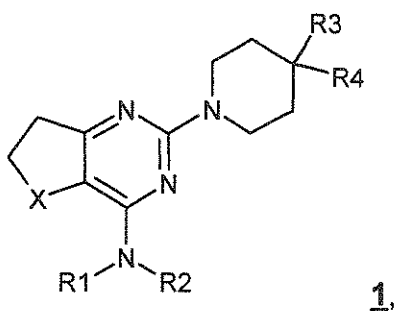


SUBSTITUTED PIPERIDINO-DIHYDROTHIENOPYRIMIDINES

The invention relates to new piperidino-dihydrothienopyrimidinesulphoxides of formula **1**, as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof,



wherein X is SO or SO₂, but preferably SO, and wherein R¹, R², R³ and R⁴ have the meanings stated in claim 1, as well as pharmaceutical compositions which contain these compounds.

These new piperidino-dihydrothienopyrimidinesulphoxides 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.

PRIOR ART

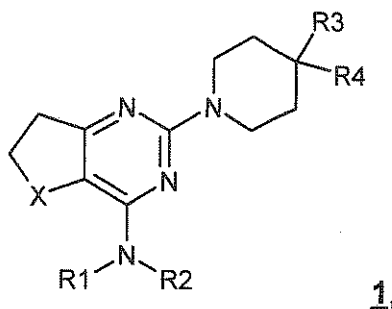
US 3,318,881 and BE 663693 disclose the preparation of piperazino-dihydrothieno-[3,2-d]pyrimidines which have cardiovascular and sedative properties. WO 2006/111549 and EP06112779.1 (EP1847543) each disclose dihydrothienopyrimidinesulphoxides which are substituted by piperazine instead of piperidine.

DESCRIPTION OF THE INVENTION

Surprisingly it has been found that, besides piperazino-dihydrothienopyrimidine-sulphoxides, piperidino-dihydrothienopyrimidinesulphoxides of formula **1**, wherein R³

and R⁴ have the meanings stated in claim 1, particularly those wherein X denotes SO, are particularly suitable for the treatment of inflammatory diseases and are superior to the corresponding piperazino-dihydrothienopyrimidinesulphoxides from the prior art.

The present invention therefore relates to compounds of formula 1



wherein

X denotes SO or SO₂,

R¹ denotes H, C₁₋₆-alkyl,

R² is H or a group selected from among C₁₋₁₀-alkyl and C₂₋₆-alkenyl, which may optionally be substituted by one or more groups selected from halogen and C₁₋₃-fluoroalkyl or which may optionally be substituted by one or more groups selected from among OR^{2.1}, COOR^{2.1}, CONR^{2.2}R^{2.3}, SR^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, C₆₋₁₀-aryl, -het, hetaryl, a mono- or bicyclic -C₃₋₁₀-cycloalkyl, CH₂-NR^{2.2}R^{2.3} and NR^{2.2}R^{2.3},

which in turn may optionally be substituted by one or more groups selected from among OH, halogen, OR^{2.1}, oxo, CF₃, CHF₂, CH₂F, C₁₋₆-alkyl, C₁₋₆-alkanol, C₆₋₁₀-aryl, COOR^{2.1}, CH₂-NR^{2.2}R^{2.3} and NR^{2.2}R^{2.3},

wherein

het denotes a three- to eleven-membered, mono- or bicyclic, saturated or partially saturated, optionally anellated or optionally bridged heterocycle is, which contains 1, 2, 3 or 4 heteroatoms selected independently of one another from among N, S or O contains,
and wherein

hetaryl is a five- to ten-membered, mono- or bicyclic, optionally anellated heteroaryl, which contains 1, 2, 3 or 4 heteroatoms selected independently of one another from among N, S or O,

and wherein

cycloalkyl may be saturated or partially saturated,

wherein $R^{2.1}$ is H or is a group selected from among C_{1-6} -alkyl, C_{1-6} -alkanol, C_{1-3} -haloalkyl, mono- or bicyclic, $-C_{3-10}$ -cycloalkyl, C_{6-10} -aryl- C_{1-6} -alkylene, hetaryl- C_{1-6} -alkylene, het- C_{1-6} -alkylene, C_{3-10} -cycloalkyl- C_{1-6} -alkylene, a mono- or bicyclic C_{6-10} -aryl, heteroaryl and a -het, which may optionally be substituted by one or more groups selected from among OH, O- $(C_{1-3}$ -alkyl), halogen, C_{1-6} -alkyl and C_{6-10} -aryl,

wherein $R^{2.2}$ and $R^{2.3}$ independently of one another denote H or a group selected from among C_{1-6} -alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} -aryl- C_{1-6} -alkylene, hetaryl- C_{1-6} -alkylene, mono- or bicyclic C_{6-10} -aryl, het, hetaryl, CO-NH₂, CO-NHCH₃, -CO-N(CH₃)₂, SO₂-(C_{1-2} -alkyl), CO- $R^{2.1}$ and COOR^{2.1}, which may optionally be substituted by one or more groups selected from among OH, halogen, C_{1-6} -alkyl, C_{6-10} -aryl and COOR^{2.1},

or

R^2 denotes a mono- or polycyclic C_{3-10} cycloalkyl, which may optionally be bridged one or more times via C_{1-3} -alkyl groups and which may optionally be substituted by a group selected from among branched or unbranched C_{1-6} -alkanol, C_{1-3} -fluoroalkyl, C_{1-3} -alkylene-OR^{2.1}, OR^{2.1}, COOR^{2.1}, -SO₂-NR^{2.2}R^{2.3}, het, -NH-CO-O- $(C_{1-6}$ -alkyl), -NH-CO- $(C_{1-6}$ -alkyl), -NH-CO-O- $(C_{6-10}$ -aryl), -NH-CO- $(C_{6-10}$ -aryl), -NH-CO-O-hetaryl, -NH-CO-hetaryl, -NH-CO-O- $(C_{1-3}$ -alkylene)- $(C_{6-10}$ -aryl), -NH-CO- $(C_{1-3}$ -alkylene)- $(C_{6-10}$ -aryl), -N(C_{1-3} -alkyl)-CO- $(C_{1-6}$ -alkyl), -N(C_{1-3} -alkyl)-CO-O- $(C_{6-10}$ -aryl), -N(C_{1-3} -alkyl)-CO- $(C_{6-10}$ -aryl), -N(C_{1-3} -alkyl)-CO-O-hetaryl, -N(C_{1-3} -alkyl)-CO-hetaryl, -N(C_{1-3} -alkyl)-CO-O- $(C_{1-3}$ -alkylene)- $(C_{6-10}$ -aryl), -N(C_{1-3} -alkyl)-CO- $(C_{1-3}$ -alkylene)- $(C_{6-10}$ -aryl), C_{6-10} -aryl, C_{1-6} -alkyl, C_{6-10} -aryl- C_{1-6} -alkylene, hetaryl- C_{1-6} -alkylene, mono- or bicyclic C_{3-10} cycloalkyl and NR^{2.2}R^{2.3}, which may optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, halogen, CF₃, CHF₂, CH₂F, C_{1-6} -alkyl, C_{6-10} -aryl and NR^{2.2}R^{2.3},

or

R^2 denotes a mono- or polycyclic C_{6-10} -aryl, which may optionally be substituted by OH, SH or halogen or by one or more groups selected from among OR^{2.1}, COOR^{2.1}, NR^{2.2}R^{2.3}, CH₂-NR^{2.2}R^{2.3}, C_{3-10} -cycloalkyl, het, C_{1-6} -alkyl, C_{1-3} -

fluoroalkyl, CF_3 , CHF_2 , CH_2F , C_{6-10} -aryl- C_{1-6} -alkylene, het- C_{1-6} -alkylene, hetaryl- C_{1-6} -alkylene, C_{6-10} -aryl, $\text{SO}_2\text{-CH}_3$, $\text{SO}_2\text{-CH}_2\text{CH}_3$ and $\text{SO}_2\text{-NR}^{2.2}\text{R}^{2.3}$, which may in turn optionally be substituted by one or more groups selected from among OH, $\text{OR}^{2.1}$, CF_3 , CHF_2 , CH_2F , oxo, halogen, CF_3 , CHF_2 , CH_2F , C_{1-6} -alkyl, C_{6-10} -aryl and $\text{NR}^{2.2}\text{R}^{2.3}$,

or

R^2 denotes a group selected from among het and hetaryl, which may optionally be substituted by one or more groups selected from among halogen, OH, oxo, CF_3 , CHF_2 and CH_2F or by one or more groups selected from among $\text{OR}^{2.1}$, C_{1-3} -alkylene- $\text{OR}^{2.1}$, $\text{SR}^{2.1}$, $\text{SO-R}^{2.1}$, $\text{SO}_2\text{-R}^{2.1}$, $\text{COOR}^{2.1}$, $\text{COR}^{2.1}$, C_{1-6} -alkanol, mono- or bicyclic C_{3-10} -cycloalkyl, C_{6-10} -aryl, C_{1-6} -alkyl, C_{6-10} -aryl- C_{1-6} -alkylene, hetaryl- C_{1-6} -alkylene, het, hetaryl, C_{1-3} -alkylene- $\text{OR}^{2.1}$ and $\text{NR}^{2.2}\text{R}^{2.3}$, which may in turn optionally be substituted by one or more groups selected from among OH, $\text{OR}^{2.1}$, oxo, halogen, CF_3 , CHF_2 , CH_2F , C_{1-6} -alkyl, C_{6-10} -aryl and $\text{NR}^{2.2}\text{R}^{2.3}$,

or wherein

NR^1R^2 together denotes a heterocyclic C_{4-7} ring, which may optionally be bridged, which contains 1, 2 or 3 heteroatoms selected from among N, O and S and which may optionally be substituted by one or more groups selected from among OH, $\text{OR}^{2.1}$, C_{1-3} -alkylene- $\text{OR}^{2.1}$, oxo, halogen, C_{1-6} -alkyl, C_{6-10} -aryl, $\text{COOR}^{2.1}$, $\text{CH}_2\text{-NR}^{2.2}\text{-COO-R}^{2.1}$, $\text{CH}_2\text{-NR}^{2.2}\text{-CO-R}^{2.1}$, $\text{CH}_2\text{-NR}^{2.2}\text{-CO-CH}_2\text{-NR}^{2.2}\text{R}^{2.3}$, $\text{CH}_2\text{-NR}^{2.2}\text{-SO}_2\text{-C}_{1-3}\text{-alkyl}$, $\text{CH}_2\text{-NR}^{2.2}\text{-SO}_2\text{-NR}^{2.2}\text{R}^{2.3}$, $\text{CH}_2\text{-NR}^{2.2}\text{-CO-NR}^{2.2}\text{R}^{2.3}$, $\text{CO-NR}^{2.2}\text{R}^{2.3}$, $\text{CH}_2\text{-NR}^{2.2}\text{R}^{2.3}$ and $\text{NR}^{2.2}\text{R}^{2.3}$,

and wherein

R^3 is a C_{6-10} -aryl, which may optionally be substituted by in the ortho, para or meta position by one, two or three groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, C_{1-6} -alkyl, C_{1-3} -fluoroalkyl, $\text{-C}_{1-3}\text{-alkylene-OR}^{2.1}$, $\text{-C}_{1-3}\text{-alkylene-NR}^{2.2}\text{R}^{2.3}$, $\text{-NR}^{2.2}\text{R}^{2.3}$, $\text{O-R}^{2.1}$, $\text{SO-R}^{2.1}$, $\text{SO}_2\text{-R}^{2.1}$, $\text{COOR}^{2.1}$, $\text{-CO-NH-(C}_{1-6}\text{-alkylene)-hetaryl}$, -CO-NH-hetaryl , $\text{-CO-N(CH}_3\text{)-het}$, $\text{-CO-N(CH}_3\text{)-(C}_{1-3}\text{-alkylene)-het}$, $\text{-CO-N(CH}_3\text{)-(C}_{1-3}\text{-alkylene)-hetaryl}$, $\text{-CO-N(C}_{3-7}\text{-cycloalkyl)-het}$, $\text{-CO-NR}^{2.2}\text{R}^{2.3}$, $\text{-CO-NH-(C}_{1-6}\text{-alkylene)-het}$, $\text{NR}^{2.2}\text{-CO-R}^{2.1}$, $\text{C}_{6-10}\text{-aryl}$, $\text{C}_{6-10}\text{-aryl-C}_{1-2}\text{-alkylene}$, het- $\text{C}_{1-2}\text{-alkylene}$, -het, -CO-het, , CO-N(CH₃)- $\text{C}_{3-7}\text{-cycloalkyl}$, $\text{C}_{3-7}\text{-cycloalkyl}$, $\text{C}_{3-7}\text{-cycloalkyl-C}_{1-2}\text{-alkylene}$, hetaryl- $\text{C}_{1-2}\text{-alkylene}$ and hetaryl, while this groups may optionally be substituted by one or more groups selected from among OH, halogen, $\text{-C}_{1-3}\text{-fluoroalkyl}$, oxo, methyl and phenyl,

or wherein

R^3 is a group selected from among het and hetaryl, which may optionally be substituted by one or more groups selected from among halogen, C_{1-3} -fluoroalkyl, CN, OH, oxo, $-C_{1-6}$ -alkyl, $-C_{1-3}$ -alkylene- $NR^{2.2}R^{2.3}$, $-NR^{2.2}R^{2.3}$, $SO-R^{2.1}$, $SO_2-R^{2.1}$, $-O-R^{2.1}$, $-COOR^{2.1}$, $SO_2-(CH_3)$, $SO_2-(CH_2-CH_3)$, C_{6-10} -aryl, het, C_{3-7} -cycloalkyl and hetaryl, which may in turn optionally be substituted by one or more groups selected from among OH, halogen, $-C_{1-3}$ -fluoroalkyl, C_{1-6} -alkyl, C_{6-10} -aryl, $-COO(C_{1-3}$ -alkyl) and $O-(C_{1-3}$ -alkyl),

or wherein

R^3 denotes $-O-R^{3.1}$,

wherein $R^{3.1}$ is a group selected from among $-C_{1-6}$ -alkyl, $-C_{6-10}$ -aryl, $-C_{1-3}$ -alkylene- C_{6-10} -aryl, hetaryl and het, which may optionally be substituted in the ortho, para or meta position by one, two or three groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, C_{1-6} -alkyl, C_{1-3} -fluoroalkyl, $CO-(C_{1-5}$ -alkyl), $-CO-(C_{1-3}$ -fluoroalkyl), $-CO-NH-(C_{1-6}$ -alkylene)-hetaryl, $-CO-N(C_{1-3}$ -alkyl)- $(C_{1-6}$ -alkylene)-hetaryl, $-CO-N(C_{1-3}$ -alkyl)-het, $-CO-N(C_{3-7}$ -cycloalkyl)-het, $-C_{1-3}$ -alkylene- $OR^{2.1}$, $-C_{1-3}$ -alkylene- $NR^{2.2}R^{2.3}$, $-NR^{2.2}R^{2.3}$, $O-R^{2.1}$, $SO-R^{2.1}$, $SO_2-R^{2.1}$, $COOH$, $COO-(C_{1-4}$ -alkyl), $-O-C_{1-3}$ -alkylene- $N(C_{1-3}$ -alkyl) $_2$, $CO-NR^{2.2}R^{2.3}$, $NR^{2.2}-CO-R^{2.1}$, C_{6-10} -aryl, C_{6-10} -aryl- C_{1-2} -alkylene, het- C_{1-2} -alkylene, $-CO$ -het, het, $-CO$ - C_{3-7} -cycloalkyl, $-CO-N(C_{1-3}$ -alkyl)- C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl- C_{1-2} -alkylene, hetaryl- C_{1-2} -alkylene and hetaryl,

which may in turn optionally be substituted by 1, 2, 3 or 4 groups selected independently of one another from among F, Cl, Br, methyl, O-methyl, ethyl, O-ethyl, OH, oxo and CF_3 .

and wherein

R^4 denotes H, CN, OH, CF_3 , CHF_2 , CH_2F , F, methyl, ethyl, $-O-(C_{1-3}$ -alkyl), $-C_{1-3}$ -alkylene-OH, $-COO(C_{1-3}$ -alkyl), $-CO$ -het, $-(C_{1-2}$ -alkylene)- $NH-SO_2-(C_{1-2}$ -alkyl), $-(C_{1-2}$ -alkylene)- $N(C_{1-3}$ -alkyl)- $SO_2-(C_{1-2}$ -alkyl), $-(C_{1-2}$ -alkylene)- $O-(C_{1-2}$ -alkylene)- C_{6-10} -aryl, $-C_{1-3}$ -alkylene- $O-C_{1-3}$ -alkyl, $-(C_{1-2}$ -alkylene)- $N(C_{1-3}$ -alkyl)- $CO-(C_{1-2}$ -alkyl), $-NH-CO-(C_{1-3}$ -alkylene)- $O-(C_{1-3}$ -alkyl), $-C_{1-3}$ -alkylene- $NH-CO-(C_{1-3}$ -alkyl), $-C_{1-3}$ -alkylene- $NH-CO-(C_{1-3}$ -alkylene)- $N(C_{1-3}$ -alkyl) $_2$, $-O-(C_{1-2}$ -alkylene)- $(C_{6-10}$ -aryl), $-C_{1-3}$ -alkylene- $NH-CO-(C_{1-3}$ -alkylene)- $O-(C_{1-3}$ -alkyl), $-CO-(C_{6-10}$ -aryl), $-(C_{1-2}$ -alkylene)- $N(C_{1-3}$ -alkyl)- $CO-(C_{1-2}$ -alkylene)- $O-(C_{1-3}$ -alkyl), wherein the aryl in the above groups may in turn optionally be substituted by one or more other groups selected from among F, Cl, Br, methyl, ethyl, propyl,

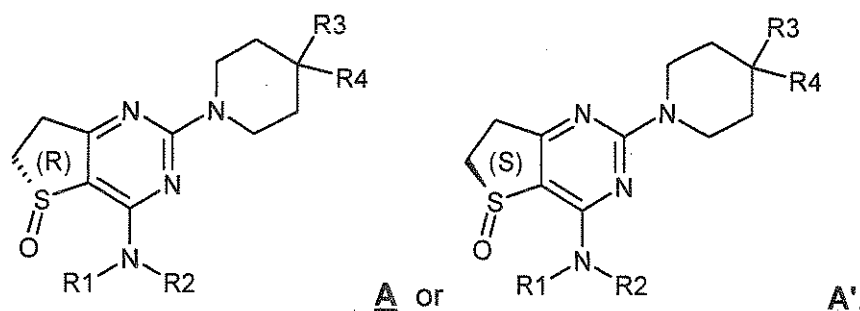
isopropyl, cyclopropyl, -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -O-cyclopropyl, -OH and CF_3

or wherein

R^3 and R^4 together form a mono- or bicyclic, unsaturated, saturated or partially saturated heterocycle, which contains 1, 2 or 3 heteroatoms selected from among N, O and S contains and which may optionally be substituted by one or more groups selected from among halogen, OH, oxo, C_{1-3} -fluoroalkyl, CN, C_{1-6} -alkyl, -O- $\text{R}^{2.1}$, $-\text{COOR}^{2.1}$, $\text{SO-R}^{2.1}$, $\text{SO}_2\text{-R}^{2.1}$, $-\text{C}_{1-3}$ -alkylene- $\text{NR}^{2.2}\text{R}^{2.3}$, $-\text{NR}^{2.2}\text{R}^{2.3}$, C_{6-10} -aryl, C_{3-7} - cycloalkyl, het and hetaryl,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

The present invention expressly relates to both the R-enantiomers of formula A and the S-enantiomers of formula A' with respect to the stereocentre at the sulfoxide-sulphur atom of the compounds of formula 1,



Also preferred are the above mentioned compounds of formula 1, wherein

X denotes SO or SO_2 ,

R^1 denotes H

R^2 denotes H or C_{1-10} -alkyl, which may optionally be substituted by one or more groups selected from halogen and C_{1-3} -fluoroalkyl or which may optionally be substituted by one or more groups selected from among $\text{OR}^{2.1}$, $\text{COOR}^{2.1}$, $\text{CONR}^{2.2}\text{R}^{2.3}$, $\text{SR}^{2.1}$, $\text{SO-R}^{2.1}$, $\text{SO}_2\text{-R}^{2.1}$, phenyl, het, hetaryl, a monocyclic C_{3-7} -cycloalkyl, $\text{CH}_2\text{-NR}^{2.2}\text{R}^{2.3}$ and $\text{NR}^{2.2}\text{R}^{2.3}$, which in turn may optionally be substituted by one or more groups selected from among OH, F, Cl, Br, $\text{OR}^{2.1}$, oxo, CF_3 , CHF_2 , CH_2F , C_{1-6} -alkyl, C_{1-6} -alkanol, phenyl, $\text{COOR}^{2.1}$, $\text{CH}_2\text{-NR}^{2.2}\text{R}^{2.3}$ and $\text{NR}^{2.2}\text{R}^{2.3}$,

wherein

het is a three- to seven-membered, monocyclic, saturated or partially saturated heterocycle or a seven- to eleven-membered, bicyclic, saturated or partially saturated heterocycle, which contains 1, 2, 3 or 4 heteroatoms selected independently of one another from among N, S or O, and wherein

hetaryl is a five- to six-membered, monocyclic, aromatic heteroaryl or a seven- to eleven-membered, bicyclic, aromatic heteroaryl, which contains in each case 1, 2, 3 or 4 heteroatoms selected independently of one another from among N, S or O,

and wherein

cycloalkyl may be saturated or partially saturated,

wherein $R^{2.1}$ is H or a group selected from among C_{1-6} -alkyl, C_{1-6} -alkanol, C_{1-3} -haloalkyl, monocyclic C_{3-7} cycloalkyl, phenyl- C_{1-6} -alkylene, hetaryl- C_{1-6} -alkylene, het- C_{1-6} -alkylene, - C_{3-7} -cycloalkyl- C_{1-6} -alkylene, phenyl, hetaryl and a het, which may optionally be substituted by one or more groups selected from among OH, F, Cl, C_{1-6} -alkyl, -O-(C_{1-3} -alkyl) and phenyl,

wherein $R^{2.2}$ and $R^{2.3}$ independently of one another denote H or a group selected from among C_{1-6} -alkyl, monocyclic C_{3-7} cycloalkyl, phenyl- C_{1-3} -alkylene, hetaryl- C_{1-3} -alkylene, phenyl, het, hetaryl, CO-NH₂, -CO-NHCH₃, -CON(CH₃)₂, SO₂-(C_{1-2} -alkyl), CO- $R^{2.1}$ and COOR^{2.1},

which may optionally be substituted by one or more groups selected from among OH, F, Cl, C_{1-6} -alkyl, phenyl and COOR^{2.1},

or

R^2 denotes a monocyclic C_{3-7} cycloalkyl, which may optionally be substituted by a group selected from among branched or unbranched C_{1-6} -alkanol, C_{1-3} -fluoroalkyl, OR^{2.1}, C_{1-3} -alkylene-OR^{2.1}, OR^{2.1}, COOR^{2.1}, SO₂-NR^{2.2}R^{2.3}, -het, -NH-CO-O-(phenyl), phenyl, C_{1-6} -alkyl, phenyl- C_{1-6} -alkylene, -hetaryl- C_{1-6} -alkylene, monocyclic C_{3-7} cycloalkyl and NR^{2.2}R^{2.3}, which may optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, F, Cl, CF₃, CHF₂, CH₂F, C_{1-6} -alkyl, phenyl and -NR^{2.2}R^{2.3},

or

R² denotes a phenyl, which may optionally be substituted by OH, SH or halogen or by one or more groups selected from among OR^{2.1}, COOR^{2.1}, NR^{2.2}R^{2.3}, CH₂-NR^{2.2}R^{2.3}, C₃₋₇-cycloalkyl, C₃₋₇ heterocycle, C₁₋₆-alkyl, C₁₋₃-fluoroalkyl, phenyl-C₁₋₆-alkylene, -het-C₁₋₆-alkylene, -hetaryl-C₁₋₆-alkylene, phenyl, SO₂-CH₃, SO₂-CH₂CH₃ and SO₂-NR^{2.2}R^{2.3}, which may in turn optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, F, Cl, CF₃, CHF₂, CH₂F, C₁₋₆-alkyl, phenyl and NR^{2.2}R^{2.3},

or

R² denotes a group selected from among het and hetaryl, which may optionally be substituted by one or more groups selected from among F, Cl, OH, oxo, CF₃, CHF₂ and CH₂F or by one or more groups selected from among OR^{2.1}, -C₁₋₃-alkylene-OR^{2.1}, SR^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, COOR^{2.1}, COR^{2.1}, C₁₋₆-alkanol, monocyclic C₃₋₇-cycloalkyl, phenyl, C₁₋₆-alkyl, phenyl-C₁₋₆-alkylene, -hetaryl-C₁₋₆-alkylene, -het, -hetaryl, and NR^{2.2}R^{2.3}, which may in turn optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, F, Cl, CF₃, CHF₂, CH₂F, C₁₋₆-alkyl, phenyl and NR^{2.2}R^{2.3},

or wherein

NR¹R² together denotes a heterocyclic C₄₋₇ ring which may optionally be bridged, which contains 1, 2 or 3 heteroatoms selected from among N, O and S and which may optionally be substituted by one or more groups selected from among OH, OR^{2.1}, C₁₋₃-alkylene-OR^{2.1}, oxo, F, Cl, C₁₋₆-alkyl, phenyl, COOR^{2.1}, CH₂-NR^{2.2}-COO-R^{2.1}, CH₂-NR^{2.2}-CO-R^{2.1}, CH₂-NR^{2.2}-CO-CH₂-NR^{2.2}R^{2.3}, CH₂-NR^{2.2}-SO₂-C₁₋₃-alkyl, CH₂-NR^{2.2}-SO₂-NR^{2.2}R^{2.3}, CH₂-NR^{2.2}-CO-NR^{2.2}R^{2.3}, CO-NR^{2.2}R^{2.3}, CH₂-NR^{2.2}R^{2.3} and NR^{2.2}R^{2.3},

and wherein

R³ is a naphthalene or phenyl, which may optionally be substituted in the ortho, para or meta position by one or two groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, C₁₋₆-alkyl, C₁₋₃-fluoroalkyl, -C₁₋₃-alkylene-OR^{2.1}, -C₁₋₃-alkylene-NR^{2.2}R^{2.3}, -NR^{2.2}R^{2.3}, O-R^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, COOR^{2.1}, -CO-NH-(C₁₋₆-alkylene)-hetaryl, -CO-NH-hetaryl, -CO-N(CH₃)-het, -CO-N(CH₃)-(C₁₋₃-alkylene)-het, -CO-N(CH₃)-(C₁₋₃-alkylene)-hetaryl, -CO-N(C₃₋₇-cycloalkyl)-het, CO-NR^{2.2}R^{2.3},

