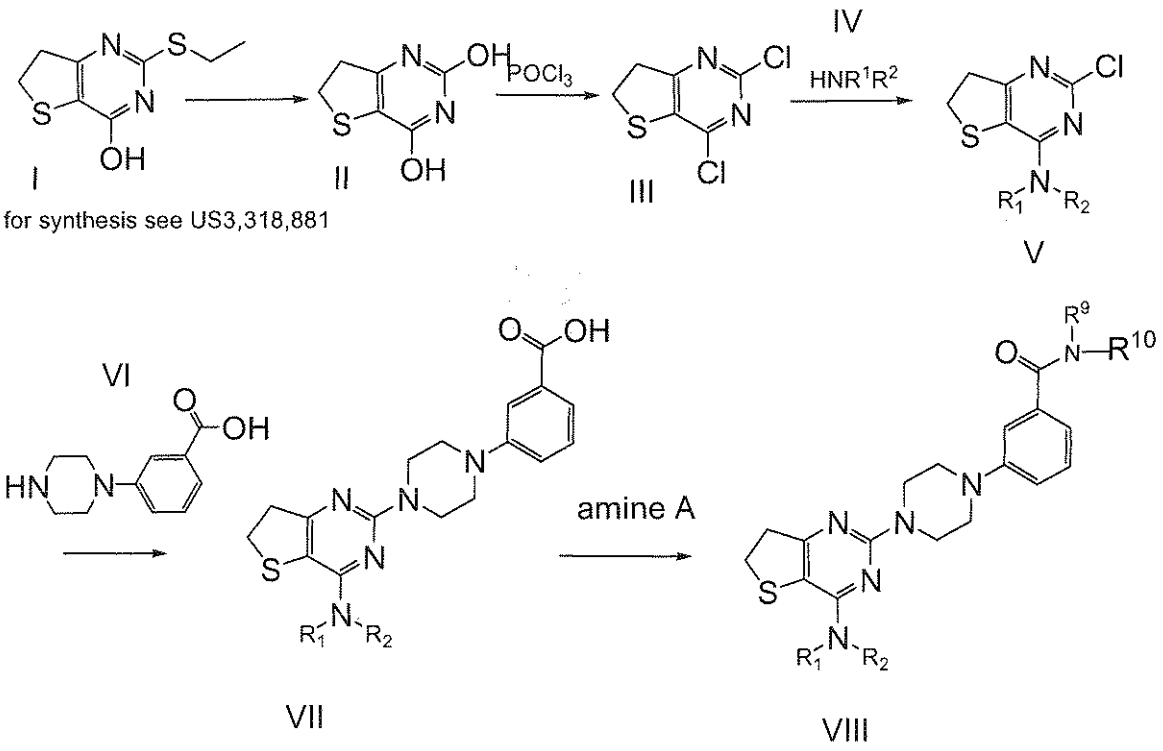
^{1}H NMR (400 MHz, DMSO): 8.71 (1H, t); 7.79 (2H, d); 7.23 (4H, s); 6.99 (2H, d); 6.43 (1H, t); 4.43 (2H, d); 3.79-3.71 (4H, m); 3.52 (2H, s); 3.23 (2H, t); 2.99 (2H, t); 2.44-2.34 (4H, m); 1.72-1.63 (4H, m); 1.61-1.48 (2H, m); 0.87 (3H, t).

N-(1-methyl-piperidin-4-yl)-4-[4-(4-propylamino-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-benzamide (VIII) (Example 87) : 0.500 g (1.3 mmol) 4-[4-(4-propylamino-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-benzoic acid (VII) are placed in 12 ml dimethylsulphoxide, 0.716 g (1.9 mmol) O-(7-azabenzotriazol-1-yl-)-N,N,N´,N´-tetramethyluronium-hexafluoro-phosphate (HATU) in 6 ml dimethylsulphoxide are added. The mixture is stirred for 1 hour at ambient temperature. Then 0.143 g (1.3 mmol) 1-methyl-piperidin-4ylamine (amine A) in 6 ml dimethylsulphoxide are added, followed by another 2.5 mmol

diisopropylethylamine. The reaction mixture is stirred for 16 hours at ambient temperature, then suction filtered through Alox. The Alox is washed with dimethylsulphoxide. The mother liquor is evaporated to dryness. The residue is stirred with water, suction filtered and dried. 0.470 g of product VIII (76%) are obtained as a powder (m.p 229-233°C).

^{1}H NMR (400 MHz, DMSO): 7.90 (1H, d); 7.75 (2H, d); 6.97 (2H, d); 6.43 (1H, d); 3.82-3.66 (5H, m); 3.23 (2H, t); 2.99 (2H, t); 2.80-2.70 (2H, m); 2.15 (3H, s); 1.92 (2H, t); 1.77-1.68 (2H, m); 1.64-1.49 (4H, m); 0.87 (3H, t).

Scheme 3:



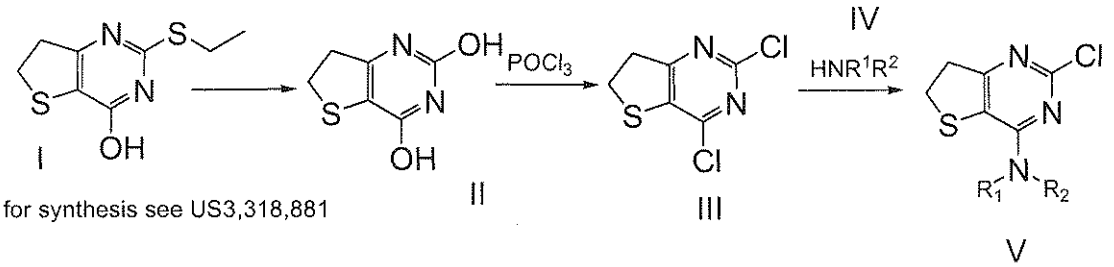
SYNTHESIS OF 3-[4-(4-PROPYLAMINO-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-2-YL)-PIPERAZIN-1-YL]-BENZOIC ACID (SCHEME 3) (in each case only the reactions of V with VI and with the amine A to yield the product VIII are described):

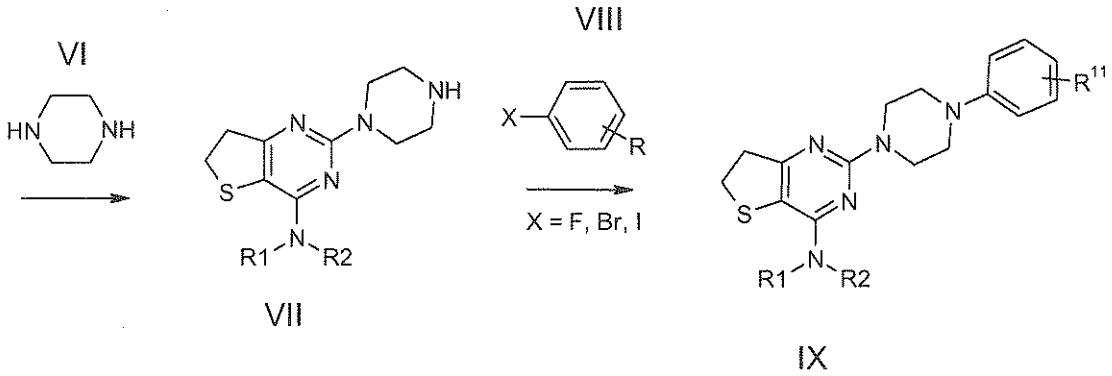
3-[4-(4-propylamino-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-benzoic acid (VIII) (Example 66) 0.900 g (3.9 mmol) (2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (V) and 1.5 g (4.7 mmol) 3-piperazin-1-yl-benzoic acid-triflate (VI) are placed in 20 ml dioxane, and 5 ml (36.7 mmol) diisopropylethylamine (amine A) are added. The suspension is stirred for 24 hours at 180°C in a pressurised glass container, then concentrated by evaporation. The residue is dissolved in acetonitrile and water, then purified by HPLC through an RP column (column: XTerra, MS-C18, 5µm, 19*100 mm, eluant: water + 0.1 % trifluoroacetic acid (A), acetonitrile + 0.1% trifluoroacetic acid (B))

gradient: minutes	% eluant A	% eluant B
0	90	10
2	90	10
11.5	0	100
13	0	100
13.5	90	10

Corresponding fractions are combined and freeze-dried. 0.43 g of product VIII (27%) are obtained.

Scheme 4:





SYNTHESIS OF 4-[4-(4-PROPYLAMINO-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-2-YL)-PIPERAZIN-1-YL]-BENZONITRILE (IX) (SCHEME 4) (only the reactions of V with VI to VII and of VII and VIII to IX are described):

(2-piperazin-1-yl-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (VII) : 1.0 g (4.4 mmol) (2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (V) and 1.9 g (21.8 mmol) piperazine (VI) are placed in 10 ml dioxane, then reacted for 0.7 hours at 150°C in the microwave. Then the reaction mixture is extracted with water and ethyl acetate, the organic phase is dried and evaporated to dryness. The residue is triturated with petroleum ether and suction filtered. 0.97 g of product VII (80%) are obtained as a powder.

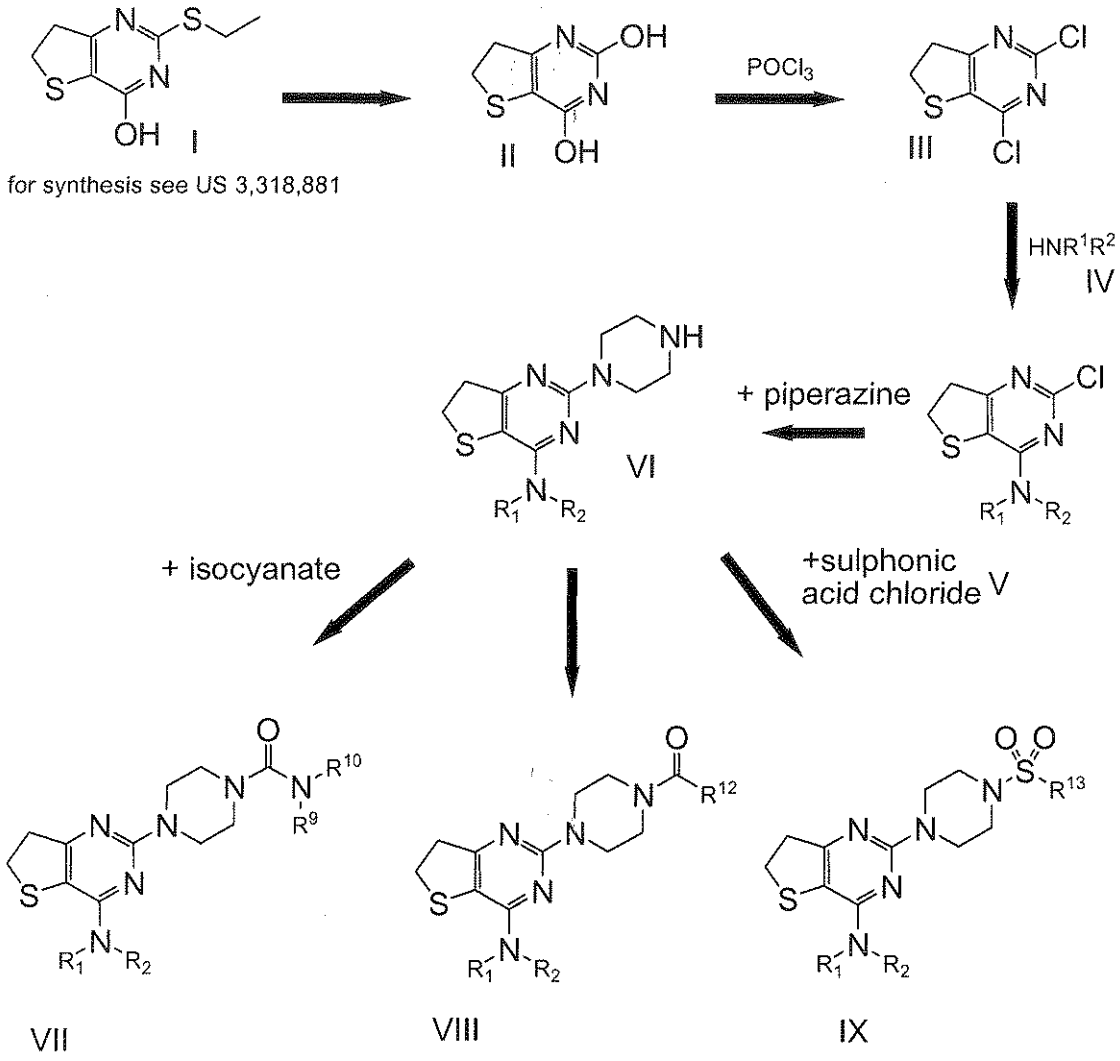
4-[4-(4-propylamino-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-benzonitrile (IX) (Example 76) : 0.150 g (0.5 mmol) (2-piperazin-1-yl-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (VII), 0.082 g (0.45 mmol) 4-bromo-benzonitrile (VIII), 0.011 g (0.05 mmol) palladium acetate, 0.041 g (0.07 mmol) Xantphos and 0.204 g (0.6 mmol) caesium carbonate are placed in 1 ml of toluene, then stirred for 24 hours at 80°C. Then the reaction mixture is combined with water and extracted with ethyl acetate. The organic phase is washed with water, dried and evaporated to dryness. The residue is purified by chromatography through an RP column using HPLC (column: Microsorb, RP-C18, 300Å, 10µm, 21.4*250 mm, eluant: acetonitrile + 0.1 % formic acid (A), water + 0.13% formic acid (B)

gradient: minutes	% eluant A	% eluant B
0	10	90
4.9	10	90
27	100	0
32	100	0
32.5	10	90
37.5	10	90

Corresponding fractions are combined and freeze-dried. 0.08 g of product IX (47%) are obtained as a powder.
^{1}H NMR (400 MHz, DMSO): 7.59 (2H, d); 7.04 (2H, d); 6.44 (1H, t); 3.78-3.71 (4H, m); 3.43-3.36 (4H, m); 3.23 (2H, t); 2.99 (2H, t); 1.60-1.49 (2H, m); 0.86 (3H, t).

{2-[4-(4-nitro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine (IX) (Example 71): 0.100 g (0.358 mmol) (2-piperazin-1-yl-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (VII) (cf. method explained previously), 0.038 ml (0.358 mmol) 1-fluoro-4-nitro-benzene (VIII) and 0.148 g (1.07 mmol) potassium carbonate are placed in 4 ml of tetrahydrofuran, then stirred for 16 hours at ambient temperature and 8 hours at 65°C and left to stand for a further 16 hours at ambient temperature. Then the solution is combined with water and extracted with ethyl acetate. The organic phase is dried and evaporated to dryness. The residue is combined with water and acetonitrile, whereupon a precipitate forms. This is suction filtered, washed and dried. 0.023 g of product IX (16%) are obtained as a powder.
^{1}H NMR (400 MHz, DMSO): 8.07 (2H, d); 7.04 (2H, d); 6.49-6.43 (1H, m); 3.81-3.73 (4H, m); 3.58-3.50 (4H, m); 3.24 (2H, t); 2.99 (2H, t); 1.61-1.49 (2H, m); 0.87 (3H, t).

Scheme 5:



STANDARD METHODS FOR THE SYNTHESIS OF AMIDES, UREAS AND SULPHONAMIDES FROM (2-PIPERAZIN-1-YL-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-4-YL)-PROPYLAMINE (SCHEME 5)

Standard method for the synthesis of amides (VIII): see above

Standard method for the synthesis of sulphonamides (IX): A solution of 0.063 mmol of the amine (VI) in 1 ml dichloromethane is combined with 30 µl diisopropylamine and 0.065 mmol sulphonic acid chloride, dissolved in 1 ml

dichloromethane, and stirred for 1 h at ambient temperature. Then the reaction mixture is evaporated to dryness and purified by preparative HPLC.

Standard method for the synthesis of ureas (VII): A solution of 0.063 mmol of the amine (VI) in 1 ml of tetrahydrofuran is combined with 30 µl diisopropylamine and 0.065 mmol isocyanate, dissolved in 1ml of tetrahydrofuran, and stirred for 1 h at ambient temperature. Then the reaction mixture is evaporated to dryness and purified by preparative HPLC.

Standard conditions for preparative HPLC purification: column: XTerra, MS-C18, 5µm, 19*100 mm, eluant: water + 0.1 % trifluoroacetic acid (A), acetonitrile + 0.1% trifluoroacetic acid (B)

gradient: minutes	% eluant A	% eluant B
0	90	10
2	90	10
11.5	0	100
13	0	100
13.5	90	10

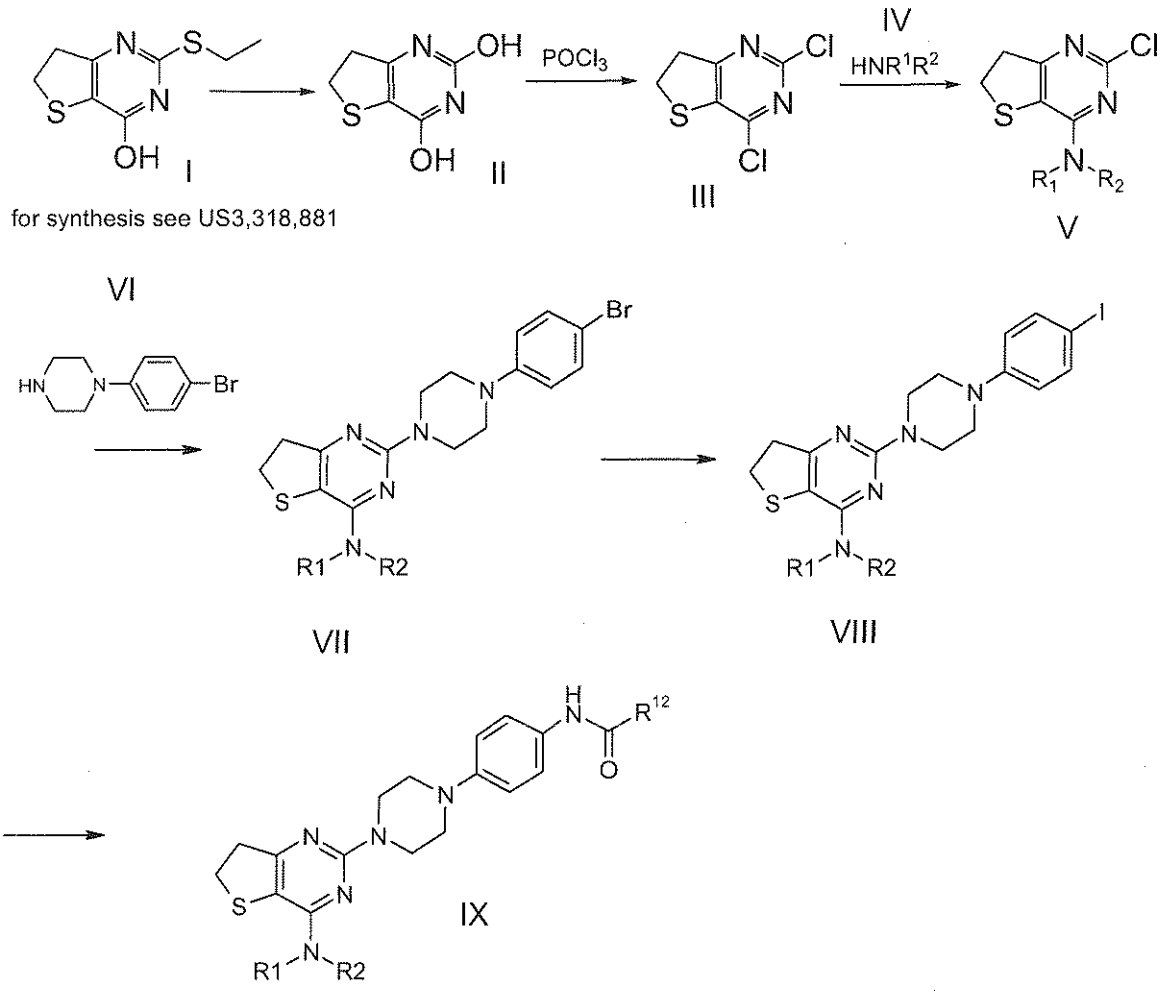
Corresponding fractions are combined and freeze-dried. The following Examples are prepared by the same method of synthesis according to Scheme 5:

4-(4-cyclohexylamino-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazine-1-carboxylic acid-phenylamide (VII) (Example 102) : 0.330 g (1.0 mmol) cyclohexyl-(2-piperazin-1-yl-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-amine (VI) and 0.115 ml (1.0 mmol) phenyl isocyanate are placed in 12.5 ml of tetrahydrofuran, then stirred for 1 hour at ambient temperature. Then the reaction mixture is concentrated by evaporation. The residue is stirred with water, suction filtered, washed with water and petroleum ether, then dried. The crude product is purified by chromatography through a 25g silica gel cartridge with a solvent mixture of

petroleum ether/ ethyl acetate 1/1. 0.240 g of product VII (53%) are obtained as a powder (m.p 207-210°C).

^{1}H NMR (400 MHz, DMSO): 8.51 (1H, s); 7.47 (2H, d); 7.23 (2H, t); 6.92 (1H, t); 6.11 (1H, d); 3.91-3.78 (1H, m); 3.69-3.59 (4H, m); 3.53-3.44 (4H, m); 3.22 (2H, t); 2.98 (2H, t); 1.92-1.78 (2H, m); 1.79-1.67 (2H, m); 1.65-1.56 (1H, m); 1.37-1.21 (4H, m); 1.18-1.04 (1H, m).

Scheme 6:



SYNTHESIS OF N-{4-[4-(4-PROPYLAMINO-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-2-YL)-PIPERAZIN-1-YL]-PHENYL}-ISONICOTINAMIDE (IX) (ACCORDING TO SCHEME 6)

{2-[4-(4-bromo-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine (VII): 1.0 g (4.4 mmol) (2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (V), 4.2 g (17.4 mmol) 1-(4-bromo-phenyl)-piperazine (VI) and 2.0 ml (11.5 mmol) diisopropylethylamine are placed in 12 ml dioxane and reacted for 2.5 hours at 160°C in the microwave. Then the reaction mixture is combined with water and dichloromethane and extracted. The organic phase is washed with water, dried and evaporated to dryness. The residue is filtered through silica gel with petroleum ether/ethyl acetate (8/2). Corresponding fractions were concentrated by evaporation. 1.9 g of product VII (100%) are obtained.

{2-[4-(4-iodo-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine (VIII): 1.55 g (3.6 mmol) {2-[4-(4-bromo-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine (VII), 1.1 g (7.2 mmol) sodium iodide and 0.036 g (0.19 mmol) copper iodide are taken, and under an argon atmosphere 0.060 ml (0.38 mmol) trans-N,N-dimethyl-1.2-cyclohexanediamine and 7 ml of anhydrous and degassed dioxane are added. The reaction mixture is heated for 1.5 hours at 140°C in the microwave, then diluted with dioxane and suction filtered through Alox. The dioxane was concentrated by evaporation. 1.70 g of product VIII (81%) are obtained as a powder.

N-{4-[4-(4-propylamino-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-phenyl}-isonicotinamide (IX) (Example 237) : 0.170 g (0.4 mmol) {2-[4-(4-iodo-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine (VIII), 0.054 g (0.4 mmol) isonicotinamide, 0.100 g (0.7 mmol) potassium carbonate and 0.004 g (0.02 mmol) copper iodide are taken, and under an argon atmosphere 1 ml of anhydrous/degassed dioxane and 0.006 ml (0.04 mmol) trans-N,N-dimethyl-1,2-cyclohexanediamine are added. The reaction mixture is reacted for 2 hours at 140°C in the microwave, then filtered through silica gel with petroleum ether/ethyl acetate (1/1) and then ethyl acetate/methanol (8/2) and concentrated by evaporation. The residue is purified by chromatography (column:

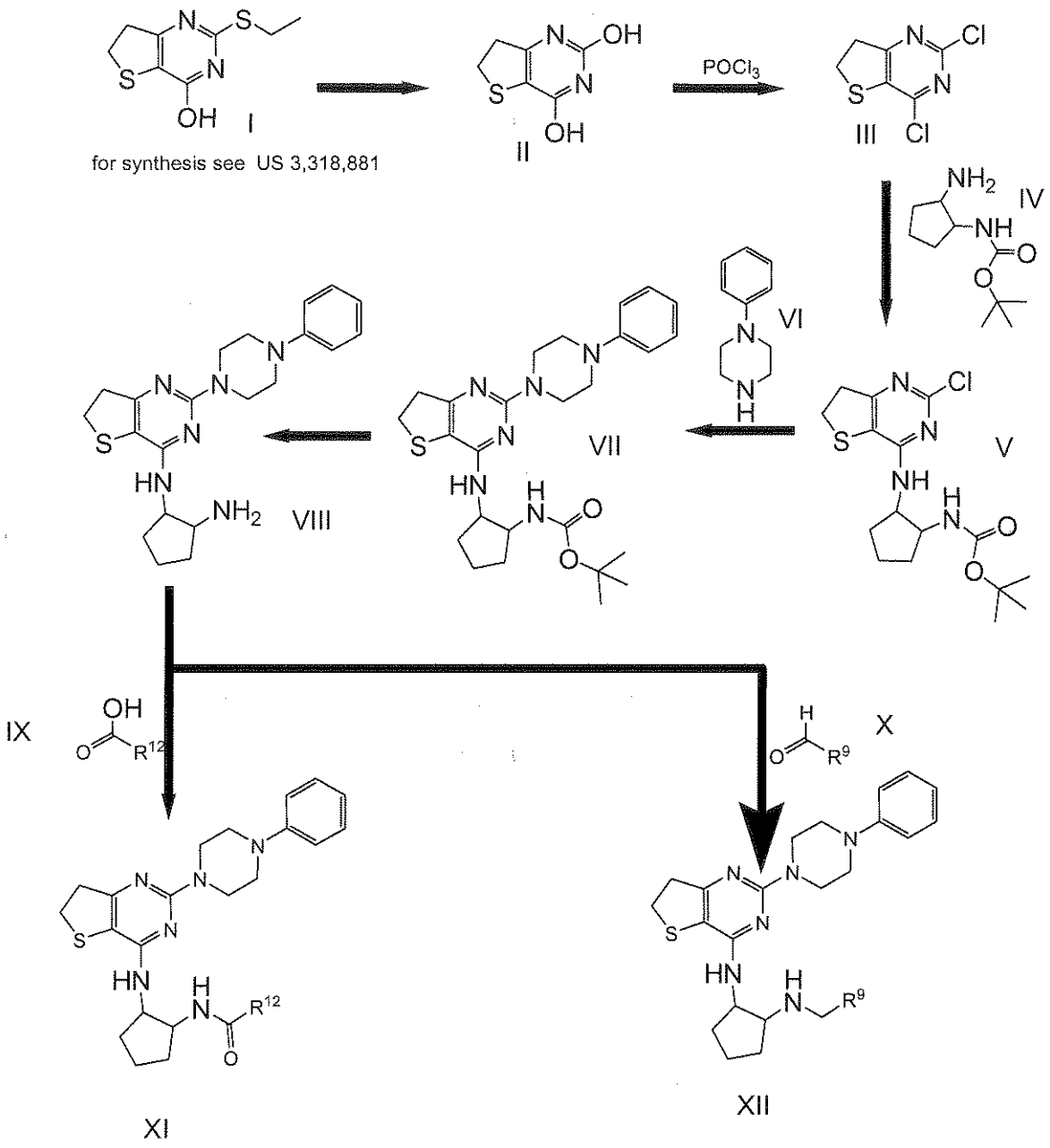
Microsorb, RP-C18, 300Å, 10µm, 21.4*250 mm, eluant: acetonitrile + 0.1 % formic acid (A), water + 0.13% formic acid (B))

gradient: minutes	% eluant A	% eluant B
0	10	90
4.9	10	90
10.5	30	70
20	30	70
21	100	0
25	100	0
26.5	10	90
31.5	10	90

0.08 g of product IX (50%) are obtained as a powder.

^{1}H NMR (400 MHz, DMSO): 10.29 (1H, s); 8.77 (2H, d); 7.85 (2H, d); 7.64 (2H, d); 7.01 (2H, d); 3.86-3.75 (4H, m); 3.23-3.07 (6H, m); 1.64-1.50 (2H, m); 0.88 (3H, t).

Scheme 7



SYNTHESIS OF ISOXAZOLE-5-CARBOXYLIC ACID-{(*1S.2S*)-2-[2-(4-PHENYL-PIPERAZIN-1-YL)-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-4-YLAMINO]-CYCLOPENTYL}-AMIDE TRIFLATE (XI) (CHIRAL) (ACCORDING TO SCHEME 7)

tert-butyl [(*1S,2S*)-2-(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino)-cyclopentyl]-carbamate (V) (chiral): 0.600 g (2.9 mmol) 2,4-dichloro-6,7-dihydro-thieno[3,2-d]pyrimidine (III), 0.580 g (2.9 mmol tert-butyl) (2-amino-cyclopentyl)-carbamate (IV) and 2.5 ml (14.5 mmol) diisopropylethylamine are placed in 30 ml of tetrahydrofuran, the mixture is stirred for 2 hours at ambient temperature and 72 hours at 80°C. The reaction mixture is concentrated by evaporation and further reacted in the crude state.

tert-butyl {(*1S,2S*)-2-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino]-cyclopentyl}-carbamate (VII) (chiral): 1.08 g (2.9 mmol) tert-butyl [(*1S,.2S*)-2-(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino)-cyclopentyl]-carbamate (V) (chiral) and 9.9 mmol 1-phenyl-piperazine (VI) are placed in 14 ml dioxane, then heated to 160°C for 2.3 hours. The reaction mixture is concentrated by evaporation, the residue is then purified by HPLC through an RP column (column: XTerra, MS-C18, 5µm, 19*100 mm
eluant: water + 0.1 % trifluoroacetic acid (A), acetonitrile + 0.1% trifluoroacetic acid (B))

gradient: minutes	% eluant A	% eluant B
0	90	10
2	90	10
11.5	0	100
13	0	100
13.5	90	10

Corresponding fractions are combined and freeze-dried. 0.97 g of product VII (67%) are obtained.