-CO-NH-(C₁₋₆-alkylene)-het, -NR^{2.2}-CO-R^{2.1}, phenyl, phenyl-C₁₋₂-alkylene, -het-C₁₋₂-alkylene, -het, -CO-het, -CO-N(CH₃)-het, CO-N(CH₃)-C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₂-alkylene, -hetaryl-C₁₋₂-alkylene and -hetaryl,

while these groups may optionally be substituted by one or more groups selected from among OH, F, Cl, -C₁₋₃-fluoroalkyl, oxo, methyl and phenyl,

or wherein

R³ denotes a group selected from among het and hetaryl, which may optionally be substituted by one or more groups selected from among F, Cl, Br, C₁₋₃-fluoroalkyl, CN, OH, oxo, -C₁₋₆-alkyl, -C₁₋₃-alkylene-NR^{2.2}R^{2.3}, -NR^{2.2}R^{2.3}, SO-R^{2.1}, SO₂-R^{2.1}, -O-R^{2.1}, -COOR^{2.1}, SO₂-(CH₃), SO₂-(CH₂-CH₃), phenyl, het, C₃₋₇-cycloalkyl and hetaryl, which may in turn optionally be substituted by one or more groups selected from among OH, F, Cl, Br, -C₁₋₃-fluoroalkyl, C₁₋₆-alkyl, phenyl, -COO(C₁₋₃-alkyl) and O-(C₁₋₃-alkyl),

or wherein

R³ denotes -O-R^{3.1},

wherein **R^{3.1}** is a group selected from among -C₁₋₆-alkyl, -phenyl, -C₁₋₃-alkylene-phenyl, hetaryl and het,

which is optionally substituted in the ortho, para or meta position by one, two or three groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, C₁₋₆-alkyl, C₁₋₃-fluoroalkyl, CO-(C₁₋₅-alkyl), -CO-(C₁₋₃-fluoroalkyl), -CO-NH-(C₁₋₆-alkylene)-hetaryl, -CO-N(CH₃)-(C₁₋₆-alkylene)-hetaryl, -CO-N(CH₃)-het, -CO-N(C₃₋₇-cycloalkyl)-het, -C₁₋₃-alkylene-OR^{2.1}, -C₁₋₃-alkylene-NR^{2.2}R^{2.3}, -NR^{2.2}R^{2.3}, O-R^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, COOH, COO-(C₁₋₄-alkyl), -O-C₁₋₃-alkylene-N(C₁₋₃-alkyl)₂, CO-NR^{2.2}R^{2.3}, NR^{2.2}-CO-R^{2.1}, phenyl, phenyl-C₁₋₂-alkylene, het-C₁₋₂-alkylene, -CO-het, het, -CO-C₃₋₇-cycloalkyl, -CO-N(CH₃)-C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₂-alkylene, hetaryl-C₁₋₂-alkylene and hetaryl,

which may in turn optionally be substituted by 1, 2, 3 or 4 groups selected independently of one another from among F, Cl, Br, methyl, O-methyl, ethyl, O-ethyl, OH, oxo and CF₃,

and wherein

R⁴ denotes H, CN, OH, CF₃, CHF₂, CH₂F, F, methyl, ethyl, O-methyl, O-ethyl, O-propyl, O-isopropyl, -C₁₋₃-alkylene-OH, -COO(C₁₋₃-alkyl), -CO-het, -(C₁₋₂-alkylene)-NH-SO₂-(C₁₋₂-alkyl), -(C₁₋₂-alkylene)-N(CH₃)-SO₂-(C₁₋₂-alkyl),

$-(C_{1-2}\text{-alkylene})-O-(C_{1-2}\text{-alkylene})\text{-phenyl}$,
 $-C_{1-3}\text{-alkylene}-O-C_{1-3}\text{-alkyl}$, $-(C_{1-2}\text{-alkylene})-N(CH_3)-CO-(C_{1-2}\text{-alkyl})$,
 $-NH-CO-(C_{1-3}\text{-alkylene})-O-(C_{1-3}\text{-alkyl})$, $-C_{1-3}\text{-alkylene}-NH-CO-(C_{1-3}\text{-alkyl})$,
 $-C_{1-3}\text{-alkylene}-NH-CO-(C_{1-3}\text{-alkylene})-N(C_{1-3}\text{-alkyl})_2$, $-O-(C_{1-2}\text{-alkylene})\text{-phenyl}$
 $-C_{1-3}\text{-alkylene}-NH-CO-(C_{1-3}\text{-alkylene})-O-(C_{1-3}\text{-alkyl})$, $-CO\text{-phenyl}$,
 $-(C_{1-2}\text{-alkylene})-N(CH_3)-CO-(C_{1-2}\text{-alkylene})-O-(C_{1-3}\text{-alkyl})$,
 wherein the phenyl in the above groups may optionally be substituted by one or more other groups selected from among F, Cl, Br, methyl, ethyl, propyl, -O-methyl, -O-ethyl, -O-propyl, -OH and CF_3

or wherein

R^3 and R^4 together form a mono- or bicyclic, unsaturated, saturated or partially saturated heterocycle, which contains 1, 2 or 3 heteroatoms selected from among N, O and S contains and which may optionally be substituted by one or more groups selected from among F, Cl, Br, OH, oxo, $C_{1-3}\text{-fluoroalkyl}$, CN, $C_{1-6}\text{-alkyl}$, $-O-R^{2.1}$, $-COOR^{2.1}$, $SO-R^{2.1}$, $SO_2-R^{2.1}$, $-C_{1-3}\text{-alkylene}-NR^{2.2}R^{2.3}$, $-NR^{2.2}R^{2.3}$, phenyl, $C_{3-7}\text{-cycloalkyl}$, het and hetaryl,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Also more preferred are the above compounds of formula 1, wherein

X denotes SO,

R^1 denotes H

R^2 denotes H or $C_{1-6}\text{-alkyl}$, which may optionally be substituted by one or more groups selected from F, Cl, CF_3 , CHF_2 or CH_2F or which may optionally be substituted by one or more groups selected from among $OR^{2.1}$, $COOR^{2.1}$, $CONR^{2.2}R^{2.3}$, $SR^{2.1}$, $SO-R^{2.1}$, $SO_2-R^{2.1}$, phenyl, het, hetaryl, a monocyclic $C_{3-7}\text{-cycloalkyl}$, $CH_2-NR^{2.2}R^{2.3}$ and $NR^{2.2}R^{2.3}$,
 which in turn may optionally be substituted by one or more groups selected from among OH, F, Cl, Br, CF_3 , CHF_2 , CH_2F , $OR^{2.1}$, oxo, methyl, ethyl, propyl, isopropyl, methanol, ethanol, phenyl, $COOR^{2.1}$, $CH_2-NR^{2.2}R^{2.3}$ and $NR^{2.2}R^{2.3}$,

wherein

het is a three- to seven-membered, monocyclic, saturated or partially saturated heterocycle, which contains 1, 2 or 3 heteroatoms selected independently of one another from among N, S or O,

and wherein

hetaryl is a five- to six-membered, monocyclic, aromatic heteroaryl which contains 1, 2 or 3 heteroatoms selected independently of one another from among N, S or O,

and wherein

cycloalkyl may be saturated or partially saturated,

wherein $R^{2.1}$ is H or a group selected from among methyl, ethyl, propyl, isopropyl, methanol, ethanol, monocyclic C_{3-7} cycloalkyl, phenyl- C_{1-2} -alkylene, -hetaryl- C_{1-2} -alkylene, -het- C_{1-2} -alkylene, C_{3-7} -cycloalkyl- C_{1-2} -alkylene, phenyl, hetaryl and a het,

which may optionally be substituted by one or more groups selected from among OH, F, Cl, methyl, ethyl, propyl, isopropyl, O-methyl, O-ethyl, O-propyl, O-isopropyl and phenyl,

wherein $R^{2.2}$ and $R^{2.3}$ independently of one another denote H or a group selected from among methyl, ethyl, propyl, isopropyl, monocyclic C_{3-7} cycloalkyl, phenyl- C_{1-3} -alkylene, hetaryl- C_{1-3} -alkylene, phenyl, -het, -hetaryl, CO-NH₂, CO-NHCH₃, CON(CH₃)₂, SO₂-(C_{1-2} -alkyl), CO- $R^{2.1}$ and COOR^{2.1},

which may optionally be substituted by one or more groups selected from among OH, F, Cl, methyl, ethyl, propyl, isopropyl, phenyl and COOR^{2.1},

or

R^2 denotes a monocyclic C_{3-7} cycloalkyl, which may optionally be substituted by a group selected from among C_{1-2} -alkanol, C_{1-3} -fluoroalkyl, C_{1-3} -alkylene-OR^{2.1}, OR^{2.1}, COOR^{2.1}, SO₂-NR^{2.2}R^{2.3}, -het, -NH-CO-O-(phenyl), methyl, ethyl, propyl, isopropyl, phenyl, phenyl- C_{1-2} -alkylene, -hetaryl- C_{1-2} -alkylene, monocyclic C_{3-7} cycloalkyl and NR^{2.2}R^{2.3},

which may optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, F, Cl, CF₃, CHF₂, CH₂F, methyl, ethyl, propyl, isopropyl, phenyl and NR^{2.2}R^{2.3},

or

R^2 denotes a phenyl, which may optionally be substituted by OH, SH, F, Cl or Br or by one or more groups selected from among OR^{2.1}, COOR^{2.1}, NR^{2.2}R^{2.3}, CH₂-NR^{2.2}R^{2.3}, monocyclic C_{3-7} -cycloalkyl, -het, methyl, ethyl, propyl, isopropyl,

CF₃, CHF₂, CH₂F, phenyl-C₁₋₂-alkylene, het-C₁₋₂-alkylene, hetaryl-C₁₋₂-alkylene, phenyl, SO₂-CH₃, SO₂-CH₂CH₃ and SO₂-NR^{2.2}R^{2.3}, which may in turn optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, F, Cl, CF₃, CHF₂, CH₂F, methyl, ethyl, propyl, isopropyl, phenyl and NR^{2.2}R^{2.3},

or

R² denotes a group selected from among het and hetaryl, which may optionally be substituted by one or more groups selected from among F, Cl, OH, oxo, CF₃, CHF₂ and CH₂F or by one or more groups selected from among OR^{2.1}, C₁₋₃-alkylene-OR^{2.1}, SR^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, COOR^{2.1}, COR^{2.1}, methanol, ethanol, monocyclic C₃₋₇-cycloalkyl, phenyl, methyl, ethyl, propyl, isopropyl, phenyl-C₁₋₂-alkylene, hetaryl-C₁₋₂-alkylene, -het, -hetaryl and NR^{2.2}R^{2.3}, which may in turn optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, F, Cl, CF₃, CHF₂, CH₂F, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl and NR^{2.2}R^{2.3},

and wherein

R³ is a naphthalene or phenyl, which may optionally be substituted in the ortho, para or meta position by one or two groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, methyl, ethyl, propyl, isopropyl, cyclopropyl, CF₃, CHF₂, CH₂F, -OCH₃, OCH₂CH₃; SO₂-CH₃, SO-CH₃, COOCH₃, COOCH₂CH₃, -CO-NH-(methylene)-hetaryl, -CO-NH-(ethylene)-hetaryl, -CO-NH-hetaryl, -CO-N(CH₃)-het, -CO-N(CH₃)-(methylene)-het, -CO-N(CH₃)-(ethylene)-het, -CO-N(CH₃)-(methylene)-hetaryl, -CO-N(CH₃)-(ethylene)-hetaryl, -CO-N(cyclopropyl)-het, CO-NH₂, CONH(CH₃), CON(CH₃)₂, -CO-NH-(methylene)-het, -CO-NH-(ethylene)-het, -NH-CO-methyl, NCH₃-CO-methyl, -NH-CO-ethyl, NCH₃-CO-ethyl, -NH-CO-propyl, NCH₃-CO-propyl, -NH-CO-isopropyl, NCH₃-CO-isopropyl, phenyl, phenyl-methylene, phenyl-ethylene, het-methylene, het-ethylene, -het, -CO-het, -CO-N(CH₃)-het, CO-N(CH₃)-cyclopropyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-methylene, C₃₋₇-cycloalkyl-ethylene, hetaryl-methylene, hetaryl-ethylene, -hetaryl, CH₂-NH₂, CH₂-NH(CH₃), CH₂-N(CH₃)₂, -NH₂, -NH(CH₃) and -N(CH₃)₂, while these groups may optionally be substituted by one or more groups selected from among OH, F, Cl, -CF₃, CHF₂, CH₂F, oxo, methyl and phenyl

or wherein

R³ denotes a group selected from among a het and hetaryl, which may optionally be substituted by one or more groups selected from among F, Cl, Br, CF₃, CHF₂, CH₂F, CN, OH, oxo, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclopropyl, -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -COO-methyl, -COO-ethyl, -COO-propyl, -COO-isopropyl, SO-(CH₃), SO-(CH₂-CH₃), SO₂-(CH₃), SO₂-(CH₂-CH₃), phenyl, CH₂-NH₂, CH₂-NH(CH₃), CH₂-N(CH₃)₂, -NH₂, -NH(CH₃), -N(CH₃)₂, het and hetaryl, which may in turn optionally be substituted by one or more groups selected from among OH, F, Cl, CF₃, CHF₂, CH₂F, methyl, ethyl, propyl, isopropyl, phenyl, -COO-methyl, -COO-ethyl and O-methyl, O-ethyl,

or wherein

R³ denotes -O-R^{3.1},

wherein **R^{3.1}** denotes a group selected from among -C₁₋₃-alkyl, -phenyl, -C₁₋₃-alkylene-phenyl, hetaryl and het,

which may optionally be substituted in the ortho, para or meta position by one, two or three groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, CF₃, CHF₂, CH₂F, CO-(methyl), CO-(ethyl), CO-(propyl), CO-(isopropyl), -CO-(CF₃), -CO-NH-(methylene)-hetaryl, -CO-NH-(ethylene)-hetaryl, -CO-N(CH₃)-(methylene)-hetaryl, -CO-N(CH₃)-(ethylene)-hetaryl, -CO-N(CH₃)-(propylene)-hetaryl, -CO-N(CH₃)-(isopropylene)-hetaryl, -CO-N(CH₃)-het, -CO-N(cyclopropyl)-het, -CO-N(C₅₋₇-cycloalkyl)-het, -methylene-O-methyl, -ethylene-O-methyl, -propylene-O-methyl, -methylene-O-ethyl, -ethylene-O-ethyl, -propylene-O-ethyl, -methylene-NH₂, -methylene-NHCH₃, -methylene-N(CH₃)₂, -ethylene-NH₂, -ethylene-NHCH₃, -ethylene-N(CH₃)₂, NH₂, N(CH₃)₂, NHCH₃, -O-methyl, O-ethyl, O-propyl, O-isopropyl, O-butyl, O-isobutyl, -SO-CH₃, SO-ethyl, -SO-propyl, -SO-isopropyl, , SO₂-methyl, -SO₂-ethyl, SO₂-propyl, SO₂-isopropyl, COOH, COO-(methyl), COO-(ethyl), COO-(propyl), COO-(isopropyl), -O-methylene-N(methyl)₂, -O-ethylene-N(methyl)₂, -O-methylene-N(ethyl)₂, -O-ethylene-N(ethyl)₂, CO-NH₂, CO-NH(CH₃), CO-N(CH₃)₂, -NH-CO-methyl, -NCH₃-CO-methyl, -NH-CO-ethyl, NCH₃-CO-ethyl, phenyl, phenyl-methylene, phenyl-ethylene, het-methylene, het-ethylene, -CO-het, het, -CO-C₅₋₇-cycloalkyl, -CO-cyclopropyl, -CO-N(CH₃)-C₅₋₇-cycloalkyl, -CO-N(CH₃)-cyclopropyl,

C₅₋₇-cycloalkyl, cyclopropyl, C₅₋₇-cycloalkyl-methylene, C₅₋₇-cycloalkyl-ethylene, cyclopropyl-methylene, cyclopropyl-ethylene, hetaryl-methylene, hetaryl-ethylene and hetaryl,

which may in turn optionally be substituted by 1, 2, 3 or 4 groups selected independently of one another from among F, Cl, Br, methyl, O-methyl, ethyl, O-ethyl, OH, oxo and CF₃,

and wherein

R⁴ denotes H, CN, OH, CF₃, CHF₂, CH₂F, F, methyl, ethyl, O-methyl or O-ethyl, -methylene-OH, -ethylene-OH, -propylene-OH, isopropylene-OH, -COO(methyl), -COO(ethyl), -COO(propyl), -COO(isopropyl), -CO-het, -(methylene)-NH-SO₂-(methyl), -(methylene)-NH-SO₂-(ethyl), -(ethylene)-NH-SO₂-(methyl), -(ethylene)-NH-SO₂-(ethyl), -(methylene)-N(CH₃)-SO₂-(methyl), -(methylene)-N(CH₃)-SO₂-(ethyl), -(ethylene)-N(CH₃)-SO₂-(methyl), -(ethylene)-N(CH₃)-SO₂-(ethyl), -(methylene)-O-(methylene)-phenyl, -(methylene)-O-(ethylene)-phenyl, -(ethylene)-O-(methylene)-phenyl, -(ethylene)-O-(ethylene)-phenyl, -methylene-O-methyl, -methylene-O-ethyl, -ethylene-O-methyl, -ethylene-O-ethyl, -(methylene)-N(CH₃)-CO-(methyl), -(methylene)-N(CH₃)-CO-(ethyl), -(ethylene)-N(CH₃)-CO-(methyl), -(ethylene)-N(CH₃)-CO-(ethyl), -NH-CO-(methylene)-O-(methyl), -NH-CO-(methylene)-O-(ethyl), -NH-CO-(ethylene)-O-(methyl), -NH-CO-(ethylene)-O-(ethyl), -methylene-NH-CO-(methyl), -methylene-NH-CO-(ethyl), -ethylene-NH-CO-(methyl), -ethylene-NH-CO-(ethyl), -methylene-NH-CO-(methylene)-N(methyl)₂, -methylene-NH-CO-(ethylene)-N(methyl)₂, -ethylene-NH-CO-(methylene)-N(methyl)₂, -ethylene-NH-CO-(ethylene)-N(methyl)₂, -methylene-NH-CO-(methylene)-O-(methyl), -methylene-NH-CO-(ethylene)-O-(methyl), -ethylene-NH-CO-(methylene)-O-(methyl), -methylene-NH-CO-(methylene)-O-(ethyl), -methylene-NH-CO-(ethylene)-O-(ethyl), -ethylene-NH-CO-(methylene)-O-(ethyl), -(methylene)-N(CH₃)-CO-(methylene)-O-(methyl), -(methylene)-N(CH₃)-CO-(ethylene)-O-(methyl), -(ethylene)-N(CH₃)-CO-(methylene)-O-(methyl), -(methylene)-N(CH₃)-CO-(methylene)-O-(ethyl),

-(methylene)-N(CH₃)-CO-(ethylene)-O-(ethyl),
 -(ethylene)-N(CH₃)-CO-(methylene)-O-(ethyl),
 -O-(methylene)-phenyl, -O-(ethylene)-phenyl,
 -CO-phenyl,

wherein the phenyl in the above groups may optionally be substituted by one or more other groups selected from among F, Cl, Br, methyl, ethyl, propyl, -O-methyl, -O-ethyl, -O-propyl, -OH and CF₃

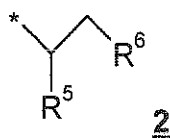
or wherein

R³ and **R⁴** together form a mono- or bicyclic, unsaturated, saturated or partially saturated heterocycle, which contains 1, 2 or 3 heteroatoms selected from among N, O and S and which may optionally be substituted by one or more groups selected from among F, Cl, Br, OH, oxo, CF₃, CHF₂, CH₂F, CN, methyl, ethyl, propyl, isopropyl, cyclopropyl, COO-methyl, -COO-ethyl, O-methyl, O-ethyl, SO₂-(CH₃), SO₂-(CH₂CH₃), SO-(CH₃), SO-(CH₂CH₃), CH₂-NH₂, CH₂-NH(CH₃), CH₂-N(CH₃)₂, -NH₂, -NH(CH₃), -N(CH₃)₂, phenyl, C₅₋₇-cycloalkyl, het and hetaryl,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

More preferably, also, the present invention relates to the above compounds of formula 1, wherein

R² denotes a group according to formula 2



and

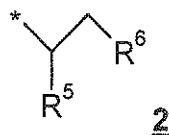
wherein **R⁶** is OH or NH₂ and

wherein **R⁵** is a group selected from among C₁₋₄-alkyl, a five- to six-membered heteroaryl with 1, 2 or 3 heteroatoms selected from among S, O and N and phenyl, which may optionally be substituted by one or more groups selected from among OH, F, Br, OR^{2.1}, oxo, methyl, ethyl, methanol, ethanol, phenyl, COOR^{2.1}, CH₂-NR^{2.2}R^{2.3} anNR^{2.2}R^{2.3}

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Preferably, also, the present invention relates to the above compounds of formula 1, wherein

R^2 is a group according to formula 2



wherein R^6 is OH or NH_2 and

wherein R^5 is methyl, ethyl, propyl, isopropyl

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Preferably, also, the present invention relates to the above compounds of formula 1, wherein