(*1S,2S*)-N-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl]-cyclopentane-1,2-diamine ditriflate (VIII) (chiral): 0.960 g (1.9 mmol) tert-butyl {(*1S,2S*)-2-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-

ylamino]-cyclopentyl}-carbamate (VII) (chiral) are dissolved in 40 ml 25% trifluoroacetic acid in dichloromethane and the mixture is stirred for 1 hour at ambient temperature. Then the reaction mixture is concentrated by evaporation, the residue is combined with acetonitrile and water and freeze-dried. 1.2 g of product VIII (100%) are obtained as a powder.

isoxazole-5-carboxylic acid-{(*1S,2S*)-2-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino]-cyclopentyl}-amide triflate (chiral) (XI) (Example 277) :

0.004 g (0.03 mmol) isoxazole-5-carboxylic acid (IX), 0.012 g (0.03 mmol) O-(7-azabenzotriazol-1-yl)-N,N,N´,N´-tetramethyluronium-hexafluoro-phosphate (HATU) and 0.017 ml (0.10 mmol) diisopropylethylamine are placed in 1 ml of dimethylformamide, stirred for 0.1 hours at ambient temperature. Then 0.020 g (0.03 mmol) N-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl]-cyclopentane-1,2-diamine ditriflate (VIII) (chiral) in 1 ml of dimethylformamide are added. The mixture is shaken for 1 hour at ambient temperature. Then the reaction mixture is purified directly by HPLC through an RP column (column: XTerra, MS-C18, 5µm, 19*100 mm, eluant: water + 0.1 % trifluoroacetic acid (A), acetonitrile + 0.1% trifluoroacetic acid (B))

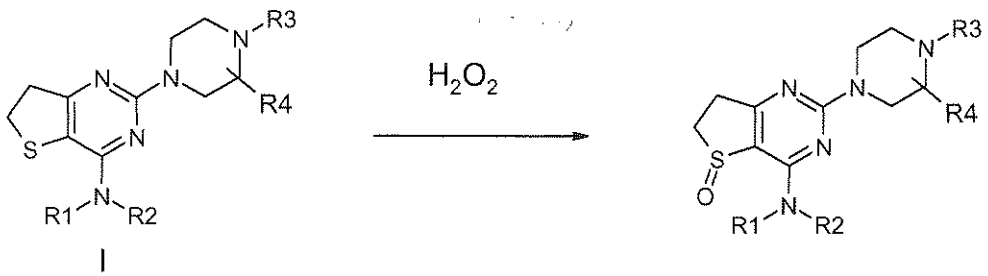
gradient: minute	% eluant A	% eluant B
0	90	10
2	90	10
11.5	0	100
13	0	100
13.5	90	10

Corresponding fractions are combined and freeze-dried. 0.003 g of product XI (18%) are obtained.

SYNTHESIS OF (*1S,2S*)-*N*-(1-METHYL-1*H*-PYRROL-2-YLMETHYL)-*N'*-[2-(4-PHENYL-PIPERAZIN-1-YL)-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-4-YL]-CYCLOPENTANE-1,2-DIAMINE TRIFLATE (CHIRAL) (EXAMPLE 310) (XII) (ACCORDING TO SCHEME 7)

0.015 g (0.02 mmol) N-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl]-cyclopentanE-1,2-diamineditriflate (VIII) (chiral), 0.015 ml (0.14 mmol) 1-methyl-1*H*-pyrrole-2-carbaldehyde (X), 0.005 ml (0.09 mmol) glacial acetic acid and molecular sieve are placed in 2 ml of dimethylformamide, and the mixture is stirred for 0.5 hours at ambient temperature. Then first of all 0.070 g (0.23 mmol) polyamine resin are added, followed, after another 0.5 hours, by 0.030 g (0.14 mmol) sodium triacetoxyborohydride. The reaction mixture is shaken for 16 hours at ambient temperature, filtered and purified through an RP-column by HPLC (column: XTerra, MS-C18, 5µm, 19*100 mm, eluant: water + 0.1% trifluoroacetic acid (A), acetonitrile + 0.1% trifluoroacetic acid (B)). Corresponding fractions are combined and lyophilised. 0.009 g of product XII (59%) are obtained. ^{1}H NMR (400 MHz, DMSO): 7.28-7.21 (2H, m); 7.00-6.95 (2H, m); 6.85-6.78 (2H, m); 6.21-6.18 (1H, m); 6.01-5.98 (1H, m); 4.74-4.67 (1H, m); 4.19-4.12 (2H, m); 3.81-3.74 (4H, m); 3.74-3.64 (1H, m); 3.59 (3H, t); 3.20-3.13 (4H, m); 3.11-3.03 (3H, m); 2.19-2.03 (3H, m); 1.78-1.70 (4H, m); 1.67-1.54 (1H, m).

Scheme 8



SYNTHESIS OF CYCLOHEXYL-[5-OXO-2-(4-PHENYL-PIPERAZIN-1-YL)-6,7-DIHYDRO-5H-5λ^4-THIENO[3,2-D]PYRIMIDIN-4-YL]-AMINE (EXAMPLE 297) (II) (ACCORDING TO SCHEME 8)

0.120 g (0.3 mmol) cyclohexyl-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl]-amine (I) are dissolved in 4 ml acetic acid and 0.27 ml of 35% hydrogen peroxide solution is added. The mixture is stirred for 16 hours at ambient temperature, then water is added. The reaction mixture is made basic and extracted with ethyl acetate. The organic phase is dried and evaporated to dryness. The residue is purified by chromatography, the product is triturated with diethyl ether and suction filtered. 0.060 g of product II (48%) are obtained.
^{1}H NMR (400 MHz, DMSO): 7.40 (1H, d); 7.23 (2H, t); 6.98 (2H, d); 6.80 (1H, t); 4.01-3.86 (5H, m); 3.48-3.37 (1H, m); 3.28-3.13 (5H, m); 3.00-2.82 (2H, m); 1.92-1.81 (2H, m); 1.80-1.69 (2H, m); 1.67-1.57 (1H, m); 1.43-1.21 (4H, m); 1.20-1.05 (1H, m).

The enantiomers were separated by analytical chiral HPLC (column: Chiralpak Diacel AD-H, 5 μM, 250*4.6 mm, flow rate: 1.0 ml/min, eluant: hexane/iPrOH (90/10)): Rt = 14.6 min: enantiomer 1 (Example 367) $[\alpha]_D^{20}$ + 183 (CH_2Cl_2); Rt = 16.4 min: enantiomer 2 (Example 368) , $[\alpha]_D^{20}$ -189 (CH_2Cl_2).

SYNTHESIS OF [5-OXO-2-(4-PHENYL-PIPERAZIN-1-YL-6,7-DIHYDRO-5H-5λ^4-THIENO[3,2-D]PYRIMIDIN-4-YL]-PROPYL-AMINE (EXAMPLE 298) (II) (ACCORDING TO SCHEME 8)

0.240 g (0.68 mmol) [2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl]-propylamine (I) are dissolved in 5 ml acetic acid, and 0.60 ml 35% hydrogen peroxide solution are added while being cooled. The mixture is stirred for 16 hours at ambient temperature, then water is added. The reaction mixture is made basic and extracted with dichloromethane. The organic phase is dried and evaporated to dryness. The residue is purified by chromatography, the product is

triturated with diethyl ether and suction filtered. 0.130 g of product II (52%) are obtained.

^{1}H NMR (400 MHz, DMSO): 7.69 (1H, t); 7.23 (2H, t); 6.98 (2H, d); 6.80 (1H, t); 3.95-3.87 (4H, m); 3.49-3.19 (4H, m); 3.22-3.13 (4H, m); 3.01-2.82 (2H, m); 1.64-1.52 (2H, m); 0.88 (3H, t).

SYNTHESIS OF [5-OXO-2-(4-PHENYL-PIPERAZIN-1-YL)-6,7-DIHYDRO-5H-5λ^4-THIENO[3,2-D]PYRIMIDIN-4-YL]-PHENYLAMINE (II) (EXAMPLE 299)
(ACCORDING TO SCHEME 8)

0.190 g (0.49 mmol) phenyl-[2-(4-phenyl-piperazin-1-yl)-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl]-amine (I) are dissolved in 5 ml acetic acid, 0.43 ml of 35% hydrogen peroxide solution are added, with cooling. The mixture is stirred for 16 hours at ambient temperature, then water is added. The reaction mixture is made basic and extracted with dichloromethane. The organic phase is dried and evaporated to dryness. The residue is purified by chromatography, the product is triturated with diethyl ether and suction filtered.
0.100 g of product II (51%) are obtained.
^{1}H NMR (400 MHz, DMSO): 9.54 (1H, s); 7.66 (2H, d); 7.35 (2H, t); 7.23 (2H, t); 7.09 (1H, t); 6.98 (2H, d); 6.80 (1H, t); 3.96-3.85 (4H, m); 3.60-3.47 (1H, m); 3.32-3.15 (4H, m); 3.12-3.02 (1H, m); 3.01-2.92 (1H, m).

The following Examples are prepared as described above according to Scheme 8:

(3-METHOXY-PHENYL)-[5-OXO-2-(4-PHENYL-PIPERAZIN-1-YL)-6,7-DIHYDRO-5*H*-5λ^4-THIENO[3,2-D]PYRIMIDIN-4-YL]-AMINE (Example 302)
(II according to SCHEME 8)

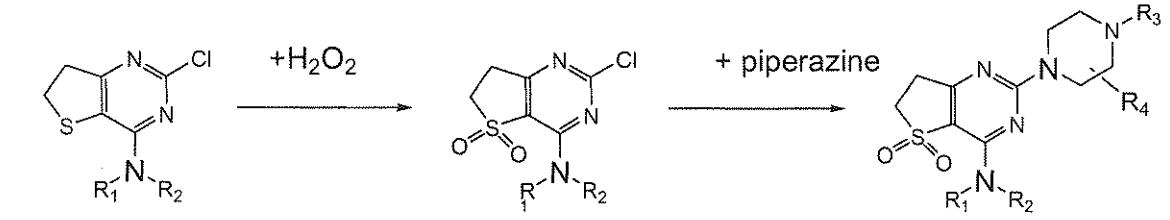
0.072 g of product II (17%) are obtained as a powder (m.p 217°-220°C).

(3-CHLORO-PHENYL)-[5-OXO-2-(4-PHENYL-PIPERAZIN-1-YL)-6,7-DIHYDRO-5*H*-5λ^4-THIENO[3,2-D]PYRIMIDIN-4-YL]-AMINE (EXAMPLE 300) (II ACCORDING TO SCHEME 8)

4.50 g of product II (73%) are obtained as a powder (m.p 230°-231°C).

The enantiomers were separated by semipreparative chiral HPLC (column: Chiralpak Diacel IA, 5 µM, 200*25 mm, flow rate: 12 ml/min, eluant: TBME/EtOH (75/25)): Rt = 16 min: Enantiomer 1 (EXAMPLE 370) , $[\alpha]_D^{20}$ + 221.3 (*c* 2.06, CH_2Cl_2).; Rt = 19 min: Enantiomer 2 (EXAMPLE 371) , $[\alpha]_D^{20}$ – 207.9 (*c* 2.24, CH_2Cl_2).

Scheme 9:



SYNTHESIS OF {2-[4-(4-CHLORO-PHENYL)-PIPERAZIN-1-YL]-5,5-DIOXO-6,7-DIHYDRO-5*H*-5λ^6 -THIENO[3,2-D]PYRIMIDIN-4-YL}-PROPYL-AMINE (EXAMPLE 377) (III ACCORDING TO SCHEME 9)

(2-chloro-5,5-dioxo-6,7-dihydro-5*H*-5λ^6-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (II): 0.805 g (3.50 mmol) (2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (I) (see Scheme 1, preparation method B) are placed at ambient temperature in 14 ml trifluoroacetic acid, then combined with 0.82 ml (8.40 mmol) hydrogen peroxide (35% in water). The reaction mixture is stirred for 16 hours at

ambient temperature and 2 hours at 45°C. After the addition of 0.5 eq hydrogen peroxide the mixture is stirred for a further 0.5 hours at 45°C, then stirred into ice water and made basic with ammonia solution. Any precipitate formed is suction filtered, washed and dried. 0.720 g of product II (79%) are obtained as a powder.

{2-[4-(4-chloro-phenyl)-piperazin-1-yl]-5,5-dioxo-6,7-dihydro-5*H*-5λ^6-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine (III): 0.262 g (1.00 mmol) (2-chloro-5,5-dioxo-6,7-dihydro-5*H*-5λ^6-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (II) and 0.433 g (2.20 mmol) 1-(4-chloro-phenyl)-piperazine are placed in 4.50 ml dioxane, then heated to 150°C in the microwave for 0.75 hours. Then the reaction mixture is concentrated by evaporation, the residue is treated with water. It is suction filtered, washed with water and dried. The product which is not yet clean is purified by chromatography (column: 10 g Chromabond SiOH cartridge, solvent: petroleum ether /ether 1:1). Corresponding fractions are combined and concentrated by evaporation. 0.295 g of product III (70%) are obtained as a powder (m.p 243°-245°C).

The following Examples are prepared as described above according to Scheme 9:

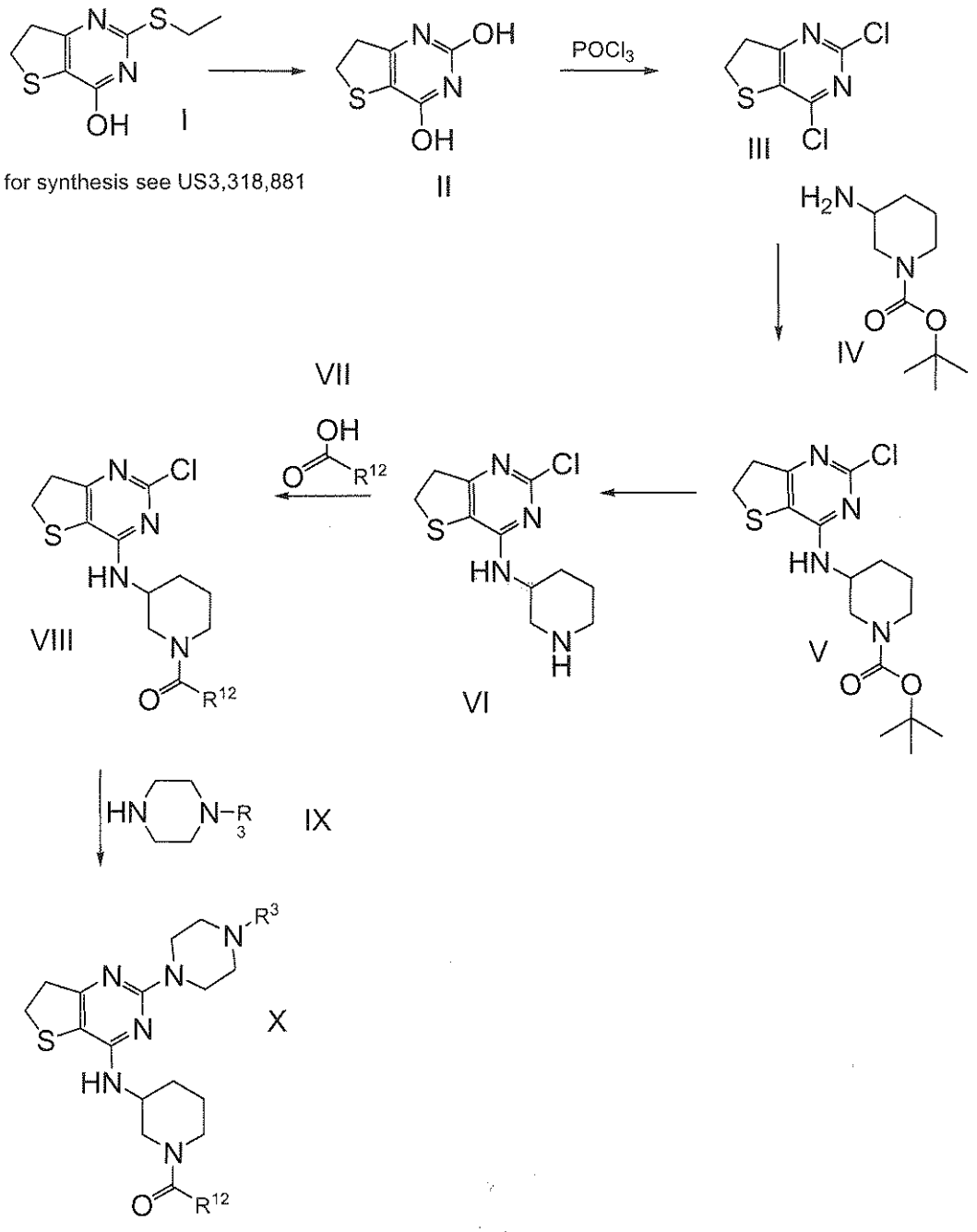
(3-CHLORO-PHENYL)-[5,5-DIOXO-2-(4-PHENYL-PIPERAZIN-1-YL)-6,7-DIHYDRO-5*H*-5λ^6-THIENO[3,2-D]PYRIMIDIN-4-YL]-AMINE (EXAMPLE 375) (III according to SCHEME 9)

0.163 g of product III (36%) are obtained as a powder (m.p 234°C).

(3-CHLORO-PHENYL)-{2-[4-(4-CHLORO-PHENYL)-PIPERAZIN-1-YL]-5,5-DIOXO-6,7-DIHYDRO-5*H*-5λ^6-THIENO[3,2-D]PYRIMIDIN-4-YL}-AMINE (EXAMPLE 376) (III ACCORDING TO SCHEME 9)

0.173 g of product III (35%) are obtained as a powder (m.p 246°C).

Scheme 10:


I
II
III
IV
V
VI
VII
VIII
IX
X
POCl3
for synthesis see US3,318,881

SYNTHESIS OF (1-METHYL-1H-PYRROL-2-YL)-{3-[2-(4-(4-CHLORO-PHENYL)-PIPERAZIN-1-YL]-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-4-YLAMINO]-PIPERIDIN-1-YL}-METHANONE (X ACCORDING TO SCHEME 10)

tert-butyl 3-(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino)-piperidine-1-carboxylate (V): 2.07 g (10.0 mmol) 2,4-dichloro-6,7-dihydro-thieno[3,2-d]pyrimidine (III), 2.0 g (10.0 mmol) tert-butyl 3-amino-piperidin-1-carboxylate (IV) and 3.4 ml (19.3 mmol) diisopropylethylamine are placed in 40 ml of tetrahydrofuran, then stirred for 40 hours at ambient temperature. Then the reaction mixture is suction filtered and the mother liquor is concentrated by evaporation. The residue is combined with water and extracted with dichloromethane. The organic phase is separated off using a phase separator and evaporated to dryness. The crude product is purified by chromatography through a Biotage silica gel cartridge 40M with petroleum ether/ethyl acetate 9:1. 1.77 g of product V (48%) is obtained.

(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-piperidin-3-yl-amine hydrochloride (VI): 1.77 g (4.8 mmol) tert-butyl 3-(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino)-piperidin-1-carboxylate (V) are placed in 21.5 ml of a 4% hydrochloric acid solution in dioxane, and methanol is added. The solution is stirred for 0.5 hours at ambient temperature, whereupon a precipitate is formed. This is suction filtered, washed with diethyl ether and dried. 1.33 g of product (VI) (91%) are obtained.

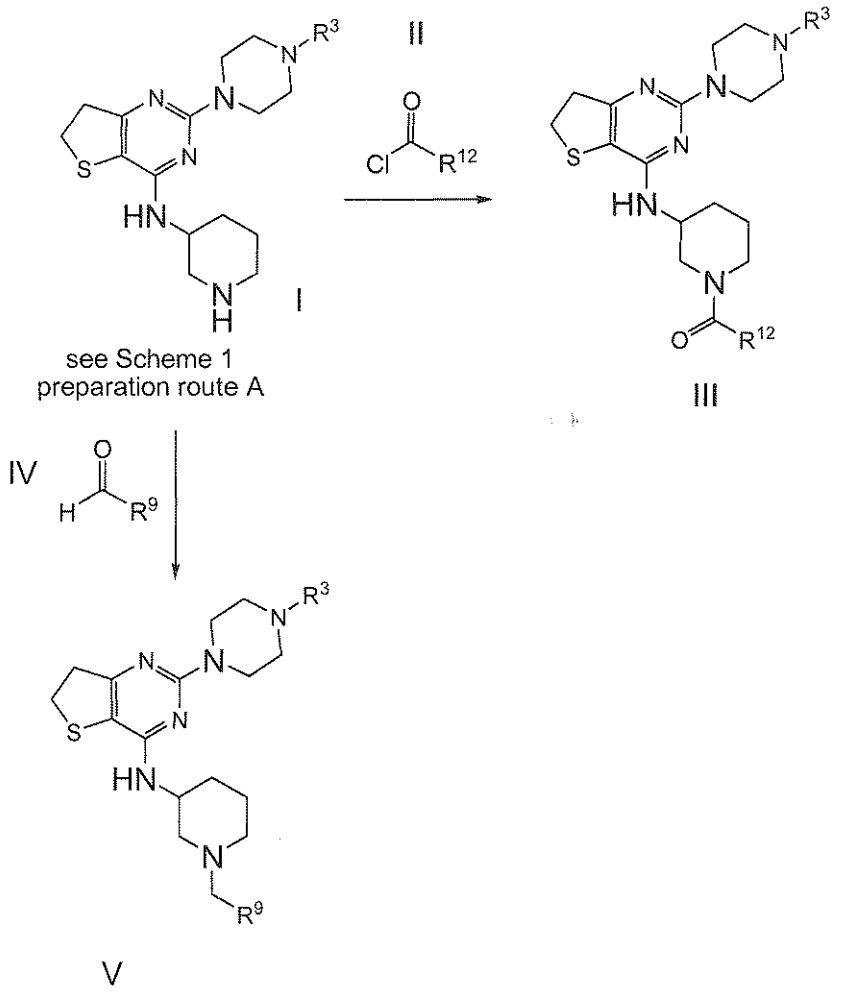
(1-methyl-1*H*-pyrrol-2-yl)-[3-(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino)-piperidin-1-yl]-methanone (VIII): 0.462 g (3.7 mmol) 1-methyl-1*H*-pyrrol-2-carboxylic acid (VII), 1.4 g (9.7 mmol) O-(7-azabenzotriazol-1-yl-)-N,N,N´,N´-tetramethyluronium-hexafluoro-phosphate (HATU) and 0.640 ml (3.7 mmol) diisopropylethylamine are placed in 10 ml dimethylsulphoxide, then stirred for 0.1 hours at ambient temperature. 0.814 g (3.0 mmol) (2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl)-piperidin-3-yl-amine hydrochloride (VI) and 3.7 mmol

diisopropylethylamine are added, then the mixture is stirred for 16 hours at ambient temperature . Then the reaction mixture is suction filtered through Alox, and the mother liquor is concentrated by evaporation. The residue is combined with 1 N sodium hydroxide solution and extracted with dichloromethane. The organic phase is separated off using a phase separator and evaporated to dryness. The crude product is purified by chromatography through a Biotage silica gel cartridge 40s with petroleum ether/ethyl acetate 1:1. 0.970 g of product VIII (85%) are obtained.

(1-methyl-1*H*-pyrrol-2-yl)-{3-[2-(4-(4-chloro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino]-piperidin-1-yl}-methanone (X according to Scheme 10) (Example 230) : 0.250 g (0.7 mmol) (1-methyl-1*H*-pyrrol-2-yl)-[3-(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino)-piperidin-1-yl]-methanone (VIII), 0.503 g (1.9 mmol) 1-(4-chloro-phenyl)-piperazine dihydrochloride (IX) and 0.430 ml (2.5 mmol) diisopropylethylamine are placed in 3.5 ml dioxane, then reacted for 2.25 hours at 160°C in the microwave. Then the reaction mixture is combined with water. Any precipitate formed is suction filtered, washed with water and dried. 0.167 g of product X (47%) are obtained as a beige powder.

^{1}H NMR (400 MHz, DMSO): 7.25 (2H, d); 6.97 (2H, d); 6.84 (1H, t); 6.34-6.31 (1H, m), 5.96 (1H, m); 4.46-4.34 (1H, m); 4.22-4.12 (1H, m); 4.04-4.92 (1H, m); 3.73-3.64 (4H, m); 3.67 (3H, s); 3.24 (2H, t); 3.16-3.09 (4H, m); 3.05-2.84 (4H, m); 1.97-1.88 (1H, m); 1.82-1.65 (2H, m); 1.55-1.43 (1H, m).

Scheme 11



SYNTHESIS OF (3-{2-[4-(4-CHLORO-PHENYL)-PIPERAZIN-1-YL]-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-4-YLAMINO}-PIPERIDIN-1-YL)-MORPHOLIN-4-YL-METHANONE TRIFLATE (EXAMPLE 357) (III ACCORDING TO SCHEME 11):

0.135 g (0.31 mmol) {2-[4-(4-chloro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl}-piperidin-3-yl-amine (I) (see Scheme 1), 0.037 ml (0.31 mmol) morpholine-4-carbonyl chloride (II), 0.119 g (0.31 mmol) O-(7-azabenzotriazol-1-yl-)-N,N,N´,N´-tetramethyluronium-hexafluoro-phosphate (HATU) and 0.218 ml

(1.25 mmol) diisopropylethylamine are stirred in 6 ml of dimethylformamide for 18 hours at ambient temperature. The reaction mixture is concentrated by evaporation, the residue is purified by chromatography (RP-HPLC). 0.040 g of the product III (19%) are obtained after freeze-drying.

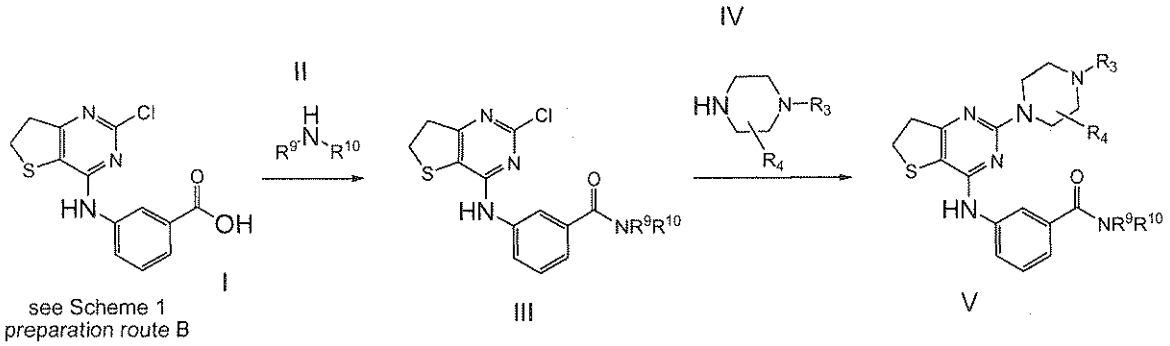
^{1}H NMR (400 MHz, DMSO): 7.26 (2H, d); 7.00 (2H, d); 4.13-3.95 (m); 3.87-3.76 (m); 3.68-3.60 (m); 3.59-3.43 (m); 3.43-3.34 (m); 3.31-3.09 (m); 2.88-2.77 (m); 1.95-1.83 (1H, m); 1.78-1.60 (2H, m); 1.57-1.40 (m).

[2-(4-PHENYL-PIPERAZIN-1-YL)-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-4-YL]-(1-PYRIDIN-3-YLMETHYL-PIPERIDIN-3-YL)-AMINE DITRIFLATE (EXAMPLE 363) (V according to Scheme11)

0.015 g (0.024 mmol) {2-[4-(4-chloro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl}-piperidin-3-yl-amine (I) (see Scheme 1), 0.015 ml (0.158 mmol) pyridine-3-aldehyde (IV) and 0.005 ml (0.087 mmol) glacial acetic acid are stirred into 2 ml DMF through a molecular sieve for 0.5 hour at ambient temperature. 0.026 mg (0.123 mmol) sodium triacetoxyborohydride are added and the reaction mixture is stirred for another 12 hours at ambient temperature. The reaction mixture is purified by chromatography (RP-HPLC). 0.009 g of the product V (50%) are obtained after freeze-drying.

^{1}H NMR (400 MHz, DMSO): 8.76-8.70 (1H, m); 8.65-8.58 (1H, m); 8.02-7.94 (1H, m); 7.56-7.49 (1H, m); 7.33-7.21 (3H, m); 7.04-6.97 (2H, m); 6.89-6.81 (1H, m); 4.57-3.78 (m); 3.75-3.40 (m); 3.37-3.28 (2H, m); 3.20-3.03 (m); 2.99-2.79 (1H, m); 2.78-2.59 (1H, m); 2.07-1.71 (3H, m); 1.69-1.52 (1H, m).

Scheme 12



SYNTHESIS OF (4-METHYL-PIPERAZIN-1-YL)-(3-{2-[4-(4-CHLORO-PHENYL)-PIPERAZIN-1-YL]-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-4-YLAMINO}-PHENYL)-METHANONE (V ACCORDING TO SCHEME 12)

3-(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino)-benzoic acid (I): 0.200 g (0.93 mmol) 2,4-dichloro-6,7-dihydro-thieno[3,2-d]pyrimidine, 0.127 g (0.93 mmol) 3-amino-benzoic acid and 0.323 ml (1.85 mmol) diisopropylethylamine are placed in 4 ml of tetrahydrofuran, stirred for 48 hours at ambient temperature and 48 hours at 70°C. Then the reaction mixture is combined with water and acidified with 1N hydrochloric acid. The precipitate formed is suction filtered and dried. 0.110 g of product I (39%) are obtained.

(4-methyl-piperazin-1-yl)-[3-(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino)-phenyl]-methanone (III): 0.600 g (1.95 mmol) 3-(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino)-benzoic acid (I), 0.741 g (1.95 mmol) O-(7-azabenzotriazol-1-yl-)-N,N,N′,N′-tetramethyluronium-hexafluoro-phosphate (HATU) and 0.680 ml (3.90 mmol) diisopropylethylamine are placed in 10 ml dimethylsulphoxide, then stirred for 0.5 hours at ambient temperature. 0.220 ml (1.95 mmol) methylpiperazine (II) are added, then the mixture is stirred for 3 hours at ambient temperature. Then the reaction mixture is concentrated by evaporation and the residue is combined with water. Any precipitate formed is suction filtered and dried. The crude product is purified by chromatography through a 50 g silica

cartridge with ethyl acetate/methanol 8:2. 0.250 g of product III (33%) are obtained.