R^2 is a monocyclic three-, four-, five-, six- or seven-membered cycloalkyl ring which may optionally be substituted in the spiro position by a group selected from among $-CH_2-$ $OR^{2.1}$, branched or unbranched C_{2-6} -alkylene- $OR^{2.1}$, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclopropyl, $-CF_3$, CHF_2 , CH_2F and C_{2-4} -fluoroalkyl, wherein

$R^{2.1}$ is selected from among methyl, ethyl, propyl, isopropyl, butyl, isobutyl,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Also preferred are the above mentioned compounds of formula 1, wherein

R^2 is a cyclopropyl which may optionally be substituted by another group selected from among $-NH_2$, CH_2-NH_2 , $-NH(CH_3)$, $-N(CH_3)_2$, methyl, ethyl, propyl, isopropyl, $-NH-CO-(tert-butyl)$, $-NH-CO-O-(tert-butyl)$, $-N(CH_3)-CO-(tert-butyl)$, $-N(CH_3)-CO-O-(tert-butyl)$, $-CF_3$, $-CHF_2$, CH_2F , F, Cl and Br,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Also preferred are the above mentioned compounds of formula 1, wherein

R^2 denotes a phenyl which may optionally be substituted in one or both meta positions by one or more groups selected from among methyl, ethyl, propyl,

isopropyl, cyclopropyl, F, Cl, Br, OH, $OR^{2.1}$, $COOR^{2.1}$, CF_3 , CHF_2 , CH_2F , NH_2 , $NH(CH_3)$ and $N(CH_3)_2$, wherein $R^{2.1}$ may be H, methyl or ethyl,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Also preferred are the above mentioned compounds of formula 1, wherein

R^2 is a group selected from among monocyclic, saturated three-, four-, five-, six- or seven-membered heterocycles with 1, 2 or 3 heteroatoms selected in each case from among N, O and S, which may optionally be substituted by one or more groups selected from among fluorine, chlorine, bromine, CF_3 , CHF_2 , CH_2F , OH and oxo or by one or more groups selected from among $OR^{2.1}$, C_{1-3} -alkylene- $OR^{2.1}$, $SR^{2.1}$, $SO-R^{2.1}$, $SO_2-R^{2.1}$, $COOR^{2.1}$, $COR^{2.1}$, C_{1-6} -alkanol, C_{3-10} -cycloalkyl, phenyl, C_{1-6} -alkyl, phenyl- C_{1-6} -alkylene, C_{5-10} -heteroaryl- C_{1-6} -alkylene, C_{5-10} heterocycle, C_{5-10} -heteroaryl and $NR^{2.2}R^{2.3}$, which may in turn optionally be substituted by one or more groups selected from among OH, $OR^{2.1}$, oxo, F, Cl, CF_3 , CHF_2 , CH_2F , C_{1-6} -alkyl, phenyl and $NR^{2.2}R^{2.3}$,

and wherein $R^{2.1}$, $R^{2.2}$ and $R^{2.3}$ are as hereinbefore defined,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

The present invention preferably also relates to the compounds of formula 1, wherein

R^2 denotes a group selected from among a monocyclic, saturated six-membered heterocycle with a heteroatom selected from among N, O and S, which may optionally be substituted by one or more groups selected from among F, Cl, Br, CF_3 , CHF_2 , CH_2F , OH, oxo, NH_2 , $NHCH_3$ and $N(CH_3)_2$, methyl, ethyl, propyl, isopropyl, cyclopropyl, methoxy and ethoxy,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

The present invention preferably also relates to the above compounds of formula 1, wherein

R^2 denotes a group selected from among piperidine or tetrahydropyran, which may optionally be substituted by one or more groups selected from among F, Cl, Br, OH, CF_3 , CHF_2 , CH_2F , NH_2 , $NHCH_3$, $N(CH_3)_2$, oxo, methyl and methoxy,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

The present invention preferably also relates to the above compounds of formula **1**, wherein

R³ is a naphthalene or phenyl, which may optionally be substituted in any position by one, two or three groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, methyl, ethyl, propyl, isopropyl, cyclopropyl, CF₃, CHF₂, CH₂F, -OCH₃, OCH₂CH₃; SO₂-CH₃, SO₂-CH₂CH₃, COOCH₃ and CO-O-CH₂CH₃,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

The present invention preferably also relates to the above compounds of formula **1**, wherein

R³ denotes a group selected from among het and hetaryl, which may optionally be substituted by one or more groups selected from among F, Cl, Br, CF₃, CHF₂, CH₂F, CN, OH, oxo, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclopropyl, C₅₋₇-cycloalkyl, -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -COO-methyl, -COO-ethyl, -COO-propyl, -COO-isopropyl, SO₂-(CH₃), SO₂-(CH₂-CH₃), SO-(CH₃), SO-(CH₂-CH₃), phenyl, -CH₂-NH₂, -CH₂-NHCH₃, -CH₂-N(CH₃)₂, NH₂, NHCH₃, N(CH₃)₂, het and hetaryl, which may in turn optionally be substituted by one or more groups selected from among OH, F, Cl, Br, CF₃, CHF₂, CH₂F, methyl, ethyl, propyl, isopropyl, phenyl, -COO-methyl, -COO-ethyl, -COO-propyl, -COO-isopropyl and O-methyl, O-ethyl, O-propyl and O-isopropyl,

and wherein

R⁴ denotes H, CN, OH, CF₃, CHF₂, CH₂F, F, methyl, ethyl, O-methyl or O-ethyl,

wherein

het is a three- to seven-membered, monocyclic, saturated or partially saturated heterocycle or a seven- to eleven-membered, bicyclic, anellated, saturated or partially saturated heterocycle which contains 1, 2 or 3 heteroatoms selected independently of one another from among N, S or O,

and wherein

hetaryl is a five- to six-membered, monocyclic, aromatic heteroaryl or a seven- to eleven-membered, bicyclic, anellated, aromatic heteroaryl, which contains in each

case 1, 2 or 3 heteroatoms selected independently of one another from among N, S or O,

and wherein

cycloalkyl may be saturated or partially saturated,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

The present invention particularly preferably also relates to the above compounds of formula **1**, wherein

R³ denotes a group selected from a bicyclic, seven- to eleven-membered, saturated or partially saturated heterocycle or a bicyclic, seven- to eleven-membered heteroaryl, which is selected from among indole, dihydroindole, quinazoline, dihydroquinazoline, tetrahydroquinazoline, benzoisoxazole, dihydrobenzoisoxazole, benzoxazine, dihydrobenzoxazine, benzothiazole, dihydrobenzothiazole, triazolopyridine, dihydrotriazolopyridine, benzofuran, dihydrobenzofuran, isobenzofuran and dihydroisobenzofuran,

which may optionally be substituted by one or more groups selected from among F, Cl, Br, CF₃, CHF₂, CH₂F, CN, OH, oxo, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclopropyl, -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -COO-methyl, -COO-ethyl, -COO-propyl, -COO-isopropyl, SO₂-(CH₃), SO₂-(CH₂-CH₃), SO-(CH₃), SO-(CH₂-CH₃), phenyl, -CH₂-NH₂, -CH₂-NHCH₃, -CH₂-N(CH₃)₂, NH₂, NHCH₃, N(CH₃)₂, furanyl and pyridinyl, which in turn may be substituted by one or more groups selected from among OH, F, Cl, Br, CF₃, CHF₂, CH₂F, methyl, ethyl, propyl, isopropyl, phenyl, -COO-methyl, -COO-ethyl and O-methyl, O-ethyl,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

The present invention particularly preferably also relates to the above compounds of formula **1**, wherein

R³ denotes a group selected from a monocyclic, saturated or partially saturated, three- to seven-membered heterocycle or a monocyclic five- to six-membered heteroaryl, which is selected from among imidazole, dihydroimidazole, oxadiazole, oxadiazolidine, pyrazole, pyridine and dihydropyrazole,

which may optionally be substituted by one or more groups selected from among F, Cl, Br, CF₃, CHF₂, CH₂F, CN, OH, oxo, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclopropyl, --O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -COO-methyl, -COO-ethyl, -COO-propyl, -COO-isopropyl, SO₂-(CH₃), SO₂-(CH₂-CH₃), SO-(CH₃), SO-(CH₂-CH₃), phenyl, -CH₂-NH₂, -CH₂-NHCH₃, -CH₂-N(CH₃)₂, NH₂, NHCH₃, N(CH₃)₂, furanyl and pyridinyl, which may in turn optionally be substituted by one or more groups selected from among OH, F, Cl, Br, CF₃, CHF₂, CH₂F, methyl, ethyl, propyl, isopropyl, phenyl, -COO-methyl, -COO-ethyl and O-methyl, O-ethyl,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

The present invention particularly preferably also relates to the above compounds of formula 1, wherein

R³ and R⁴ together form a mono- or bicyclic, unsaturated or partially saturated, three- to eleven-membered heterocycle which contains 1, 2 or 3 heteroatoms selected from among N, O and S and which may optionally be substituted by one or more groups selected from among F, Cl, Br, OH, oxo, CF₃, CHF₂, CH₂F, CN, methyl, ethyl, propyl, isopropyl, cyclopropyl, COO-methyl, -COO-ethyl, O-methyl, O-ethyl, SO₂-(CH₃), SO₂-(CH₂-CH₃), SO-(CH₃), SO-(CH₂-CH₃), phenyl, -CH₂-NH₂, -CH₂NHCH₃, -CH₂-N(CH₃)₂, NH₂, NHCH₃, N(CH₃)₂, a saturated or partially saturated, five- to six-membered heterocycle and a five- to six-membered heteroaryl,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

The present invention particularly preferably also relates to the above compounds of formula 1, wherein

R³ and R⁴ together form a bicyclic heterocycle selected from among tetrahydroquinazoline, tetrahydrobenzoxazine and dihydroindole, dihydroisobenzofuran, which may optionally be substituted by one or more groups selected from among F, Cl, Br, OH, oxo, CF₃, CHF₂, CH₂F, CN, methyl, ethyl, propyl, isopropyl, cyclopropyl, COO-methyl, -COO-ethyl, O-methyl, O-ethyl, SO₂-(CH₃), SO₂-(CH₂-CH₃), phenyl, -CH₂-NH₂, -CH₂NHCH₃, -CH₂-N(CH₃)₂, NH₂, NHCH₃, N(CH₃)₂, a saturated or partially saturated, five- to six-membered heterocycle and a five- to six-membered heteroaryl,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

The invention preferably further relates to those compounds according to formula 1, wherein

R^3 is $-O-R^{3.1}$,

wherein $R^{3.1}$ is a group selected from among methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, -phenyl, -methylene-phenyl, -ethylene-phenyl, -propylene-phenyl, -isopropylene-phenyl, hetaryl and het, which may optionally be substituted in the ortho, para or meta position by one, two or three groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, $-CF_3$, CHF_2 , CH_2F , CO-(methyl), CO-(ethyl), CO-(propyl), CO-(isopropyl), CO-(butyl), CO-(isobutyl), $-CO-(CF_3)$, $-CO-(CH_2F)$, $-CO-(CHF_2)$, $-CO-NH-(methylene)-hetaryl$, $-CO-NH-(ethylene)-hetaryl$, $-CO-NH-(propylene)-hetaryl$, $-CO-NH-(isopropylene)-hetaryl$, $-CO-N(CH_3)-(methylene)-hetaryl$, $-CO-N(CH_3)-(ethylene)-hetaryl$, $-CO-N(CH_3)-(propylene)-hetaryl$, $-CO-N(CH_3)-(isopropylene)-hetaryl$, $-CO-N(CH_3)-het$, $-CO-N(C_{3-7}\text{-cycloalkyl})-het$, -methylene-O-methyl, -ethylene-O-methyl, -methylene-O-ethyl, -ethylene-O-ethyl, -methylene-NH₂, -ethylene-NH₂, -methylene-NHCH₃, -ethylene-NHCH₃, -methylene-N(CH₃)₂, -ethylene-N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -SO-CH₃, -SO-(CH₂CH₃), -SO₂-CH₃, -SO₂-(CH₂CH₃), COOH, COO-(methyl), COO-(ethyl), COO-(propyl), COO-(isopropyl), -O-methylene-N(methyl)₂, -O-ethylene-N(methyl)₂, -O-methylene-N(ethyl)₂, -O-ethylene-N(ethyl)₂, CO-NH₂, CO-NHCH₃, CO-N(CH₃)₂, NH-CO-methyl, NCH₃-CO-methyl, NH-CO-ethyl, N(CH₃)-CO-ethyl, phenyl, phenyl-methylene, phenyl-ethylene, het-methylene, het-ethylene, -CO-het, het, -CO-C₄₋₇-cycloalkyl, -CO-cyclopropyl, -CO-N(CH₃)-cyclopropyl, -CO-N(CH₃)-C₄₋₇-cycloalkyl, C₄₋₇-cycloalkyl, cyclopropyl, C₄₋₇-cycloalkyl-methylene, cyclopropyl-methylene, C₄₋₇-cycloalkyl-ethylene, cyclopropyl-ethylene, hetaryl-methylene, hetaryl-ethylene and hetaryl, which may in turn optionally be substituted by 1, 2, 3 or 4 groups selected independently of one another from among F, Cl, Br, methyl, O-methyl, ethyl, O-ethyl, OH, oxo and CF₃,

and wherein the other variables are as hereinbefore defined,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Also preferred within the scope of the invention are the compounds of formula 1, wherein

R⁴ denotes H, CN, OH, CF₃, CHF₂, CH₂F, F, methyl, ethyl, O-methyl or O-ethyl, -methylene-OH, -ethylene-OH, -propylene-OH, isopropylene-OH, -COO(methyl), -COO(ethyl), -COO(propyl), -COO(isopropyl), -CO-het, -(methylene)-NH-SO₂-(methyl), -(methylene)-NH-SO₂-(ethyl), -(ethylene)-NH-SO₂-(methyl), -(ethylene)-NH-SO₂-(ethyl), -(methylene)-N(CH₃)-SO₂-(methyl), -(methylene)-N(CH₃)-SO₂-(ethyl), -(ethylene)-N(CH₃)-SO₂-(methyl), -(ethylene)-N(CH₃)-SO₂-(ethyl), -(methylene)-O-(methylene)-phenyl, -(methylene)-O-(ethylene)-phenyl, -(ethylene)-O-(methylene)-phenyl, -(ethylene)-O-(ethylene)-phenyl, -methylene-O-methyl, -methylene-O-ethyl, -ethylene-O-methyl -ethylene-O-ethyl, -(methylene)-N(CH₃)-CO-(methyl), -(methylene)-N(CH₃)-CO-(ethyl), -(ethylene)-N(CH₃)-CO-(methyl), -(ethylene)-N(CH₃)-CO-(ethyl), -NH-CO-(methylene)-O-(methyl), -NH-CO-(methylene)-O-(ethyl), -NH-CO-(ethylene)-O-(methyl), -NH-CO-(ethylene)-O-(ethyl), -methylene-NH-CO-(methyl), -methylene-NH-CO-(ethyl), -ethylene-NH-CO-(methyl), -ethylene-NH-CO-(ethyl), -methylene-NH-CO-(methylene)-N(methyl)₂, -methylene-NH-CO-(ethylene)-N(methyl)₂, -ethylene-NH-CO-(methylene)-N(methyl)₂, -ethylene-NH-CO-(ethylene)-N(methyl)₂, -methylene-NH-CO-(methylene)-O-(methyl), -methylene-NH-CO-(ethylene)-O-(methyl), -ethylene-NH-CO-(methylene)-O-(methyl), -methylene-NH-CO-(methylene)-O-(ethyl), -methylene-NH-CO-(ethylene)-O-(ethyl), -ethylene-NH-CO-(methylene)-O-(ethyl), -(methylene)-N(CH₃)-CO-(methylene)-O-(methyl), -(methylene)-N(CH₃)-CO-(ethylene)-O-(methyl), -(ethylene)-N(CH₃)-CO-(methylene)-O-(methyl), -(methylene)-N(CH₃)-CO-(methylene)-O-(ethyl),

-(methylene)-N(CH₃)-CO-(ethylene)-O-(ethyl),
-(ethylene)-N(CH₃)-CO-(methylene)-O-(ethyl),
-O-(methylene)-phenyl, -O-(ethylene)-phenyl,
-CO-phenyl,

while the phenyl in the above groups may optionally be substituted by one or more other groups selected from among F, Cl, Br, methyl, ethyl, propyl, -O-methyl, -O-ethyl, -O-propyl, -OH and CF₃,

and wherein the other variables are as hereinbefore defined,

as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

Also preferred within the scope of the invention are those compounds of formula 1 wherein

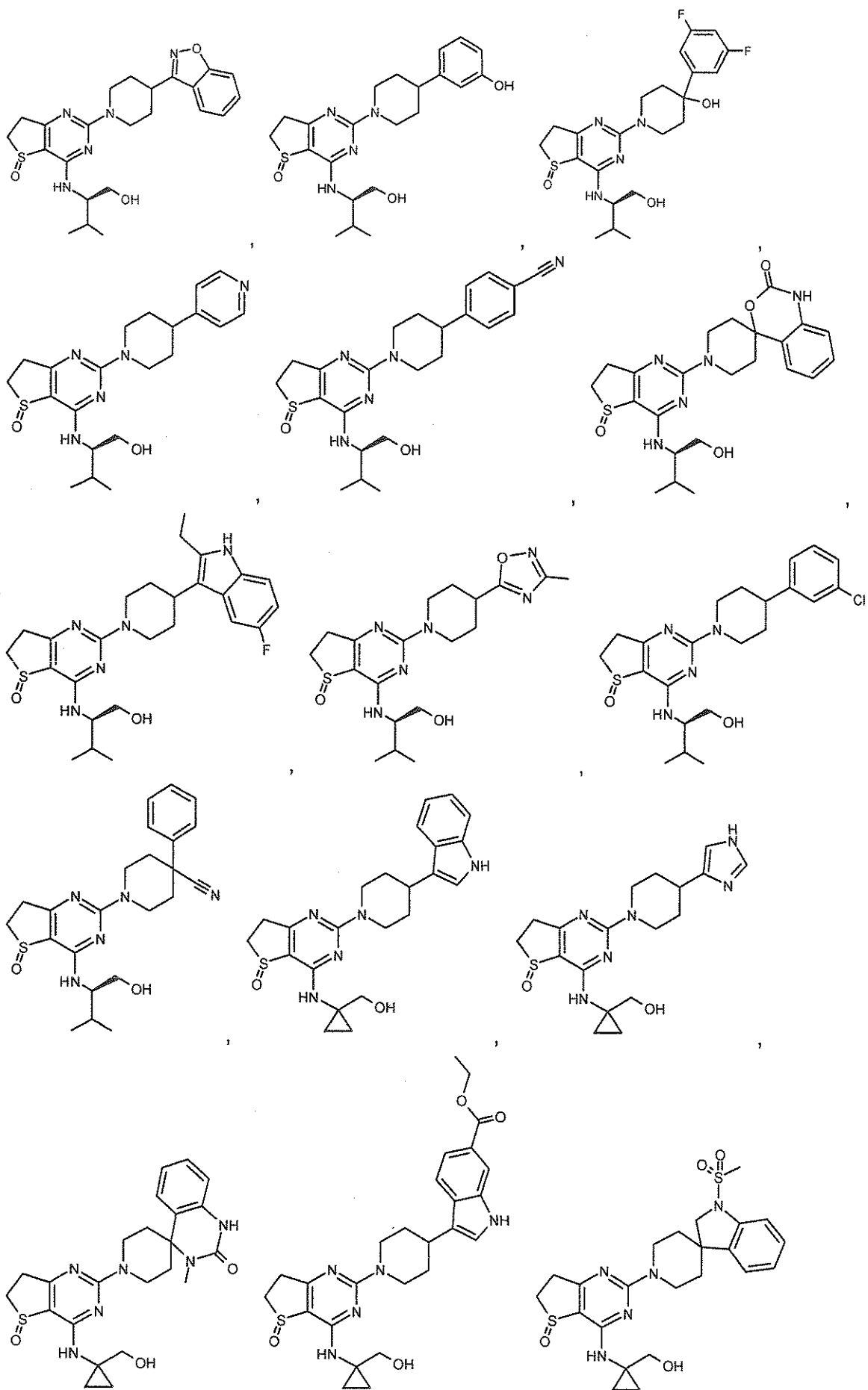
R³ is a group selected from among oxazole, imidazole and thiazole, while these groups may optionally be substituted by one, two or three further groups selected independently of one another from among methyl, ethyl, propyl, isopropyl, O-methyl, O-ethyl, O-propyl, O-isopropyl, OH, F, Cl, Br, CF₃, phenyl, hetaryl and C₃₋₆-cycloalkyl,

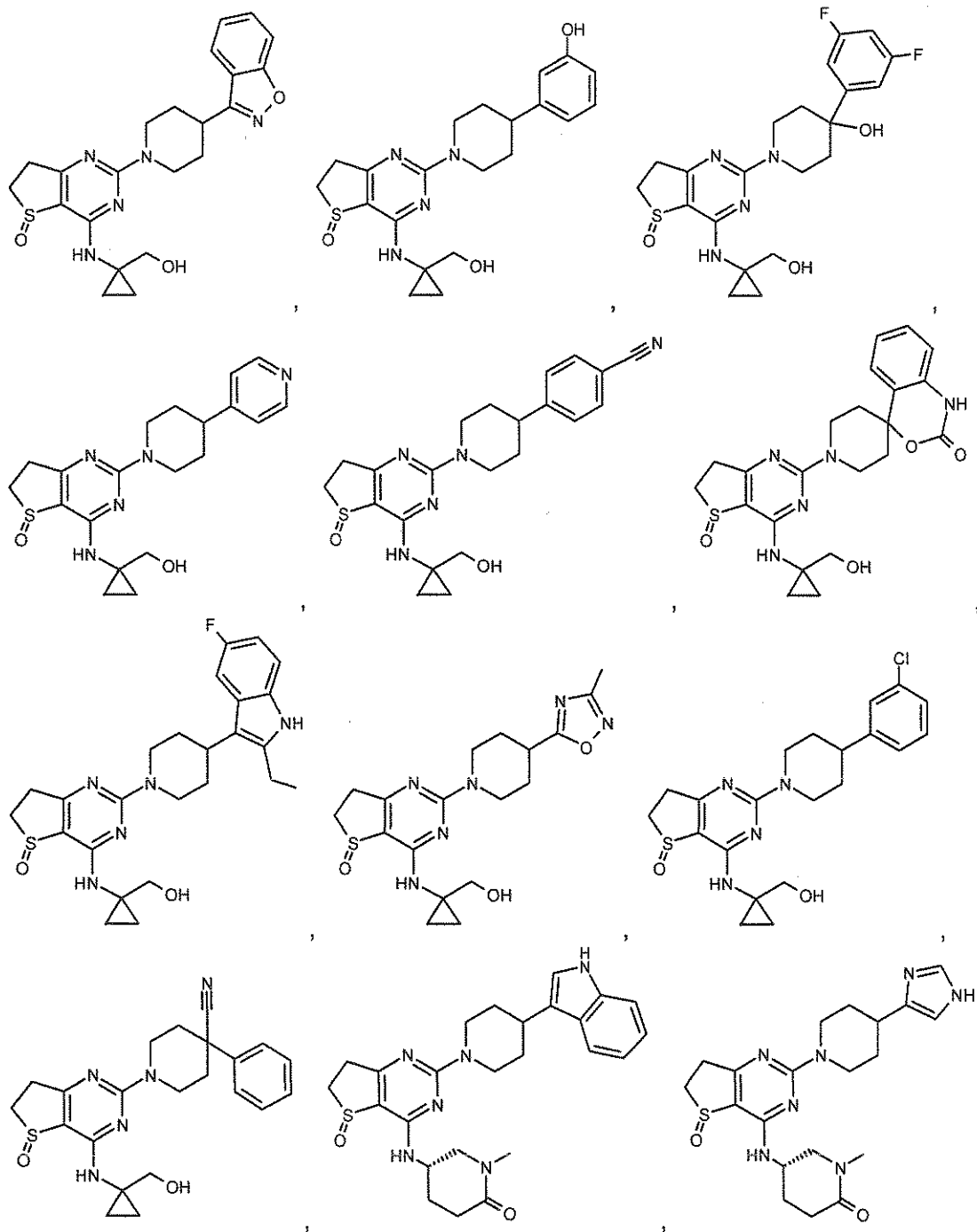
and wherein the other variables are as hereinbefore defined,
as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