(4-methyl-piperazin-1-yl)-(3-{2-[4-(4-chloro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino}-phenyl)-methanone (V) (Example 236) :

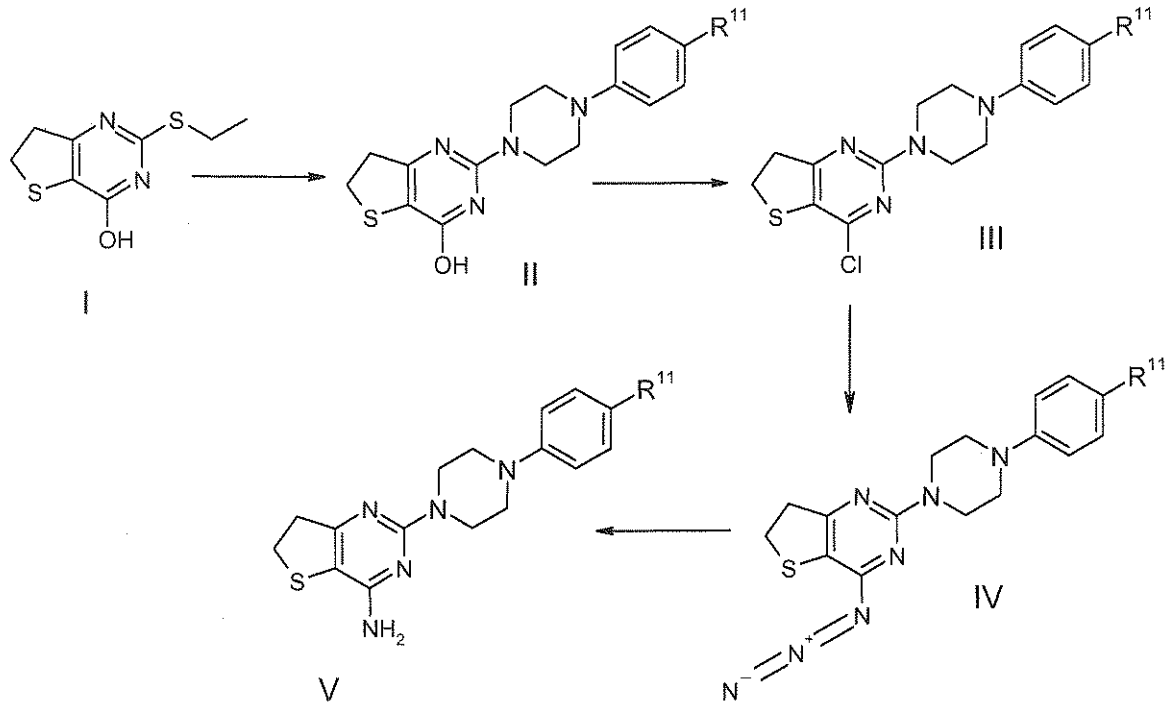
0.100 g (0.26 mmol) (4-methyl-piperazin-1-yl)-[3-(2-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamino)-phenyl]-methanone (III), 0.207 g (0.77 mmol) 1-(4-chloro-phenyl)-piperazine (IV) and 0.180 ml (1.02 mmol) diisopropylethylamine are placed in 3.5 ml dioxane, then reacted for a total of 2 hours at 160°C in the microwave. Then the reaction mixture is combined with water and extracted with ethyl acetate. The organic phase is dried and evaporated to dryness. The residue is purified by chromatography using HPLC through an RP column (column: Microsorb, RP-C18, 300Å, 10µm, 21.4*250 mm, eluant: acetonitrile + 0.1 % formic acid (A), water + 0.13% formic acid (B))

gradient: minutes	% eluant A	% eluant B
0	10	90
4.9	10	90
27	100	0
32	100	0
32.5	10	90
37.5	10	90

Corresponding fractions are combined and freeze-dried. 0.014 g of product V (10%) are obtained.

^{1}H NMR (400 MHz, DMSO): 8.60 (1H, s); 7.76-7.70 (2H, m); 7.37 (1H, t); 7.25 (2H, d); 7.03 (1H, d); 6.98 (2H, d); 3.81-3.72 (5H, m); 3.72-3.37 (3H, m); 3.21-3.14 (4H, m); 3.10 (3H, t); 2.97-2.62 (4H, m).

Scheme 13:



SYNTHESIS OF 4-[4-(4-AMINO-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-2-YL)-PIPERAZIN-1-YL]-PHENOL (V ACCORDING TO SCHEME 13)

2-[4-(4-hydroxy-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ol (II): 1.70 g (9.54 mmol) 4-piperazin-1-yl-phenol are placed in 0.55 ml (9.62 mmol) glacial acetic acid and heated to 180°C in the heating block. 0.800 g (3.73 mmol) 2-ethylsulphanyl-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ol (I) are added, then the mixture is left to stand for 1.5 hours at 180°C and 16 hours at ambient temperature. Then the reaction mixture is combined with water and treated in the ultrasound bath. The precipitate is suction filtered, washed and dried. 1.1 g of product II are obtained as a powder.

4-[4-(4-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-phenol (III): 1.11 g (3.36 mmol) 2-[4-(4-hydroxy-phenyl)-piperazin-1-yl]-6,7-dihydro-

thieno[3,2-d]pyrimidin-4-ol (II) are placed in 5 ml phosphorus oxychloride, then stirred for 4 hours at 120°C. Excess phosphorus oxychloride is then distilled off and the residue is combined with water. The precipitate formed is suction filtered, washed with plenty of water and dried. 1.18 g of product III are obtained as a brown powder.

4-[4-(4-azido-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-phenol (IV): 1.18 g (2.75 mmol) 4-[4-(4-chloro-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-phenol (III) are placed in 25 ml of dimethylformamide, 1.20 g (18.46 mmol) sodium azide are added. The reaction mixture is stirred for 4.5 hours at 100°C. Then it is concentrated by evaporation, the residue is cooled in the ice bath and combined with water. The precipitate formed is suction filtered, washed and dried. 0.800 g of product IV are obtained and used further as a crude product.

4-[4-(4-amino-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-phenol (V) (Example 218) : 0.800 g (1.80 mmol) 4-[4-(4-azido-6,7-dihydro-thieno[3,2-d]pyrimidin-2-yl)-piperazin-1-yl]-phenol (IV) are placed in 10 ml of tetrahydrofuran and 0.500 g molecular sieve are added. 3.80 ml (3.80 mmol) lithium aluminium hydride (1 M solution in tetrahydrofuran) are slowly added dropwise. The reaction mixture is stirred for 3 hours at ambient temperature. Then 0.55 ml 1N sodium hydroxide solution and 0.50 ml of water are added, the mixture is boiled for 0.3 hours, then cooled again. It is filtered, the filtrate is dried and evaporated to dryness. The residue is extracted with ethyl acetate and 1 N hydrochloric acid, the aqueous phase is made basic and extracted with ethyl acetate. The organic phase is washed with water, dried and evaporated to dryness. 0.280 g of product V are obtained as a light brown foam.

^{1}H NMR (400 MHz, DMSO): 8.80 (1H, s); 6.82 (2H, d); 6.66 (2H, d); 6.26 (2H, s); 3.77-3.66 (4H, m); 3.21 (2H, t); 2.98 (2H, t); 2.98-2.90 (4H, m).

SYNTHESIS OF 2-[4-(4-CHLORO-PHENYL)-PIPERAZIN-1-YL]-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-4-YLAMINE (V ACCORDING TO SCHEME 13)

2-[4-(4-chloro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ol (II):

1.9 g (9.66 mmol) 1-(4-chlorophenyl)piperazine are placed in 0.55 ml (9.62 mmol) glacial acetic acid and heated to 180°C in the heating block. 0.800 g (3.73 mmol) 2-ethylsulphanyl-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ol (I) are added, then the mixture is left to stand for 1.5 hours at 180°C and 16 hours at ambient temperature. Then the reaction mixture is combined with water and treated in the ultrasound bath. The precipitate is suction filtered, washed and dried. 1.25 g 2 of product II are obtained and used further in the crude state.

4-chloro-2-[4-(4-chloro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidine (III): 1.25 g (3.05 mmol) 2-[4-(4-chloro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ol (II) are placed in 4.50 ml phosphorus oxychloride, then stirred for 4 hours at 120°C. Then excess phosphorus oxychloride is distilled off, the residue is combined with water. The precipitate formed is suction filtered, washed with plenty of water and dried, then stirred with methanol. 0.960 g of product III (85%) are obtained.

4-azido-2-[4-(4-chloro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidine (IV): 0.950 g (2.59 mmol) 4-chloro-2-[4-(4-chloro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidine (III) are placed in 20 ml of dimethylformamide and 0.900 g (13.84 mmol) sodium azide are added. The reaction mixture is stirred for 4 hours at 100°C. It is then concentrated by evaporation, the residue is cooled in the ice bath and combined with water. The precipitate formed is suction filtered, washed and dried. 0.920 g of product IV (76%) are obtained and used further in the crude state.

2-[4-(4-chloro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-ylamine (Example 219) (V) : 0.820 g (1.76 mmol) 4-azido-2-[4-(4-chloro-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidine (IV) are placed in 10 ml of tetrahydrofuran and 3.80 ml (3.80 mmol) lithium aluminium hydride (1 molar solution in tetrahydrofuran) are slowly added dropwise. The reaction mixture is stirred for 4 hours at ambient temperature. Then 0.55 ml 1N sodium hydroxide solution and 0.50 ml of water are added, the mixture is boiled for 0.3 hours, then cooled again. It is filtered, the filtrate is dried and evaporated to dryness. The residue is extracted with ethyl acetate and 1 N hydrochloric acid. The product precipitates out, is suction filtered, then extracted with ethyl acetate and 1 N sodium hydroxide solution. The organic phase is washed with water, dried and evaporated to dryness. The residue is stirred with petroleum ether. 0.513 g of product V (84%) are obtained as a solid (m.p 176-178°C).

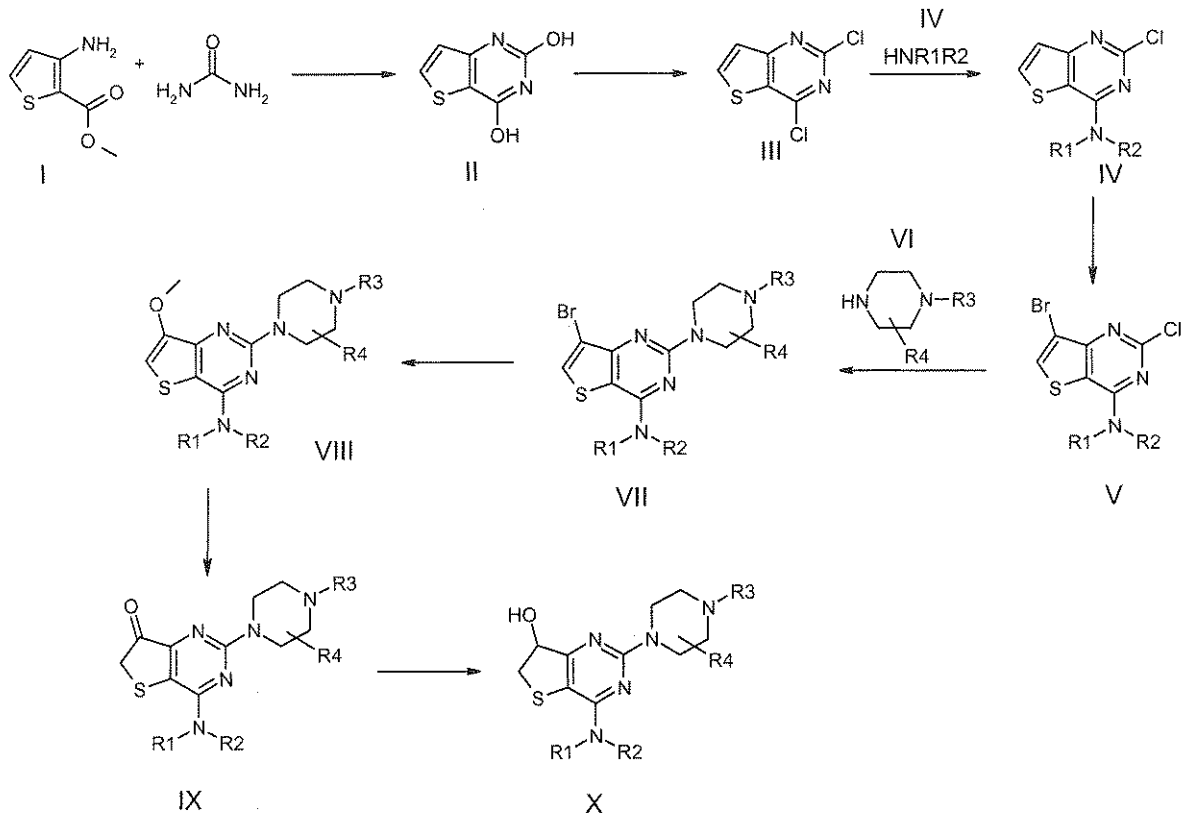
^{1}H NMR (400 MHz, DMSO): 7.24 (2H, d); 6.98 (2H, d); 6.30 (2H, s); 3.77-3.68 (4H, m); 3.22 (2H, t); 3.17-3.09 (4H, m); 2.99 (2H, t).

SYNTHESIS OF MONO-{4-[4-(4-PROPYLAMINO-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-2-YL)-PIPERAZIN-1-YL]-PHENYL} SULPHATE (V ACCORDING TO SCHEME 13) (EXAMPLE 291)

0.100 g (0.269 mmol) {2-[4-(4-hydroxy-phenyl)-piperazin-1-yl]-6,7-dihydro-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine are dissolved in 3 ml of pyridine at ambient temperature, and 0.009 g (0.0540 mmol) potassium iodide are added. Then 0.089 ml (1.34 mmol) chlorosulphonic acid are added dropwise while cooling with ice. After the addition the reaction mixture is solid and 3 ml of tetrahydrofuran are added. Then it is combined with water and dichloromethane, the precipitate formed is suction filtered and dried. 0.049 g of the product (33%) are obtained as a powder.

^{1}H NMR (400 MHz, DMSO+DCl): 9.01-8.92 (1H, m); 8.21-8.10 (1H, m); 7.90-7.80 (1H, m); 7.79-7.70 (1H, m); 7.40-7.31 (1H, m); 7.02-6.92 (1H, m); 4.49-4.27 (4H, m); 3.82-3.64 (4H, m); 3.57-3.30 (6H, m); 1.65-1.50 (2H, m); 0.96-0.77 (3H, m).

Scheme 14:



SYNTHESIS OF 2-[4-(4-CHLORO-PHENYL)-PIPERAZIN-1-YL]-4-PROPYLAMINO-6,7-DIHYDRO-THIENO[3,2-D]PYRIMIDIN-7-OL TRIFLATE ((EXAMPLE 378) (X according to Scheme 14)

thieno[3,2-d]pyrimidine-2,4-diol (II): 10.0 g (64.0 mmol) methylester 3-aminothiophene-2-carboxylate (I) and 19.0 g (31.60 mmol) urea are mixed and melted for 2 hours at 200°C. After cooling the reaction mixture is dissolved in 1 molar sodium hydroxide solution and decolorised with activated charcoal. It is filtered, the filtrate is cooled and acidified with 4-molar hydrochloric acid. The precipitate formed is suction filtered and dried. 8.03 g of product II (75%) are obtained as a powder.

2,4-dichloro-thieno[3,2-d]pyrimidine (III): 7.97 g (47.0 mmol) thieno[3,2-d]pyrimidine-2,4-diol (II) are placed in 50 ml (54.5 mmol) phosphorus oxychloride, then refluxed for 14 hours, with stirring. The mixture is then concentrated by evaporation, the residue is combined with ice water. The precipitate formed is suction filtered and dried. 9.00 g of product III (93%) are obtained as a powder.

(2-chloro-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (IV): 3.95 g (19.26 mmol) 2,4-dichloro-thieno[3,2-d]pyrimidine (III), 1.90 ml (23.11 mmol) propylamine and 6.71 ml (38.52 mmol) diisopropylethylamine are stirred for 16 hours in 40 ml of tetrahydrofuran at ambient temperature. Then the reaction mixture is concentrated by evaporation, the residue is combined with water. The precipitate formed is suction filtered and dried. 4.03 g of product IV (92%) are obtained as a powder.

(7-bromo-2-chloro-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (V): 8.34 g (36.63 mmol) (2-chloro-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (IV) are dissolved in 60 ml acetonitrile and 7.89 g (44.32 mmol) N-bromosuccinimide are added. The reaction mixture is stirred for 16 hours at ambient temperature and for 6 hours at 50°C. Then it is concentrated by evaporation and the residue is combined with water. The precipitate formed is suction filtered, washed and dried. 7.25 g of product V (61%) are obtained as a powder.

{7-bromo-2-[4-(4-chloro-phenyl)-piperazin-1-yl]-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine (VII): 2.00 g (6.20 mmol) (7-bromo-2-chloro-thieno[3,2-d]pyrimidin-4-yl)-propyl-amine (V), 4.64 g (23.59 mmol) 1-(4-chloro-phenyl)-piperazine (VI) and 2.13 ml (12.39 mmol) diisopropylethylamine are placed in 15 ml dioxane, and heated to 100°C in the microwave for 0.75 hours. As only 50% reacted, the reaction mixture is heated to 160°C in the microwave for another 1.5 hours. Then the precipitate formed is suction filtered, washed with water and stirred with petroleum ether. After suction filtering again, 3.19 g of product VII (100%) are obtained.

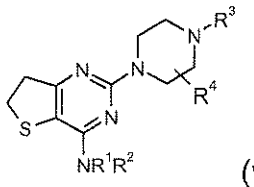
{2-[4-(4-chloro-phenyl)-piperazin-1-yl]-7-methoxy-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine (VIII): 2.00 g (4.28 mmol) {7-bromo-2-[4-(4-chloro-phenyl)-piperazin-1-yl]-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine (VII) are placed in 15 ml of methanol and cooled to some extent. First 0.995 g (18.42 mmol) sodium methoxide, then 0.187 g (2.36 mmol) copper(II)oxide and 0.040 g (0.27 mmol) sodium iodide are added. The reaction mixture is heated to 160°C in the microwave for 0.75 hours. Then it is suction filtered through silica gel and the mother liquor is concentrated by evaporation. The residue is dissolved, and any insoluble matter is removed by suction filtering. Further purification is carried out by preparative HPLC. 0.23 g of product VIII (20%) are obtained.

2-[4-(4-chloro-phenyl)-piperazin-1-yl]-4-propylamino-thieno[3,2-d]pyrimidin-7-ol triflate (IX): 0.430 g (1.03 mmol) {2-[4-(4-chloro-phenyl)-piperazin-1-yl]-7-methoxy-thieno[3,2-d]pyrimidin-4-yl}-propyl-amine (VIII) are dissolved in 4 ml dichloromethane and cooled somewhat. Under a nitrogen atmosphere 1.13 ml (1.13 mmol) boron tribromide solution (1 molar in heptane) are added dropwise. The reaction mixture is stirred for 48 hours at ambient temperature. After the addition of 0.50 ml boron tribromide solution the mixture is stirred for another 24 hours at ambient temperature. Then saturated potassium carbonate solution is added and the mixture is stirred for 0.4 hours. After the addition of dichloromethane the organic phase is separated off through the phase separator and evaporated to dryness. The residue is purified by chromatography (HPLC), corresponding fractions are lyophilised. 0.150 g of product IX (28%) are obtained.

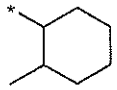
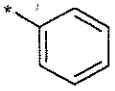
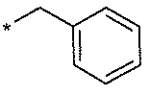
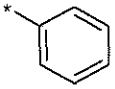
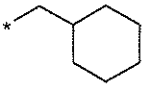
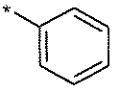
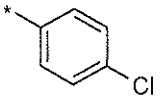
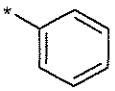
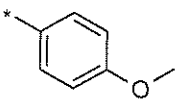
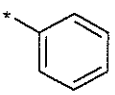
2-[4-(4-chloro-phenyl)-piperazin-1-yl]-4-propylamino-6,7-dihydro-thieno[3,2-d]pyrimidin-7-ol triflate (X): 0.050 g (0.12 mmol) 2-[4-(4-chloro-phenyl)-piperazin-1-yl]-4-propylamino-thieno[3,2-d]pyrimidin-7-ol triflate (IX) are dissolved in 1 ml of methanol and 0.020 g (0.53 mmol) sodium borohydride are added. The reaction mixture is stirred for 16 hours at ambient temperature, then concentrated by evaporation. The residue is purified by chromatography using HPLC through an

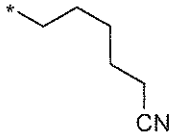
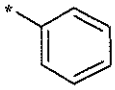
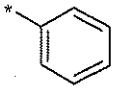
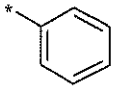
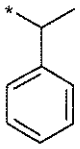
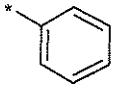
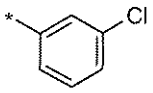
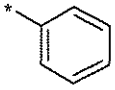
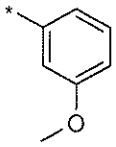
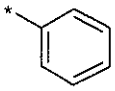
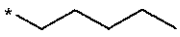
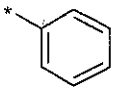
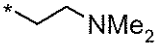
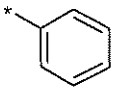
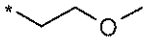
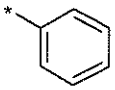
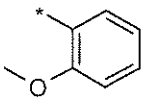
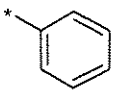
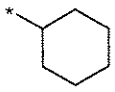
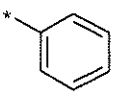
RP column (column: Microsorb, RP-C18). Corresponding fractions are combined and lyophilised. 0.013 g of product X (20%) are obtained as a powder.
^{1}H NMR (400 MHz, DMSO): 7.26 (2H, d); 7.00 (2H, d); 5.15-5.09 (1H, m); 3.86-3.79 (4H, m), 3.63-3.55 (2H, m); 3.42-3.33 (2H, m); 3.28-3.22 (4H, m); 3.18-3.11 (1H, m); 1.63-1.52 (2H, m); 0.88 (3H, t).

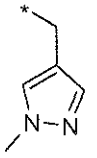
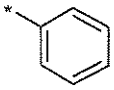
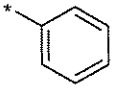
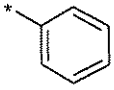
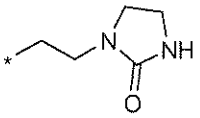
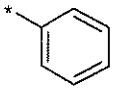
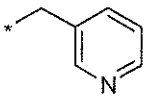
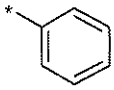
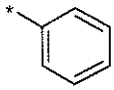
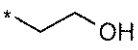
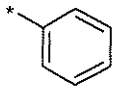
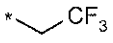
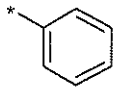
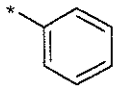
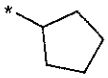
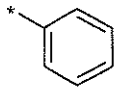
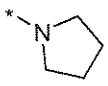
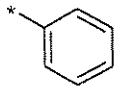
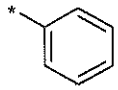
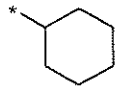
The following Examples may be prepared analogously to the methods of synthesis described above illustrated in Schemes 1 to 14 (as indicated). The compounds are suitable as PDE4-inhibitors and have IC_{50} values of less than or equal to 1 µmol.

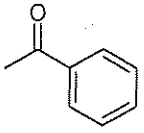
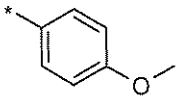
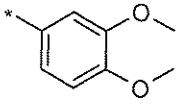
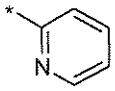
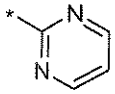
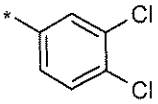
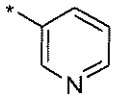
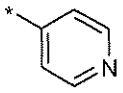
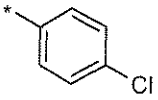
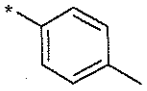
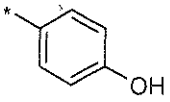
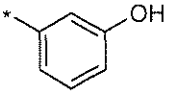


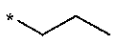
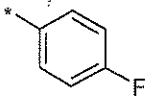
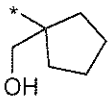
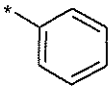
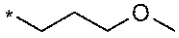
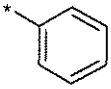
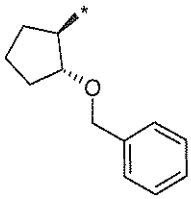
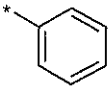
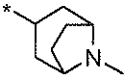
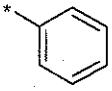
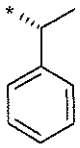
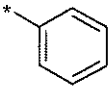
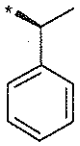
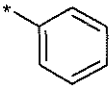
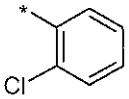
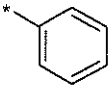
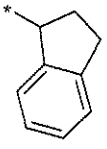
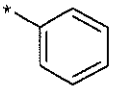
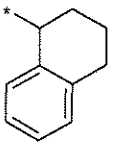
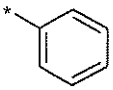
(wherein R^4 = H)

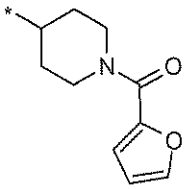
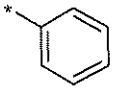
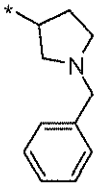
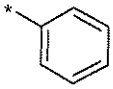
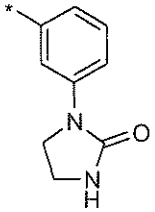
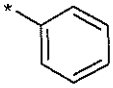
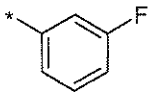
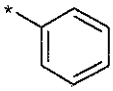
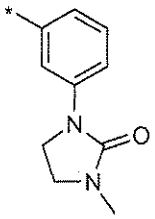
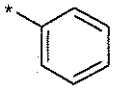
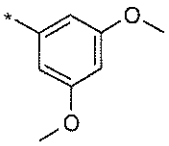
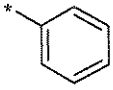
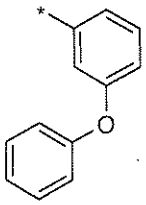
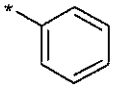
#	R^1	R^2	R^3	Preparation
1.	H			**Scheme 1**
2.	H			**Scheme 1**
3.	H			**Scheme 1**
4.	H			**Scheme 1**
5.	H			**Scheme 1**

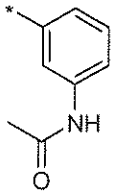
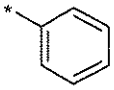
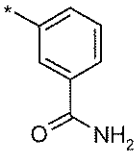
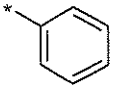
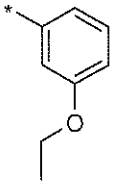
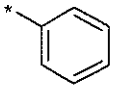
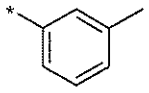
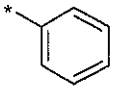
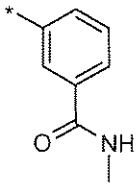
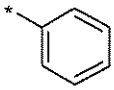
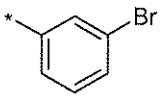
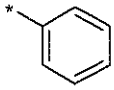
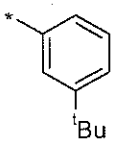
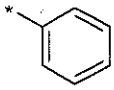
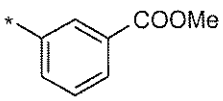
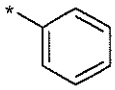
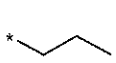
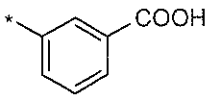
#	R^1	R^2	R^3	Preparation
6.	H			**Scheme 1**
7.	H			Scheme 1
8.	H			Scheme 1
9.	H			Scheme 1
10.	H			Scheme 1
11.	H			Scheme 1
12.	H			Scheme 1
13.	H			Scheme 1
14.	H			Scheme 1
15.	H			Scheme 1
16.	H			Scheme 1

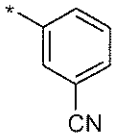
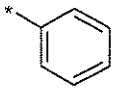
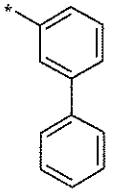
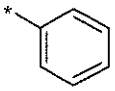
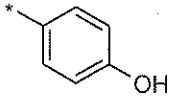
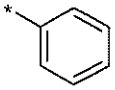
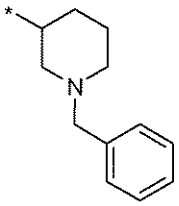
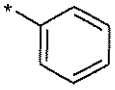
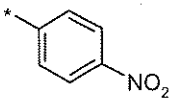
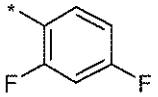
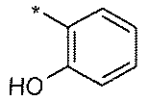
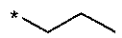
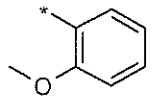
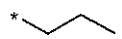
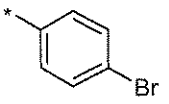
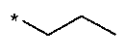
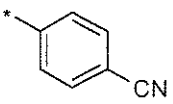
#	R^1	R^2	R^3	Preparation
17.	H			Scheme 1
18.	H			Scheme 1
19.	H			Scheme 1
20.	H			Scheme 1
21.	H			Scheme 1
22.	H			Scheme 1
23.	H			Scheme 1
24.	H			Scheme 1
25.	H			Scheme 1
26.	H			Scheme 1
27.	H			Scheme 1
28.	H			Scheme 1

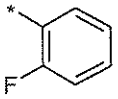
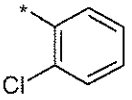
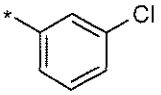
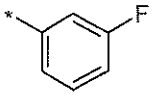
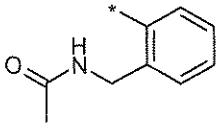
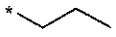
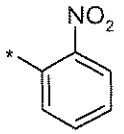
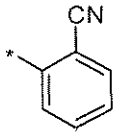
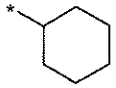
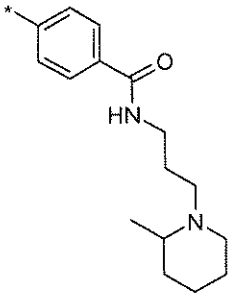
#	R^1	R^2	R^3	Preparation
29.	H			Scheme 1
30.	H			Scheme 1
31.	H			Scheme 1
32.	H			Scheme 1
33.	H			Scheme 1
34.	H			Scheme 1
35.	H			Scheme 1
36.	H			Scheme 1
37.	H			Scheme 1
38.	H			Scheme 1
39.	H			Scheme 1
40.	H			Scheme 1

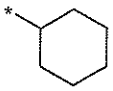
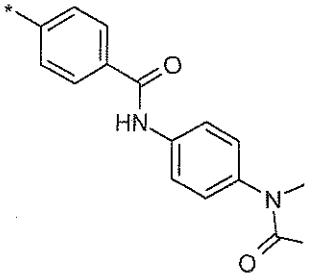
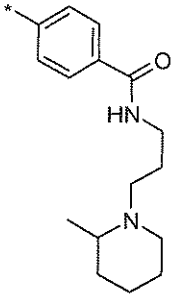
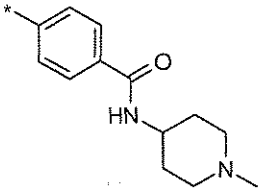
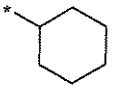
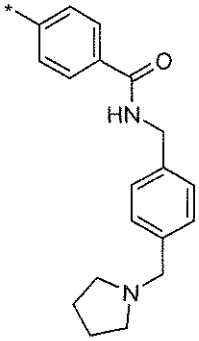
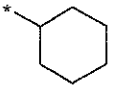
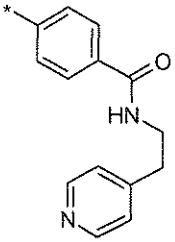
#	R^1	R^2	R^3	Preparation
41.	H			Scheme 1
42.	H			Scheme 1
43.	H			Scheme 1
44.	H			Scheme 1
45.	H			Scheme 1
46.	H			Scheme 1
47.	H			Scheme 1
48.	H			Scheme 1
49.	H			Scheme 1
50.	H			Scheme 1

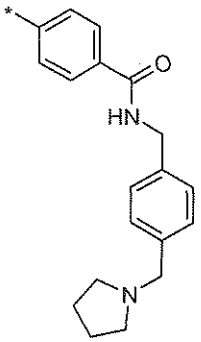
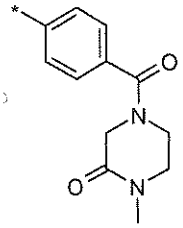
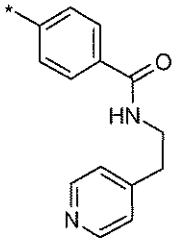
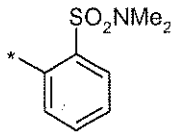
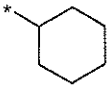
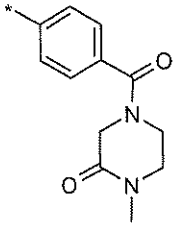
#	R^1	R^2	R^3	Preparation
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52.	H			Scheme 1
53.	H			Scheme 1
54.	H			Scheme 1
55.	H			Scheme 1
56.	H			Scheme 1
57.	H			Scheme 1

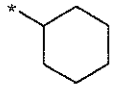
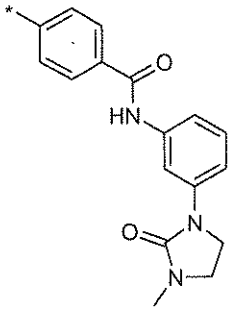
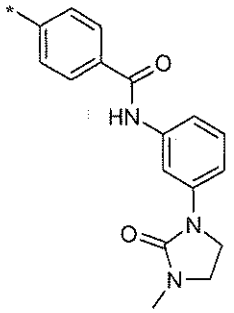
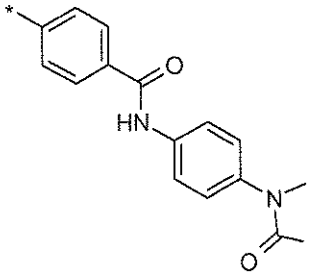
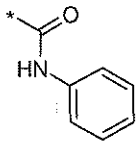
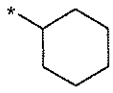
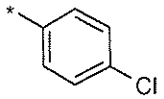
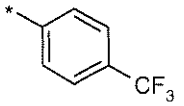
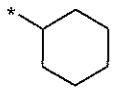
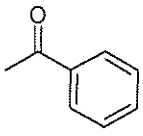
#	R^1	R^2	R^3	Preparation
58.	H			Scheme 1
59.	H			Scheme 1
60.	H			Scheme 1
61.	H			Scheme 1
62.	H			Scheme 1
63.	H			Scheme 1
64.	H			Scheme 1
65.	H			Scheme 1
66.	H			Scheme 1

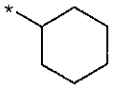
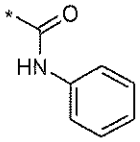
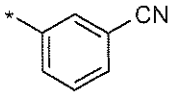
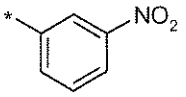
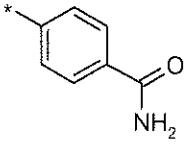
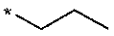
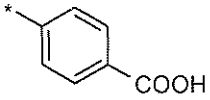
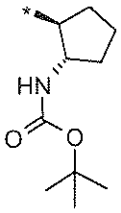
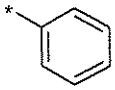
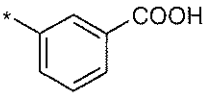
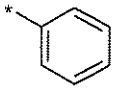
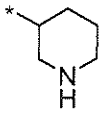
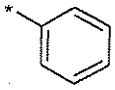
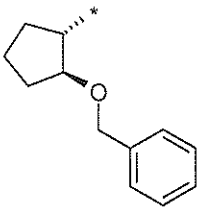
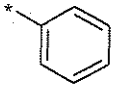
#	R^1	R^2	R^3	Preparation
67.	H			Scheme 1
68.	H			Scheme 1
69.	H			Scheme 1
70.	H			Scheme 1
71.	H			Scheme 1
72.	H			Scheme 1
73.	H			Scheme 1
74.	H			Scheme 1
75.	H			Scheme 1
76.	H			Scheme 1

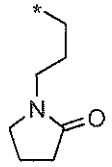
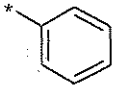
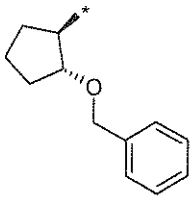
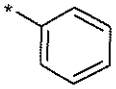
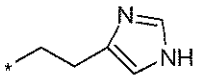
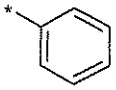
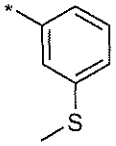
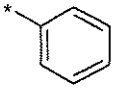
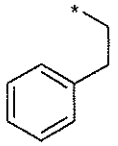
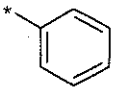
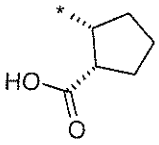
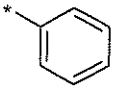
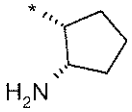
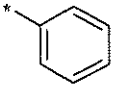
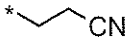
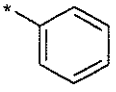
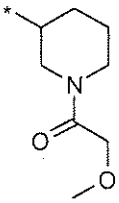
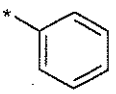
#	R^1	R^2	R^3	Preparation
77.	H			Scheme 1
78.	H			Scheme 1
79.	H			Scheme 1
80.	H			Scheme 1
81.	H			Scheme 1
82.	H			Scheme 1
83.	H			Scheme 1
84.	H			Scheme 2

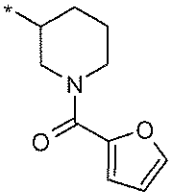
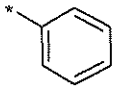
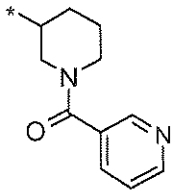
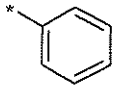
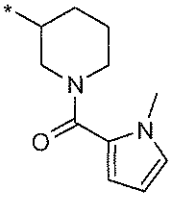
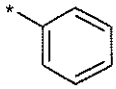
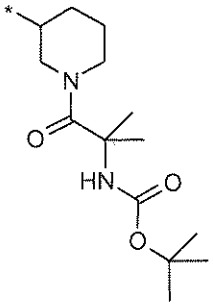
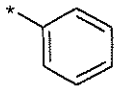
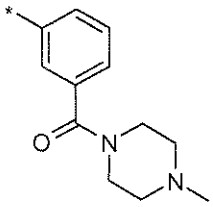
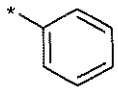
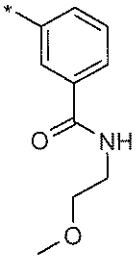
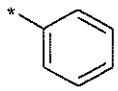
#	R^1	R^2	R^3	Preparation
85.	H			Scheme 2
86.	H			Scheme 2
87.	H			Scheme 2
88.	H			Scheme 2
89.	H			Scheme 2

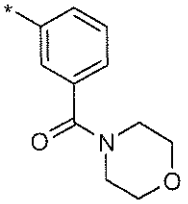
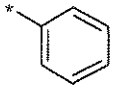
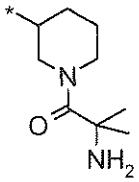
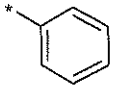
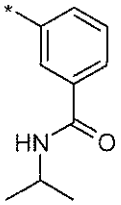
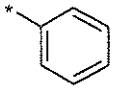
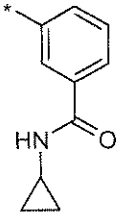
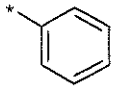
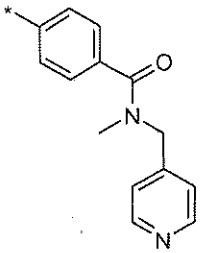
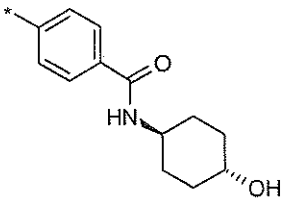
#	R^1	R^2	R^3	Preparation
90.	H			Scheme 2
91.	H			Scheme 2
92.	H			Scheme 2
93.	H			Scheme 1
94.	H			Scheme 2

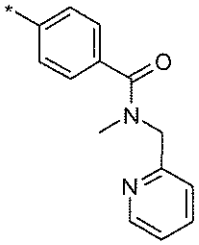
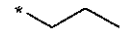
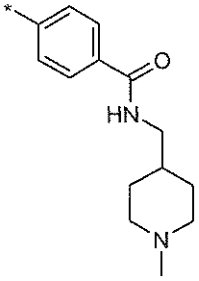
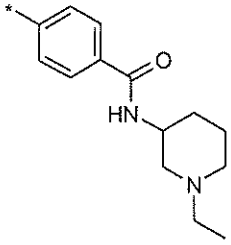
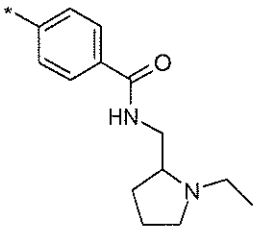
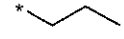
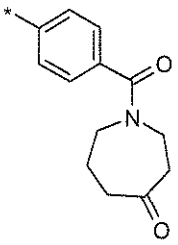
#	R^1	R^2	R^3	Preparation
95.	H			Scheme 2
96.	H			Scheme 2
97.	H			Scheme 2
98.	H			Scheme 5
99.	H			Scheme 1
100.	H			Scheme 1
101.	H			Scheme 5

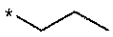
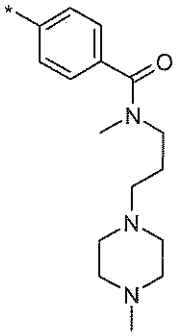
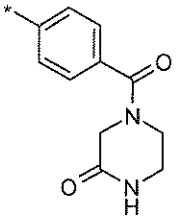
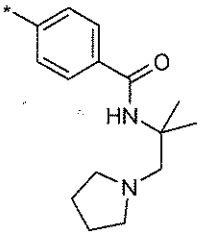
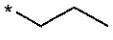
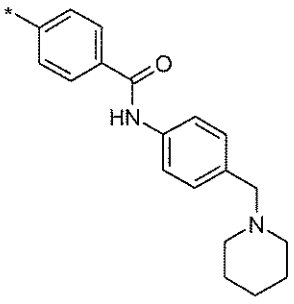
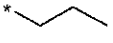
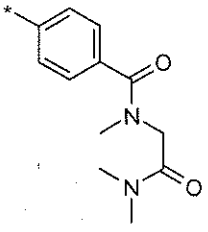
#	R^1	R^2	R^3	Preparation
102.	H			Scheme 5
103.	H			Scheme 1
104.	H			Scheme 1
105.	H			Scheme 1
106.	H			Scheme 1
107.	H			Scheme 7
108.	H			Scheme 1
109.	H			Scheme 11
110.	H			Scheme 1

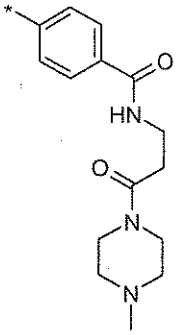
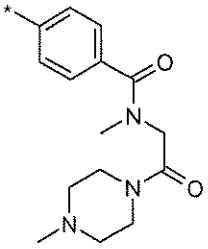
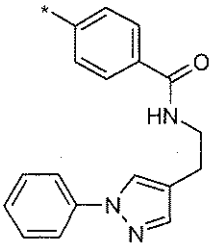
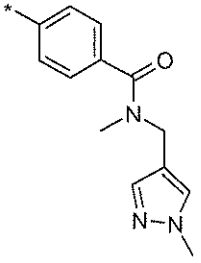
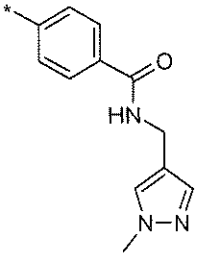
#	R^1	R^2	R^3	Preparation
111.	H			Scheme 1
112.	H			Scheme 1
113.	H			Scheme 1
114.	H			Scheme 1
115.	H			Scheme 1
116.	H			Scheme 1
117.	H			Scheme 1
118.	H			Scheme 1
119.	H			Scheme 10

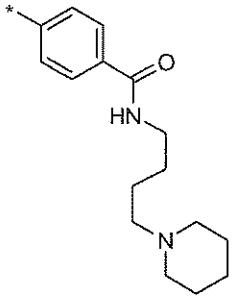
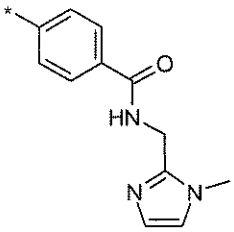
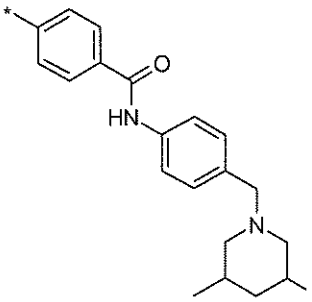
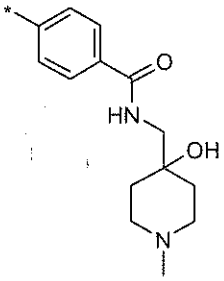
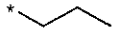
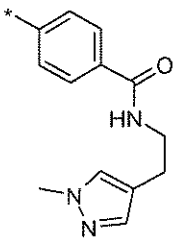
#	R^1	R^2	R^3	Preparation
120.	H			Scheme 10
121.	H			Scheme 10
122.	H			Scheme 10
123.	H			Scheme 10
124.	H			Scheme 12
125.	H			Scheme 12

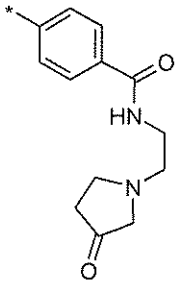
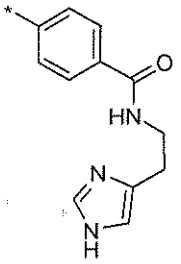
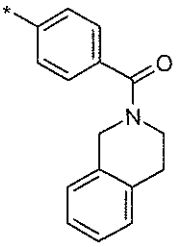
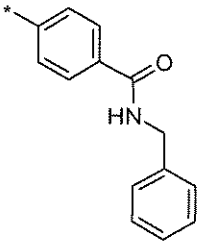
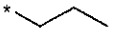
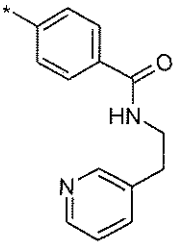
#	R^1	R^2	R^3	Preparation
126.	H			Scheme 12
127.	H			Scheme 10
128.	H			Scheme 12
129.	H			Scheme 12
130.	H			Scheme 2
131.	H			Scheme 2

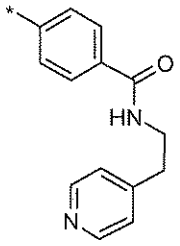
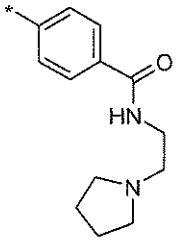
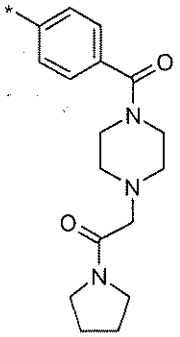
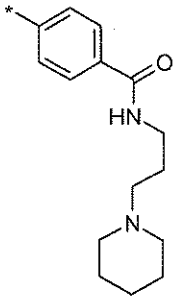
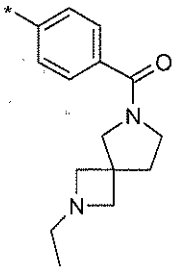
#	R^1	R^2	R^3	Preparation
132.	H			Scheme 2
133.	H			Scheme 2
134.	H			Scheme 2
135.	H			Scheme 2
136.	H			Scheme 2

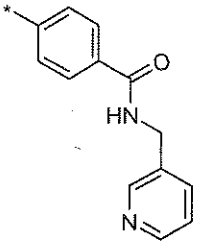
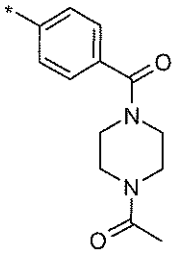
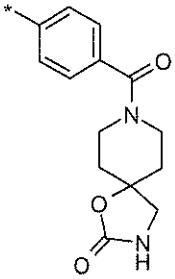
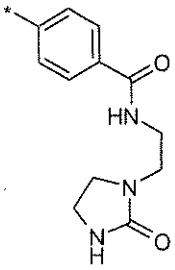
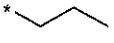
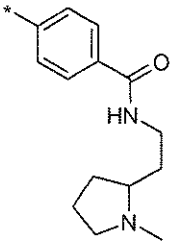
#	R^1	R^2	R^3	Preparation
137.	H			Scheme 2
138.	H			Scheme 2
139.	H			Scheme 2
140.	H			Scheme 2
141.	H			Scheme 2

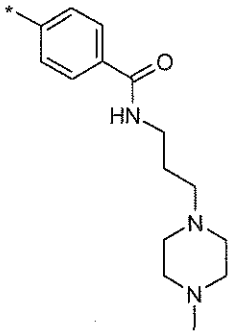
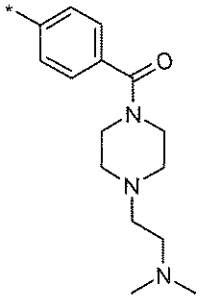
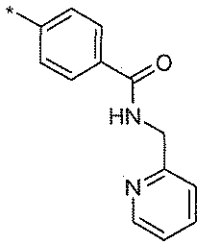
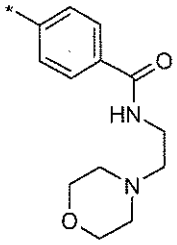
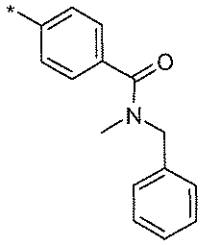
#	R^1	R^2	R^3	Preparation
142.	H			Scheme 2
143.	H			Scheme 2
144.	H			Scheme 2
145.	H			Scheme 2
146.	H			Scheme 2

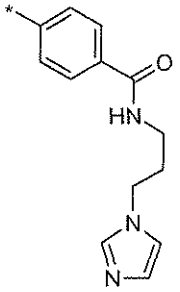
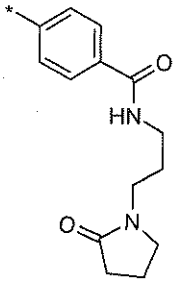
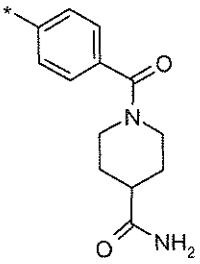
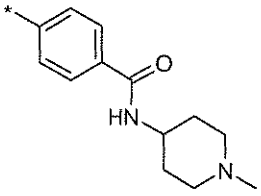
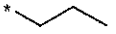
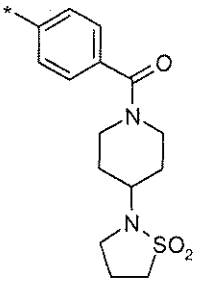
#	R^1	R^2	R^3	Preparation
147.	H			Scheme 2
148.	H			Scheme 2
149.	H			Scheme 2
150.	H			Scheme 2
151.	H			Scheme 2

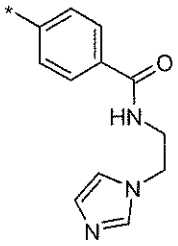
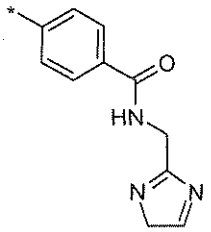
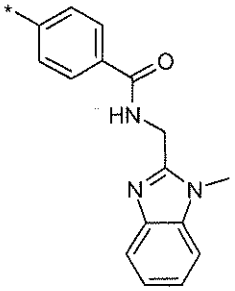
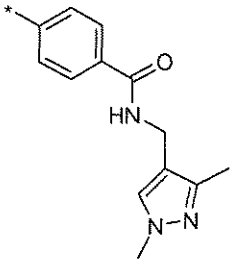
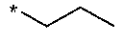
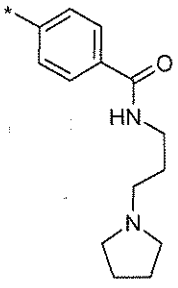
#	R^1	R^2	R^3	Preparation
152.	H			Scheme 2
153.	H			Scheme 2
154.	H			Scheme 2
155.	H			Scheme 2
156.	H			Scheme 2

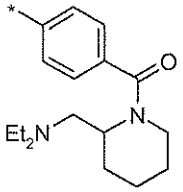
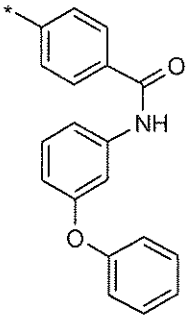
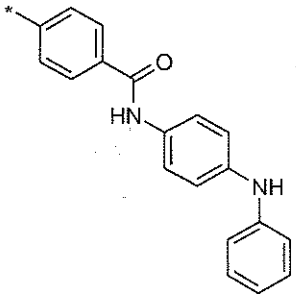
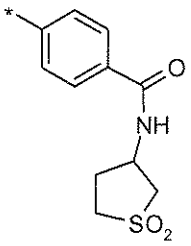
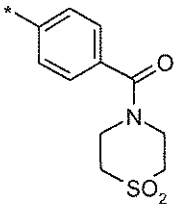
#	R^1	R^2	R^3	Preparation
157.	H			Scheme 2
158.	H			Scheme 2
159.	H			Scheme 2
160.	H			Scheme 2
161.	H			Scheme 2

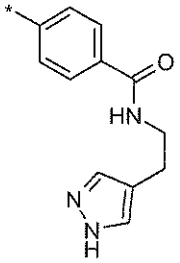
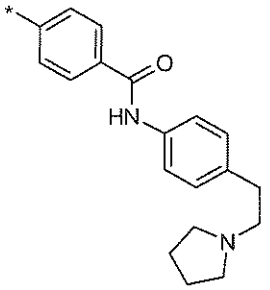
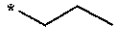
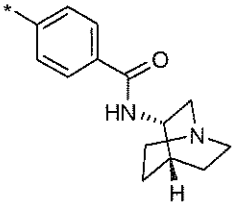
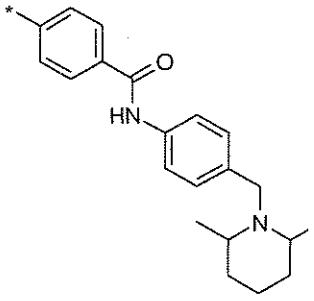
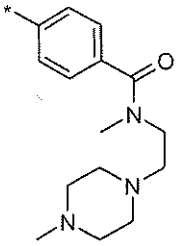
#	R^1	R^2	R^3	Preparation
162.	H			Scheme 2
163.	H			Scheme 2
164.	H			Scheme 2
165.	H			Scheme 2
166.	H			Scheme 2

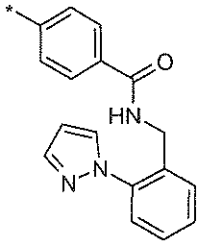
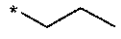
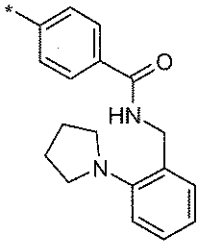
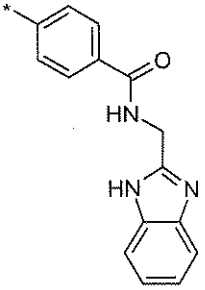
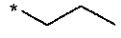
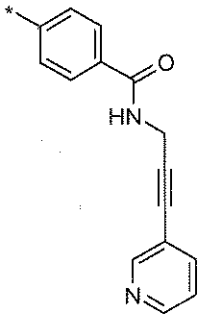
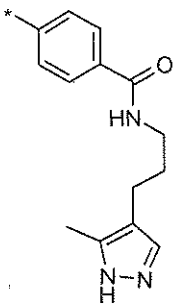
#	R^1	R^2	R^3	Preparation
167.	H			Scheme 2
168.	H			Scheme 2
169.	H			Scheme 2
170.	H			Scheme 2
171.	H			Scheme 2

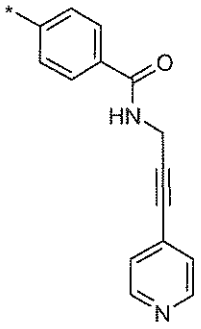
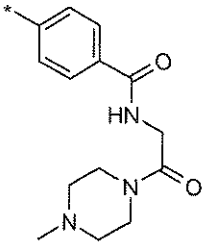
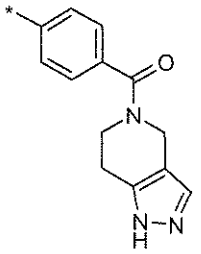
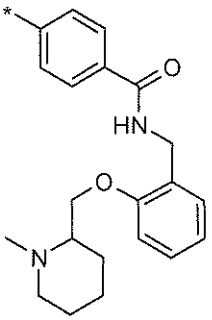
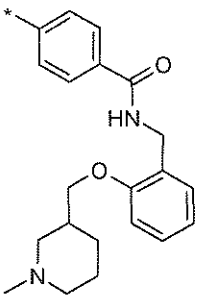
#	R^1	R^2	R^3	Preparation
172.	H			Scheme 2
173.	H			Scheme 2
174.	H			Scheme 2
175.	H			Scheme 2
176.	H			Scheme 2

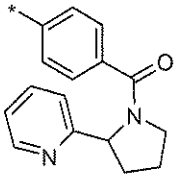
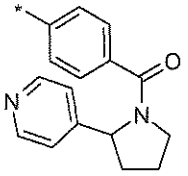
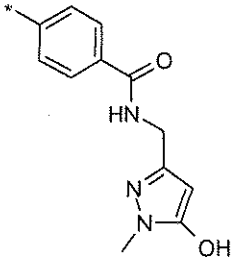
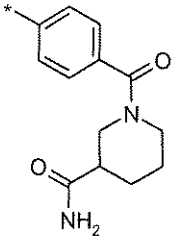
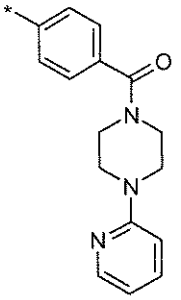
#	R^1	R^2	R^3	Preparation
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178.	H			Scheme 2
179.	H			Scheme 2
180.	H			Scheme 2
181.	H			Scheme 2

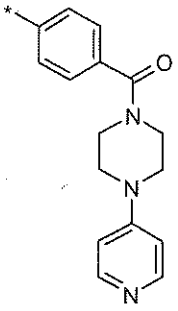
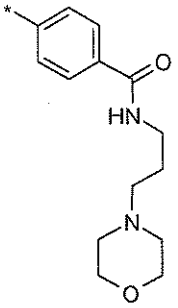
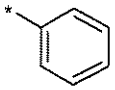
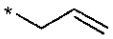
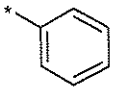
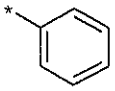
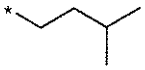
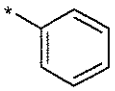
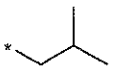
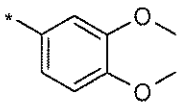
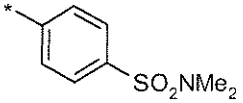
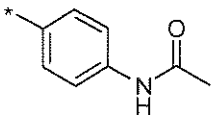
#	R^1	R^2	R^3	Preparation
182.	H			Scheme 2
183.	H			Scheme 2
184.	H			Scheme 2
185.	H			Scheme 2
186.	H			Scheme 2

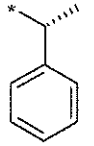
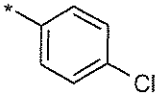
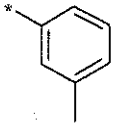
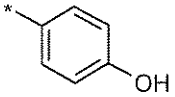
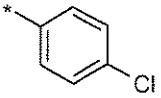
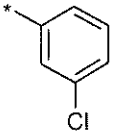
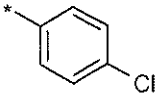
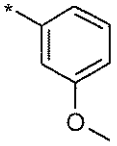
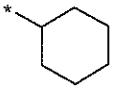
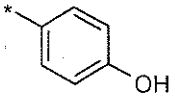
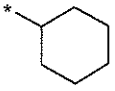
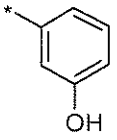
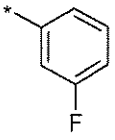
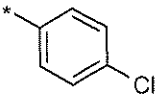
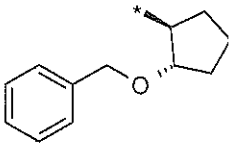
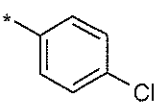
#	R^1	R^2	R^3	Preparation
187.	H			Scheme 2
188.	H			Scheme 2
189.	H			Scheme 2
190.	H			Scheme 2
191.	H			Scheme 2