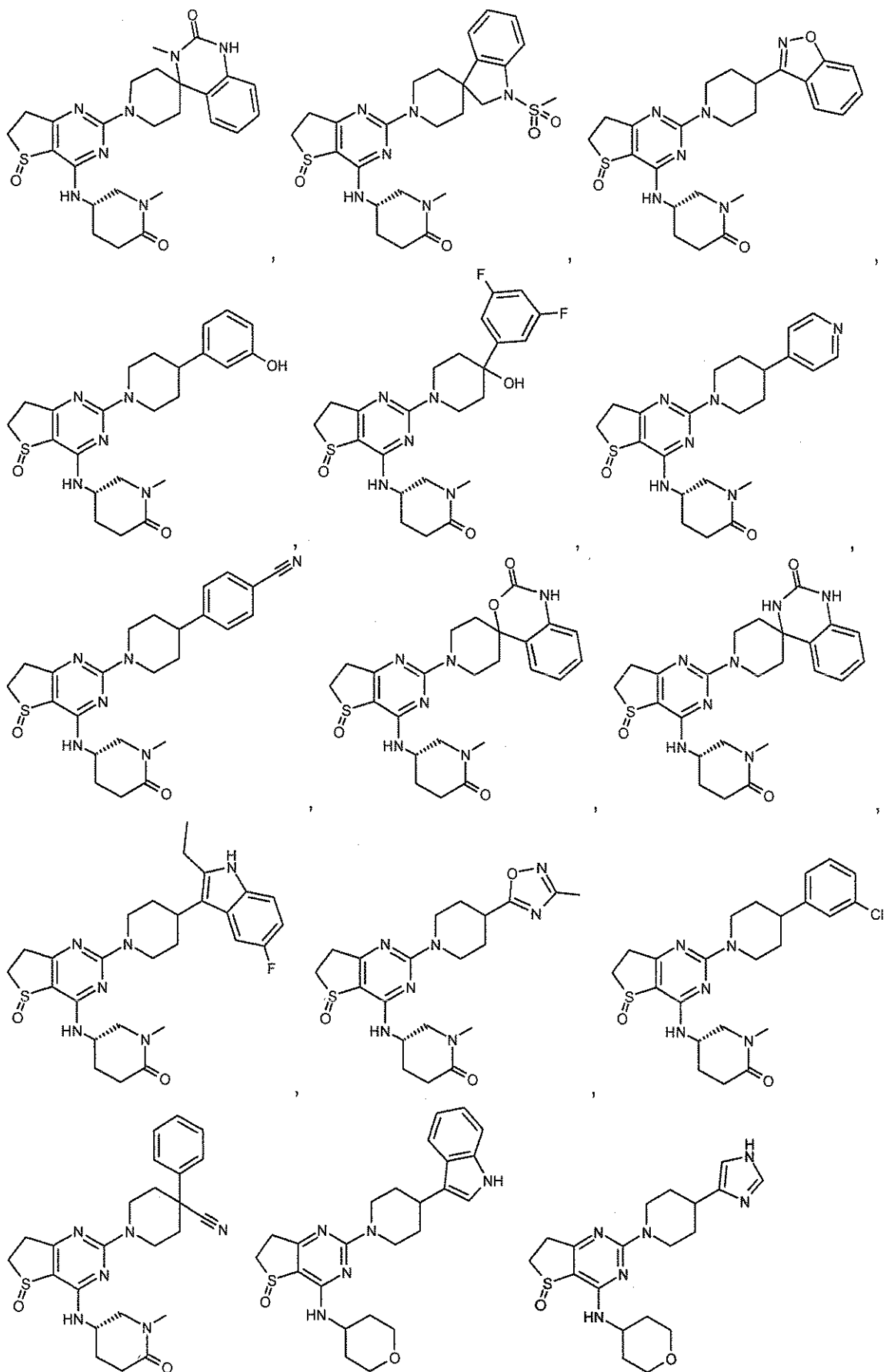
The present invention preferably also relates to the above compounds of formula 1, wherein X is SO₂,

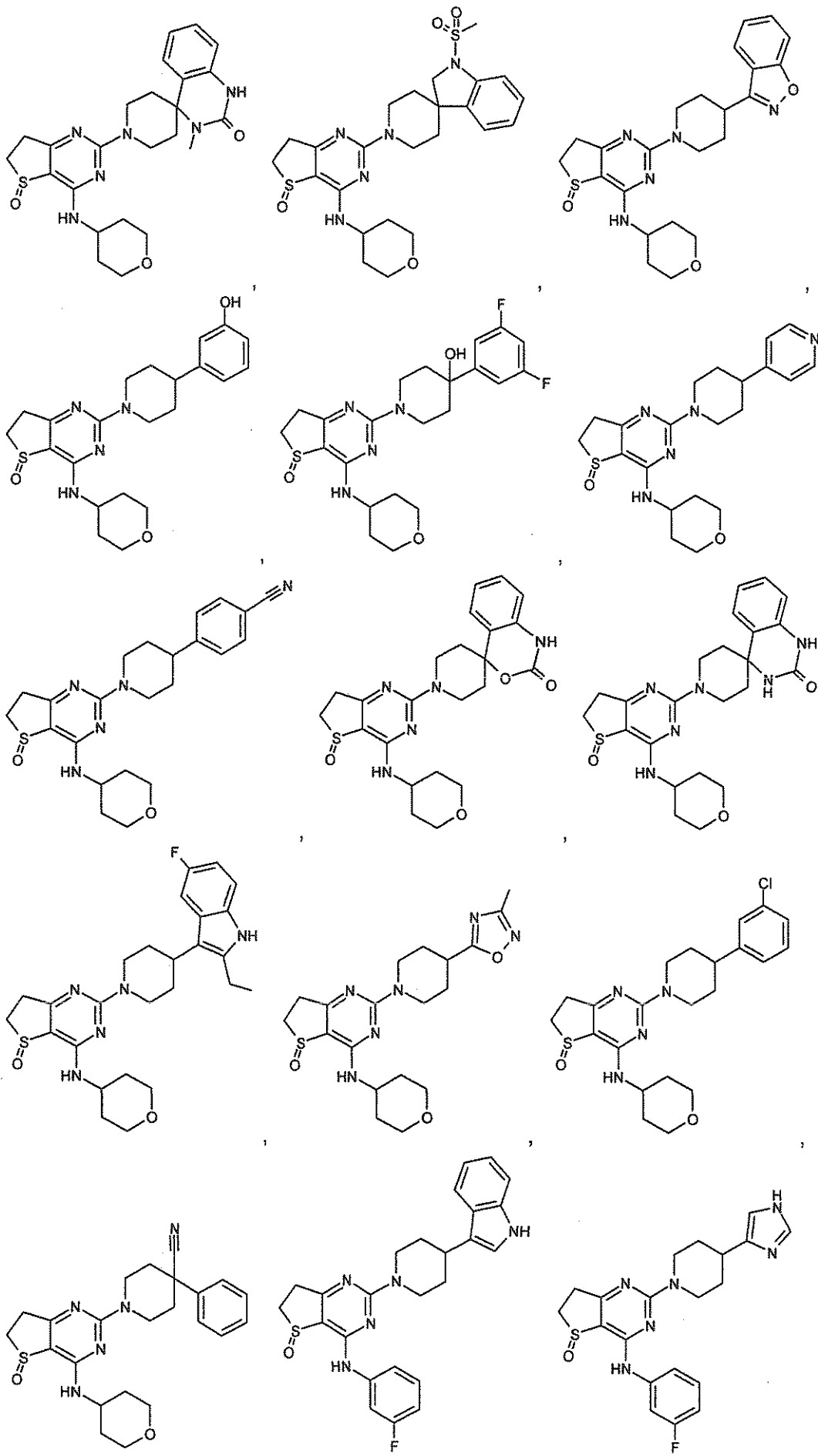
and wherein the other variables are as hereinbefore defined,
as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof.

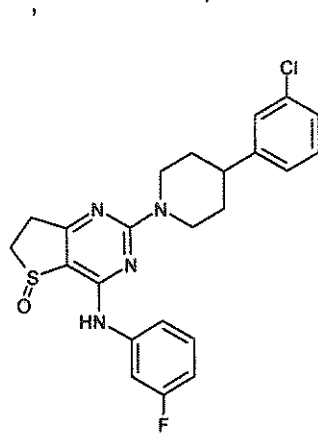
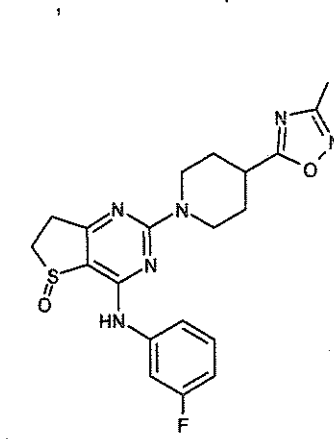
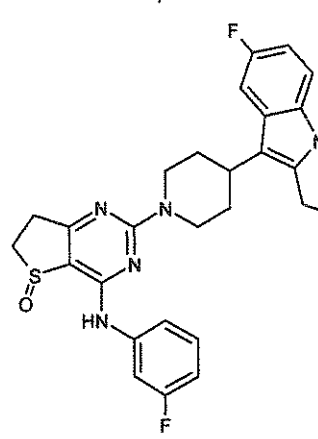
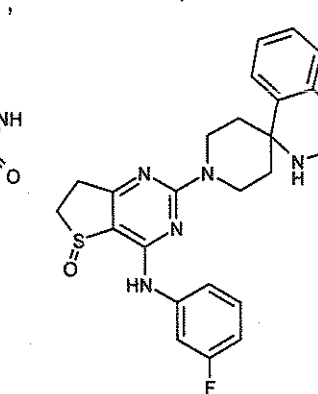
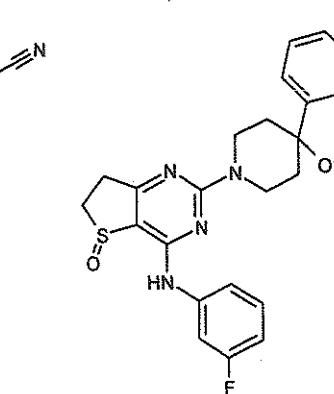
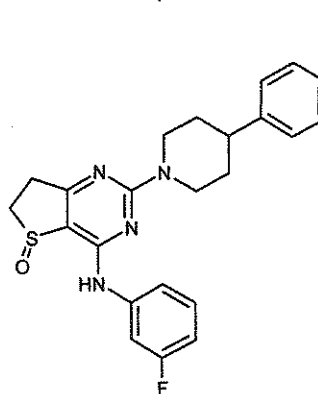
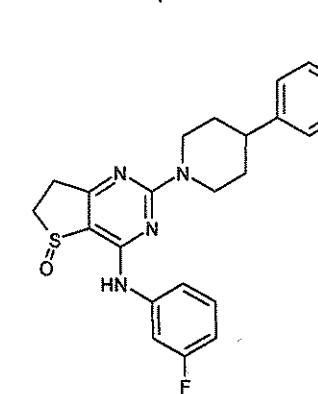
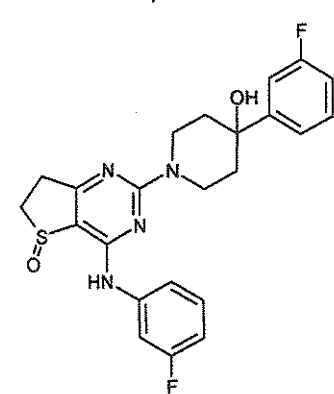
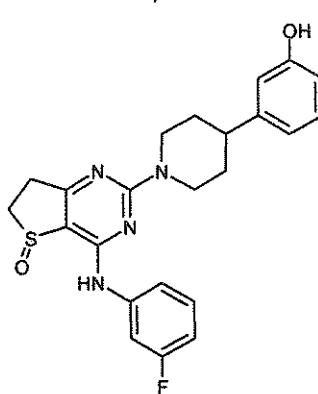
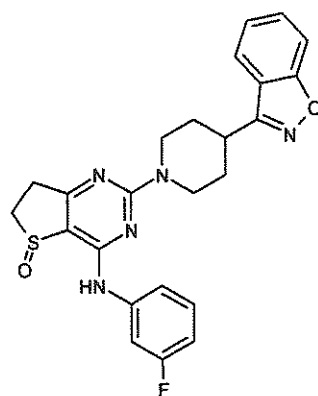
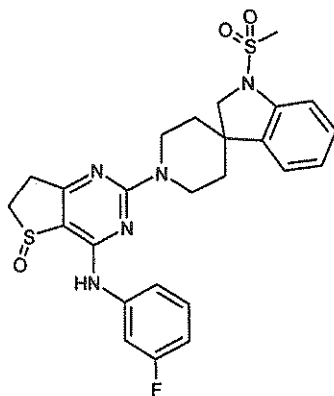
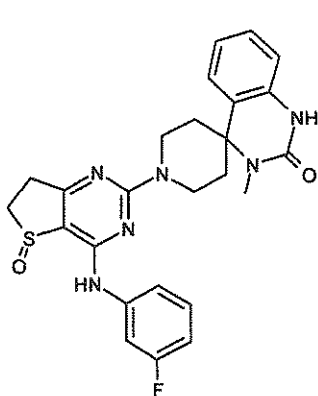
The invention particularly relates to compounds according to formula 1, which are selected from among

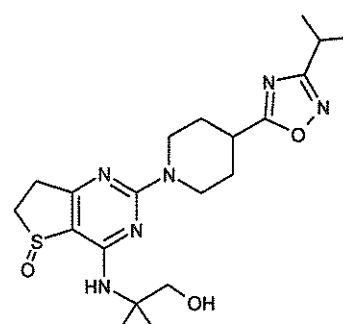
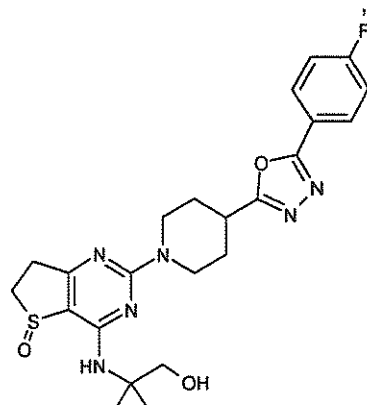
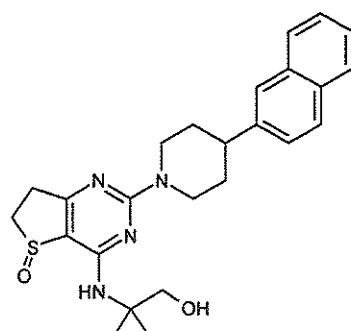
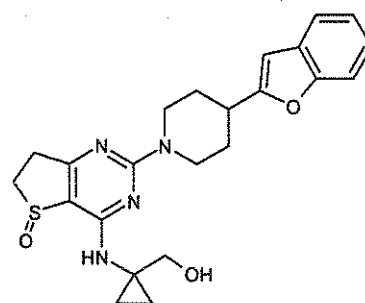
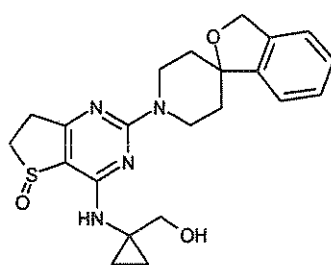
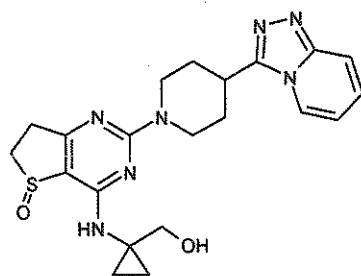
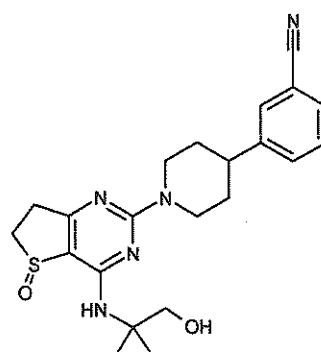
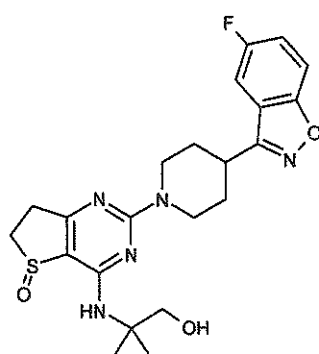
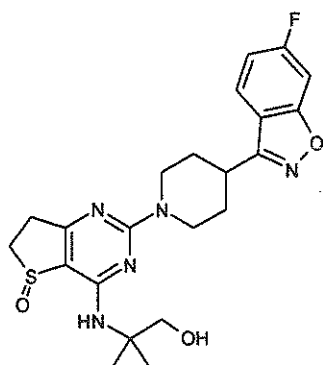
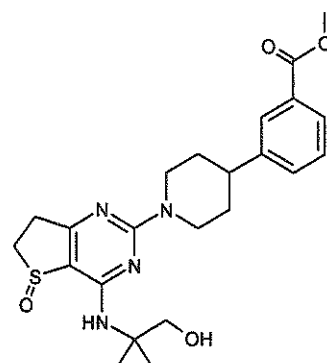
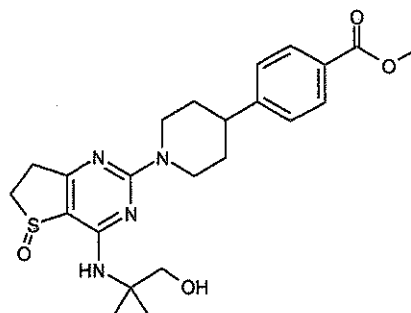
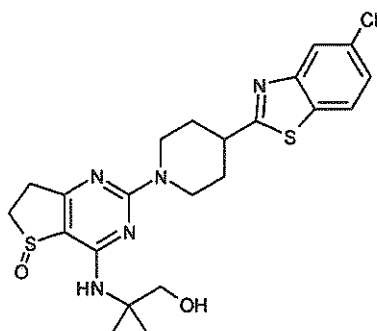
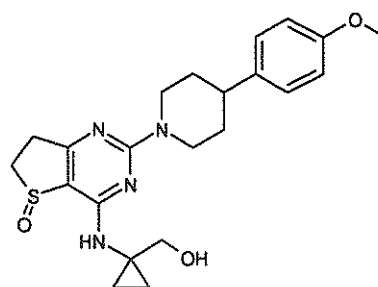
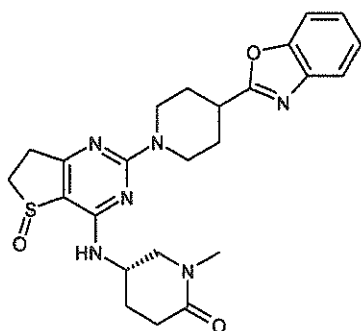


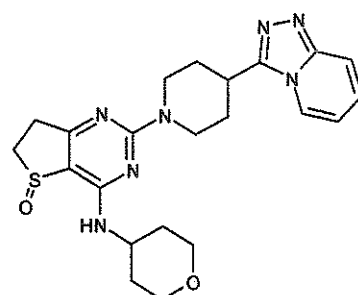
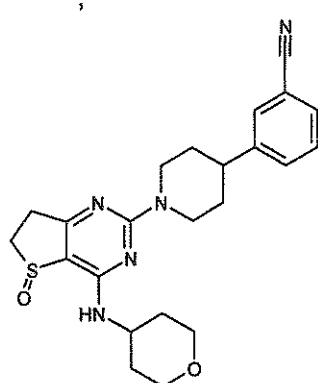
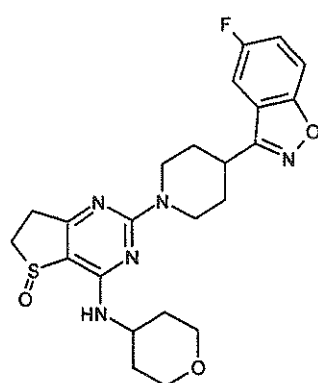
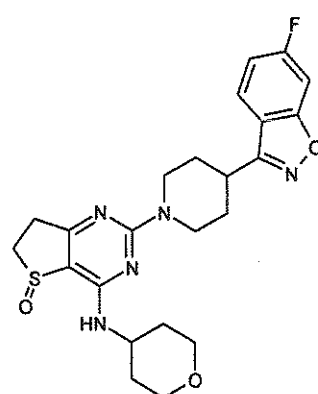
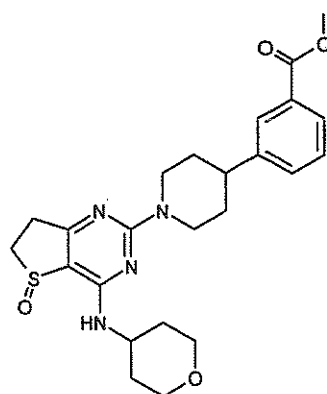
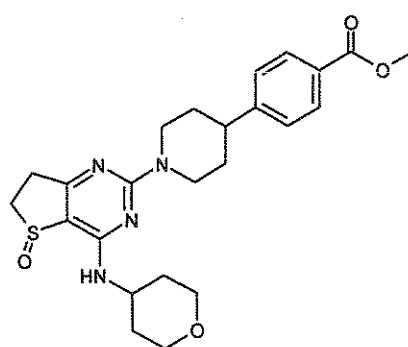
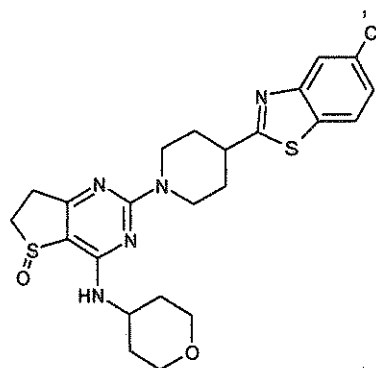
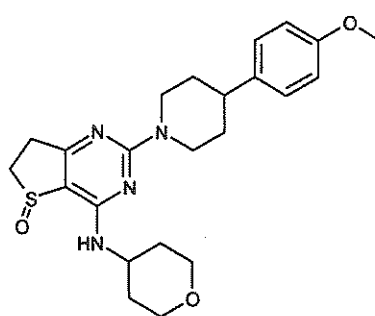
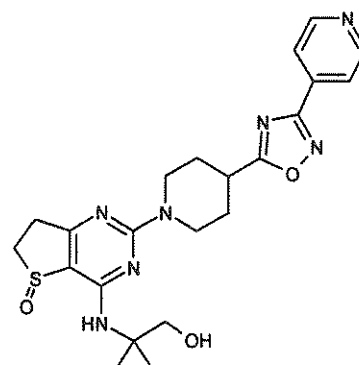
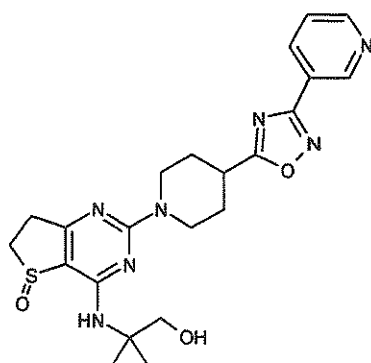
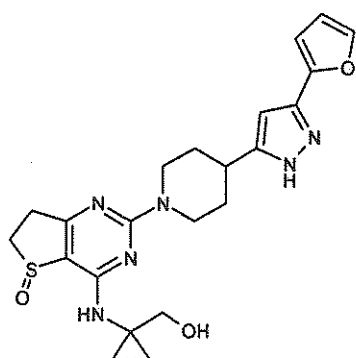


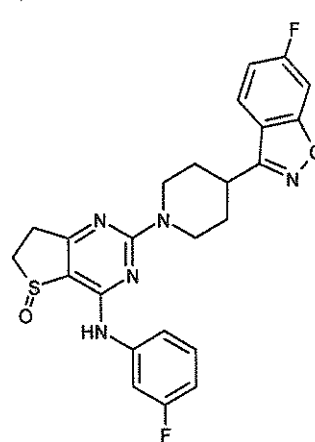
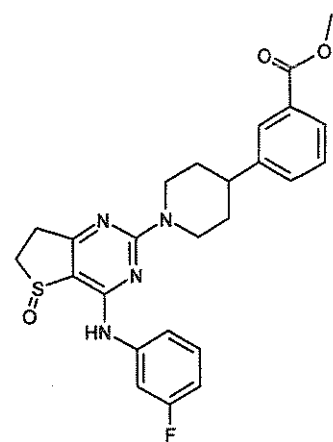
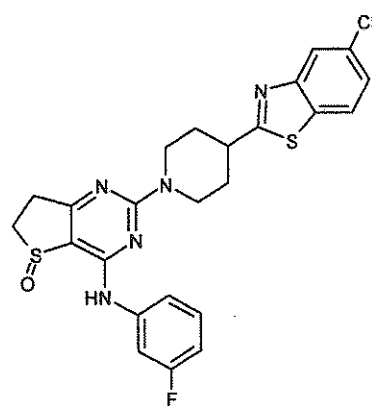
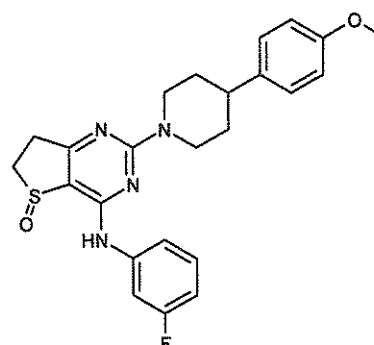
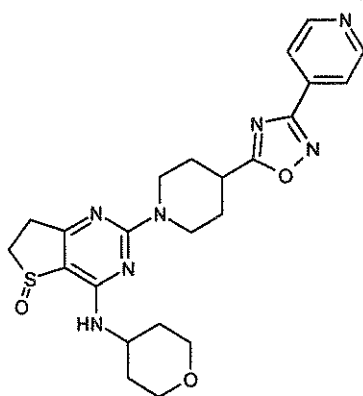
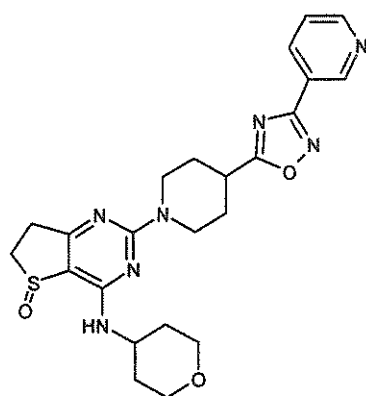
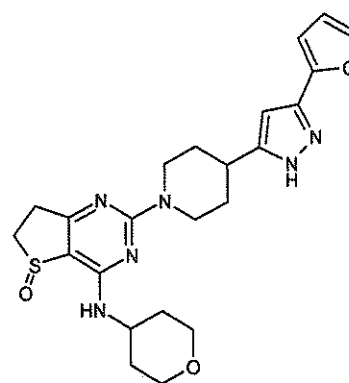
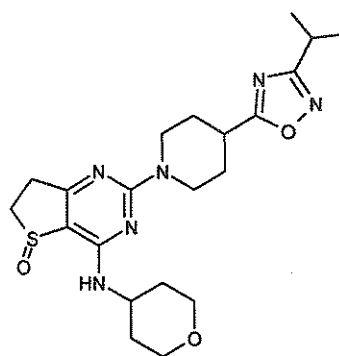
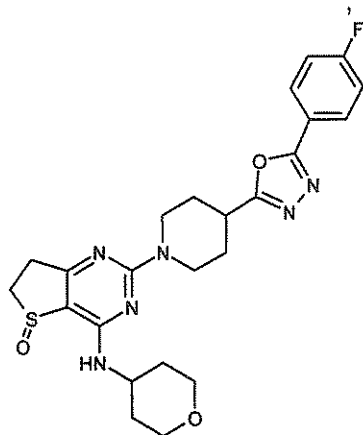
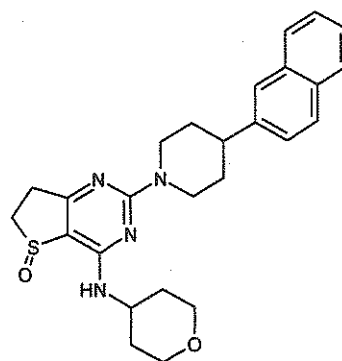
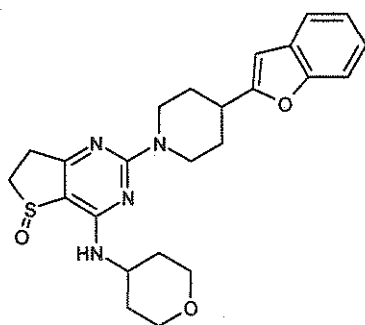
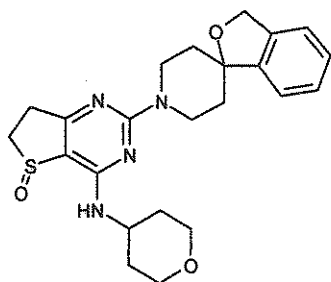