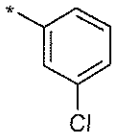
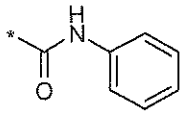
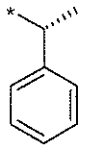
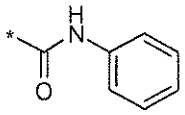
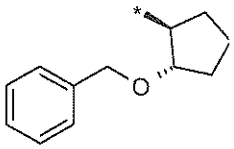
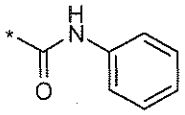
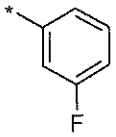
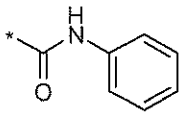
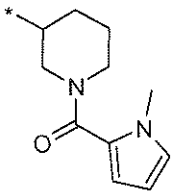
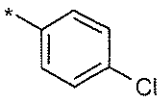
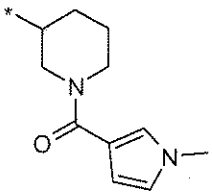
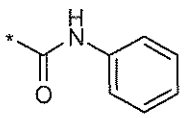
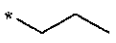
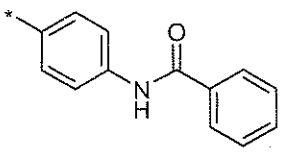
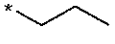
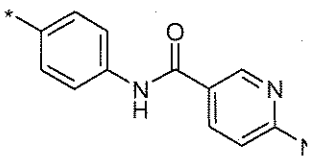
#	R^1	R^2	R^3	Preparation
192.	H			Scheme 2
193.	H			Scheme 2
194.	H			Scheme 2
195.	H			Scheme 2
196.	H			Scheme 2

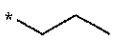
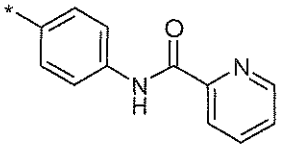
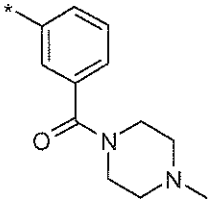
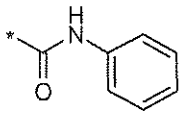
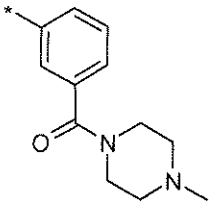
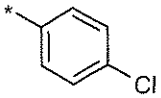
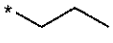
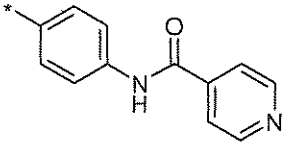
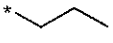
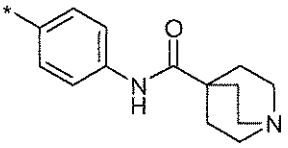
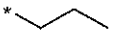
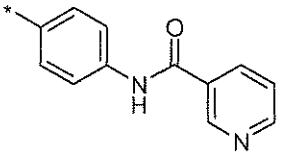
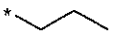
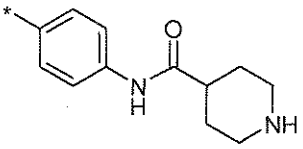
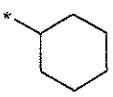
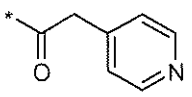
#	R^1	R^2	R^3	Preparation
197.	H			Scheme 2
198.	H			Scheme 2
199.	H			Scheme 2
200.	H			Scheme 2
201.	H			Scheme 2

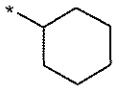
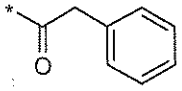
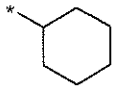
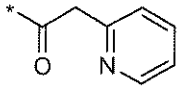
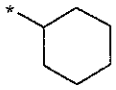
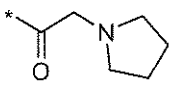
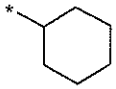
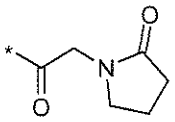
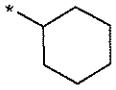
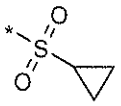
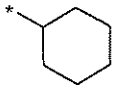
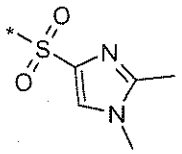
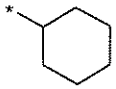
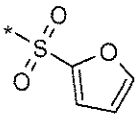
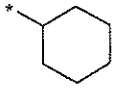
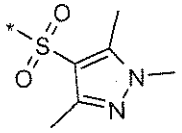
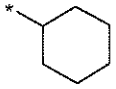
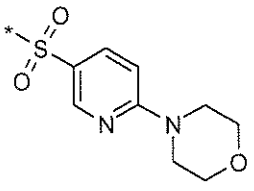
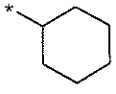
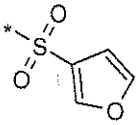
#	R^1	R^2	R^3	Preparation
202.	H			Scheme 2
203.	H			Scheme 2
204.	H			Scheme 2
205.	H			Scheme 2
206.	H			Scheme 2

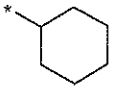
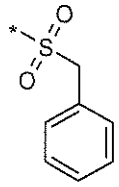
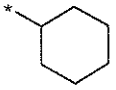
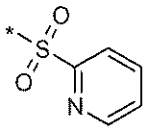
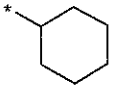
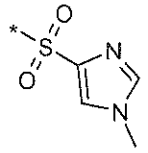
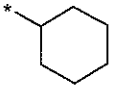
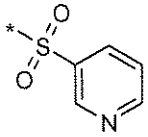
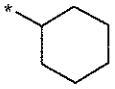
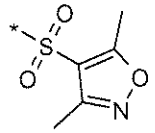
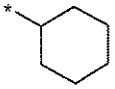
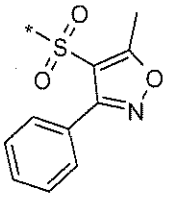
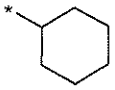
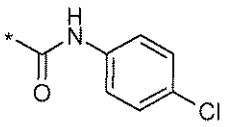
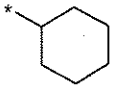
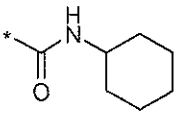
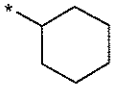
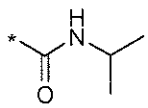
#	R^1	R^2	R^3	Preparation
207.	H			Scheme 2
208.	H			Scheme 2
209.	H			Scheme 1
210.	H			Scheme 1
211.	H			Scheme 1
212.	H			Scheme 1
213.	H			Scheme 1
214.	H			Scheme 1
215.	H			Scheme 4

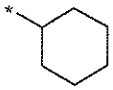
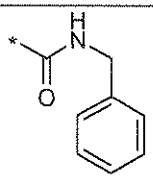
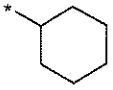
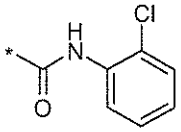
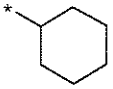
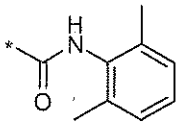
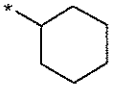
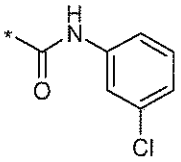
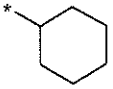
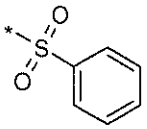
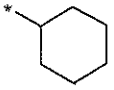
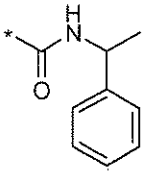
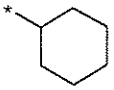
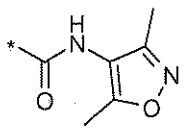
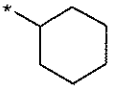
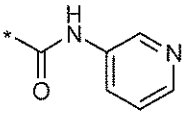
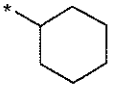
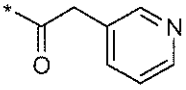
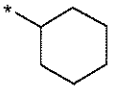
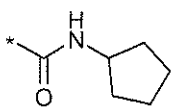
#	R^1	R^2	R^3	Preparation
216.	H			Scheme 1
217.	H			Scheme 1
218.	H	H		Scheme 1
219.	H	H		Scheme 1
220.	H			Scheme 1
221.	H			Scheme 1
222.	H			Scheme 1
223.	H			Scheme 1
224.	H			Scheme 1
225.	H			Scheme 1

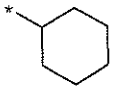
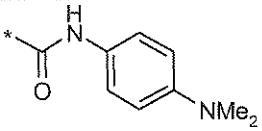
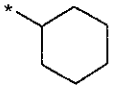
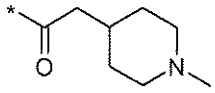
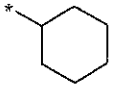
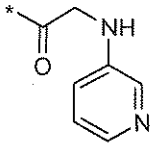
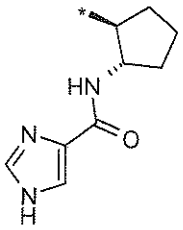
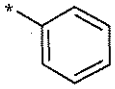
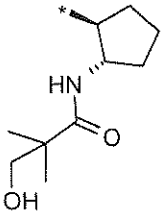
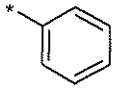
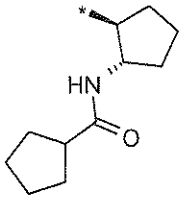
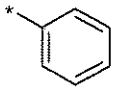
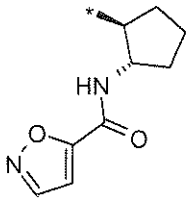
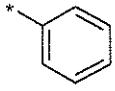
#	R^1	R^2	R^3	Preparation
226.	H			Scheme 5
227.	H			Scheme 5
228.	H			Scheme 5
229.	H			Scheme 5
230.	H			Scheme 10
231.	H			Scheme 5
232.	H			Scheme 5
233.	H			Scheme 5

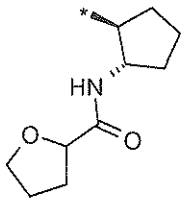
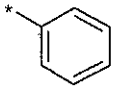
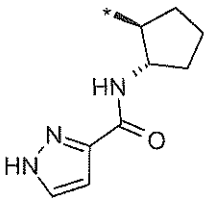
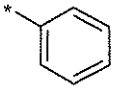
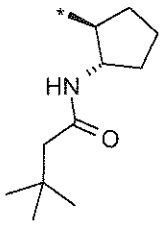
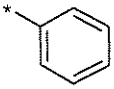
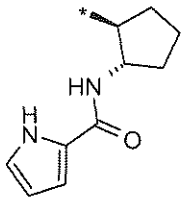
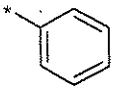
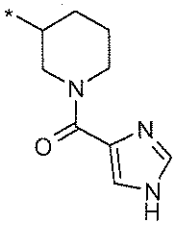
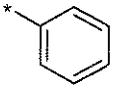
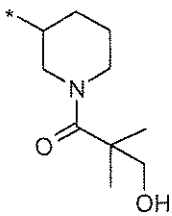
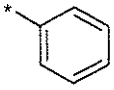
#	R^1	R^2	R^3	Preparation
234.	H			Scheme 5
235.	H			Scheme 5
236.	H			Scheme 12
237.	H			Scheme 4
238.	H			Scheme 4
239.	H			Scheme 4
240.	H			Scheme 4
241.	H			Scheme 5

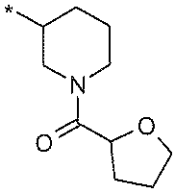
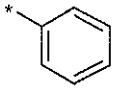
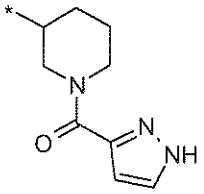
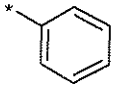
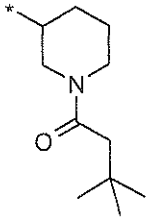
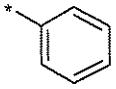
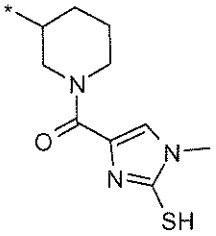
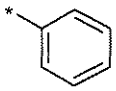
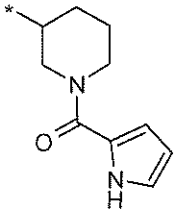
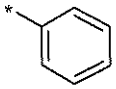
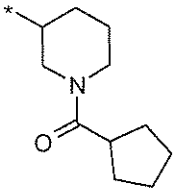
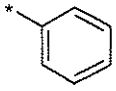
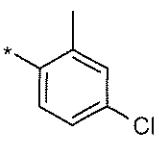
#	R^1	R^2	R^3	Preparation
242.	H			Scheme 5
243.	H			Scheme 5
244.	H			Scheme 5
245.	H			Scheme 5
246.	H			Scheme 5
247.	H			Scheme 5
248.	H			Scheme 5
249.	H			Scheme 5
250.	H			Scheme 5
251.	H			Scheme 5

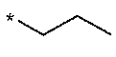
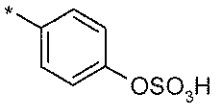
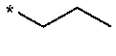
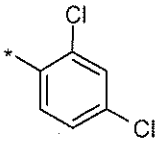
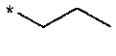
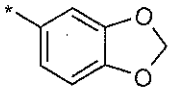
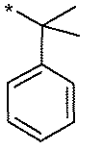
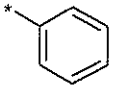
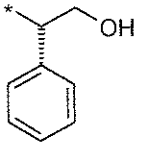
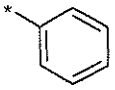
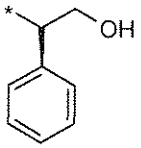
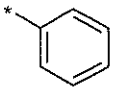
#	R^1	R^2	R^3	Preparation
252.	H			Scheme 5
253.	H			Scheme 5
254.	H			Scheme 5
255.	H			Scheme 5
256.	H			Scheme 5
257.	H			Scheme 5
258.	H			Scheme 5
259.	H			Scheme 5
260.	H			Scheme 5

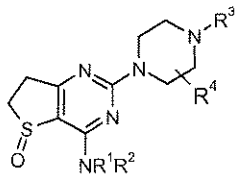
#	R^1	R^2	R^3	Preparation
261.	H			Scheme 5
262.	H			Scheme 5
263.	H			Scheme 5
264.	H			Scheme 5
265.	H			Scheme 5
266.	H			Scheme 5
267.	H			Scheme 5
268.	H			Scheme 5
269.	H			Scheme 5
270.	H			Scheme 5

#	R^1	R^2	R^3	Preparation
271.	H			Scheme 5
272.	H			Scheme 5
273.	H			Scheme 5
274.	H			Scheme 7
275.	H			Scheme 7
276.	H			Scheme 7
277.	H			Scheme 7

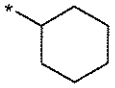
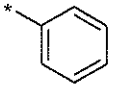
#	R^1	R^2	R^3	Preparation
278.	H			Scheme 7
279.	H			Scheme 7
280.	H			Scheme 7
281.	H			Scheme 7
282.	H			Scheme 10
283.	H			Scheme 10

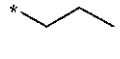
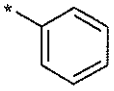
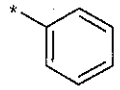
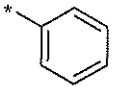
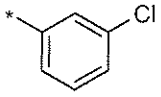
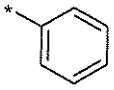
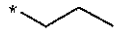
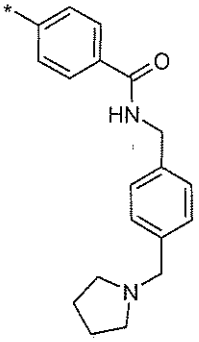
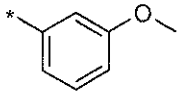
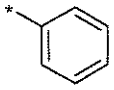
#	R^1	R^2	R^3	Preparation
284.	H			Scheme 10
285.	H			Scheme 10
286.	H			Scheme 10
287.	H			Scheme 10
288.	H			Scheme 10
289.	H			Scheme 10
290.	H			Scheme 1

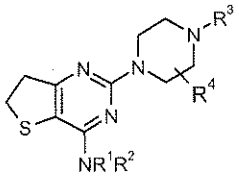
#	R^1	R^2	R^3	Preparation
291.	H			Scheme 1
292.	H			Scheme 1
293.	H			Scheme 1
294.	H			Scheme 1
295.	H			Scheme 1
296.	H			Scheme 1



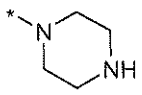
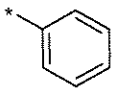
(wherein R^4 = H)

#	R^1	R^2	R^3	Preparation
297	H			Scheme 8

298	H			Scheme 8
299	H			Scheme 8
300	H			Scheme 8
301	H			Scheme 8
302	H			Scheme 8

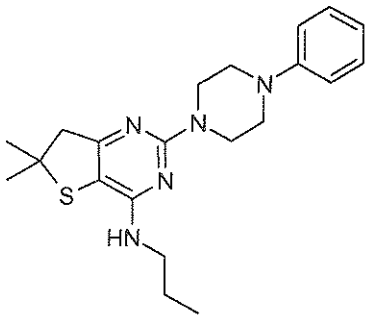
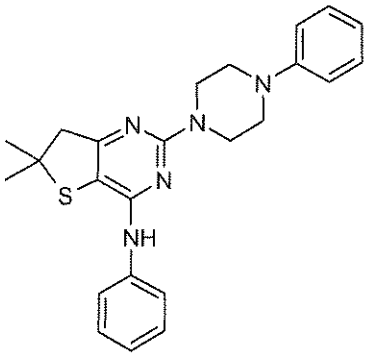
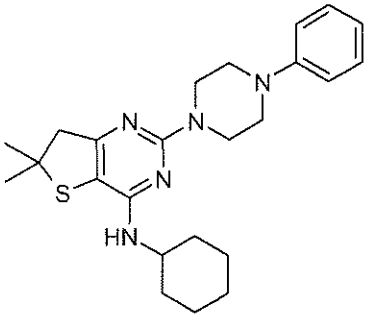
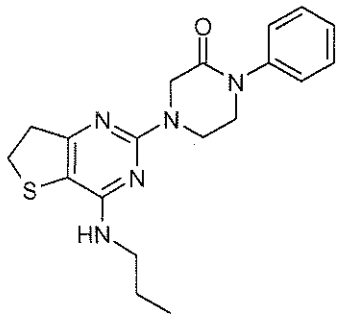


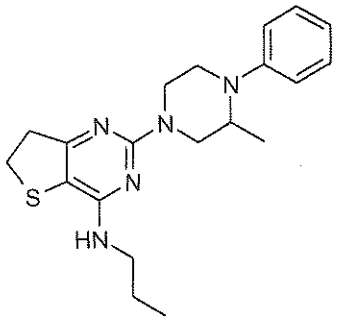
(wherein R^4 = H)

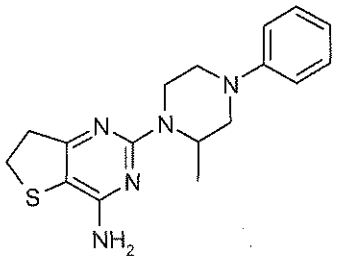
#	NR^1R^2	R^3	Preparation
303.			**Scheme 1**

Further Examples include:

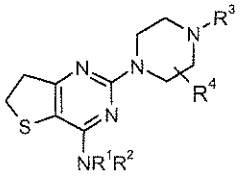
#	Structure	Preparation

304.		Scheme 1
305.		
306.		Scheme 1
307.		Scheme 1

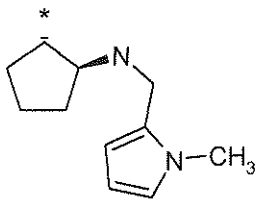
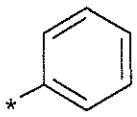
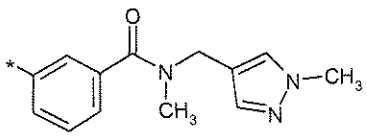
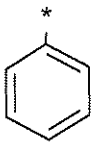
308.  Scheme 1

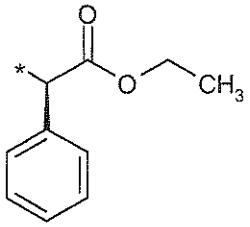
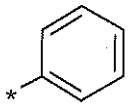
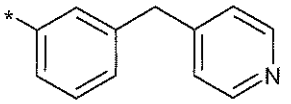
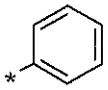
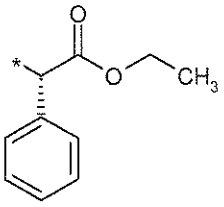
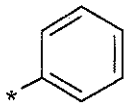
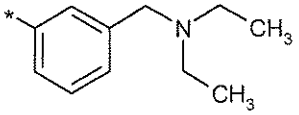
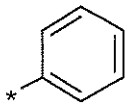
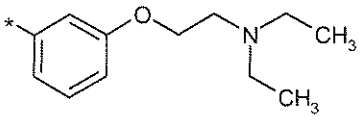
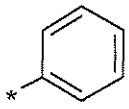
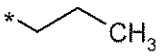
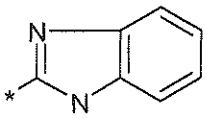
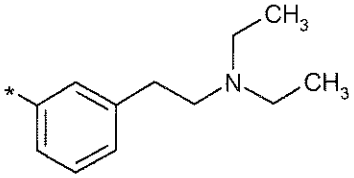
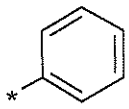
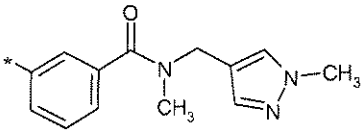
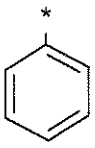
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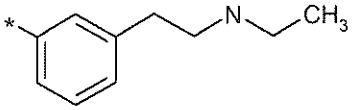
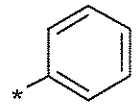
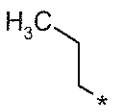
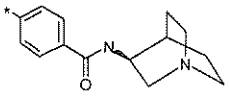
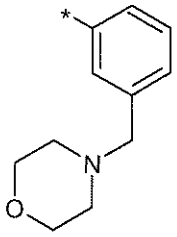
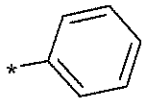
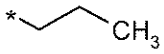
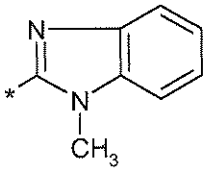
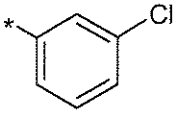
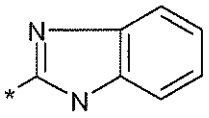
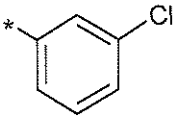
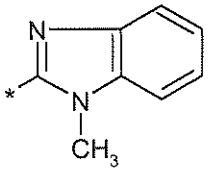
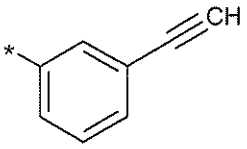
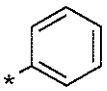
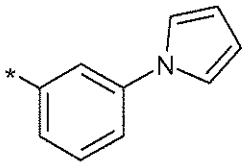
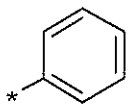
Examples A1

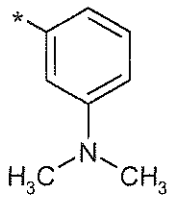
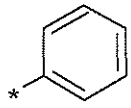
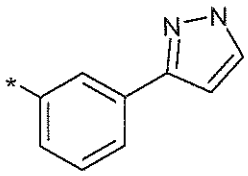
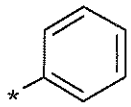
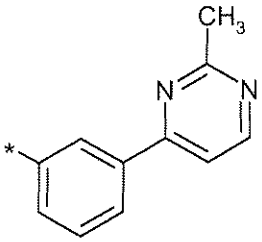
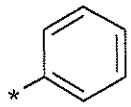
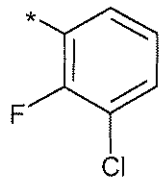
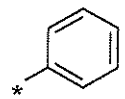
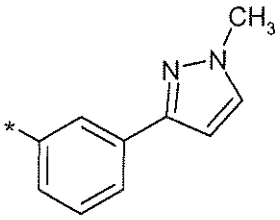
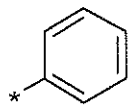
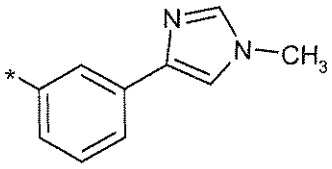
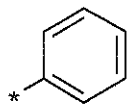
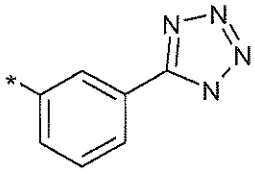
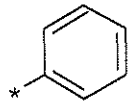
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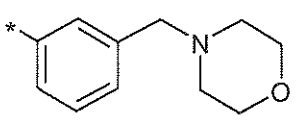
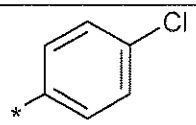
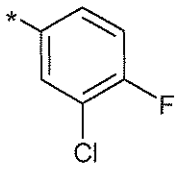
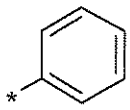
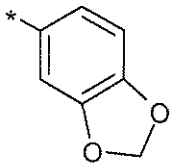
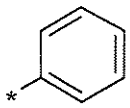
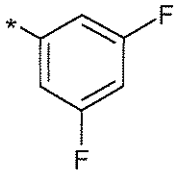
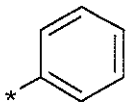
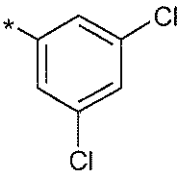
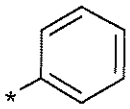
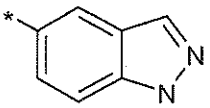
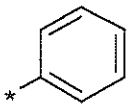
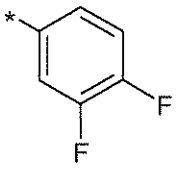
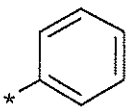
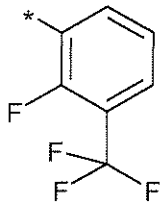
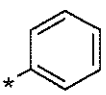
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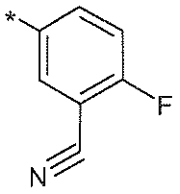
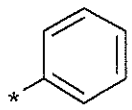
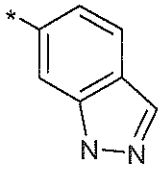
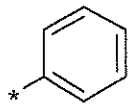
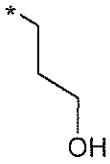
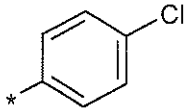
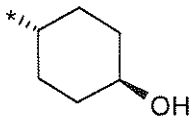
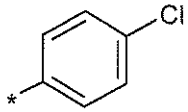
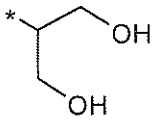
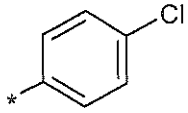
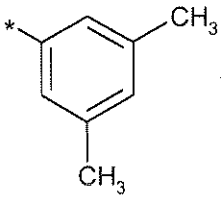
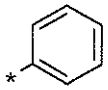
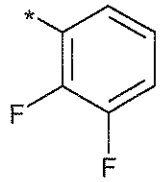
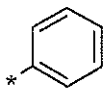
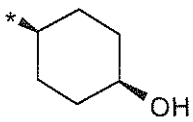
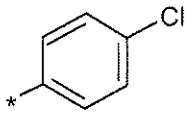
#	R^1	R^2	R^3	Preparation
310.	H	 chiral		Scheme 7
311.	H			Scheme 12

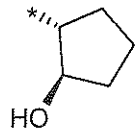
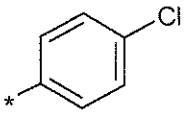
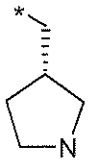
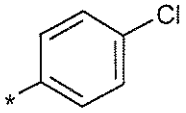
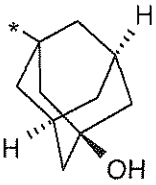
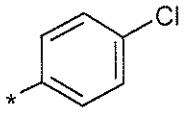
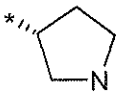
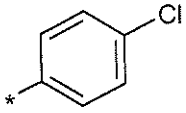
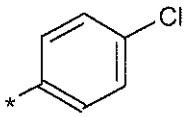
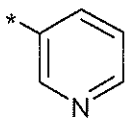
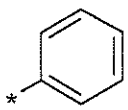
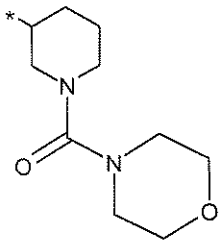
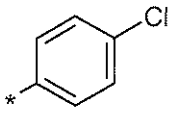
#	R^1	R^2	R^3	Preparation
312.	H	 chiral		Scheme 1
313.	H			Scheme 1
314.	H	 chiral		Scheme 1
315.	H			Scheme 1
316.	H			Scheme 1
317.	H			Scheme 1
318.	H			Scheme 1
319.	H			Scheme 12

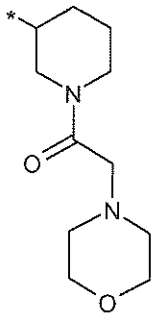
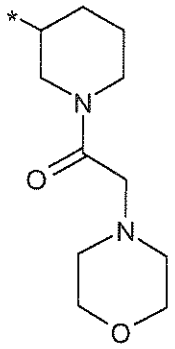
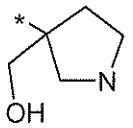
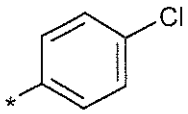
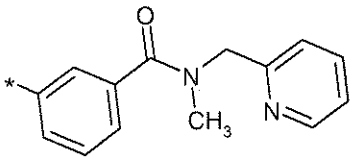
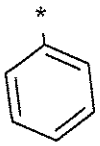
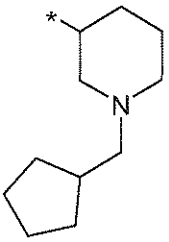
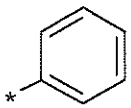
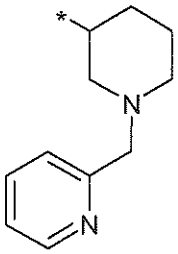
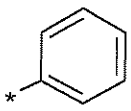
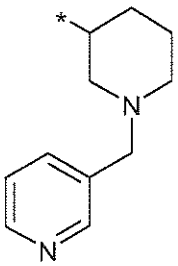
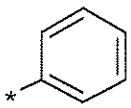
#	R^1	R^2	R^3	Preparation
320.	H			Scheme 1
321.	H		 chiral	Scheme 2
322.	H			Scheme 1
323.	H			Scheme 1
324.	H			Scheme 1
325.	H			Scheme 1
326.	H			Scheme 1
327.	H			Scheme 1

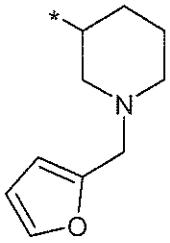
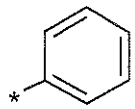
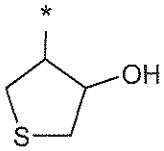
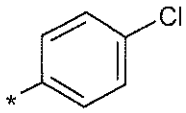
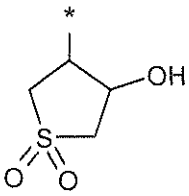
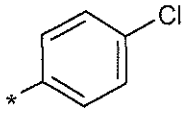
#	R^1	R^2	R^3	Preparation
328.	H			Scheme 1
329.	H			Scheme 1
330.	H			Scheme 1
331.	H			Scheme 1
332.	H			Scheme 1
333.	H			Scheme 1
334.	H			Scheme 1

#	R^1	R^2	R^3	Preparation
335.	H			Scheme 1
336.	H			Scheme 1
337.	H			Scheme 1
338.	H			Scheme 1
339.	H			Scheme 1
340.	H			Scheme 1
341.	H			Scheme 1
342.	H			Scheme 1

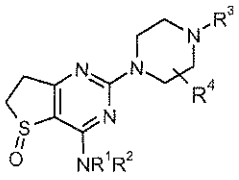
#	R^1	R^2	R^3	Preparation
343.	H			Scheme 1
344.	H			Scheme 1
345.	H			Scheme 1
346.	H			Scheme 1
347.	H			Scheme 1
348.	H			Scheme 1
349.	H			Scheme 1
350.	H			Scheme 1

#	R^1	R^2	R^3	Preparation
351.	H	 chiral		Scheme 1
352.	H	 chiral		Scheme 1
353.	H			Scheme 1
354.	H	 chiral		Scheme 1
355.	H	 chiral		Scheme 1
356.	H			Scheme 1
357.	H			Scheme 11

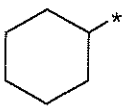
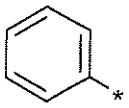
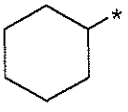
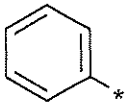
#	R^1	R^2	R^3	Preparation
358.	H			Scheme 11
359.	H			Scheme 1
360.	H			Scheme 12
361.	H			Scheme 11
362.	H			Scheme 11
363.	H			Scheme 11

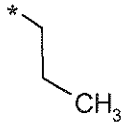
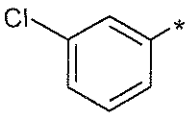
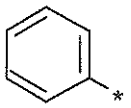
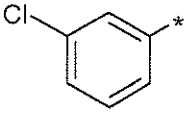
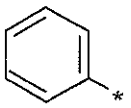
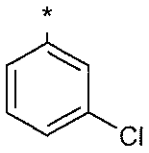
#	R^1	R^2	R^3	Preparation
364.	H			Scheme 11
365.	H			Scheme 1
366.	H			Scheme 1

Example B1

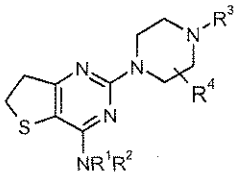


, wherein R^4 = H

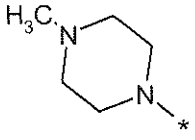
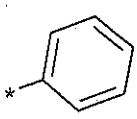
#	R^1	R^2	R^3	Preparation
367.	H			Scheme 1
368.	H			Scheme 1 Enantiomer 2 of racemate 297

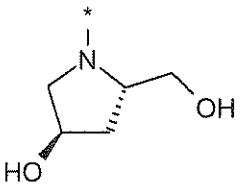
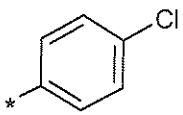
#	R^1	R^2	R^3	Preparation
369.	H			Scheme 1
370.	H			Scheme 1 Enantiomer 1 of racemate 300
371.	H			Scheme 1 Enantiomer 2 of racemate 300
372.	H			Scheme 1

Example C1



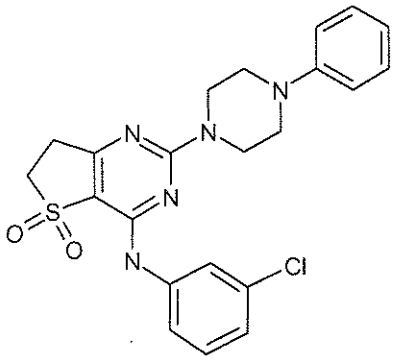
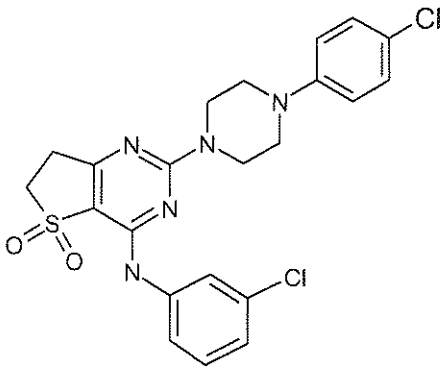
, wherein R^4 = H,

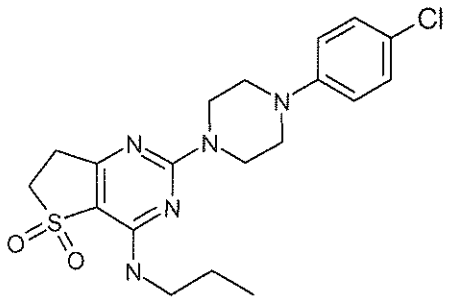
#	NR^1R^2	R^3	Preparation
373.			Scheme 1

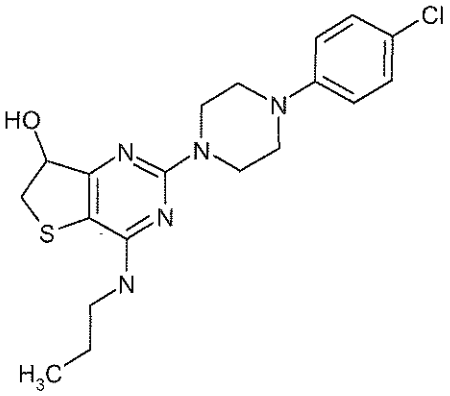
#	NR^1R^2	R^3	Preparation
374.	 chiral		Scheme 1

Further Examples include:

Examples D1:

#	Structure	Preparation
375.		Scheme 9
376.		Scheme 9

377.  Scheme 9

378.  Scheme 14

INDICATIONS

As has been found, the compounds of formula **1** are characterised by their wide range of applications in the therapeutic field. Particular mention should be made of those applications for which the compounds according to the invention of formula **1** are preferably suited on account of their pharmaceutical efficacy as PDE4 inhibitors. Examples include respiratory or gastrointestinal diseases or complaints, inflammatory diseases of the joints, skin or eyes, cancers, and also diseases of the peripheral or central nervous system.

Particular mention should be made of the prevention and treatment of diseases of the airways and of the lung which are accompanied by increased mucus production, inflammations and/or obstructive diseases of the airways. Examples include acute, allergic or chronic bronchitis, chronic obstructive bronchitis (COPD), coughing, pulmonary emphysema, allergic or non-allergic rhinitis or sinusitis, chronic rhinitis or sinusitis, asthma, alveolitis, Farmer´s disease, hyperreactive airways, infectious bronchitis or pneumonitis, paediatric asthma, bronchiectases, pulmonary fibrosis, ARDS (acute adult respiratory distress syndrome), bronchial oedema, pulmonary oedema, bronchitis, pneumonia or interstitial pneumonia triggered by various causes, such as aspiration, inhalation of toxic gases, or bronchitis, pneumonia or interstitial pneumonia as a result of heart failure, irradiation, chemotherapy, cystic fibrosis or mucoviscidosis, or alpha1-antitrypsin deficiency.

Also deserving special mention is the treatment of inflammatory diseases of the gastrointestinal tract. Examples include acute or chronic inflammatory changes in gall bladder inflammation, Crohn's disease, ulcerative colitis, inflammatory pseudopolyps, juvenile polyps, colitis cystica profunda, pneumatosis cystoides intestinales, diseases of the bile duct and gall bladder, e.g. gallstones and

conglomerates, for the treatment of inflammatory diseases of the joints such as rheumatoid arthritis or inflammatory diseases of the skin and eyes.

Preferential mention should also be made of the treatment of cancers. Examples include all forms of acute and chronic leukaemias such as acute lymphatic and acute myeloid leukaemia, chronic lymphatic and chronic myeloid leukaemia, and bone tumours such as osteosarcoma and all types of glioma such as oligodendroglioma and glioblastoma.

Preferential mention should also be made of the prevention and treatment of diseases of the peripheral or central nervous system. Examples of these include depression, bipolar or manic depression, acute and chronic anxiety states, schizophrenia, Alzheimer's disease, Parkinson's disease, acute and chronic multiple sclerosis or acute and chronic pain as well as injuries to the brain caused by stroke, hypoxia or craniocerebral trauma.

Particularly preferably the present invention relates to the use of compounds of formula **1** for preparing a pharmaceutical composition for the treatment of inflammatory or obstructive diseases of the upper and lower respiratory tract including the lungs, such as for example allergic rhinitis, chronic rhinitis, bronchiectasis, cystic fibrosis, idiopathic pulmonary fibrosis, fibrosing alveolitis, COPD, chronic bronchitis, chronic sinusitis, asthma, Crohn's disease, ulcerative colitis, particularly COPD, chronic bronchitis and asthma.

It is most preferable to use the compounds of formula **1** for the treatment of inflammatory and obstructive diseases such as COPD, chronic bronchitis, chronic sinusitis, asthma, Crohn's disease, ulcerative colitis, particularly COPD, chronic bronchitis and asthma.

It is also preferable to use the compounds of formula **1** for the treatment of diseases of the peripheral or central nervous system such as depression, bipolar

or manic depression, acute and chronic anxiety states, schizophrenia, Alzheimer's disease, Parkinson's disease, acute and chronic multiple sclerosis or acute and chronic pain as well as injuries to the brain caused by stroke, hypoxia or craniocerebral trauma.

An outstanding aspect of the present invention is the reduced profile of side effects. This means, within the scope of the invention, being able to administer a dose of a pharmaceutical composition without inducing vomiting, preferably nausea and most preferably malaise in the patient. It is particularly preferable to be able to administer a therapeutically effective quantity of substance without inducing emesis or nausea, at every stage of the disease.

COMBINATIONS

The compounds of formula **1** may be used on their own or in conjunction with other active substances of formula **1** according to the invention. If desired the compounds of formula **1** may also be used in combination with other pharmacologically active substances. It is preferable to use for this purpose active substances selected for example from among betamimetics, anticholinergics, corticosteroids, other PDE4-inhibitors, LTD4-antagonists, EGFR-inhibitors, dopamine agonists, H1-antihistamines, PAF-antagonists and PI3-kinase inhibitors or double or triple combinations thereof, such as for example combinations of

- betamimetics with corticosteroids, PDE4-inhibitors, EGFR-inhibitors or LTD4-antagonists,
- anticholinergics with betamimetics, corticosteroids, PDE4-inhibitors, EGFR-inhibitors or LTD4-antagonists,
- corticosteroids with PDE4-inhibitors, EGFR-inhibitors or LTD4-antagonists
- PDE4-inhibitors with EGFR-inhibitors or LTD4-antagonists
- EGFR-inhibitors with LTD4-antagonists
- MRP4-inhibitors.

The invention also encompasses combinations of three active substances, each selected from one of the above-mentioned categories of compounds.

Suitable betamimetics used are preferably compounds selected from among albuterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, fenoterol, formoterol, arformoterol, zinterol, hexoprenaline, ibuterol, isoetharine, isoprenaline, levosalbutamol, mabuterol, meluadrine, metaproterenol, orciprenaline, pirbuterol, procaterol, reproterol, rimiterol, ritodrine, salmeterol, salmefamol, soterenol, sulphonterol, tiaramide, terbutaline, tolubuterol, CHF-1035, HOKU-81, KUL-1248, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzyl-sulphonamide, 5-[2-(5.6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1.4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-

4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3.4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3.4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 1-(4-ethoxy-carbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol, optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

Preferably the betamimetics are selected from among bambuterol, bitolterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, pirbuterol, procaterol, reproterol, salmeterol, sulphonterol, terbutaline, tolubuterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide, 5-[2-(5.6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-tert.-butylamino)ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl-4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-

hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1.1dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol, optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

Particularly preferred betamimetics are selected from among fenoterol, formoterol, salmeterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide, 5-[2-(5.6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinoline-2-one, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-

[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

Of these betamimetics the particularly preferred ones according to the invention are formoterol, salmeterol, 3-(4-{6-[2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide, 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1.1dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one, 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid, 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and 5-[2-(5,6-diethyl-indan-2-ylamino)-1-

hydroxy-ethyl]-8-hydroxy-1H-quinoline-2-one, optionally in the form of the racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof.

According to the invention the acid addition salts of the betamimetics are preferably selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably the hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate. Of the above-mentioned acid addition salts the salts of hydrochloric acid, methanesulphonic acid, benzoic acid and acetic acid are particularly preferred according to the invention.

The anticholinergics used are preferably compounds selected from among the tiotropium salts, oxitropium salts, flutropium salts, ipratropium salts, glycopyrronium salts, trospium salts, tropenol 2,2-diphenylpropionate methobromide, scopine 2,2-diphenylpropionate methobromide, scopine 2-fluoro-2,2-diphenylacetate methobromide, tropenol 2-fluoro-2,2-diphenylacetate methobromide, tropenol 3,3',4,4'-tetrafluorobenzilate methobromide, scopine 3,3',4,4'-tetrafluorobenzilate methobromide, tropenol 4,4'-difluorobenzilate methobromide, scopine 4,4'-difluorobenzilate methobromide, tropenol 3,3'-difluorobenzilate methobromide, scopine 3,3'-difluorobenzilate methobromide, tropenol 9-hydroxy-fluorene-9-carboxylate -methobromide, tropenol 9-fluoro-fluorene-9-carboxylate -methobromide, scopine 9-hydroxy-fluoren-9-carboxylate methobromide, scopine 9-fluoro-fluorene-9-carboxylate methobromide, tropenol 9-methyl-fluorene-9-carboxylate methobromide, scopine 9-methyl-fluorene-9-carboxylate methobromide, cyclopropyltropine benzilate methobromide, cyclopropyltropine 2,2-diphenylpropionate methobromide, cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide, cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide, cyclopropyltropine 9-methyl-xanthene-9-

carboxylate methobromide, cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide, methyl cyclopropyltropine 4,4'-difluorobenzilate methobromide, tropenol 9-hydroxy-xanthene-9-carboxylate -methobromide, scopine 9-hydroxy-xanthene-9-carboxylate methobromide, tropenol 9-methyl-xanthene-9-carboxylate methobromide, scopine 9-methyl-xanthene-9-carboxylate methobromide, tropenol 9-ethyl-xanthene-9-carboxylate methobromide, tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide, scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide, optionally in the form of the solvates or hydrates thereof.

In the above-mentioned salts the cations tiotropium, oxitropium, flutropium, ipratropium, glycopyrronium and trospium are the pharmacologically active ingredients. As anions, the above-mentioned salts may preferably contain chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate or p-toluenesulphonate, while chloride, bromide, iodide, sulphate, methanesulphonate or p-toluenesulphonate are preferred as counter-ions. Of all the salts, the chlorides, bromides, iodides and methanesulphonate are particularly preferred.

Of particular importance is tiotropium bromide. In the case of tiotropium bromide the pharmaceutical combinations according to the invention preferably contain it in the form of the crystalline tiotropium bromide monohydrate, which is known from WO 02/30928. If the tiotropium bromide is used in anhydrous form in the pharmaceutical combinations according to the invention, it is preferable to use anhydrous crystalline tiotropium bromide, which is known from WO 03/000265.

Corticosteroids used here are preferably compounds selected from among prednisolone, prednisone, butixocortpropionate, flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, dexamethasone, betamethasone, deflazacort, RPR-106541, NS-126, (S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-

androsta-1,4-diene-17-carbothionate and (S)-(2-oxo-tetrahydro-furan-3S-yl) 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-propionyloxy-androsta-1,4-diene-17-carbothionate, optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Particularly preferred is the steroid selected from among flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, dexamethasone, NS-126, (S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-androsta-1,4-diene-17-carbothionate and (S)-(2-oxo-tetrahydro-furan-3S-yl) 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-propionyloxy-androsta-1,4-diene-17-carbothionate, optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Particularly preferred is the steroid selected from among budesonide, fluticasone, mometasone, ciclesonide and (S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-androsta-1,4-diene-17-carbothionate, optionally in the form of the racemates, enantiomers or diastereomers thereof and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Any reference to steroids includes a reference to any salts or derivatives, hydrates or solvates thereof which may exist. Examples of possible salts and derivatives of the steroids may be: alkali metal salts, such as for example sodium or potassium salts, sulfobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates thereof.

Other PDE4 inhibitors which may be used are preferably compounds selected from among enprofyllin, theophyllin, roflumilast, ariflo (cilomilast), tofimilast, pumafentrin, lirimilast, arofyllin, atizoram, D-4396 (Sch-351591), AWD-12-281

(GW-842470), NCS-613, CDP-840, D-4418, PD-168787, T-440, T-2585, V-11294A, Cl-1018, CDC-801, CDC-3052, D-22888, YM-58997, Z-15370,N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide, (-)p-[(4aR*.10bS*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methyl-benzo[s][1.6]naphthyridin-6-yl]-N,N-diisopropylbenzamide, (R)-(+)-1-(4-bromo-benzyl)-4-[(3-cyclopentyloxy)-4-methoxyphenyl]-2-pyrrolidone, 3-(cyclopentyloxy-4-methoxyphenyl)-1-(4-N'-[N-2-cyano-S-methyl-isothioureido]benzyl)-2-pyrrolidone, cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid], 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexane-1-one, cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol], (R)-(+)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate, (S)-(-)-ethyl[4-(3-cyclopentyloxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate, 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine and 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine, optionally in the form of the racemates, enantiomers or diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

Particularly preferably the PDE4-inhibitor is selected from among enprofyllin, roflumilast, ariflo (cilomilast), arofyllin, atizoram, AWD-12-281 (GW-842470), T-440, T-2585, PD-168787, V-11294A, Cl-1018, CDC-801, D-22888, YM-58997, Z-15370, N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropyl-methoxybenzamide, cis[4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexane-1-carboxylic acid], 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol], 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine and 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine, optionally in the form of the racemates, enantiomers or diastereomers

and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

Particularly preferably the PDE4-inhibitor is selected from among roflumilast, ariflo (cilomilast), arofyllin, AWD-12-281 (GW-842470), 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one, cis[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol], atizoram, Z-15370, 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(2-thienyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine and 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(tert-butyl)-9H-pyrazolo[3,4-c]-1,2,4-triazolo[4,3-a]pyridine, optionally in the form of the racemates, enantiomers or diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof.

By acid addition salts with pharmacologically acceptable acids which the above-mentioned PDE4-inhibitors might be in a position to form are meant, for example, salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate.

LTD4-antagonists which may be used are preferably compounds selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707, L-733321, 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2- hydroxy-2-propyl)phenyl)thio)-methylcyclopropane-acetic acid, 1-(((1(R)-3(3-(2-(2.3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)-propyl)thio)methyl)cyclopropane-acetic acid and [2-[[2-(4-tert-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]acetic acid, optionally in the form of the racemates,

enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Preferably the LTD4-antagonist is selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001, MEN-91507 (LM-1507), VUF-5078, VUF-K-8707 and L-733321, optionally in the form of the racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

Particularly preferably the LTD4-antagonist is selected from among montelukast, pranlukast, zafirlukast, MCC-847 (ZD-3523), MN-001 and MEN-91507 (LM-1507), optionally in the form of the racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts and optionally in the form of the salts and derivatives, solvates and/or hydrates thereof.

By acid addition salts with pharmacologically acceptable acids which the LTD4-antagonists may be capable of forming are meant, for example, salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate. By salts or derivatives which the LTD4-antagonists may be capable of forming are meant, for example: alkali metal salts, such as, for example, sodium or potassium salts, alkaline earth metal salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.

The EGFR-inhibitors used are preferably compounds selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-

quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methanesulphonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-

fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methanesulphonylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulphonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy- quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-

quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2,2,1]hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-

methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, cetuximab, trastuzumab, ABX-EGF and Mab ICR-62, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

Preferred EGFR-inhibitors are selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-diethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-2-methoxymethyl-6-oxo-morpholin-4-yl)-1-oxo-2-buten-1-

yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(N,N-bis-(2-methoxy-ethyl)-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-ethyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((R)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-7-[3-(morpholin-4-yl)-propyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-{[3-chloro-4-(3-fluoro-benzyloxy)-phenyl]amino}-6-(5-{[(2-methanesulphonyl-ethyl)amino]methyl}-furan-2-yl)quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-

fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(methoxymethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-((S)-tetrahydrofuran-3-yloxy)-7-hydroxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(dimethylamino)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulphonylamino]-cyclohexan-1-yloxy}-7-methoxy-

quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-acetylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-(2-methanesulphonylamino-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-aminocarbonylmethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(tetrahydropyran-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulphonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-acetylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(tert.-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(4-methyl-piperazin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-

piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(cis-2,6-dimethyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methyl-morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(S,S)-(2-oxa-5-aza-bicyclo[2,2,1]hept-5-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(3-methoxypropyl-amino)-carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-

chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, and cetuximab, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

It is particularly preferable within the scope of the present invention to use those EGFR-inhibitors which are selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-({4-[N-(tetrahydropyran-4-yl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopentyloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-(4-hydroxy-phenyl)-7H-pyrrolo[2,3-d]pyrimidine, 3-cyano-4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N,N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-ethoxy-quinoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-

morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(piperidin-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-acetylamino-ethyl)-piperidin-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-4-yloxy)-7-ethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(piperidin-1-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(2-methoxy-acetyl)-piperidin-4-yloxy]-7-(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(tetrahydropyran-4-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(piperidin-1-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexan-1-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(N-methyl-N-2-

methoxyethyl-amino)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-ethyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

Particularly preferred EGFR-inhibitors according to the invention are the compounds selected from among 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N-(2-methoxy-ethyl)-N-methyl-amino]-1-oxo-2-buten-1-yl}amino)-7-cyclopropylmethoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6,7-bis-(2-methoxy-ethoxy)-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-

[(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(tetrahydropyran-3-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-ethynyl-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(2-methoxyethyl)carbonyl]-piperidin-4-yloxy}-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexan-1-yloxy]-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline and 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-cyano-piperidin-4-yloxy)-7-methoxy-quinazoline, optionally in the form of the racemates, enantiomers or diastereomers thereof, optionally in the form of the pharmacologically acceptable acid addition salts thereof, the solvates and/or hydrates thereof.

By acid addition salts with pharmacologically acceptable acids which the EGFR-inhibitors may be capable of forming are meant, for example, salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate.

Examples of dopamine agonists which may be used preferably include compounds selected from among bromocriptine, cabergoline, alpha-dihydroergocryptine, lisuride, pergolide, pramipexol, roxindol, ropinirol, talipexol, terguride and viozan. Any reference to the above-mentioned dopamine agonists within the scope of the present invention includes a reference to any pharmacologically acceptable acid addition salts and optionally hydrates thereof which may exist. By the physiologically acceptable acid addition salts which may be formed by the above-mentioned dopamine agonists are meant, for example, pharmaceutically acceptable salts which are selected from the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and maleic acid.

Examples of H1-antihistamines preferably include compounds selected from among epinastine, cetirizine, azelastine, fexofenadine, levocabastine, loratadine, mizolastine, ketotifen, emedastine, dimetinden, clemastine, bamipin, cexchlorpheniramine, pheniramine, doxylamine, chlorophenoxamine, dimenhydrinate, diphenhydramine, promethazine, ebastine, desloratidine and meclozine. Any reference to the above-mentioned H1-antihistamines within the scope of the present invention includes a reference to any pharmacologically acceptable acid addition salts which may exist.

Examples of PAF-antagonists preferably include compounds selected from among 4-(2-chlorophenyl)-9-methyl-2-[3(4-morpholinyl)-3-propanon-1-yl]-6H-thieno-[3,2-f]-[1,2,4]triazolo[4,3-a][1,4]diazepines, 6-(2-chlorophenyl)-8,9-dihydro-1-methyl-8-[(4-morpholinyl)carbonyl]-4H,7H-cyclo-penta-[4,5]thieno-[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepines.

MRP4-inhibitors used are preferably compounds selected from among *N*-acetyl-dinitrophenyl-cysteine, cGMP, cholate, diclofenac, dehydroepiandrosterone 3-glucuronide, dehydroepiandrosterone 3-sulphate, dilazep, dinitrophenyl-*s*-glutathione, estradiol 17-β-glucuronide, estradiol 3,17-disulphate, estradiol 3-glucuronide, estradiol 3-sulphate, estrone 3-sulphate, flurbiprofen, folate, N5-formyl-tetrahydrofolate, glycocholate, clycolithocholic acid sulphate, ibuprofen, indomethacin, indoprofen, ketoprofen, lithocholic acid sulphate, methotrexate, MK571 ((*E*)-3-[[[3-[2-(7-chloro-2-quinolinyl)ethenyl]phenyl]-[[3-dimethylamino)-3-oxopropyl]thio]methyl]thio]-propanoic acid), α-naphthyl-β-D-glucuronide, nitrobenzyl mercaptopurine riboside, probenecid, PSC833, sildenafil, sulfinpyrazone, taurochenodeoxycholate, taurocholate, taurodeoxycholate, taurolithocholate, taurolithocholic acid sulphate, topotecan, trequinsin and zaprinast, dipyridamole, optionally in the form of the racemates, enantiomers, diastereomers and the pharmacologically acceptable acid addition salts and hydrates thereof.

Preferably the invention relates to the use of MRP4-inhibitors for preparing a pharmaceutical composition for the treatment of respiratory complaints, containing the PDE4B-inhibitors and MRP4-inhibitors, the MRP4-inhibitors preferably being selected from among *N*-acetyl-dinitrophenyl-cysteine, dehydroepiandrosterone 3-sulphate, dilazep, dinitrophenyl-*S*-glutathione, estradiol 3,17-disulphate, flurbiprofen, glycocholate, glycolithocholic acid sulphate, ibuprofen, indomethacin, indoprofen, lithocholic acid sulphate, MK571, PSC833, sildenafil, taurochenodeoxycholate, taurocholate, taurolithocholate, taurolithocholic acid sulphate, trequinsin and zaprinast, dipyridamole, optionally in the form of the

racemates, enantiomers, diastereomers and the pharmacologically acceptable acid addition salts and hydrates thereof.

The invention relates more preferably to the use of MRP4-inhibitors for preparing a pharmaceutical composition for treating respiratory complaints, containing the PDE4B-inhibitors and MRP4-inhibitors according to the invention, the MRP4-inhibitors preferably being selected from among dehydroepiandrosterone 3-sulphate, estradiol 3,17-disulphate, flurbiprofen, indomethacin, indoprofen, MK571, taurocholate, optionally in the form of the racemates, enantiomers, diastereomers and the pharmacologically acceptable acid addition salts and hydrates thereof. The separation of enantiomers from the racemates can be carried out using methods known from the art (e.g. chromatography on chiral phases, etc.) .

By acid addition salts with pharmacologically acceptable acids are meant, for example, salts selected from among the hydrochlorides, hydrobromides, hydroiodides, hydrosulphates, hydrophosphates, hydromethanesulphonates, hydronitrates, hydromaleates, hydroacetates, hydrobenzoates, hydrocitrates, hydrofumarates, hydrotartrates, hydrooxalates, hydrosuccinates, hydrobenzoates and hydro-*p*-toluenesulphonates, preferably the hydrochlorides, hydrobromides, hydrosulphates, hydrophosphates, hydrofumarates and hydromethanesulphonates.

The invention further relates to pharmaceutical preparations which contain a triple combination of the PDE4B-inhibitors, MRP4-inhibitors and another active substance according to the invention, such as, for example, an anticholinergic, a steroid, an LTD4-antagonist or a betamimetic, and the preparation thereof and the use thereof for treating respiratory complaints.

FORMULATIONS

Suitable forms for administration are for example tablets, capsules, solutions, syrups, emulsions or inhalable powders or aerosols. The content of the pharmaceutically effective compound(s) in each case should be in the range from 0.1 to 90 wt.%, preferably 0.5 to 50 wt.% of the total composition, i.e. in amounts which are sufficient to achieve the dosage range specified hereinafter.

The preparations may be administered orally in the form of a tablet, as a powder, as a powder in a capsule (e.g. a hard gelatine capsule), as a solution or suspension. When administered by inhalation the active substance combination may be given as a powder, as an aqueous or aqueous-ethanolic solution or using a propellant gas formulation.

Preferably, therefore, pharmaceutical formulations are characterised by the content of one or more compounds of formula **1** according to the preferred embodiments above.