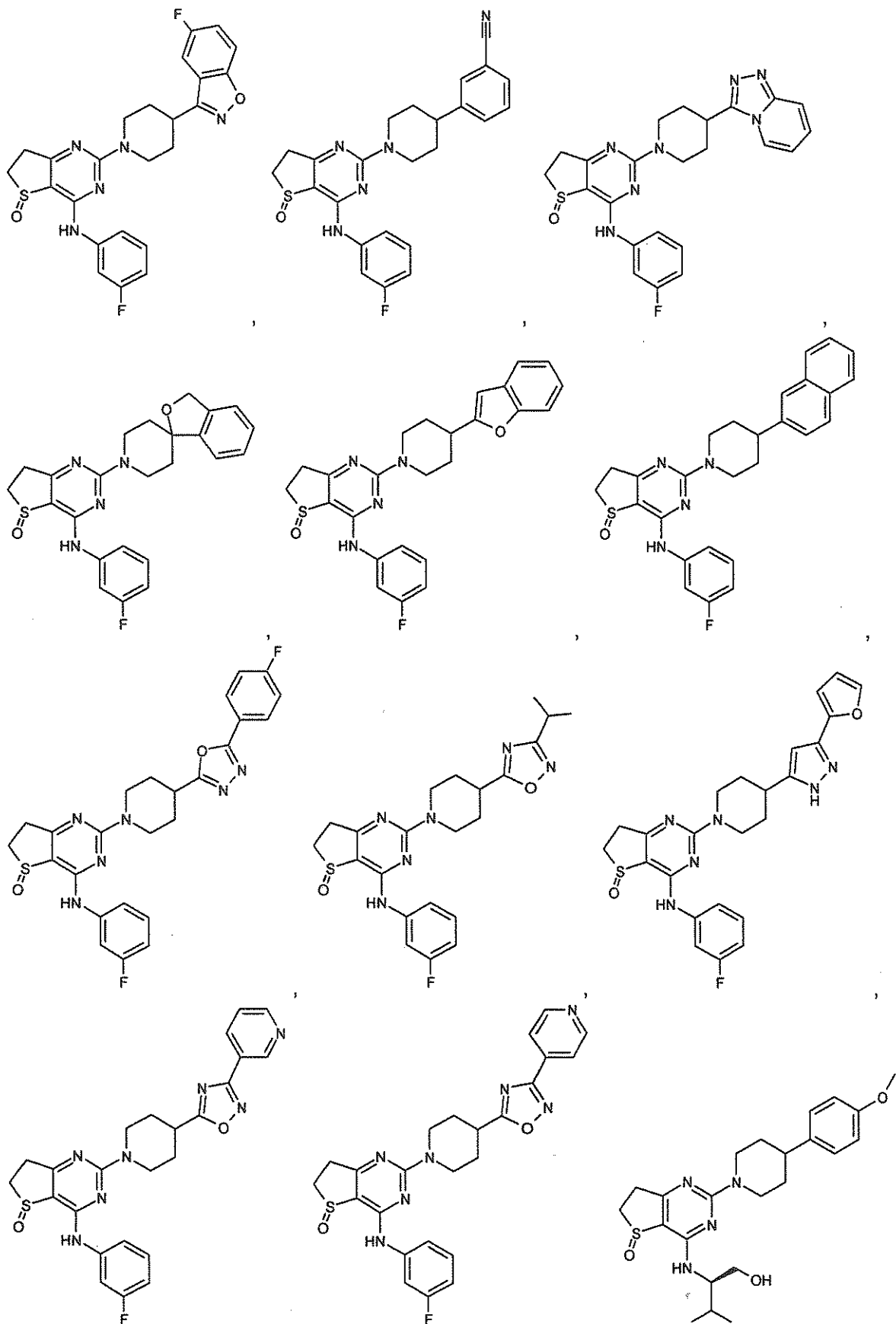


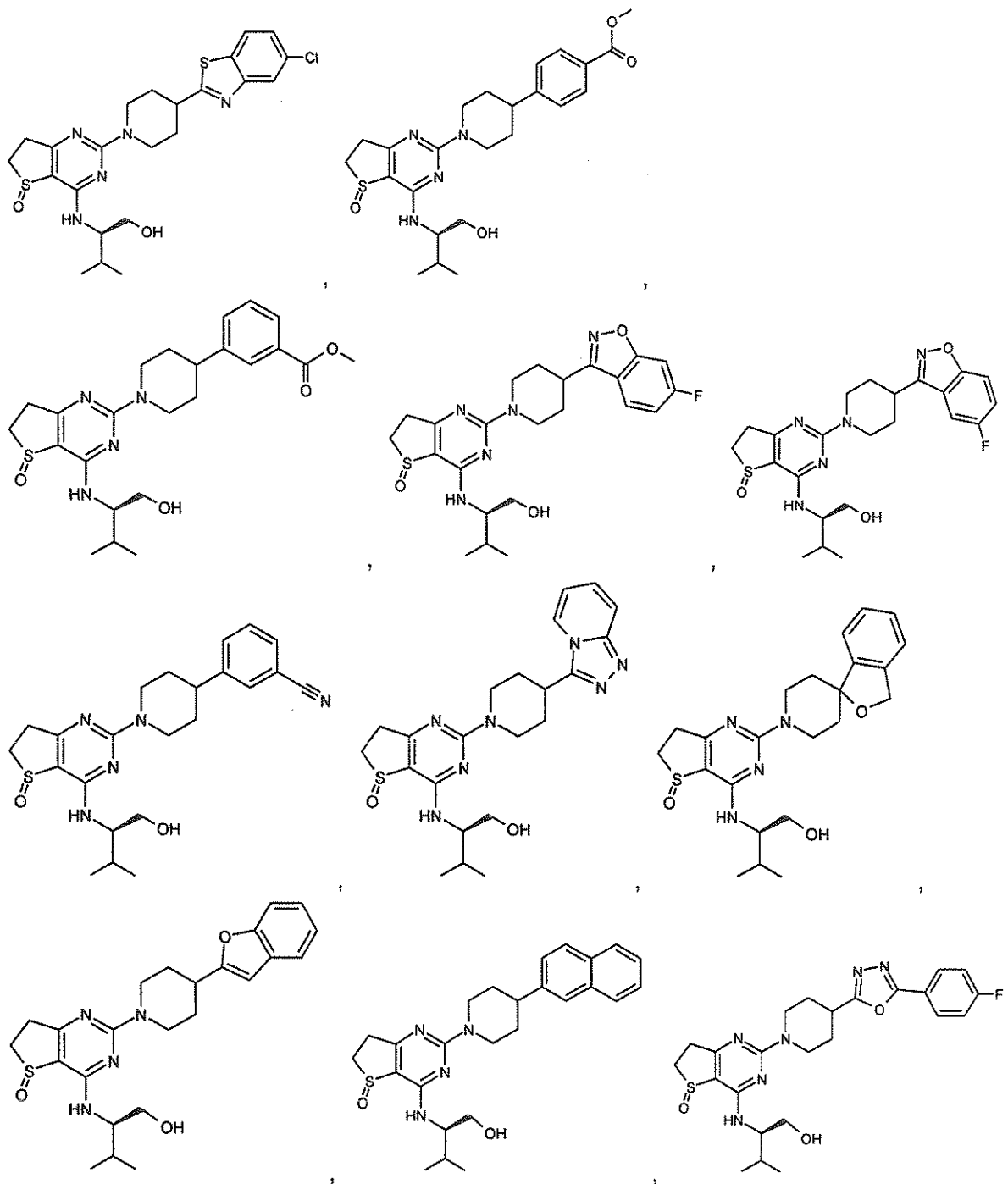


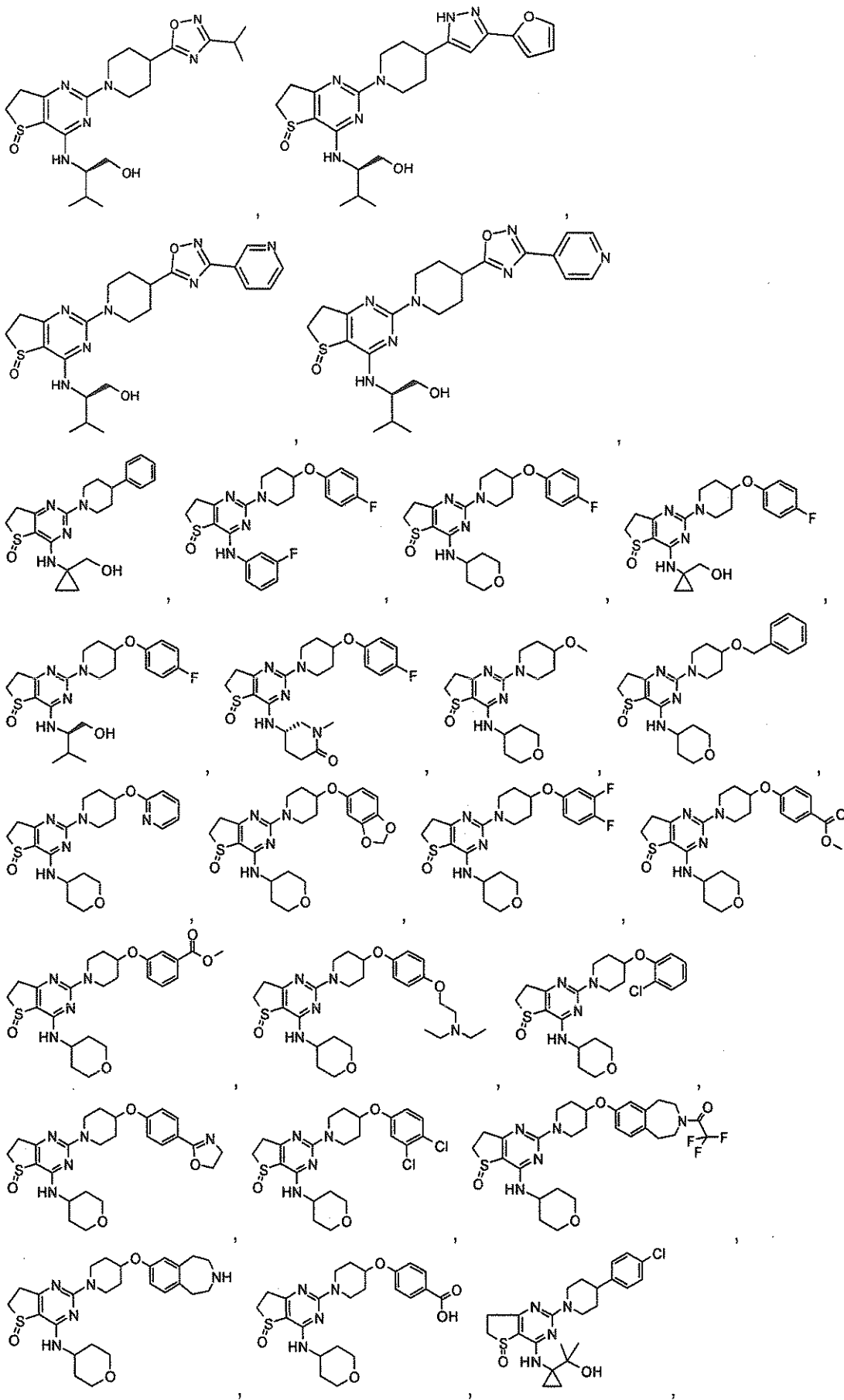


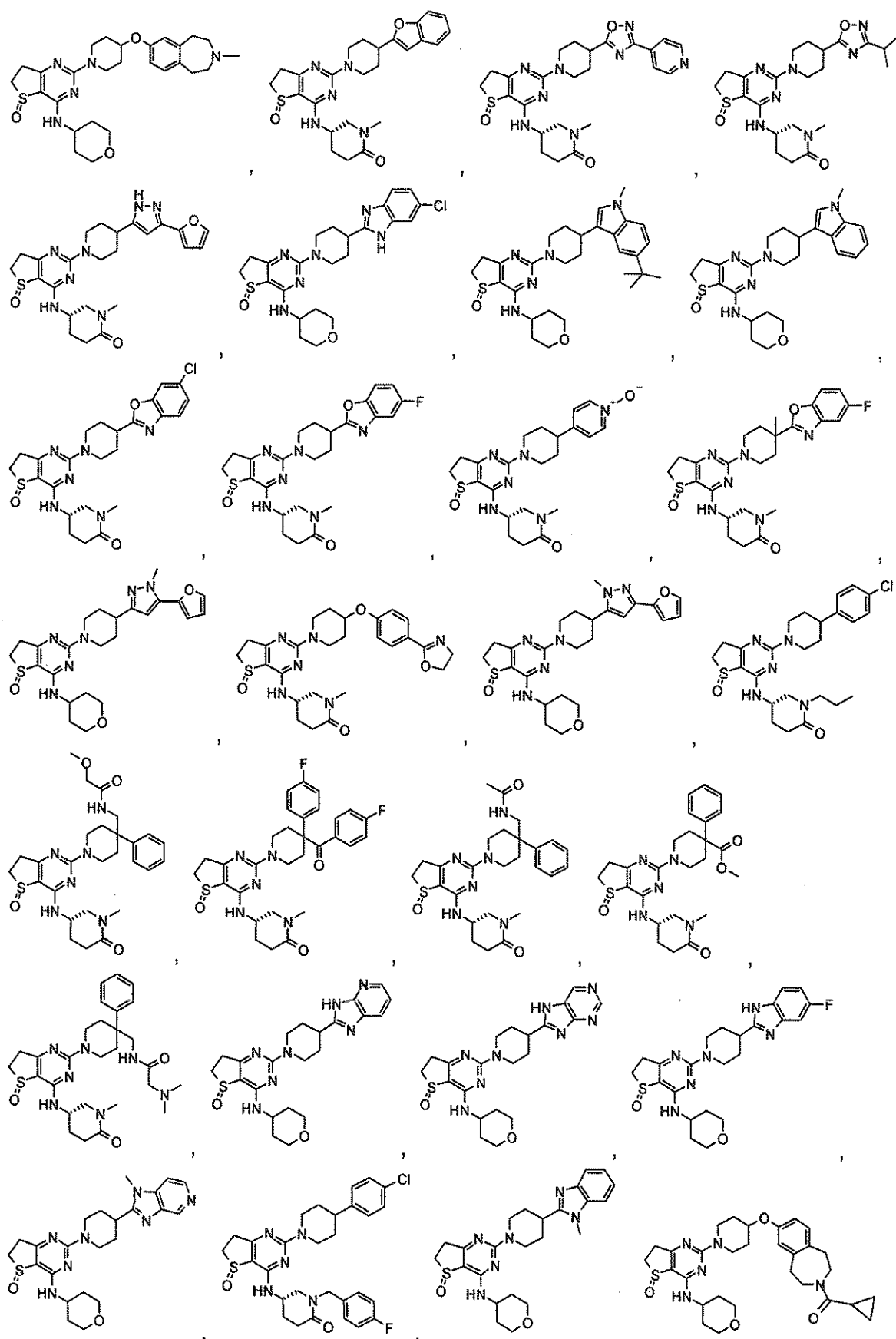


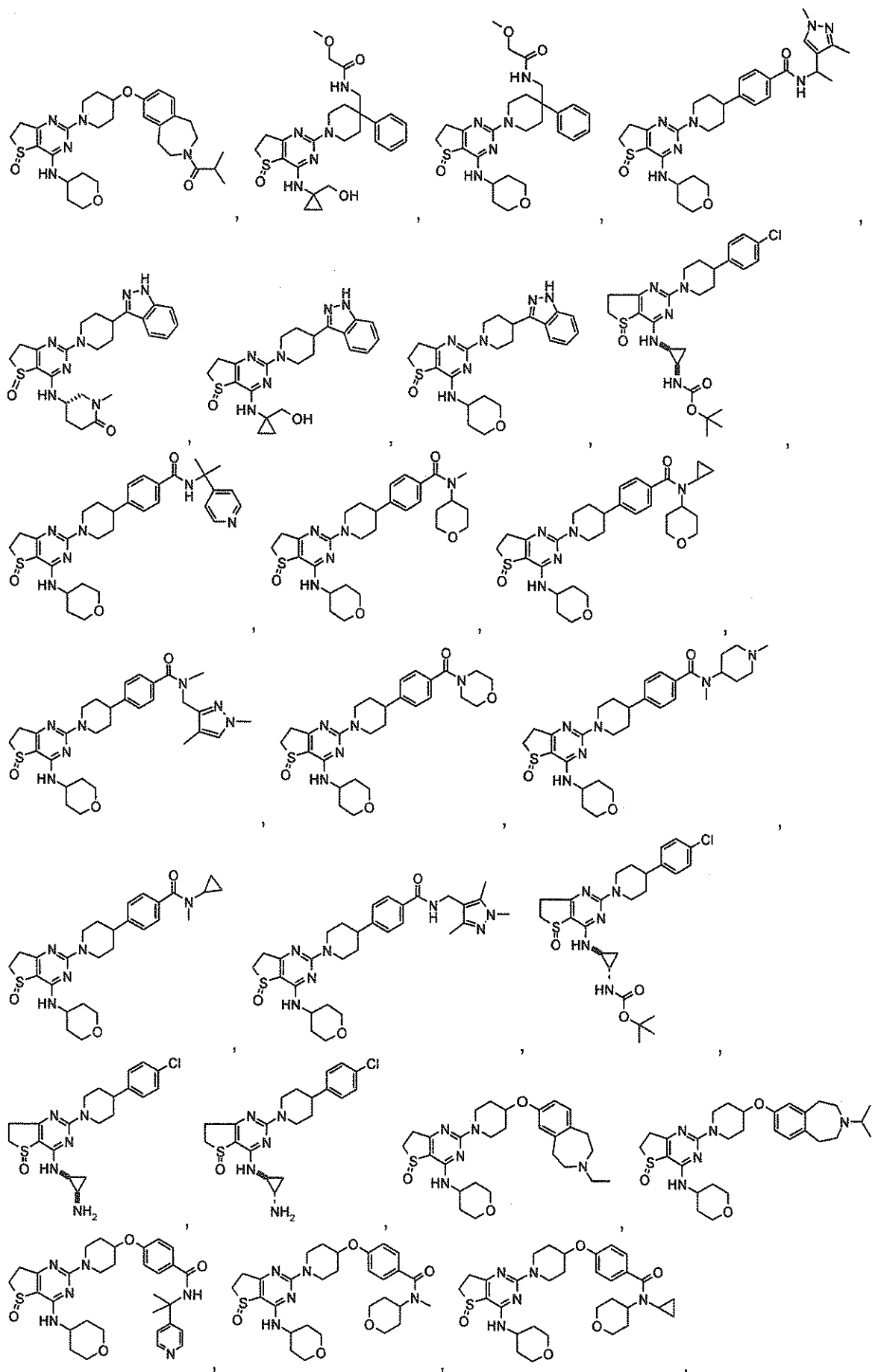


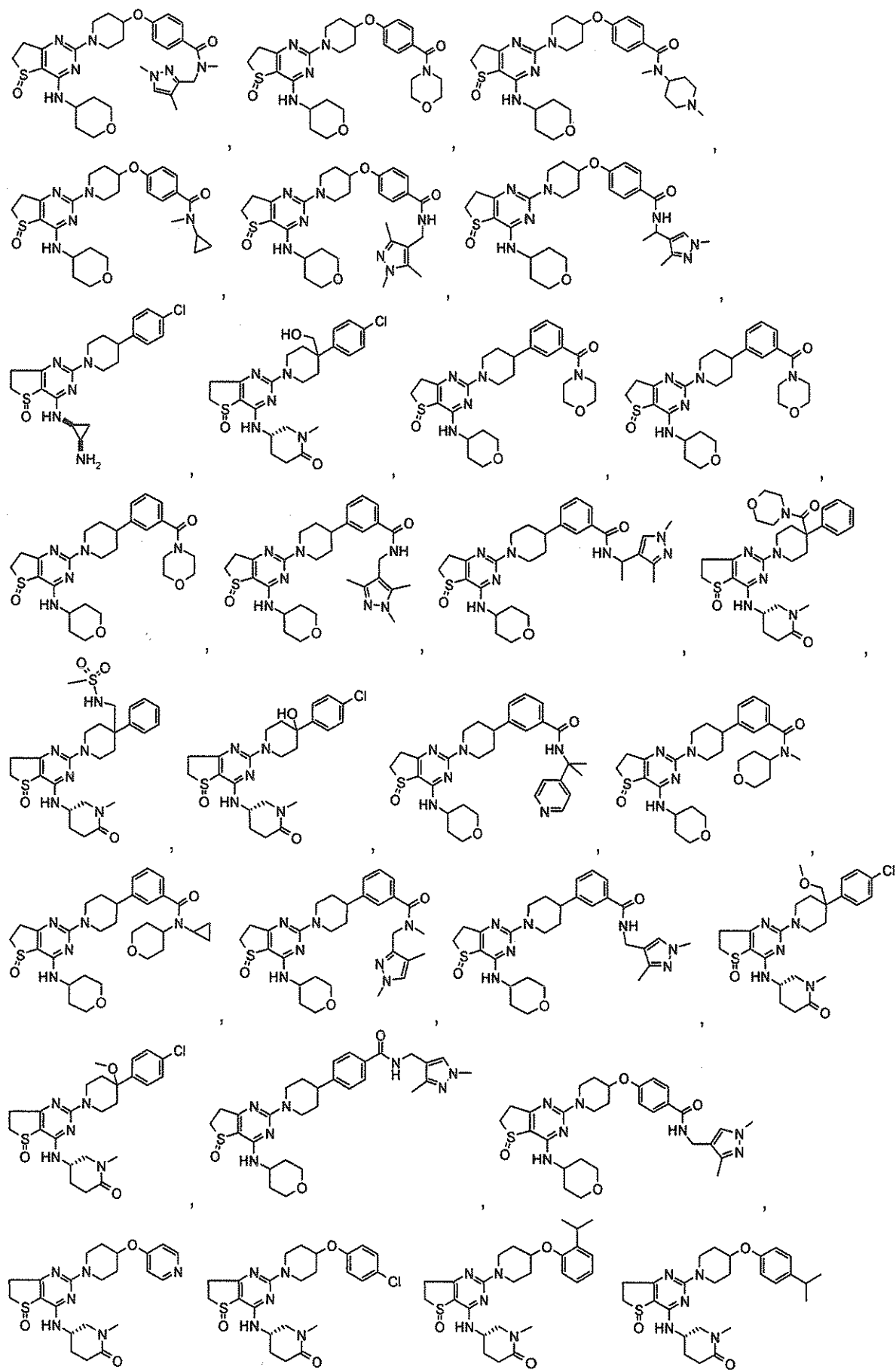


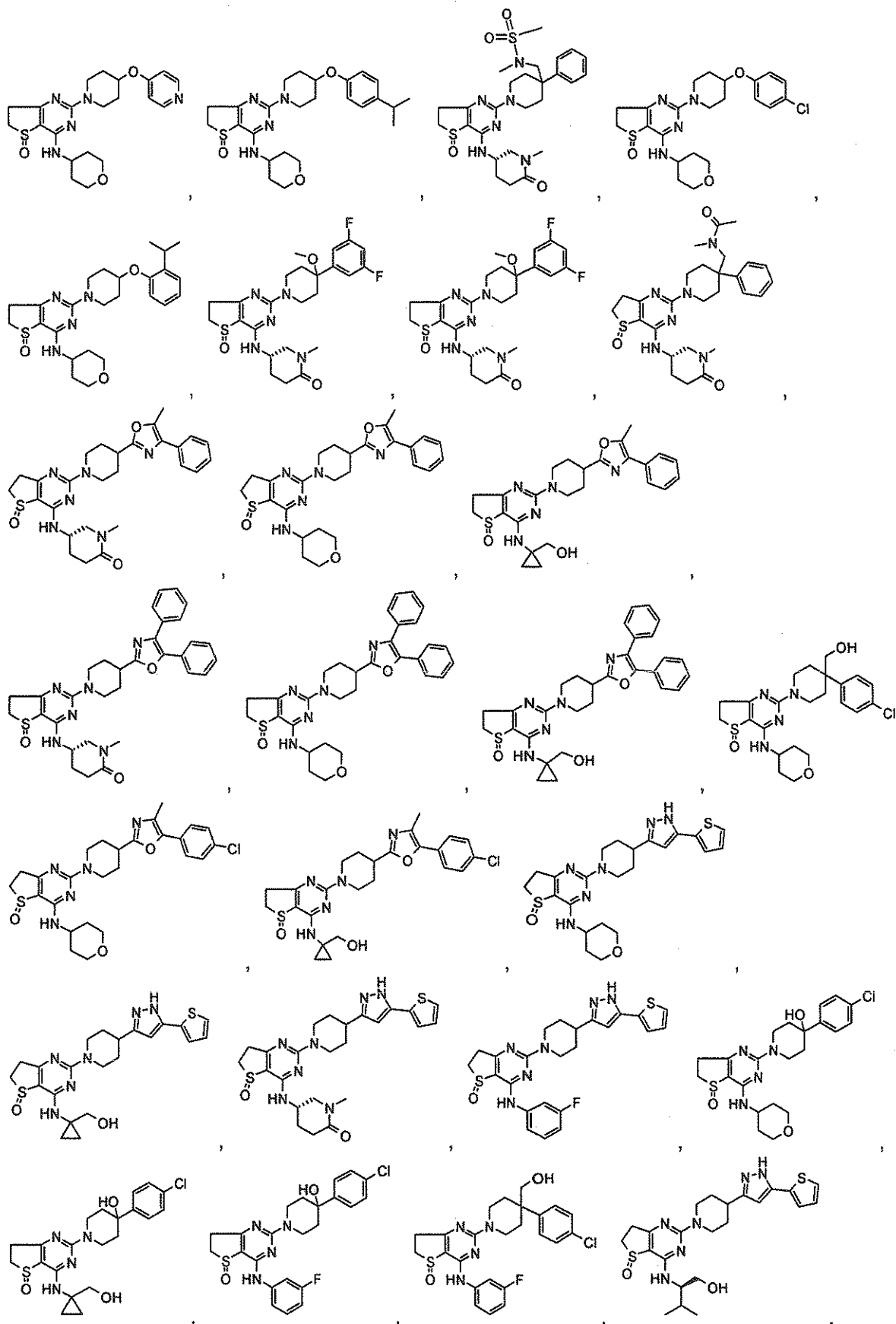


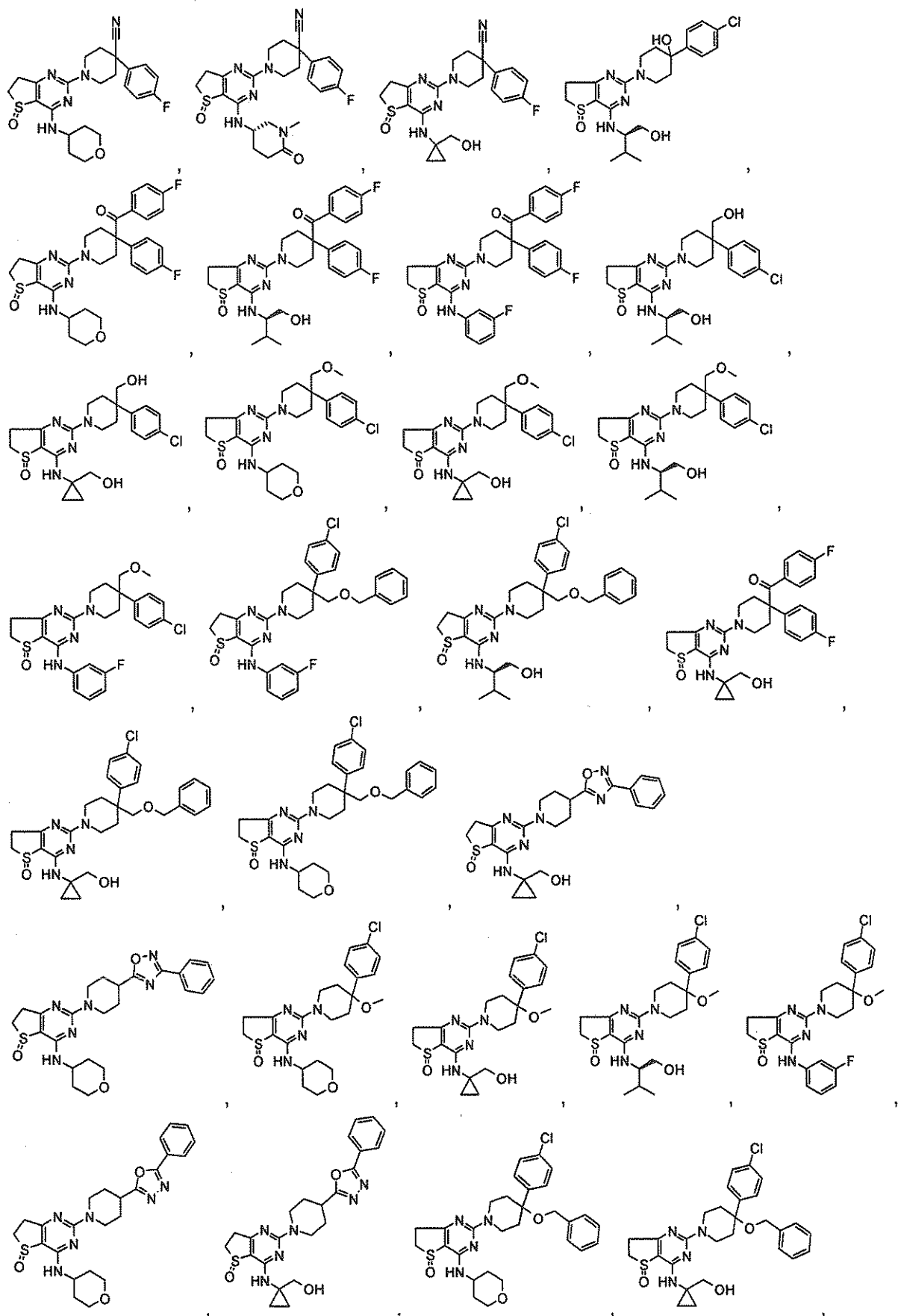


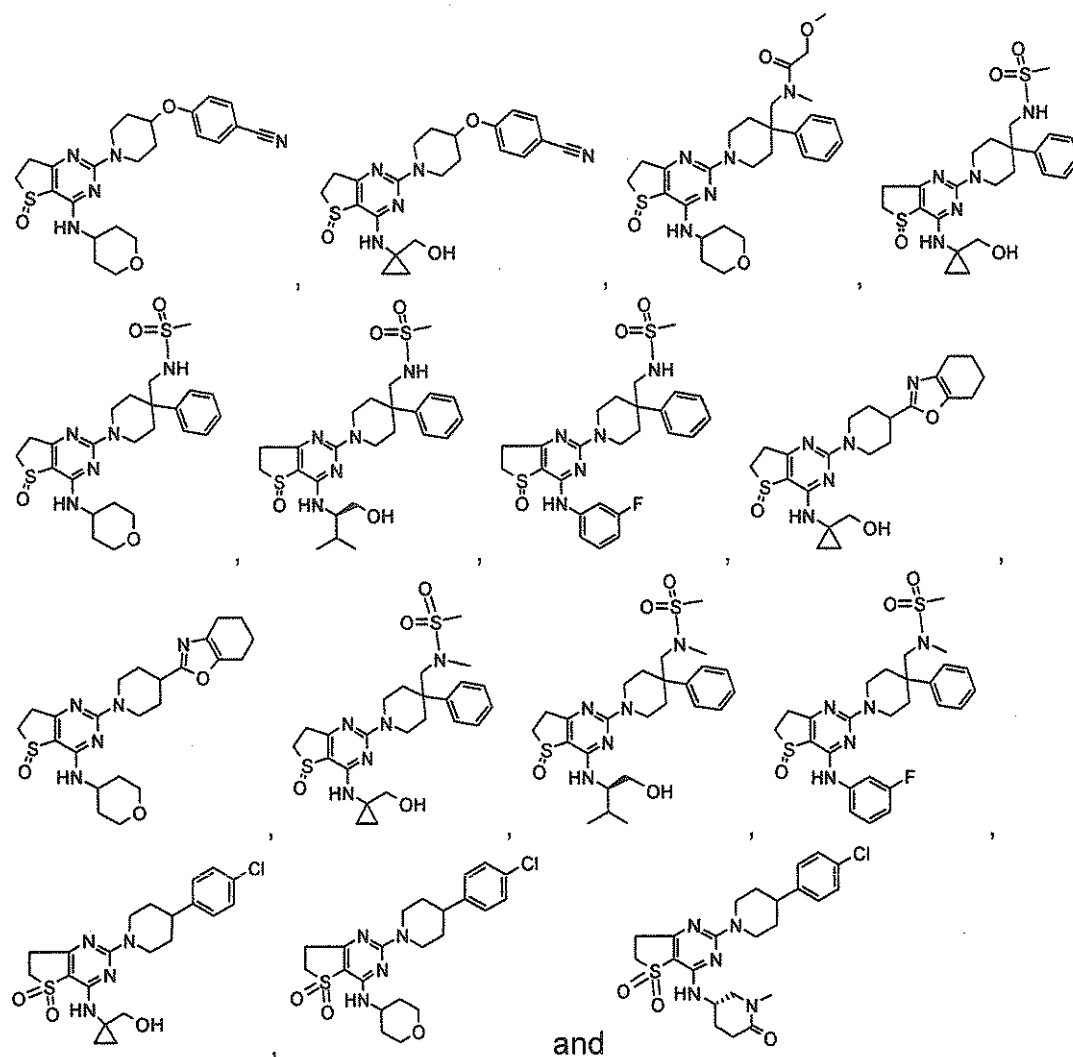












as well as pharmacologically acceptable salts, diastereomers, enantiomers, racemates, hydrates or solvates thereof, particularly the R-enantiomers and the S-enantiomers with respect to the stereocentre at the sulfoxide sulphur atom of the above compounds.

The invention further relates to the above compounds of formula **1** as pharmaceutical compositions.

The invention further relates to the use of the above compounds according to formula **1** for preparing a medicament for the treatment of diseases which can be treated by inhibition of the PDE4 enzyme.

The invention further relates to the use of the above compounds according to formula **1** for preparing a medicament for the treatment of respiratory or gastrointestinal diseases or complaints, as well as inflammatory diseases of the joints, skin or eyes, cancers, and diseases of the peripheral or central nervous system.

The invention further relates to the use of the above compounds according to formula 1 for preparing a medicament for the prevention and/or treatment of respiratory or pulmonary diseases which are accompanied by increased mucus production, inflammations and/or obstructive diseases of the respiratory tract.

The invention further relates to the use of the above compounds according to formula 1 for preparing a medicament for the treatment of inflammatory and/or obstructive diseases such as COPD, chronic sinusitis, asthma, Crohn's disease and ulcerative colitis.

The invention further relates to the use of the above compounds according to formula 1 for preparing a medicament for the treatment of inflammatory diseases of the gastrointestinal tract.

The invention further relates to the use of the above compounds according to formula 1 for preparing a medicament for 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 and brain damage caused by stroke, hypoxia or cranio-cerebral trauma.

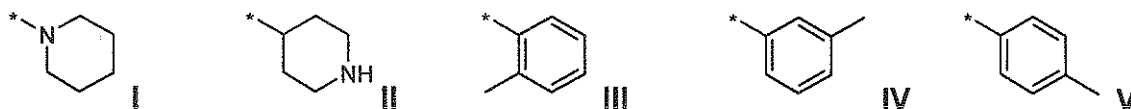
The invention further relates to pharmaceutical formulations which contain one or more of the above compounds according to formula 1.

The invention further relates to pharmaceutical formulations containing one or more compounds of formula 1 in combination with one or more active substances selected from among betamimetics, corticosteroids, other PDE4-inhibitors, EGFR-inhibitors and LTD4-antagonists, CCR3-inhibitors, iNOS-inhibitors and SYK-inhibitors.

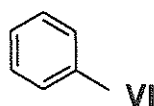
TERMS AND DEFINITIONS USED

Unless otherwise stated, all the substituents are independent of one another. If for example a plurality of C₁₋₆-alkyl groups are possible substituents in one group, in the case of three substituents C₁₋₆-alkyl, for example, one may represent methyl, one *n*-propyl and one *tert*-butyl, for example.

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-piperidinyI (I), 4-piperidinyI (II), 2-tolyl (III), 3-tolyl (IV) and 4-tolyl (V) are shown as follows:



If there is no asterisk (*) in the structural formula of the substituent, each hydrogen atom may be removed at the substituent and the valency thus freed may serve as a binding site to the rest of a molecule, unless the linking point to the remainder of the molecule is otherwise designated or defined. Thus, for example, VI may represent 2-tolyl, 3-tolyl, 4-tolyl and benzyl.

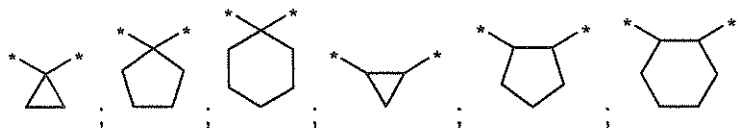


By the term "C₁₋₁₀-alkyl" (including those which are part of other groups) are meant branched and unbranched alkyl groups with 1 to 10 carbon atoms and by the term "C₁₋₆-alkyl" are meant, accordingly, branched and unbranched alkyl groups with 1 to 6 carbon atoms. "C₁₋₄-Alkyl" accordingly denotes branched 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 "C₁₋₆-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 "C₁₋₄-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 "C₂₋₆-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 "C₂₋₄-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 "C₂₋₆-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 "C₂₋₄-alkenylene" are meant branched and unbranched alkylene groups with 2 to 4 carbon atoms. Alkenylene groups with 2 to 4 carbon atoms are preferred. Examples of these 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 "C₂₋₆-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 "C₂₋₄-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 "C₂₋₆-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 "C₂₋₄-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 "C₂₋₆-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 "C₂₋₄-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-methylethyhylylene, butynylene, 1-methylpropynylene, 1,1-dimethylethyhylylene, 1,2-dimethylethyhylylene, 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

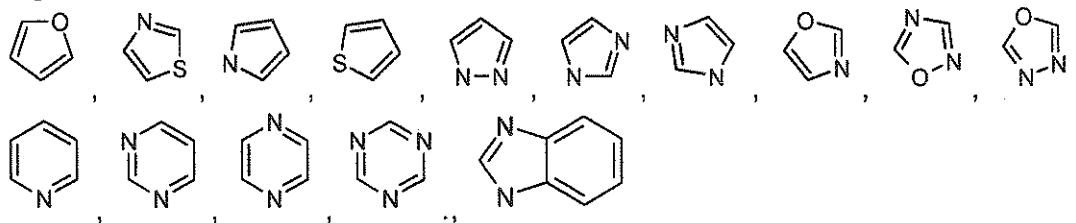
example propynyl also includes 1-methylethynylene and butynylene includes 1-methylpropynylene, 1,1-dimethylethynylene, 1, 2-dimethylethynylene.

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-C₁₋₆-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.

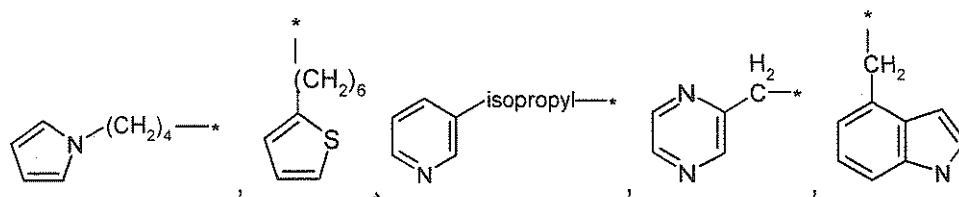
By the term "heteroaryl-C₁₋₆-alkylene" (including those which are part of other groups) are meant - even though they are already included under "aryl-C₁₋₆-alkylene" - branched and unbranched alkylene groups with 1 to 6 carbon atoms, which are substituted by a heteroaryl.

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 or bicyclic heteroaryl rings:



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-C₁₋₆-alkylenes:

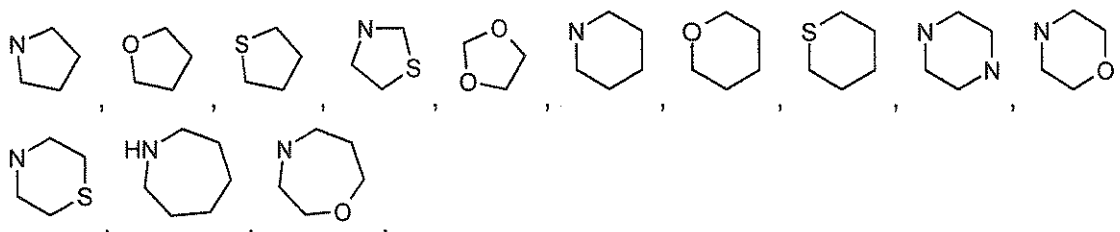


By the term "C₁₋₆-haloalkyl" (including those which are part of other groups) are meant branched and unbranched alkyl groups with 1 to 6 carbon atoms, which are substituted by one or more halogen atoms. By the term "C₁₋₄-alkyl" are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms, which are substituted by one or more halogen atoms. Alkyl groups with 1 to 4 carbon atoms are preferred. Examples include: CF₃, CHF₂, CH₂F, CH₂CF₃.

By the term "C₃₋₇-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 stated, 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.

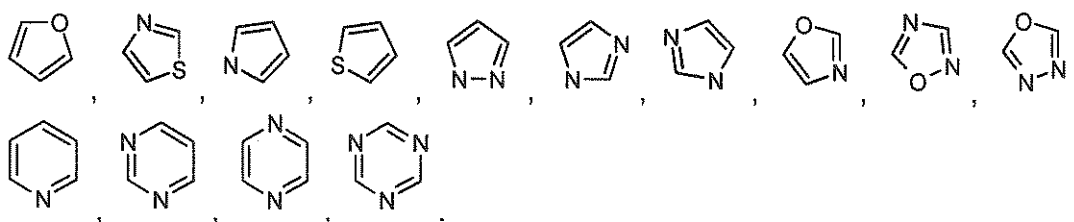
By the term "C₃₋₁₀-cycloalkyl" are also meant monocyclic alkyl groups with 3 to 7 carbon atoms and also bicyclic alkyl groups with 7 to 10 carbon atoms, or monocyclic alkyl groups which are bridged by at least one C₁₋₃-carbon bridge.