It is particularly preferable if the compounds of formula **1** are administered orally, and it is also particularly preferable if they are administered once or twice a day. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To

achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as *p*-hydroxybenzoates.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules. Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

For oral administration the tablets may, of course, contain, apart from the abovementioned carriers, additives such as sodium citrate, calcium carbonate and

dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tabletting process. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

It is also preferred if the compounds of formula **1** are administered by inhalation, particularly preferably if they are administered once or twice a day. For this purpose, the compounds of formula **1** have to be made available in forms suitable for inhalation. Inhalable preparations include inhalable powders, propellant-containing metered-dose aerosols or propellant-free inhalable solutions, which are optionally present in admixture with conventional physiologically acceptable excipients.

Within the scope of the present invention, the term propellant-free inhalable solutions also includes concentrates or sterile ready-to-use inhalable solutions. The preparations which may be used according to the invention are described in more detail in the next part of the specification.

Inhalable powders

If the active substances of formula **1** are present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare the inhalable powders according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose), oligo- and polysaccharides (e.g. dextran), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose

is the particularly preferred excipient, while lactose monohydrate is most particularly preferred. Methods of preparing the inhalable powders according to the invention by grinding and micronising and by finally mixing the components together are known from the prior art.

Propellant-containing inhalable aerosols

The propellant-containing inhalable aerosols which may be used according to the invention may contain **1** dissolved in the propellant gas or in dispersed form. The propellant gases which may be used to prepare the inhalation aerosols according to the invention are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as preferably fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The propellant gases mentioned above may be used on their own or in mixtures thereof. Particularly preferred propellant gases are fluorinated alkane derivatives selected from TG134a (1,1,1,2-tetrafluoroethane), TG227 (1,1,1,2,3,3,3-heptafluoropropane) and mixtures thereof. The propellant-driven inhalation aerosols used within the scope of the use according to the invention may also contain other ingredients such as co-solvents, stabilisers, surfactants, antioxidants, lubricants and pH adjusters. All these ingredients are known in the art.

Propellant-free inhalable solutions

The compounds of formula **1** according to the invention are preferably used to prepare propellant-free inhalable solutions and inhalable suspensions. Solvents used for this purpose include aqueous or alcoholic, preferably ethanolic solutions. The solvent may be water on its own or a mixture of water and ethanol. The solutions or suspensions are adjusted to a pH of 2 to 7, preferably 2 to 5, using suitable acids. The pH may be adjusted using acids selected from inorganic or organic acids. Examples of particularly suitable inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and/or phosphoric acid. Examples of particularly suitable organic acids include ascorbic acid, citric

acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and/or propionic acid etc. Preferred inorganic acids are hydrochloric and sulphuric acids. It is also possible to use the acids which have already formed an acid addition salt with one of the active substances. Of the organic acids, ascorbic acid, fumaric acid and citric acid are preferred. If desired, mixtures of the above acids may also be used, particularly in the case of acids which have other properties in addition to their acidifying qualities, e.g. as flavourings, antioxidants or complexing agents, such as citric acid or ascorbic acid, for example. According to the invention, it is particularly preferred to use hydrochloric acid to adjust the pH.

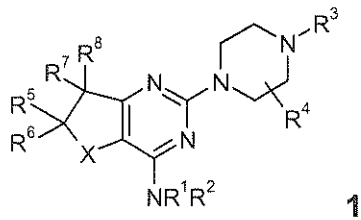
Co-solvents and/or other excipients may be added to the propellant-free inhalable solutions used for the purpose according to the invention. Preferred co-solvents are those which contain hydroxyl groups or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance which is not an active substance but which can be formulated with the active substance or substances in the pharmacologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Preferably, these substances have no pharmacological effect or, in connection with the desired therapy, no appreciable or at least no undesirable pharmacological effect. The excipients and additives include, for example, surfactants such as soya lecithin, oleic acid, sorbitan esters, such as polysorbates, polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants and/or preservatives which guarantee or prolong the shelf life of the finished pharmaceutical formulation, flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents. The preferred excipients include antioxidants such as ascorbic acid, for example, provided that it has not already been used to adjust the pH, vitamin A, vitamin E,

tocopherols and similar vitamins or provitamins occurring in the human body. Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium chloride, benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art.

For the treatment forms described above, ready-to-use packs of a medicament for the treatment of respiratory complaints are provided, containing an enclosed description including for example the words respiratory disease, COPD or asthma, a pteridine and one or more combination partners selected from those described above.

Patent Claims

1. Compounds of formula **1**,



1

wherein

X denotes O, S, SO or SO_2;

$\mathbf{R^1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{6-10}-aryl or C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene;

$\mathbf{R^2}$ denotes H or an optionally mono- or polysubstituted group selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, an optionally mono- or poly-bridged mono- or bicyclic C_{3-10}-cycloalkyl, C_{6-10}-aryl, an aromatic or non-aromatic, heterocyclic C_{3-10} ring, a bicyclic ring and a C_{6-10}-aryl fused to a C_{3-10} heterocycle;

or $\mathbf{NR^1R^2}$ together denote a heterocyclic ring which is optionally substituted by one or more groups selected from C_{1-4}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, straight-chain or branched C_{1-6}-alkanol and oxo;

$\mathbf{R^3}$ denotes a mono- or polysubstituted group selected from among a heterocyclic C_{6-10} ring, C_{3-7}-cycloalkyl, C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene, a fused, bicyclic ring which may optionally contain 1-4 heteroatoms selected independently of one another from N, O, S,

or $\mathbf{R^3}$ denotes optionally substituted phenyl;

or $\mathbf{R^3}$ denotes a group $COR^{3.7}$, $COCH_2R^{3.8}$, $CONHR^{3.8}$ or $SO_2R^{3.8}$;

wherein

$R^{3.7}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl or C_{6-10}-aryl;

$R^{3.8}$ denotes C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-7}-cycloalkyl or a group selected from among C_{6-10}-aryl, a heterocyclic C_{3-10} ring and a bicyclic ring, which is optionally substituted by one or more groups selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, halogen, $NR^{3.8.1}R^{3.8.2}$, C_{6-10}-aryl and a heterocyclic C_{3-10} ring ;

wherein

$R^{3.8.1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

$R^{3.8.2}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

$\mathbf{R^4}$ denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, or oxo;

$\mathbf{R^5}$ denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl or C_{2-4}-alkynyl;

$\mathbf{R^6}$ denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl or C_{2-4}-alkynyl;

$\mathbf{R^7}$ denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, C_{6-10}-aryl, or OH;

$\mathbf{R^8}$ denotes H, C_{1-4}-alkyl, C_{2-4}-alkenyl, C_{2-4}-alkynyl, C_{6-10}-aryl or OH;

or $\mathbf{R^7}$ and $\mathbf{R^8}$ together form oxo;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

2. Compounds of formula **1**, according to claim 1, wherein

X denotes O, S, SO or SO_2;

$\mathbf{R^1}$ denotes H, C_{1-6}-alkyl, C_{6-10}-aryl, C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene,

R^2 denotes H or C_{1-6}-alkyl, which may optionally be substituted by one or more groups selected from among C_{1-6}-haloalkyl, CN, $OR^{2.1}$, $NR^{2.1}R^{2.2}$, $COOR^{2.1}$, $CONR^{2.1}R^{2.2}$, C_{3-7}-cycloalkyl optionally substituted by C_{1-4}-alkyl or oxo, an aromatic or non-aromatic heterocycle optionally substituted by C_{1-4}-alkyl, oxo, OH or halogen, C_{6-10}-aryl optionally substituted by C_{1-4}-alkyl or oxo and C_{6-10}-aryl fused to a C_{5-6} heterocycle, while this fused ring system may optionally be substituted by C_{1-4}-alkyl or oxo

wherein

$R^{2.1}$ denotes H or C_{1-6}-alkyl which is optionally substituted by a C_{3-7}-cycloalkyl, C_{3-10} heterocycle or C_{6-10}-aryl, each of which is optionally substituted,

$R^{2.2}$ denotes H or C_{1-6}-alkyl;

or **R^2** denotes a group selected from optionally mono- or poly-bridged C_{3-10}-cycloalkyl or a C_{3-10}-cycloalkyl, which may optionally be fused to a C_{6-10}-aryl ring which is optionally substituted by one or more groups selected from among C_{1-6}-alkyl, OH, $CH_2OR^{2.3}$, $COOR^{2.3}$, $COR^{2.3}$, $CONR^{2.3}R^{2.4}$, O-C_{1-6}-alkyl, O-C_{7-11}-aralkyl, $NR^{2.3}R^{2.4}$ and $NHCOR^{2.5}$,

wherein

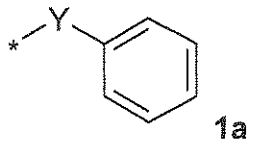
$R^{2.3}$ is H or a heterocycle or a C_{1-6}-alkyl, which may optionally be substituted by a group selected from C_{3-7}-cycloalkyl, C_{3-10} heterocycle and C_{6-10}-aryl, while this group may optionally be substituted in each case by one or more groups selected from among C_{1-6}-alkyl, halogen, OH and O-C_{1-6}-alkyl;

wherein

$R^{2.4}$ denotes H or C_{1-6}-alkyl;

$R^{2.5}$ denotes a group selected from among C_{3-7}-cycloalkyl, a heterocyclic C_{3-10} ring and C_{1-6}-alkyl, which may optionally be substituted by OH;

or R^2 denotes a group of formula **1a**,



1a

Y denotes C_{1-6}-alkylene, optionally substituted by one or two $R^{2.7}$ wherein $R^{2.7}$ are in each case selected independently of one another from C_{1-6}-alkyl, COOH, $CONH_2$, $OR^{2.1}$, and $COOR^{2.1}$; or $R^{2.7}$ together with one or two carbon atoms of Y forms a carbocyclic ring with 3 carbon atoms

or R^2 denotes C_{6-10}-aryl, which may optionally be substituted by one or more groups selected independently of one another from among C_{1-6}-alkyl, C_{1-6}-haloalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$, NHCOMe, $CONR^{2.3}R^{2.4}$, a C_{1-4} alkylene group substituted by $NR^{2.1}R^{2.2}$, or $NR^{2.1}R^{2.2}$,

or R^2 denotes C_{6-10}-aryl, which may optionally be substituted by one or more groups selected independently of one another from among C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene, C_{3-7}-cycloalkyl, a C_{3-7}-cycloalkyl-C_{1-4}-alkylene, C_{6-10}-aryl, and a heterocyclic C_{3-10} ring, while these groups may each optionally be substituted by one or more groups selected from C_{1-6}-alkyl, C_{1-6}-haloalkyl, $COOR^{2.8}$, CN, halogen, $OR^{2.8}$, $NHCOR^{2.8}$, oxo, a C_{3-10} heterocycle, a C_{3-7}-cycloalkyl-C_{1-4} alkylene, a C_{5-10} heterocycle -C_{1-4}-alkylene and a $NR^{2.1}R^{2.2}$ -C_{1-4} alkylene,

wherein

$R^{2.8}$ denotes H, C_{1-6}-alkyl, C_{6-10}-aryl, a $NR^{2.1}R^{2.2}$-C_{1-4} alkylene group;

$R^{2.10}$ denotes $NHR^{2.10.1}$ or a heterocyclic C_{3-10} ring which may optionally be substituted by C_{1-4}-alkyl;

$R^{2.10.1}$ denotes H, C_{3-7}-cycloalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl,C_{1-6}-alkyl or C_{1-6}-alkyl-O-C_{1-4}-alkyl

or **R^2** denotes C_{6-10}-aryl, to which an aromatic or non-aromatic C_{3-10} heterocycle is fused;

or **R^2** denotes an aromatic or non-aromatic heterocyclic C_{3-10} ring which may optionally be substituted by one or more groups selected from among halogen, OH, oxo, CN, C_{1-6}-alkyl, C_{1-6}-alkanol, C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene, $COR^{2.11}$, C_{3-7}-cycloalkyl-C_{1-4}-alkylene and C_{3-10} heterocycle-C_{1-4}-alkylene;
wherein
$R^{2.11}$ denotes a group selected from among C_{3-10} heterocycle- C_{1-4}-alkylene, C_{3-7}-cycloalkyl and a heterocyclic aromatic or non-aromatic C_{3-10} ring,
which may optionally be substituted by C_{1-6}-alkyl, which may in turn optionally be substituted by OH, CH_2OH, OMe, NH_2, a C_{3-10} heterocycle or NHCOO-^{t}Bu;

or **R^2** denotes a group selected from among C_{2-6}-alkenyl or a bicyclic ring, which may optionally be substituted by methyl;

or **NR^1R^2** denotes a heterocyclic ring which may optionally be substituted by one or more groups selected from among C_{1-4}-alkyl, OH and C_{1-4}-alkanol;

R^3 denotes a group selected from among a heterocyclic C_{3-10} ring, a C_{3-7}-cycloalkyl, a bicyclic, fused aromatic or non-aromatic ring system, which optionally contains 1 to 4 heteroatoms selected from S, N, O, or it denotes C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene and CH_2-benzo[1, 3]dioxolyl, which may optionally be substituted by one or more groups

selected from OH, halogen, C_{1-6}-alkyl, O-C_{1-6}-alkyl, C_{1-6}-haloalkyl and CO-$R^{3.1}$,

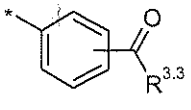
or **R^3** denotes phenyl, which may optionally be substituted by one or more groups selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-4}-haloalkyl, C_{1-6}-alkylene-$NR^{3.1}R^{3.2}$, CN, $COOR^{3.1}$, $CONR^{3.1}R^{3.2}$, $NR^{3.1}R^{3.2}$, $NHCOR^{3.1}$, CF_3, $OR^{3.1}$, halogen, $NHCOR^{3.1}$, NO_2, $SO_2NR^{3.1}R^{3.2}$ and C_{1-6}-alkylene-$NHCOR^{3.1}$;

wherein

$R^{3.1}$ denotes H,C_{1-6}-alkyl; C_{2-6}-alkenyl or C_{2-6}-alkynyl, optionally bridged, mono-or bicyclic C_{3-10} heterocycle or C_{3-10} heterocycle-C_{1-4}-alkylene group;

$R^{3.2}$ denotes H, C_{1-6}-alkyl,, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

or **R^3** denotes a group of formula 1b



1b;

wherein

$R^{3.3}$ denotes a group selected from among a heterocyclic C_{3-10} ring which may optionally be substituted by one or more groups selected from among C_{1-6}-alkyl, oxo, $COR^{3.3.1}$, $COR^{3.3.2}$, C_{1-6}-alkylene-$R^{3.3.2}$, CH_2CO-pyrrolidine and a heterocyclic C_{3-10} ring, wherein a sulphur atom optionally contained in the heterocyclic ring, may optionally be in the form of the oxide or dioxide;

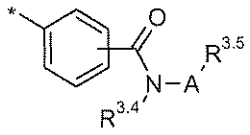
wherein

$R^{3.3.1}$ denotes C_{1-6}-alkyl;

$R^{3.3.2}$ denotes NH_2, $NH(C_{1-6}$-alkyl), $N(C_{1-6}$-alkyl$)_2$;

or $R^{3.3}$ denotes a bicyclic ring or heterocyclic spiro ring;

or $\mathbf{R^3}$ denotes a group of formula **1c**;



1c;

wherein

A may be a bond or C_{1-6}-alkyl, which may optionally be substituted by oxo or NMe_2;

$R^{3.4}$ denotes H or C_{1-6}-alkyl;

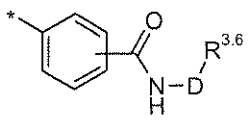
$R^{3.5}$ denotes a group selected from among

C_{1-6}-alkyl, which may optionally be substituted by one or more groups selected from C_{3-7}-cycloalkyl, C_{6-10}-aryl and a C_{3-10} heterocycle, while this group may also optionally be substituted in each case by a group selected from among OH, oxo, C_{1-6}-alkyl, O-C_{1-6}-alkyl and C_{1-6}-haloalkyl,

or a group selected from a heterocyclic C_{3-10} ring and a bicyclic ring, which is optionally substituted by one or more groups selected independently of one another from among oxo, C_{1-6}-alkyl, OH, C_{6-10}-aryl, a heterocyclic C_{3-10} ring, C_{1-6}-alkylene-$R^{3.5.1}$, O-C_{1-6}-alkylene-$R^{3.5.1}$ and NH-C_{1-6}-alkylene-$R^{3.5.1}$,

$R^{3.5.1}$ denotes a group selected from among C_{6-10}-aryl and a heterocyclic C_{3-10} ring which may optionally be substituted by C_{1-6}-alkyl;

or $\mathbf{R^3}$ denotes a group of formula **1d**;



1d;

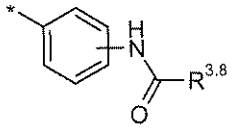
wherein

D denotes C_{2-4}-alkynyl; an optionally bridged, bicyclic C_{3-10}-cycloalkyl group, which may optionally be substituted by one or more groups selected from C_{1-6}-alkyl, halogen, OH, C_{1-6}-haloalkyl and O-C_{1-6}-alkyl,

$R^{3.6}$ denotes pyridinyl;

or **R^3** denotes a group selected from among $COR^{3.7}$, $COCH_2R^{3.8}$, $CONHR^{3.8}$, $SO_2R^{3.8}$ and a heterocyclic group fused to a C_{6-10}-aryl group, which may optionally be substituted by methyl,

or **R^3** denotes a group of formula **1e**;



1e;

$R^{3.7}$ denotes H, C_{1-6}-alkyl, C_{6-10}-aryl;

$R^{3.8}$ denotes a group selected from among C_{1-6}-alkyl, C_{3-7}-cycloalkyl or a group selected from among C_{6-10}-aryl, a heterocyclic C_{3-10} ring and a bicyclic ring, which may optionally be substituted by one or more groups selected from among C_{1-6}-alkyl, halogen, $NR^{3.8.1}R^{3.8.2}$, C_{6-10}-aryl and a heterocyclic C_{3-10} ring;

$R^{3.8.1}$ denotes H or C_{1-6}-alkyl;

$R^{3.8.2}$ denotes H or C_{1-6}-alkyl;

R^4 denotes H, C_{1-4}-alkyl or oxo;

R^5 denotes H or C_{1-4}-alkyl;

R^6 denotes H or C_{1-4}-alkyl;

R^7 denotes H, C_{1-4}-alkyl, C_{6-10}-aryl or OH;

R^8 denotes H, C_{1-4}-alkyl, C_{6-10}-aryl or OH;

or R^7 and R^8 together form oxo;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

3. Compounds of formula **1**, according to one of claims 1 or 2, wherein

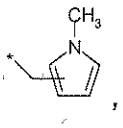
X denotes O, S, SO or SO_2;

R^1 denotes H, methyl, ethyl or propyl;

R^2 denotes H or C_{1-6}-alkyl, which may optionally be substituted by one or more groups selected from among CF_3, CN, OH, NMe_2, OMe, COOH and $CONMe_2$,

or R^2 denotes C_{1-6}-alkyl, which may optionally be substituted by one or more groups selected from cyclopropyl, cyclopentyl, cyclohexyl, phenyl, pyrrolidinyl, imidazolidinyl, pyrazolyl, imidazolyl and pyridinyl, which may optionally be substituted by methyl or oxo;

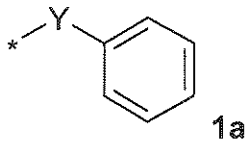
or R^2 denotes C_{3-7}-cycloalkyl, which may optionally be substituted by a group selected from among methyl, $OR^{2.3}$,$CH_2OR^{2.3}$, COOH, $CONR^{2.3}R^{2.4}$, CONH-^{t}Bu, O-benzyl, $NR^{2.3}R^{2.4}$ and $NHCOR^{2.5}$,
wherein

$R^{2.3}$ denotes H or methyl, ,

$R^{2.4}$ denotes H or methyl;

$R^{2.5}$ denotes $CH_2C(CH_3)_3$, $CH_2C(CH_3)_2(CH_2OH)$, cyclopentyl, tetrahydrofuranyl, pyrrolyl, pyrazolyl, imidazolyl or isoxazolyl;

or R^2 denotes a group of formula **1a**,



1a

Y denotes C_{1-4}-alkylene, optionally substituted by one or two $R^{2.7}$

$R^{2.7}$ each independently of one another denote C_{1-4}-alkyl, COOH, $CONH_2$; or $R^{2.7}$ together with one or two carbon atoms of Y forms a carbocyclic ring with 3 carbon atoms

or **R^2** denotes C_{6-10}-aryl, which may optionally be substituted by one or more groups selected independently of one another from among methyl, *tert*-butyl, CN, F, Cl, Br, OH, OMe, OEt, O-phenyl, COOH, COOMe, $COR^{2.10}$, NHCOMe and morpholine-substituted C_{1-4}-alkylene,

wherein

$R^{2.10}$ denotes NH_2, NHMe, NH-^{i}Pr, NH-cyclopropyl, $NHCH_2CH_2OMe$ or a heterocyclic, non-aromatic C_{3-10} ring, which may contain one, two or three heteroatoms selected from among oxygen and nitrogen;

or **R^2** denotes C_{6-10}-aryl, which may optionally be substituted by a group selected from among phenyl and a heterocyclic C_{3-10} ring, which may optionally be substituted by one or more groups selected from among methyl, *tert*-butyl, COOH, COOMe, CN, F, Cl, Br, OH, OMe, OEt and NHCOMe, oxo;

or **R^2** denotes a heterocyclic non-aromatic C_{3-10} ring which may optionally be substituted by a group selected from among benzyl and $COR^{2.11}$;

wherein

$R^{2.11}$ denotes a group selected from among cyclopentyl, tetrahydrofuranyl, furan, pyridyl, pyrrolyl, pyrrazolyl, imidazolyl, which may optionally be substituted by one or two methyl groups, or by one or more groups selected from among $CH_2C(CH_3)_3$, $C(CH_3)_2(CH_2OH)$, CH_2OMe, $C(CH_3)_2NH_2$ and $C(CH_3)_2NHCOO\text{-}^tBu$;

or **R^2** denotes a group selected from among C_{2-6}-alkenyl, indanyl, 1,2,3,4-tetrahydro-naphthalyl and 8-methyl-8-aza-bicyclo[3.2.1]octane;

or **NR^1R^2** denotes a group selected from among pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, which may optionally be substituted by methyl;

R^3 denotes a group selected from among pyridinyl, pyrimidine, benzyl, and CH_2-benzo[1, 3]dioxolyl;

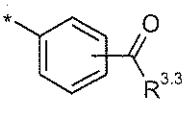
or **R^3** denotes phenyl, which may optionally be substituted by one, two or three groups selected from among methyl, CH_2NH_2, CN, COOH, $CONH_2$, CF_3, OH, F, Cl, Br, OMe, NHCOMe, $NR^{3.1}COR^{3.2}$, $CONR^{3.1}R^{3.2}$, NO_2, $SONMe_2$ and $CH_2NHCOMe$;

wherein

$R^{3.1}$ denotes H, C_{1-6}-alkyl or an optionally bridged, mono- or bicyclic C_{3-10} heterocycle

$R^{3.2}$ denotes H or C_{1-6}-alkyl;

or **R^3** denotes a group of formula **1b**



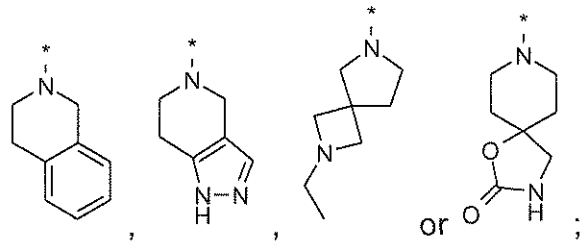
1b;

wherein

$R^{3.3}$ denotes a group selected from among piperidinyl, piperazinyl, azepanyl, which may optionally be substituted by one or more groups

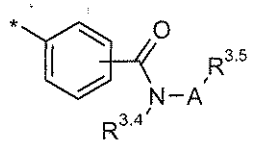
selected independently of one another from among methyl, oxo, $COCH_3$, $CONH_2$, CH_2NEt_2, $CH_2CH_2NMe_2$, CH_2CO-pyrrolidine, pyridinyl, isothiazolidinyl-1,1-dioxide and thiazolidinyl-1,1-dioxide;

or $R^{3.3}$ denotes a group of formula



;

or **R^3** denotes a group of formula **1c**;



1c;

wherein

A denotes a bond or C_{1-4}-alkyl, which may optionally be substituted by oxo or NMe_2,

$R^{3.4}$ denotes H or methyl;

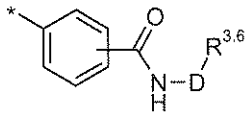
$R^{3.5}$ denotes a group selected from among pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, cyclohexyl, imidazolyl, pyrazolyl, phenyl, pyridinyl, benzimidazolyl, imidazolidin-2-one, pyrrolidin-2-one, pyrrolidin-3-one, tetrahydro-thiophene-1,1-dioxide and 1-aza-bicyclo[2,2,2]octane, which may optionally be substituted by one or more groups selected independently of one another from among methyl, ethyl, OH, phenyl, pyridinyl, pyrazolyl, pyrrolidinyl, $(CH_2)_o$-$R^{3.5.1}$, O-$(CH_2)_o$-$R^{3.5.1}$ and NH-$(CH_2)_o$-$R^{3.5.1}$;

wherein

o denotes 0, 1 or 2

$R^{3.5.1}$ denotes a group selected from among phenyl, pyrrolidinyl, piperidinyl and imidazolidin-2-one, which may optionally be substituted by methyl;

or **R^3** denotes a group of formula **1d**;



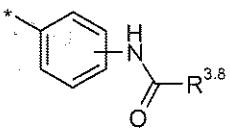
1d;

wherein

D denotes C_{2-4}-alkynyl;

$R^{3.6}$ denotes pyridinyl;

or **R^3** denotes a group $COR^{3.7}$, $COCH_2R^{3.8}$, $CONHR^{3.8}$, $SO_2R^{3.8}$ or a group of formula **1e**;



1e;

wherein

$R^{3.7}$ denotes H, methyl, phenyl;

$R^{3.8}$ denotes a group selected from among *iso*-propyl, cyclopropyl, cyclopentyl, cyclohexyl, pyrrolidinyl, pyrrolidin-2-one, furanyl and azabicyclo[2,2,2]octanyl or a group selected from among piperidinyl, pyrazolyl, imidiazolyl, isoxazolyl, pyridinyl, phenyl, benzyl, which may optionally be substituted by one or more groups selected from among methyl, chlorine, NH_2, NMe_2, phenyl and morpholinyl;

R^4 denotes H, methyl or oxo;

R^5 denotes H or methyl;

R^6 denotes H or methyl;

R^7 denotes H, methyl or OH; preferably H or methyl;

R^8 denotes H, methyl or OH; preferably H or methyl;

or R^7 and R^8 together form oxo;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

4. Compounds of formula **1**, according to one of claims 1 to 3, wherein

R^1 denotes H;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

5. Compounds of formula **1**, according to one of claims 1 to 4, wherein

X denotes SO;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

6. Compounds of formula **1**, according to one of claims 1 to 5, wherein

R^5, R^6, R^7, R^8 denote H;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

7. Compounds of formula **1**, according to one of claims 1 to 6, wherein

R^4 denotes H;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

8. Compounds of formula **1**, according to one of claims 1 to 7, wherein

R^2 denotes C_{6-10}-aryl, which may optionally be substituted by one or more groups selected independently of one another from among C_{1-6}-alkyl, C_{1-4}-haloalkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$, $NR^{2.8}R^{2.9}$, $NHCOR^{2.8}$, $SR^{2.8}$, $SOR^{2.8}$, $SO_2R^{2.8}$ and $SO_2NR^{2.8}R^{2.9}$

or R^2 denotes C_{6-10}-aryl, which may optionally be substituted by one or more groups selected from among C_{6-10}-aryl-C_{1-6}-alkylene, C_{5-10}-heteroaryl-C_{1-6}-alkylene, C_{6-10}-aryl and a heterocyclic C_{3-10} ring, which may optionally be substituted by a group selected from among C_{1-6}-alkyl, C_{1-6}-haloalkyl, $COOR^{2.8}$, CN, halogen, $OR^{2.8}$, $NHCOR^{2.8}$, oxo, a C_{3-7}-cycloalkyl-C_{1-4} alkylene, a heterocycle-C_{1-4} alkylene and a $NR^{2.1}R^{2.2}$-C_{1-4} -alkylene,

wherein

$R^{2.8}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, a $NR^{2.1}R^{2.2}$-C_{1-4} -alkylene or C_{6-10}-aryl;

$R^{2.9}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

$R^{2.10}$ denotes $NHR^{2.10.1}$,C_{1-6}-alkylene-O-C_{1-4}-alkyl, or a heterocyclic C_{3-10} ring which may optionally be substituted by C_{1-4}-alkyl;

$R^{2.10.1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl or C_{3-7}-cycloalkyl;

or R^2 denotes C_{6-10}-aryl, to which an aromatic or non-aromatic C_{3-10} heterocycle is fused;

or R^2 denotes C_{6-10}-aryl, which may optionally be substituted by a group selected from among C_{6-10}-aryl and a heterocyclic C_{3-10} ring, which is optionally substituted by one or more groups selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-4}-haloalkyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$ $NR^{2.8}R^{2.9}$, $NHCOR^{2.8}$, $SR^{2.8}$, $SOR^{2.8}$, $SO_2R^{2.8}$, $SO_2NR^{2.8}R^{2.9}$ and oxo;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

9. Compounds of formula **1**, according to one of claims 1 to 8, wherein

R^2 denotes C_{6-10}-aryl, which may optionally be substituted by one or more groups selected from among C_{1-4}-alkyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$ and NHCOMe

$R^{2.8}$ denotes C_{1-4}-alkyl or C_{6-10}-aryl;
$R^{2.10}$ denotes $NHR^{2.10.1}$, morpholinyl, methyl-piperazinyl;

$R^{2.10.1}$ denotes H, cyclopropyl or C_{1-4}-alkyl, which may optionally be substituted by one or more groups selected from O-C_{1-4}-alkyl, OH or C_{6-10}-aryl;

or R^2 denotes C_{6-10}-aryl, which may optionally be substituted by a group selected from among phenyl and a heterocyclic C_{3-10} ring, which may optionally be substituted by C_{1-4}-alkyl, $COOR^{2.8}$, CN, halogen, $OR^{2.8}$, NHCOMe and oxo;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