By the term "heterocyclic rings" or "heterocycle" 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:

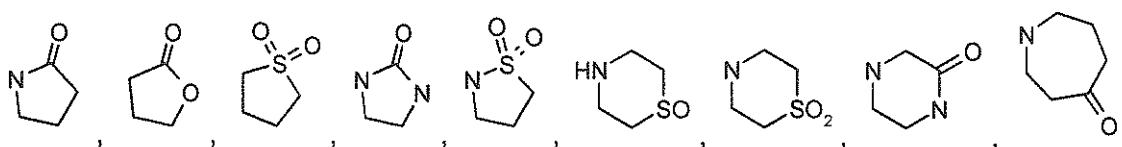


Although included by the term "heterocyclic rings" or "heterocycles", the term "heterocyclic aromatic rings" or "heteroaryl" refers to five- or six-membered heterocyclic aromatic groups or 5-10-membered, bicyclic heteroaryl rings which may contain one, two, three or four heteroatoms, selected from among oxygen, sulphur

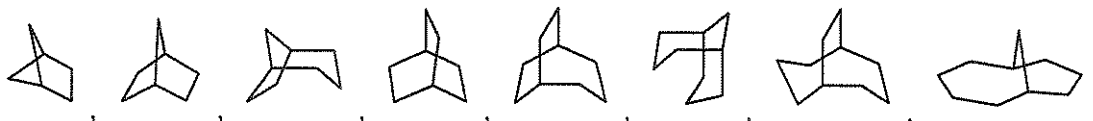
and nitrogen, and contain so many conjugated double bonds that an aromatic system is formed. Examples of five- or six-membered heterocyclic aromatic groups include:



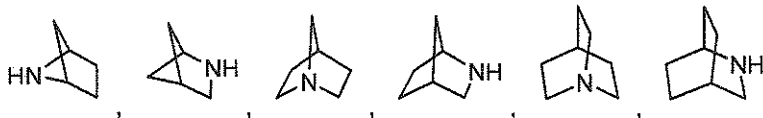
Unless otherwise mentioned, a heterocyclic ring (or heterocycle) may be provided with a keto group. Examples include:



Although covered by the term "cycloalkyl", the term "bicyclic cycloalkyls" generally denotes eight-, nine- or ten-membered bicyclic carbon rings. Examples include



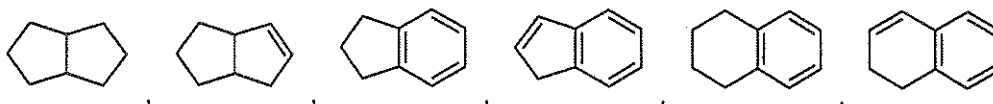
Although already included by the term "heterocycle", the term "bicyclic heterocycles" generally denotes eight-, nine- or ten-membered bicyclic rings which may contain one or more heteroatoms, preferably 1-4, more preferably 1-3, even more preferably 1-2, particularly one heteroatom, selected from among 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:



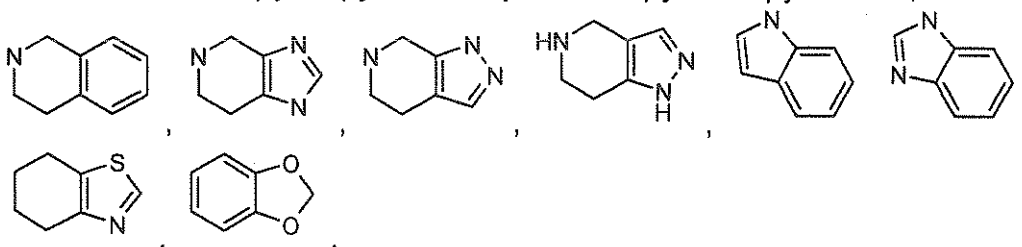
Although already included by the term "aryl", the term "bicyclic aryl" denotes a 5-10 membered, bicyclic aryl ring which contains sufficient conjugated double bonds to form an aromatic system. One example of a bicyclic aryl is naphthyl.

Although already included under "heteroaryl", the term "bicyclic heteroaryl" denotes a 5-10 membered, bicyclic heteroaryl ring which may contain one, two, three or four heteroatoms, selected from among oxygen, sulphur and nitrogen, and contains sufficient conjugated double bonds to form an aromatic system.

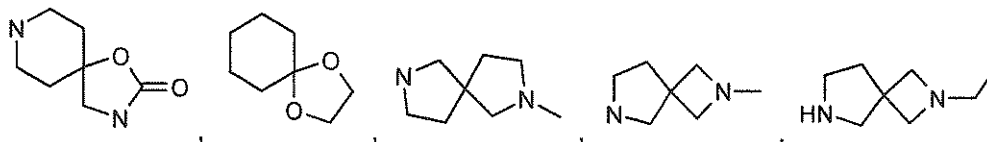
Although included by the term "bicyclic cycloalkyls" or "bicyclic aryl", the term "fused cycloalkyl" or "fused aryl" denotes bicyclic rings wherein the bridge separating the rings denotes a direct single bond. The following are examples of a fused, bicyclic cycloalkyl:



Although included by the term "bicyclic heterocycles" or "bicyclic heteroaryls", the term "fused bicyclic heterocycles" or "fused bicyclic heteroaryls" 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. The "fused bicyclic heteroaryls" moreover contain sufficient conjugated double bonds to form an aromatic system. Examples include pyrrolizine, indole, indolizine, isoindole, indazole, purine, quinoline, isoquinoline, benzimidazole, benzofuran, benzopyran, benzothiazole, benzothiazole, benzoisothiazole, pyridopyrimidine, pteridine, pyrimidopyrimidine,



By the term "heterocyclic spiro rings" (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 if available through a nitrogen atom. Unless otherwise mentioned, a spirocyclic ring may be provided with an oxo, methyl or ethyl group. Examples of this 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 usable inorganic acids such as 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 usable bases such as alkali metal or alkaline earth metal hydroxides or carbonates, zinc or ammonium hydroxides or organic amines such as e.g. diethylamine, triethylamine, triethanolamine, *inter alia*.

As mentioned previously, 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 be present on the one hand as physiologically and pharmacologically acceptable acid addition salts of the compounds of formula 1 with inorganic or organic acids. On the other hand, the compound of formula 1 when R is hydrogen may 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. To prepare the alkali and alkaline earth metal salts of the compound of formula 1 wherein R denotes hydrogen, it is preferable to use the alkali and alkaline earth metal hydroxides and hydrides, of which the hydroxides and hydrides of the alkali metals, particularly sodium and potassium, are preferred, while sodium and potassium hydroxide are particularly preferred.

The compounds of general formula 1 may optionally be converted into the salts thereof, particularly for pharmaceutical use into the pharmacologically acceptable acid addition salts with an inorganic or organic acid. Examples of suitable acids for this purpose include 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 be present as racemates, but may also be obtained as pure enantiomers, i.e. In the (R) or (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.

The invention relates to the respective compounds of formula 1 in the form of the pharmacologically acceptable salts thereof as hereinbefore described. These pharmacologically acceptable salts of the compounds of formula 1 may also be present in the form of their respective hydrates (e.g. monohydrated, dihydrates, etc.) as well as in the form of their respective solvates.

By a hydrate of the compound according to the formula 1 is meant, for the purposes of the invention, a crystalline salt of the compound according to formula 1, containing water of crystallisation.

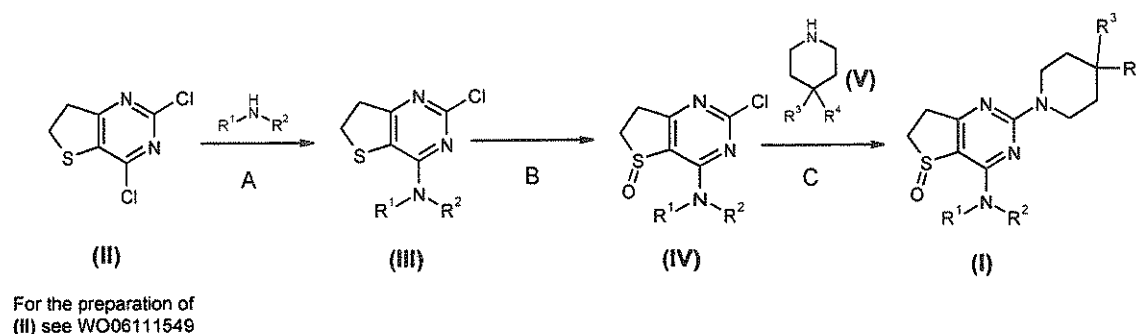
By a solvate of the compound according to the formula 1 is meant, for the purposes of the invention, a crystalline salt of the compound according to formula 1, which contains solvent molecules (e.g. Ethanol, methanol etc) in the crystal lattice.

The skilled man will be familiar with the standard methods of obtaining hydrates and solvates (e.g. recrystallisation from the corresponding solvent in the case of solvates or from water in the case of hydrates).

METHODS OF SYNTHESIS

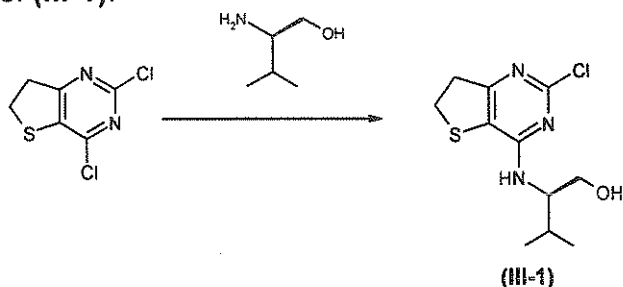
The compounds of general formula (I) may be prepared according to the following general synthesis scheme, wherein the substituents of general formula (I) have the meanings given hereinbefore. These methods are to be understood as being an illustration of the invention without restricting it to the subject-matter thereof.

GENERAL SYNTHESIS SCHEME



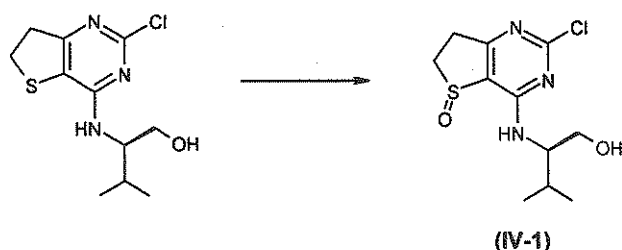
1. SYNTHESIS OF (R)-2-[2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YLAMINO]-3-METHYLBUTAN-1-OL (EXAMPLE 1)

1.1 (R)-2-(2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-ylamino)-3-methylbutan-1-ol (III-1):



7.2 g of 2,4-dichloro-6,7-dihydrothieno[3,2-d]pyrimidin (II) are in 36 ml dioxane placed, and then first 18 ml diisopropylethylamine, then 6.1 g (R)-(-)-2-amino-3-methyl-1-butanol are added. The reaction mixture is heated to 100°C, until there is no further reaction and cooled, then evaporated down. The residue is treated with petroleum ether/ethyl acetate (9:1) in the ultrasound bath and the solid is suction filtered and dried. 8.3 g (III-1) are obtained as a solid. Analytical HPLC (method A): RT = 2.75 min

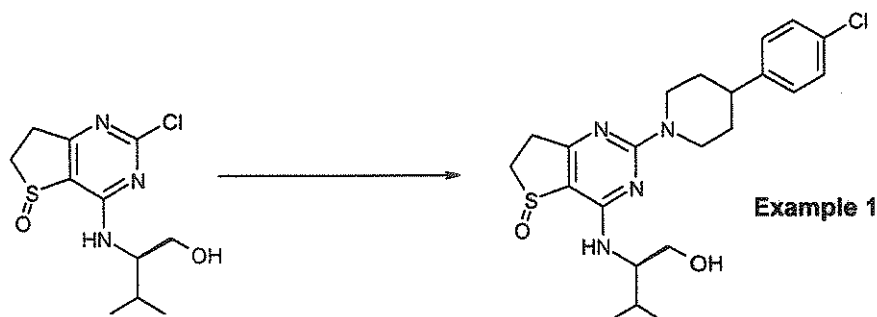
1.2 (R)-2-(2-chloro-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-ylamino)-3-methylbutan-1-ol (IV-1):



4.1 g S-(-)-1,1'-bi-2-naphthol are placed in 15 ml chloroform under argon, then 0.44 ml titanium(IV)-isopropoxide and 0.54 ml of water are added. The reaction mixture is stirred for 1 hour at ambient temperature. Then a suspension of 4.1 g **(III-1)** in 107 ml dichloromethane is added. The reaction mixture is cooled to -2°C and after 30 minutes 2.7 ml tert-butylhydroperoxide 5-6 M in decane are added dropwise. The reaction mixture is stirred further at -2°C, until there is no further reaction, and made basic with NH₄OH. The product is extracted with dichloromethane and purified by chromatography (silica gel, ethyl acetate/methanol 100/0 to 86/14). 2.45 g **(IV-1)** are obtained as a solid.

Analytical HPLC (method A): RT = 2.37 min

1.3 (R)-2-{2-[4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5λ⁴-thieno[3,2-d]pyrimidin-4-ylamino}-3-methylbutan-1-ol (**Example 1**)



0.2 g **(IV-1)** is placed in 3 ml dioxane and 360 µl diisopropylethylamine, combined with 0.16 g 4-(4-chlorophenyl)-piperidine and heated in the microwave at 120°C, until there is no further reaction. The reaction mixture is mixed with water, extracted with dichloromethane and the product is purified by chromatography (silica gel, dichloromethane/methanol 100/0 to 92/8). 0.33 g **Example 1** are obtained as a solid. Analytical HPLC-MS (method A): RT = 1.24 min.

2. SYNTHESIS OF (1-{2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5λ⁴-THIENO[3,2-d]PYRIMIDIN-4-YLAMINO}-CYCLOPROPYL)-METHANOL (**EXAMPLE 2**)

2.1 tert-butyl (1-hydroxymethylcyclopropyl)-carbamidate:



1 g 1-(BOC-amino)-cyclopropanecarboxylic acid is dissolved in 20 ml dimethoxyethane and cooled to -70°C . Then 0.65 ml N-methylmorpholine are added and 0.71 ml isobutylchloroformate in 5 ml dimethoxyethane are added dropwise. The reaction mixture is heated to -5°C . The precipitate is suction filtered. The eluate is cooled to -15°C and 0.303 g sodiumborohydride are slowly added. The reaction mixture is then stirred for 30 minutes at ambient temperature, mixed with water and the product is extracted with dichloromethane. The organic phase is dried and evaporated to dryness. 1.04 g product are obtained as a solid. ^1H NMR (400 MHz, DMSO): 1.36 (9H, s); 0.61 (2H, t); 0.52 (2H, t).

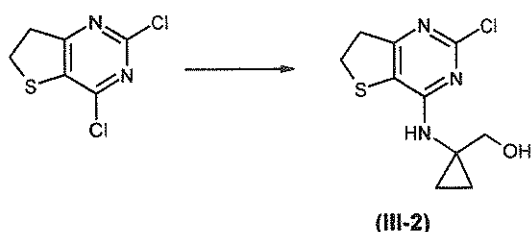
2.2 1-aminocyclopropanemethanol:



1.04 g tert-butyl (1-hydroxymethylcyclopropyl)-carbamidate are placed in 5 ml dioxane. 2.5 ml HCl in dioxane (4 mol/l) are added dropwise. The reaction mixture is stirred for 15 h at ambient temperature. The solvent is evaporated down by half and the precipitated solid is suction filtered. 0.5 g product are obtained as the hydrochloride.

^1H NMR (400 MHz, DMSO): 5.27 (1H, t); 0.91 (2H, t); 0.71 (2H, t).

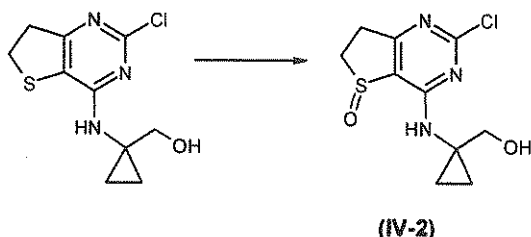
2.3 [1-(2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-ylamino)-cyclopropyl]-methanol (III-2):



1.4 g (II) are placed in 10 ml dioxane, then 3.6 ml diisopropylethylamine and then 1 g of 1-aminocyclopropanemethanol (see 2.2) are added. The reaction mixture is heated to 160°C , until there is no further reaction, and cooled, then evaporated down. The residue is treated with cyclohexane/ethyl acetate (4:1) in the ultrasound bath, the

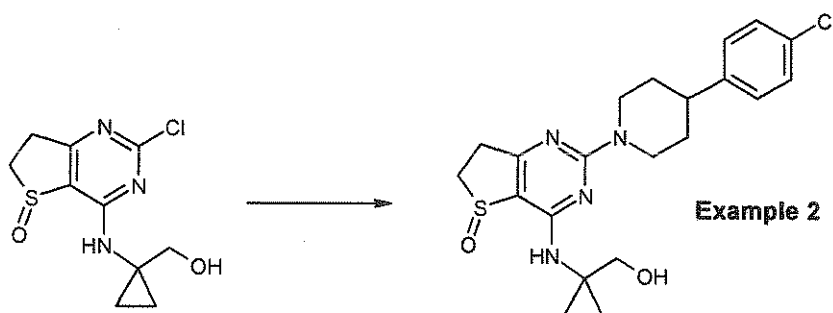
solid is suction filtered and dried. 1.24 g (**III-2**) are obtained as a solid. Analytical HPLC-MS (method A): RT = 1.01 min.

2.4 [1-(2-chloro-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-ylamino)-cyclopropyl]-methanol (**IV-2**):



0.28 g S-(-)-1,1'-bi-2-naphthol are placed in 20 ml chloroform under argon, then 0.14 ml titanium(IV)-isopropoxide and 0.17 ml of water are added. The reaction mixture is stirred for 1 hour at ambient temperature. Then a suspension of 1.2 g (**III-2**) in 40 ml dichloromethane and 2 ml of methanol is added. The reaction mixture is cooled to -5°C and after 30 minutes 0.91 ml tert-butylhydroperoxide 5-6 M in decane are added dropwise. The reaction mixture is stirred further at -5°C, until there is no further reaction, and made basic with NH₄OH. The aqueous phase is washed with dichloromethane and freeze-dried. 1 g (**IV-2**) is obtained as a solid. Analytical HPLC-MS (method A) RT = 0.85 min

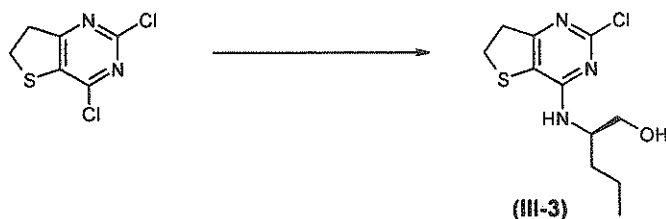
2.5 (1-{2-[4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-ylamino}-cyclopropyl)-methanol (**Example 2**)



Starting from 0.17 g (**IV-2**) and 0.15 g 4-(4-chlorophenyl)-piperidine 0.14 g **Example 2** are prepared and purified analogously to Example 1 (see 1.3). Analytical HPLC-MS (method B): RT = 1.32 min.

3. SYNTHESIS OF (R)-2-{2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YLAMINO}-PENTAN-1-OL (**EXAMPLE 3**)

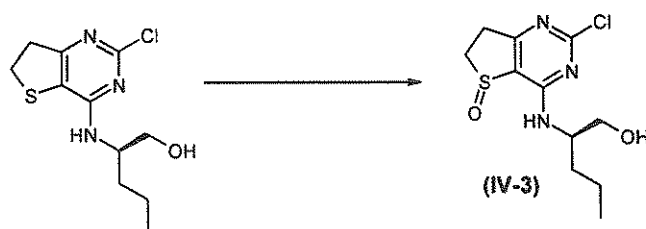
3.1 (R)-2-(2-chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-ylamino)-pentan-1-ol (**III-3**):



1.4 g 2,4-dichloro-6,7-dihydrothieno[3,2-*d*]pyrimidine (**II**) are placed in 9 ml dioxane, then first 3.5 ml diisopropylethylamine, then 0.9 g D-norvalinol are added. The reaction mixture is heated in the microwave at 120°C, until there is no further reaction, and cooled, then evaporated down. The residue is treated with petroleum ether/ethyl acetate 9:1 in the ultrasound bath, the solid is suction filtered and dried. 1.5 g (**III-3**) are obtained as a solid.

¹H NMR (400 MHz, DMSO): 4.67 (1H, t); 0.86 (3H, t).

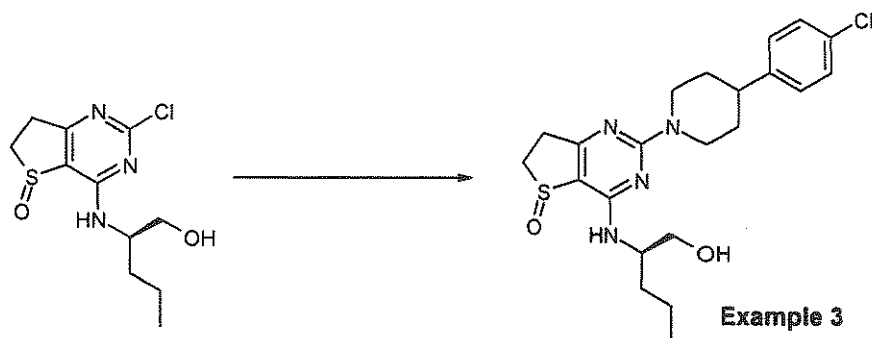
3.2 (R)-2-(2-chloro-5-oxo-6,7-dihydro-5*H*-5λ⁴-thieno[3,2-*d*]pyrimidin-4-ylamino)-pentan-1-ol (**IV-3**):



0.3 g S-(-)-1,1'-bi-2-naphthol are placed in 5 ml chloroform under argon, then 0.15 ml titanium(IV)-isopropoxide and 0.19 ml of water are added. The reaction mixture is stirred for 1 hour at ambient temperature. Then a suspension of 1.4 g (**III-3**) in 20 ml dichloromethane is added. The reaction mixture is cooled to -5°C and after 30 minutes 0.95 ml tert-butylhydroperoxide 5-6 M in decane are added dropwise. The reaction mixture is stirred further at -5°C, until there is no further reaction, and made basic with NH₄OH. The product is extracted with dichloromethane and purified by chromatography (ethyl acetate/methanol 100/0 to 80/20). 1.17 g (**IV-3**) are obtained as a solid.

Analytical HPLC (method A): RT = 2.41 min

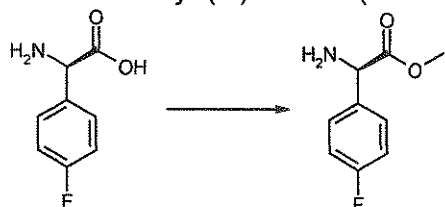
3.3 (R)-2-{2-[4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5*H*-5λ⁴-thieno[3,2-*d*]pyrimidin-4-ylamino}-pentan-1-ol (**Example 3**)



0.2 g (**IV-3**) are placed in 4 ml dioxane and 237 μ l diisopropylethylamine, combined with 0.149 g 4-(4-chlorophenyl)-piperidine and heated to 130°C in the microwave for 30 min. The reaction mixture is mixed with water and the product is extracted with dichloromethane. The residue is treated with acetonitrile in the ultrasound bath and the solid is suction filtered. 0.104 g **Example 3** are obtained as a solid. Analytical HPLC-MS (method A): RT = 1.29 min.

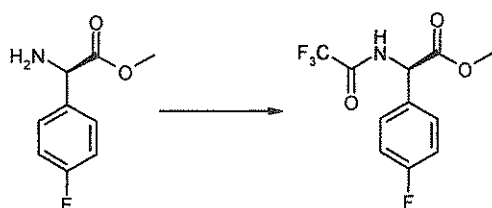
4. SYNTHESIS OF (R)-1-{2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YLAMINO}-1-(4-FLUOROPHENYL)-2-METHYLPROPAN-2-OL (**EXAMPLE 4**)

4.1 methyl (R)-amino-(4-fluorophenyl)-acetate:



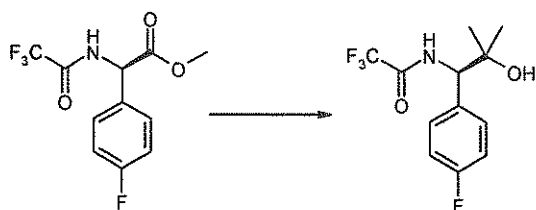
4 g (R)-4-fluorophenylglycine are suspended in 80 ml of methanol. While cooling with the ice bath 3.28 ml of thionyl chloride are slowly added dropwise, so that the temperature is maintained between 15°C and 20°C. The reaction mixture is stirred for 12 hours at ambient temperature and then evaporated to dryness. 5.1 g of the product are obtained as the hydrochloride. Analytical HPLC-MS (method A): RT = 0.8 min.