10. Compounds of formula **1**, according to one of claims 1 to 7, wherein

R^2 denotes a group selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkynyl, which may optionally be substituted by a group selected from among C_{1-6}-haloalkyl, CN, $OR^{2.1}$, $NR^{2.1}R^{2.2}$, $NHCOR^{2.1}$, $SR^{2.1}$, $SOR^{2.1}$, $SO_2R^{2.1}$, $SO_2NR^{2.1}R^{2.2}$, $COOR^{2.1}$ and $CONR^{2.1}R^{2.2}$, which may optionally be substituted by a group selected from among C_{3-7}-cycloalkyl, C_{6-10}-aryl and a heterocyclic C_{3-10} ring, which may in turn optionally be substituted by one or more groups selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl or oxo;
wherein
$R^{2.1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;
$R^{2.2}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

11. Compounds of formula **1**, according to one of claims 1 to 7 and 10, wherein

R^2 denotes C_{1-6}-alkyl, which may optionally be substituted by a group selected from among C_{1-4}-haloalkyl, CN, $OR^{2.1}$, $NR^{2.1}R^{2.2}$, $COOR^{2.1}$ and $CONR^{2.1}R^{2.2}$ or which may optionally be substituted by a group selected from among C_{3-7}-cycloalkyl, C_{6-10}-aryl and a heterocyclic, aromatic C_{3-10} ring, which may in turn optionally be substituted by methyl or oxo;
wherein
$R^{2.1}$ denotes H or C_{1-4}-alkyl;
$R^{2.2}$ denotes H or C_{1-4}-alkyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

12. Compounds of formula **1**, according to one of claims 1 to 9, wherein

R^2 denotes C_{6-10}-aryl, which may optionally be substituted in the *meta* position by one or more groups selected independently of one another from among C_{1-4}-alkyl, CN, halogen, $OR^{2.8}$, $COOR^{2.8}$, $COR^{2.10}$ and NHCOMe wherein

$R^{2.8}$ denotes C_{1-4}-alkyl or C_{6-10}-aryl;

$R^{2.10}$ denotes $NHR^{2.10.1}$, morpholinyl, methyl-piperazinyl;

$R^{2.10.1}$ denotes H, cyclopropyl or C_{1-4}-alkyl, wherein the C_{1-4}-alkyl may optionally be substituted by one or more groups selected from among O-C_{1-4}-alkyl, OH and C_{6-10}-aryl;

or **R^2** denotes $NH(R^{2.10.1})$, cyclohexyl

or **NR^1R^2** denotes a heterocyclic C_{5-6} ring selected from among pyrrolidine and piperazine, which may optionally be substituted by one or more groups selected from among C_{1-4}-alkyl, OH and C_{1-4}-alkanol

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

13. Compounds of formula **1**, according to one of claims 1 to 9 and 12, wherein

R^3 denotes phenyl, which may optionally be substituted by one or more groups selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-4}-haloalkyl, C_{1-6}-alkylene-$NR^{3.1}R^{3.2}$, CN, halogen, $OR^{3.1}$, $COOR^{3.1}$, $CONR^{3.1}R^{3.2}$, $NR^{3.1}R^{3.2}$, $NHCOR^{3.1}$, NO_2, $SR^{3.1}$, $SOR^{3.1}$, $SO_2R^{3.1}$, $SO_2NR^{3.1}R^{3.2}$ and C_{1-6}-alkylene-$NHCOR^{3.1}$;

wherein

$R^{3.1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

$R^{3.2}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

14. Compounds of formula **1**, according to one of claims 1 to 9 and 12 to 13, wherein

R^3 denotes phenyl, which may optionally be substituted in the *para* position by a group selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{1-4}-haloalkyl, C_{1-6}-alkylene-$NR^{3.1}R^{3.2}$, CN, halogen, $OR^{3.1}$, $COOR^{3.1}$, $CONR^{3.1}R^{3.2}$, $NR^{3.1}R^{3.2}$, $NHCOR^{3.1}$, NO_2, $SR^{3.1}$, $SOR^{3.1}$, $SO_2R^{3.1}$, $SO_2NR^{3.1}R^{3.2}$ and C_{1-6}-alkylene-$NHCOR^{3.1}$,

wherein

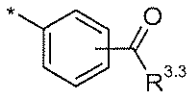
$R^{3.1}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

$R^{3.2}$ denotes H, C_{1-6}-alkyl, C_{2-6}-alkenyl or C_{2-6}-alkynyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

15. Compounds of formula **1**, according to one of claims 1 to 9 and 12 to 14, wherein

R^3 denotes a group of formula **1b**



1b;

wherein

$R^{3.3}$ denotes a heterocyclic C_{3-10} ring which may optionally be substituted by one or more groups selected from among C_{1-6}-alkyl, oxo, $COR^{3.3.1}$, $COR^{3.3.2}$, C_{1-6}-alkylene-$R^{3.3.2}$, CH_2CO-pyrrolidine and a heterocyclic C_{3-10} ring ,

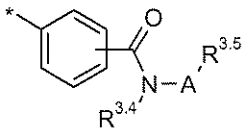
wherein a sulphur atom optionally contained in the heterocyclic C_{3-10} ring may optionally also be present as the oxide or dioxide;
wherein
$R^{3.3.1}$ denotes C_{1-6}-alkyl;
$R^{3.3.2}$ denotes NH_2, $NH(C_{1-6}$-alkyl) or $N(C_{1-6}$-alkyl)$_2$;

or $R^{3.3}$ denotes a bicyclic ring or a heterocyclic spiro ring;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

16. Compounds of formula **1**, according to one of claims 1 to 9 and 12 to 15, wherein

R^3 denotes a group of formula **1c**;



1c;

wherein
A denotes a bond or C_{1-6}-alkyl, which may optionally be substituted by oxo or NMe_2;
$R^{3.4}$ denotes H or C_{1-6}-alkyl;
$R^{3.5}$ denotes a group selected from among
C_{1-6}-alkyl, which may optionally be substituted by a group selected from among C_{3-7}-cycloalkyl, C_{6-10}-aryl and a C_{5-10} heterocycle, which may also optionally be substituted in each case by one or more groups selected from among halogen, OH, oxo, C_{1-6}-alkyl, O-C_{1-6}-alkyl, C_{1-6}-haloalkyl, a heterocyclic C_{3-10} ring and a bicyclic ring, while these groups may each optionally be substituted by one or more groups selected from among oxo, C_{1-6}-alkyl, OH, C_{6-10}-aryl, a heterocyclic ring, C_{1-6}-alkylene-$R^{3.5.1}$, O-C_{1-6}-alkylene-$R^{3.5.1}$ and NH-C_{1-6}-alkylene-$R^{3.5.1}$,

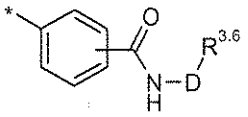
wherein

$R^{3.5.1}$ denotes a group selected from among C_{6-10}-aryl and heterocyclic C_{3-10} ring which may optionally be substituted by C_{1-6}-alkyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

17. Compounds of formula **1** according to one of claims 1 to 9 and 12 to 16, wherein

R^3 denotes a group of formula **1d**;



1d;

wherein

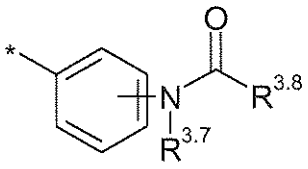
D denotes C_{2-4}-alkynyl;

$R^{3.6}$ denotes pyridinyl;

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

18. Compounds of formula **1**, according to one of claims 1 to 9 and 12 to 17, wherein

R^3 denotes a group of formula **1e**;



1e;

wherein

$R^{3.7}$ denotes H, halogen, C_{1-6}-alkyl, C_{2-6}-alkenyl;C_{2-6}-alkynyl or C_{1-6}-haloalkyl;

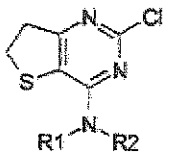
$R^{3.8}$ denotes H, OH, halogen or a group selected from among C_{1-6}-alkyl, C_{2-6}-alkenyl;C_{2-6}-alkynyl, C_{1-6}-haloalkyl, O-C_{1-6}-alkyl, C_{6-10}-aryl, a heterocyclic C_{3-10} ring and a bicyclic ring which may optionally be

substituted by one or more groups selected from among halogen, C_{1-6}-alkyl, OH, C_{1-6}-haloalkyl and O-C_{1-6}-alkyl ,

and the pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

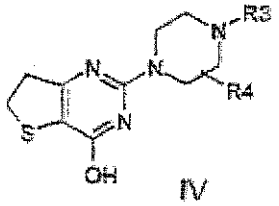
19. Intermediate products selected from among:

- compounds according to formula VIII according to preparation method B as illustrated in Scheme 1



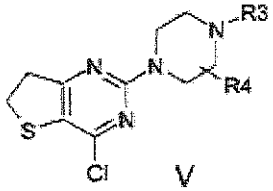
VIII

- compounds according to formula IV and V according to preparation method A as illustrated in Scheme 1



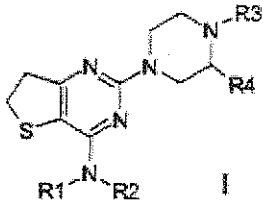
IV

and



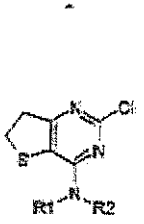
V

- compounds according to formula I as illustrated in Scheme 1

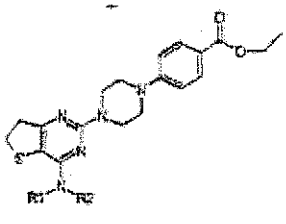


I

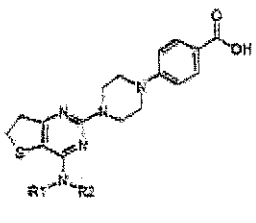
- compounds according to formula IV, VI, VII and VIII as illustrated in Scheme 2



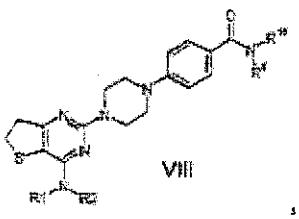
IV ,



VI ,

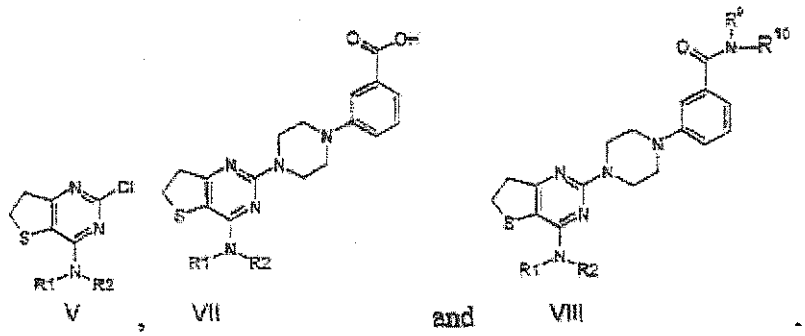


VII and

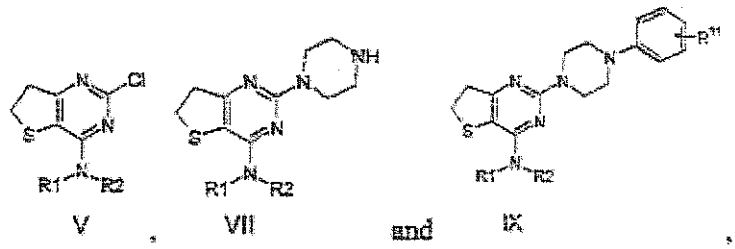


VIII ,

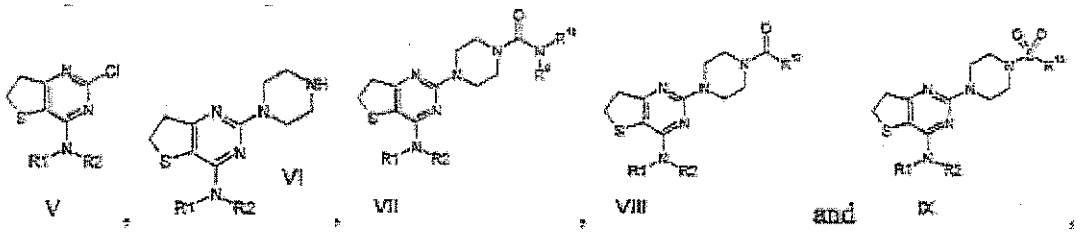
- compounds according to formula V, VII and VIII as illustrated in Scheme 3



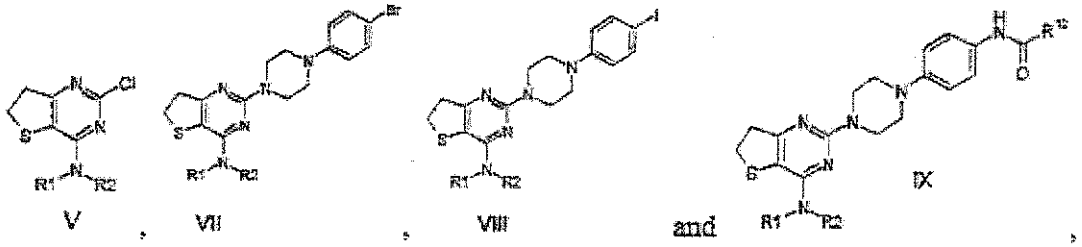
- compounds according to formula V, VII and IX as illustrated in Scheme 4



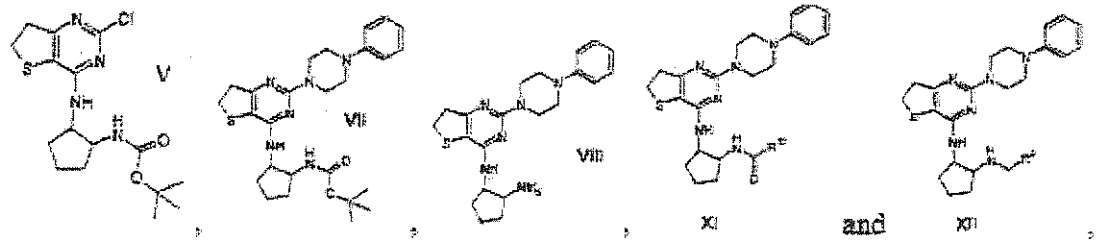
- compounds according to formula V, VI, VII, VIII and IX as illustrated in Scheme 5



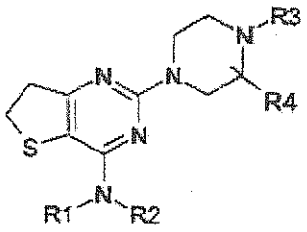
- compounds according to formula V, VII, VIII and IX as illustrated in Scheme 6



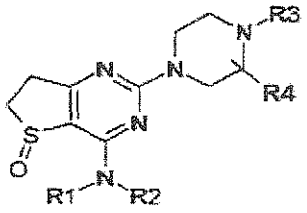
- compounds according to formula V, VII, VIII, XI and XII as illustrated in Scheme 7



- compounds according to formula I and II as illustrated in Scheme 8



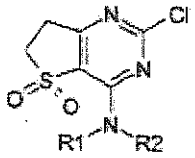
I



II

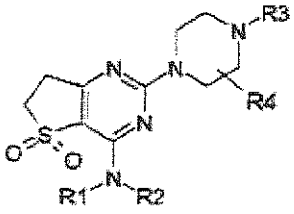
and

- compounds according to formula II and III as illustrated in Scheme 9



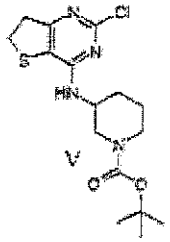
II

and

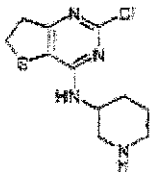


III

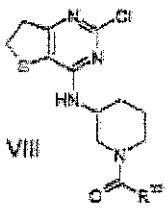
- compounds according to formula V, VI, VIII and X as illustrated in Scheme 10



V

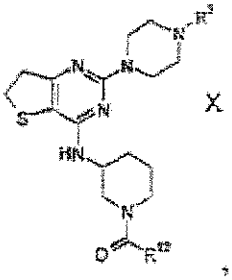


VI



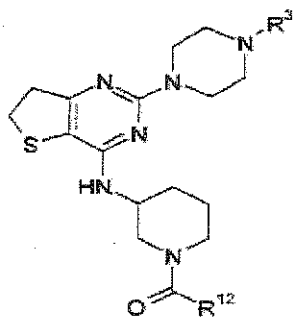
VIII

and

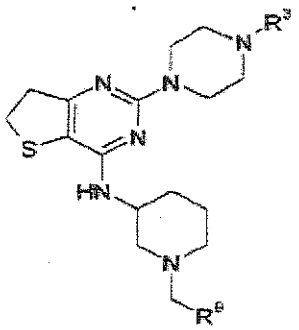


X

- compounds according to formula III and V as illustrated in Scheme 11



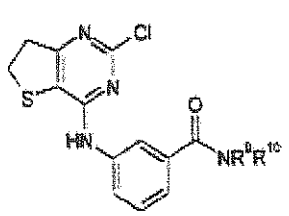
III



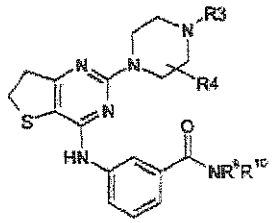
V

and

- compounds according to formula III and V as illustrated in Scheme 12



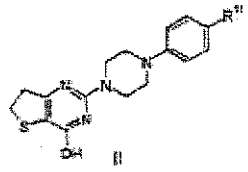
III



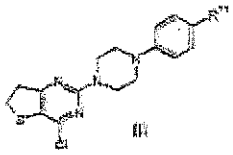
V

and

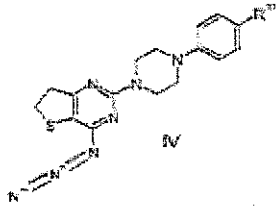
- compounds according to formula II, III, IV and V as illustrated in Scheme 13



II ,

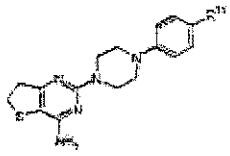


III ,



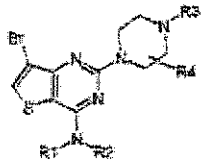
IV

and

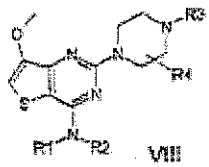


V ,

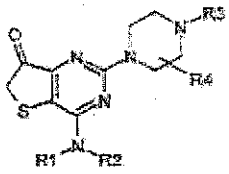
- compounds according to formula VII, VIII, IX and X as illustrated in Scheme 14,



VII ,

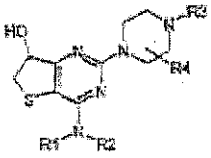


VIII ,



IX

and



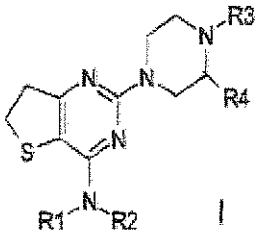
X ,

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and X have the meanings defined in claims 1 to 18,

and wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and X have the meanings defined hereinbefore and wherein R^9, R^{10}, R^{11}, R^{12} in each case independently of one another denote a group selected from among H, halogen, C_{1-6}-alkyl, C_{1-6}-haloalkyl, C_{6-10}-aryl, C_{3-7}-cycloalkyl, aromatic or non-aromatic C_{3-10} heterocycle, C_{6-10}-aryl-C_{1-6}-alkylene, C_{3-7}-cycloalkyl- C_{1-6}-alkylene and C_{3-10} heterocycle-C_{1-6}-alkylene, which may optionally be substituted by one or more groups selected from among OH, oxo, C_{1-6}-alkyl, phenyl C_{3-7}-cycloalkyl, C_{3-7} heterocycle and halogen,
and wherein R^{13} is selected from among OH, halogen, O-C_{1-6}-alkyl, C_{1-6}-alkyl, phenyl and C_{3-7}-cycloalkyl and C_{3-7} heterocycle.

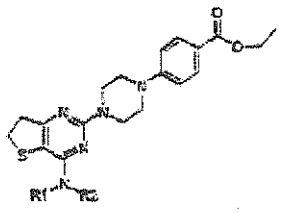
20. Intermediate products according to claim 19 selected from among:

- compounds according to formula I as illustrated in Scheme 1

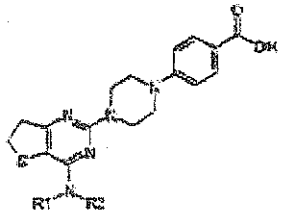


I

- compounds according to formula VI, VII and VIII as illustrated in Scheme 2

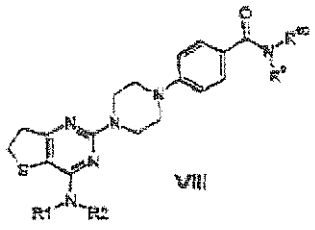


VI



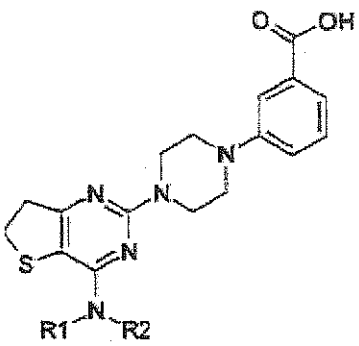
VII

and



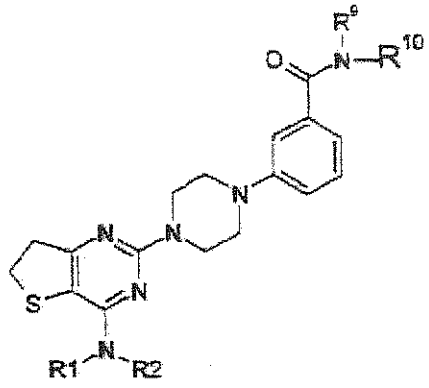
VIII

- compounds according to formula VII and VIII as illustrated in Scheme 3



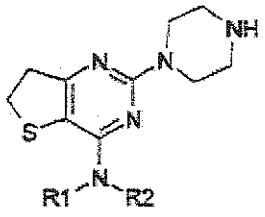
VII

and



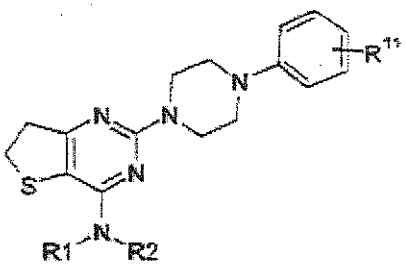
VIII

- compounds according to formula VII and IX as illustrated in Scheme 4



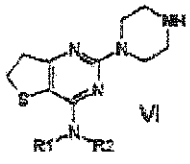
VII

and

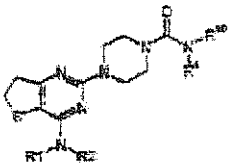


IX

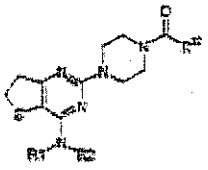
- compounds according to formula VI, VII, VIII and IX as illustrated in Scheme 5



VI

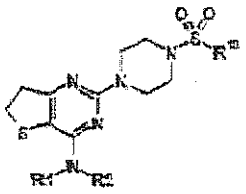


VII



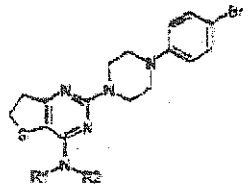
VIII

and

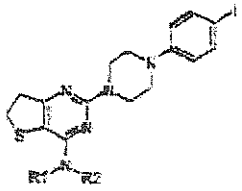


IX

- compounds according to formula VII, VIII and IX as illustrated in Scheme 6

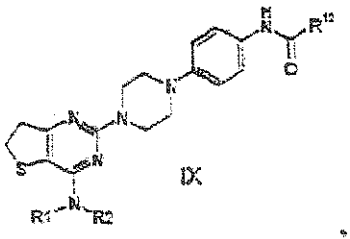


VII



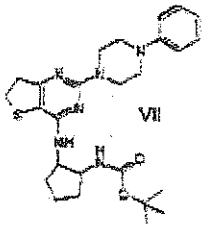
VIII

and

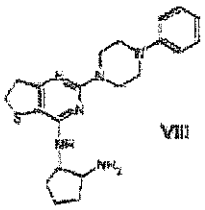


IX

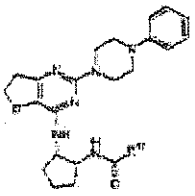
- compounds according to formula VII, VIII, XI and XII as illustrated in Scheme 7



VII

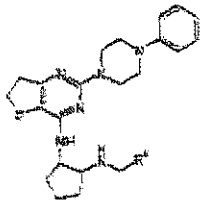


VIII



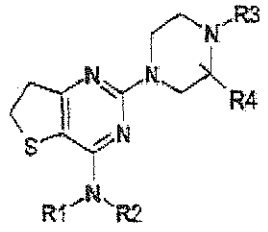
XI

and

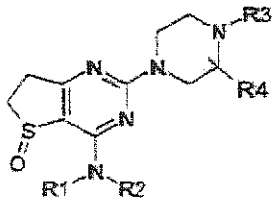


XII

- compounds according to formula I and II as illustrated in Scheme 8



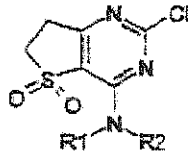
I



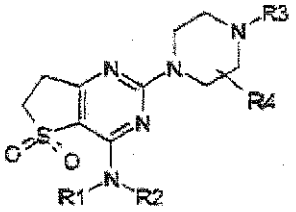
II

and

- compounds according to formula II and III as illustrated in Scheme 9



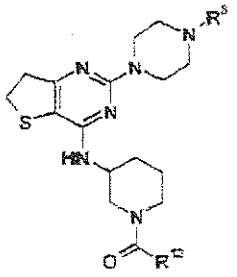
II



III

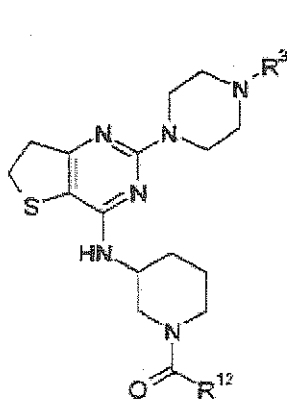
and

- compounds according to formula X as illustrated in Scheme 10

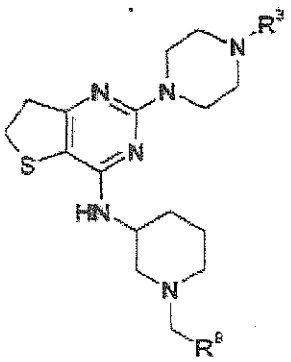


X

- compounds according to formula III and V as illustrated in Scheme 11



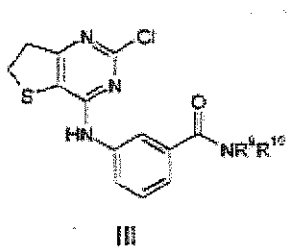
III



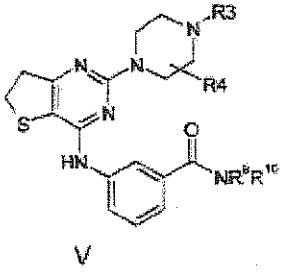
V

and

- compounds according to formula III and V as illustrated in Scheme 12



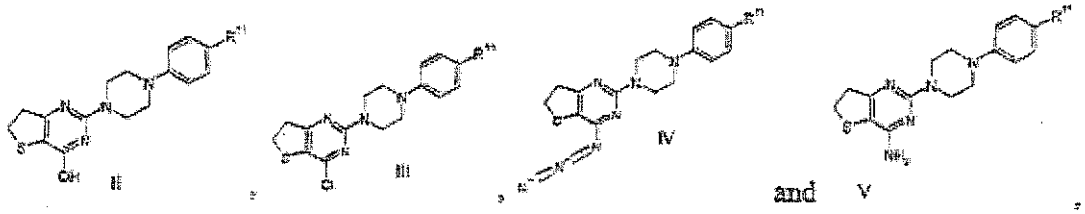
III



V

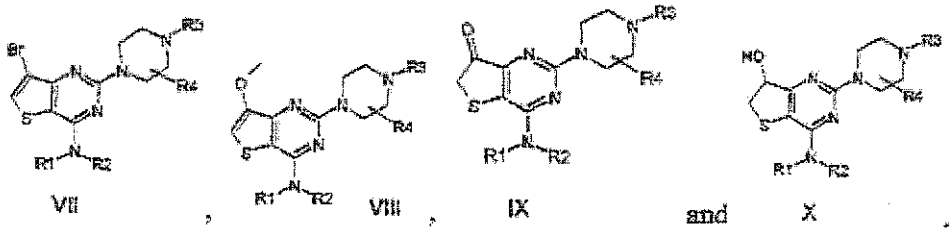
and

- compounds according to formula II, III, IV and V as illustrated in Scheme 13



II , III , IV and V ,

- compounds according to formula VII, VIII, IX and X as illustrated in Scheme 14.



VII , VIII , IX and X .

21. Compounds according to one of claims 1 to 18 as pharmaceutical compositions.

22. Use of the compounds according to one of claims 1 to 18 for preparing a medicament for the treatment of a disease selected from among respiratory or gastrointestinal complaints or diseases, inflammatory diseases of the joints, skin or eyes, cancers, and diseases of the peripheral or central nervous system.

23. Use of claim 22, wherein the medicament is directed to the prevention and treatment of respiratory or pulmonary diseases which are accompanied by increased mucus production, inflammation and/or obstructive diseases of the airways.

24. Use of any one of claims 22 to 23, wherein the medicament is directed to the treatment of inflammatory and obstructive diseases such as COPD, chronic sinusitis, asthma, Crohn's disease, ulcerative colitis.

25. Use of any one of claims 22 to 24, wherein the medicament is directed to the treatment of inflammatory diseases of the gastrointestinal tract.

26. Use of claim 22, wherein the medicament is directed to the prevention and treatment of diseases of the peripheral or central nervous system such as depression, bipolar or manic depression, acute and chronic anxiety states, schizophrenia, Alzheimer's disease, Parkinson's disease, acute and chronic multiple sclerosis or acute and chronic pain as well as injuries to the brain caused by stroke, hypoxia or craniocerebral trauma.

27. Pharmaceutical formulations, characterised in that they contain one or more compounds of formula **1** according to one of claims 1 to 18.

28. Pharmaceutical formulation suitable for administration by inhalation, characterised in that it contains a compound of formula **1** according to one of claims 1 to 18.