4.2 methyl (R)-(4-fluorophenyl)-(2,2,2-trifluoroacetyl-amino)-acetate:



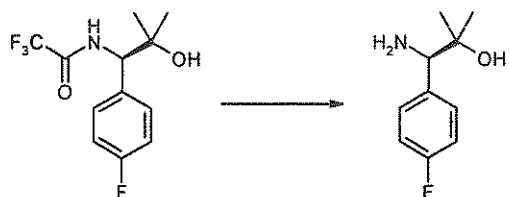
5.1 g methyl (R)-amino-(4-fluorophenyl)-acetate are placed in 36.5 ml abs. Tetrahydrofuran, then 3.9 ml triethylamine added. The reaction mixture is cooled to -70°C. 3.9 ml trifluoroacetic anhydride are then slowly added dropwise, so that the temperature does not exceed -60°C. The reaction mixture is stirred for 12 hours at ambient temperature and then mixed with water. Then potassium hydrogen carbonate is added until no further foaming can be observed and the product is extracted with ethyl acetate. 6.2 g of the product are obtained as an oil. Analytical HPLC-MS (method A): RT = 1.28 min.

4.3 2,2,2-trifluoro-*N*-[(R)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]-acetamide:



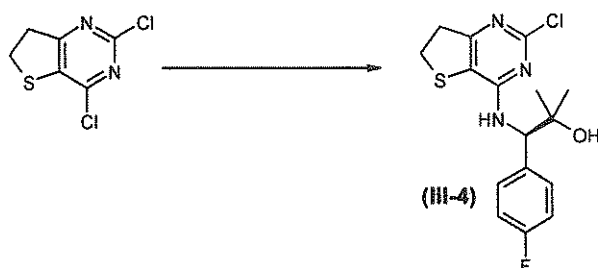
6.2 g methyl (R)-amino-(4-fluorophenyl)-acetate are placed in 195 ml abs. Tetrahydrofuran and the reaction mixture is cooled to +3°C. 37.2 ml of a methylmagnesium iodide solution (3 M) are slowly added dropwise, so that the temperature does not exceed +10°C. The reaction mixture is stirred for 12 hours at ambient temperature and then stirred into ice water. Ammonium chloride is added until the precipitate has dissolved and the product is extracted with ethyl acetate. 5.6 g of the product are obtained as an oil. Analytical HPLC-MS (method A): RT = 1.19 min

4.4 (R)-1-amino-1-(4-fluorophenyl)-2-methylpropan-2-ol:



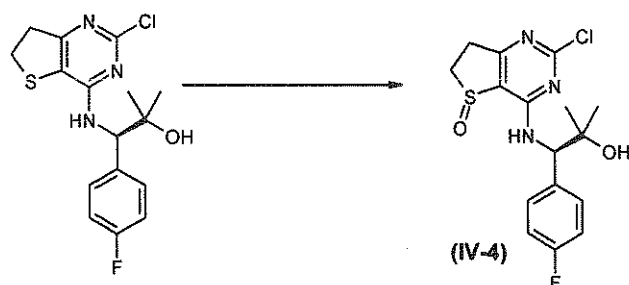
5.6 g 2,2,2-trifluoro-*N*-[(R)-1-(4-fluorophenyl)-2-hydroxy-2-methylpropyl]-acetamide and 2.27 g KOH are suspended in 60 ml of methanol. The reaction mixture is stirred for 20 hours at 60°C, then mixed with water and the product is extracted with dichloromethane. 3.2 g product are obtained as an oil. Analytical HPLC-MS (method A): RT = 0.79 min.

4.5 (R)-1-(2-chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-ylamino)-1-(4-fluorophenyl)-2-methylpropan-2-ol (III-4):



0.533 g (II), 0.850 g (R)-1-amino-1-(4-fluorophenyl)-2-methylpropan-2-ol and 1.3 ml diisopropylethylamine are suspended in 9.8 ml dioxane. The reaction mixture is heated to 80°C in the microwave for 2 hours and then evaporated to dryness. The residue is mixed with water. The precipitate formed is suction filtered and purified by chromatography (silica gel, petroleum ether/ethyl acetate 100/0 to 60/40). 0.260 g (III-4) are obtained as a solid. Analytical HPLC-MS (method A): 1.39 min.

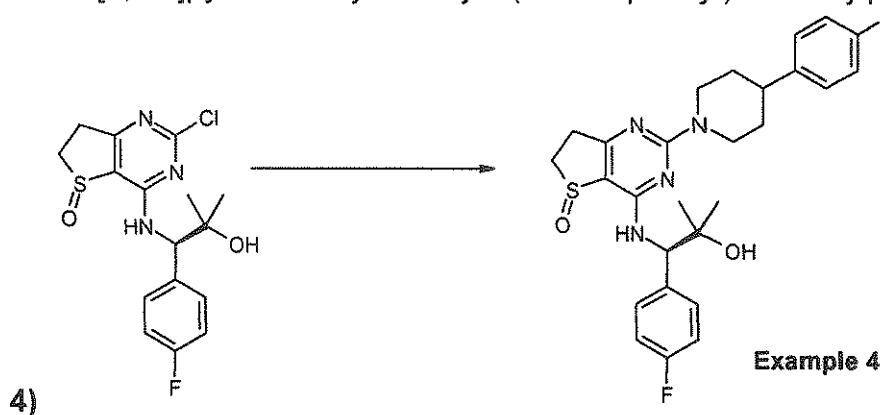
4.6 (R)-1-(2-chloro-5-oxo-6,7-dihydro-5H-5λ⁴-thieno[3,2-d]pyrimidin-4-ylamino)-1-(4-fluorophenyl)-2-methylpropan-2-ol (IV-4):



0.24 g S-(-)-1,1'-bi-2-naphthol are placed in 4 ml chloroform under argon, then 0.125 ml titanium(IV)-isopropoxide and 0.15 ml of water are added. The reaction mixture is stirred for 1 hour at ambient temperature. Then a suspension of 1.51 g (III-4) in 26 ml chloroform is added. The reaction mixture is cooled to -6°C and after 30 minutes 0.78 ml tert-butylhydroperoxide 5-6 M in decane are added dropwise. The reaction mixture is stirred further at -6°C until there is no further reaction, and made basic with NH₄OH. The product is extracted with dichloromethane and purified by chromatography (dichloromethane/methanol 100/0 to 95/5). 0.62 g (IV-4) are obtained as a solid.

Analytical HPLC-MS (method A): RT = 1.19 min.

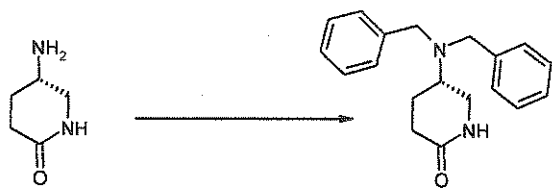
4.7 (R)-1-[2-[4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H- λ^4 -thieno[3,2-*d*]pyrimidin-4-ylamino]-1-(4-fluorophenyl)-2-methylpropan-2-ol (**Example 4**)



Starting from 0.24 g (**IV-4**) and 0.15 g 4-(4-chlorophenyl)-piperidine 0.19 g **Example 4** are prepared analogously to Example 1 (see 1.3). The product is purified by chromatography (dichloromethane/methanol 100/0 to 96/4). Analytical HPLC-MS (method A): RT = 1.36 min.

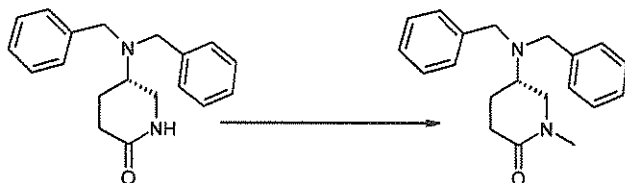
5. SYNTHESIS OF (S)-5-[2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H- λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO]-1-METHYLPYPERIDIN-2-ONE (**EXAMPLE 5**)

5.1 (S)-5-dibenzylaminopiperidin-2-one:



0.600 g 4-(S)-amino-delta-valerolactam hydrochloride, 0.970 ml benzylbromide and 1.5 g sodium hydrogen carbonate are suspended in 30 ml of ethanol. The reaction mixture is then stirred for 8 hours at 80°C and then evaporated to dryness. The residue is suspended in water and the product is extracted with dichloromethane and purified by chromatography (silica gel, dichloromethane/methanol 100/0 to 95/5). 0.500 g product are obtained as an oil. Analytical HPLC-MS (method A): RT = 1.01 min.

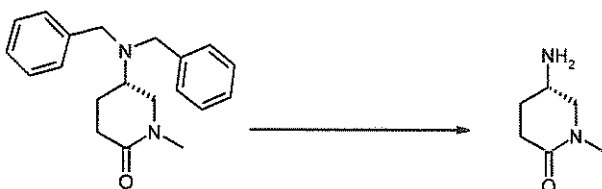
5.2 (S)-5-dibenzylamino-1-methylpiperidin-2-one:



0.500 g (S)-5-dibenzylaminopiperidin-2-one are suspended in 15 ml of tetrahydrofuran. While cooling with the ice bath 0.175 g potassium-*tert*-butoxide are added. The reaction mixture is then stirred for 30 minutes at ambient temperature. While cooling with the ice bath 0.095 ml methyl iodide are added. The reaction mixture is then stirred for 48 hours at ambient temperature and then combined with a saturated NaCl solution. The product is extracted with ethyl acetate. 0.450 g product are obtained as an oil.

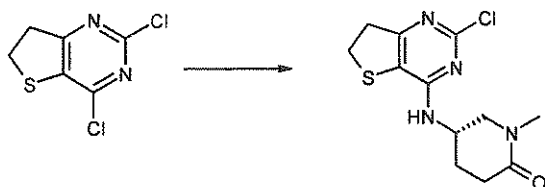
Analytical HPLC-MS (method A): RT = 1.07 min.

5.3 (S)-5-amino-1-methylpiperidin-2-one:



0.450 g (S)-5-dibenzylamino-1-methylpiperidin-2-one are suspended in 25 ml of methanol and hydrogenated with 0.150 g Pd/C 10% at a pressure of 3 bar and a temperature of 60°C. After 16 hours the catalyst is suction filtered and the filtrate is evaporated to dryness. 0.190 g of the product are obtained as an oil. ¹H NMR (400 MHz, DMSO): 2.76 (3H, s).

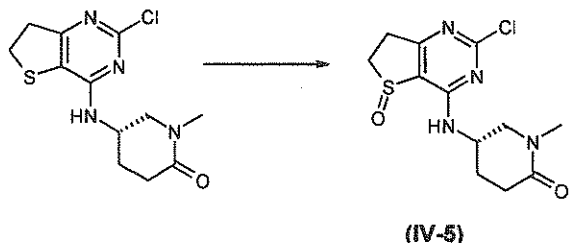
5.4 (S)-5-(2-chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-ylamino)-1-methylpiperidin-2-one (III-5):



(III-5)

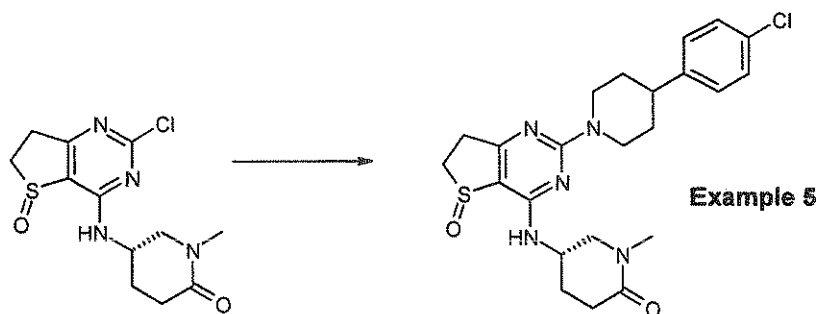
0.27 g (II) are placed in 3 ml dioxane, then first 0.45 ml diisopropylethylamine, then 0.25 g (S)-5-amino-1-methylpiperidin-2-one are added. The reaction mixture is heated to 130°C, until there is no further reaction, and cooled, then evaporated down. The product is extracted with dichloromethane and purified by chromatography (preparative HPLC, method A). 0.26 g (III-5) are obtained as a solid. Analytical HPLC-MS (method A): RT = 1.06 min.

5.5 (S)-5-(2-chloro-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-ylamino)-1-methylpiperidin-2-one (**IV-5**):



0.04 g S-(-)-1,1'-bi-2-naphthol are placed in 5 ml chloroform under argon, then 0.02 ml titanium(IV)-isopropoxide and 0.025 ml of water are added. The reaction mixture is stirred for 1 hour at ambient temperature. Then a suspension of 0.2 g (**III-5**) in 4 ml dichloromethane is added. The reaction mixture is cooled to -5°C and after 20 minutes 0.12 ml tert-butylhydroperoxide 5-6 M in decane are added dropwise. The reaction mixture is stirred further at -5°C, until there is no further reaction, and made basic with NH₄OH. The product is purified by chromatography (silica gel, ethyl acetate/methanol 100/0 to 60/40). 0.09 g (**IV-5**) are obtained as a solid. Analytical HPLC-MS (method A): RT = 0.83 min.

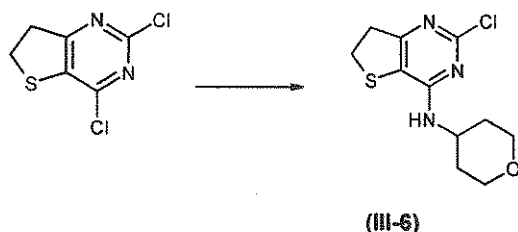
5.6 (S)-5-{2-[4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-ylamino}-1-methylpiperidin-2-one (**Example 5**)



Starting from 0.2 g (**IV-5**) and 0.18 g 4-(4-chlorophenyl)-piperidine 0.17 g **Example 5** are prepared analogously to Example 1 (see 1.3). The product is purified by chromatography (preparative HPLC, method A). The product fractions are made basic with ammonia and freeze-dried. Analytical HPLC-MS (method A): RT = 1.18 min

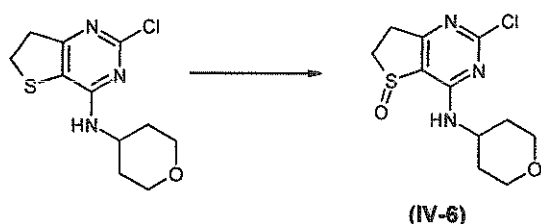
6. SYNTHESIS OF {2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YL}-(TETRAHYDROPYRAN-4-YL)-AMINE (**EXAMPLE 6**)

6.1 (2-chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)-(tetrahydropyran-4-yl)-amine (**III-6**):



0.68 g (**II**) are placed in 6 ml dioxane, then first 1.72 ml diisopropylethylamine, then 0.6 g 4-aminotetrahydropyran are added. The reaction mixture is heated to 130°C, until there is no further reaction, and cooled, then evaporated down. The product is treated with water in the ultrasound bath, then suction filtered and dried. 0.66 g (**III-6**) are obtained as a solid. Analytical HPLC-MS (method C): RT = 1.08 min.

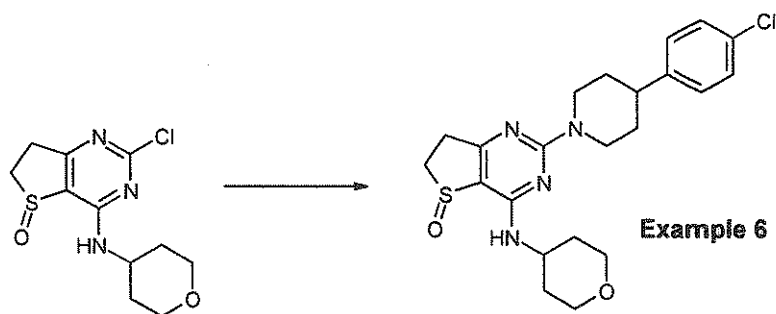
6.2 (2-chloro-5-oxo-6,7-dihydro-5*H*-5λ⁴-thieno[3,2-*d*]pyrimidin-4-yl)-(tetrahydropyran-4-yl)-amine (**IV-6**):



0.14 g S-(-)-1,1'-bi-2-naphthol are placed in 5 ml chloroform under argon, then 0.072 ml titanium(IV)-isopropoxide and 0.087 ml of water are added. The reaction mixture is stirred for 45 minutes at ambient temperature. Then a suspension of 0.66 g (**III-6**) in 25 ml chloroform is added. The reaction mixture is cooled to -10°C and after 60 minutes 0.444 ml tert-butylhydroperoxide 5-6 M in decane are added dropwise. The reaction mixture is stirred further at -10 to -4°C, until there is no further reaction, and mixed with water. The product is extracted with dichloromethane and purified by chromatography (silica gel, ethyl acetate/methanol 100/0 to 80/20). 0.42 g (**IV-6**) are obtained as a solid.

Analytical HPLC-MS (method A): RT = 0.94 min.

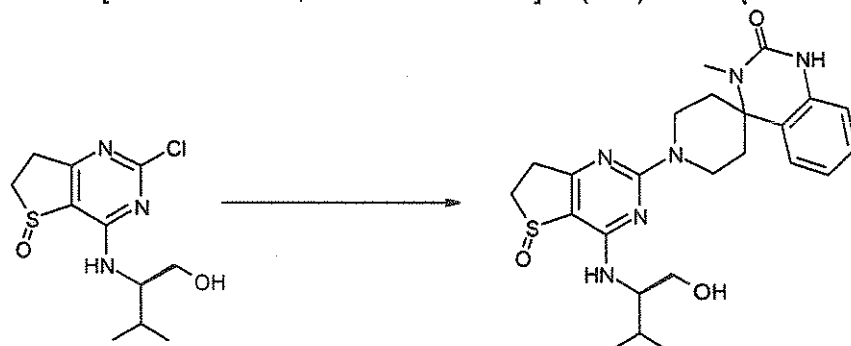
6.3 {2-[4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5*H*-5λ⁴-thieno[3,2-*d*]pyrimidin-4-yl)-(tetrahydropyran-4-yl)-amine (**Example 6**)



Starting from 0.18 g (**IV-6**) and 0.17 g 4-(4-chlorophenyl)-piperidine 0.23 g **Example 6** are prepared analogously to Example 1 (see 1.3). The product is treated with water in the ultrasound bath and the solid is suction filtered.

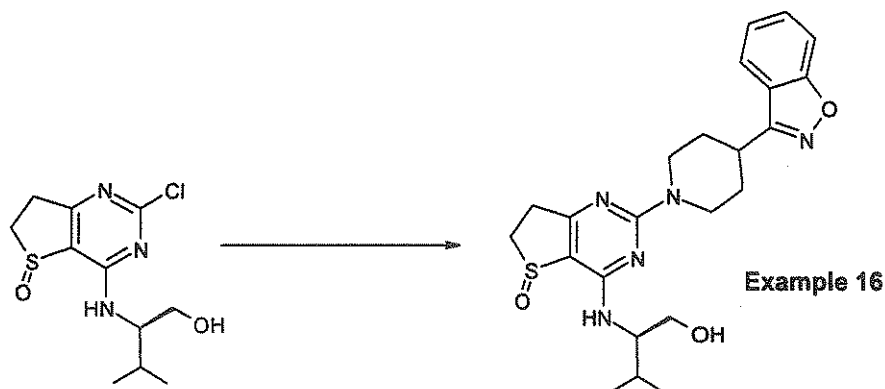
Analytical HPLC-MS (method A): RT = 1.24 min

7 SYNTHESIS OF (R)-1-(4-(1-HYDROXY-3-METHYLBUTAN-2-YLAMINO)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL)-3'-METHYL-1'*H*-SPIRO[PIPERIDIN-4,4'-QUINAZOLIN]-2'(3'*H*)-ONE (EXAMPLE 14)



(**IV-1**) (see 1.2, 0.1 mmol) is placed in 750 μ l N-methyl-2-pyrrolidone (NMP) and 50 μ l diisopropylethylamine, combined with a solution of 3'-methyl-1'*H*-spiro[piperidin-4,4'-quinazolin]-2'(3'*H*)-one (*Chem. Pharm. Bull.* **1988**, 4659) (0.1 mmol) in 400 μ l NMP and heated for 30 min at 120°C in the microwave. Then 600 μ l DMF are added, the reaction solution is purified by preparative HPLC-MS (method A) and the product fractions are freeze-dried. Analytical HPLC-MS (method C): RT = 1.58 min.

8. SYNTHESIS OF (R)-2-[2-(4-BENZO[*d*]ISOXAZOL-3-YL-PIPERIDIN-1-YL)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO]-3-METHYLBUTAN-1-OL (EXAMPLE 16)

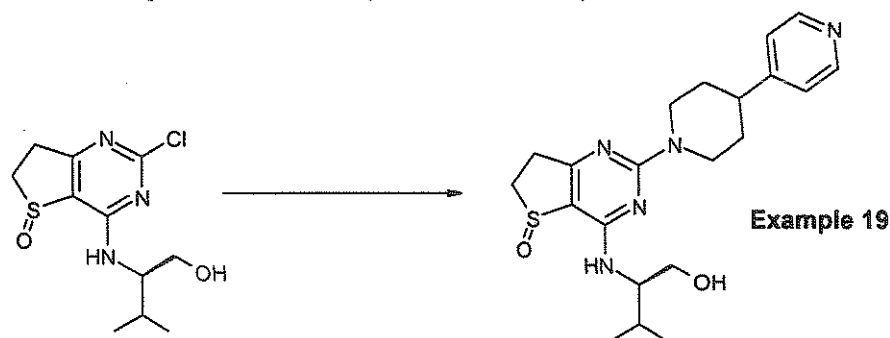


Starting from (IV-1) (see 1.2) and 3-piperidin-4-yl-benzo[d]isoxazole

Example 16 may be prepared and purified analogously to Example 14 (see 7.).

Analytical HPLC-MS (method C): RT = 1.74 min.

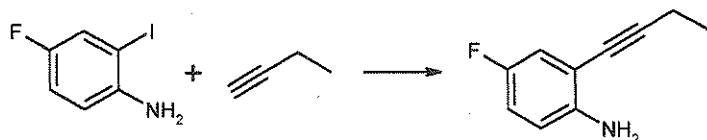
9. SYNTHESIS OF (R)-3-METHYL-2-[5-OXO-2-(3,4,5,6-TETRAHYDRO-2H-[4,4']BIPYRIDINYL-1-YL)-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YLAMINO]-BUTAN-1-OL (**EXAMPLE 19**)



Starting from (IV-1) (see 1.2) and 4-piperidin-4-yl-pyridin **Example 19** may be prepared and purified analogously to Example 14 (see 7). Analytical HPLC-MS (method C): RT = 1.33 min.

10. SYNTHESIS OF (R)-2-{2-[4-(2-ETHYL-5-FLUORO-1H-INDOL-3-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YLAMINO}-3-METHYLBUTAN-1-OL (**EXAMPLE 22**)

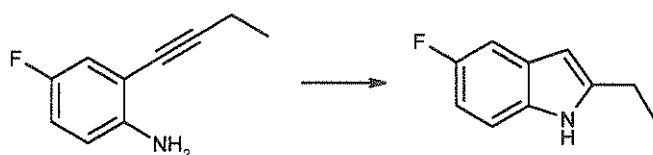
10.1 2-but-1-ynyl-4-fluorophenylamine



80 ml of tetrahydrofuran is placed under argon. 5 g of 4-fluoro-2-iodophenylamine, 0.74 g dichlorobis(triphenylphosphine) palladium(II), 0.2 g copper iodide and 8.8 ml triethylamine are added. 4 g of gaseous 1-butyne are passed through the suspension. The reaction mixture is stirred under argon for 15 hours at ambient temperature, then filtered through Celite and evaporated to dryness. 3.4 g product are obtained as a solid.

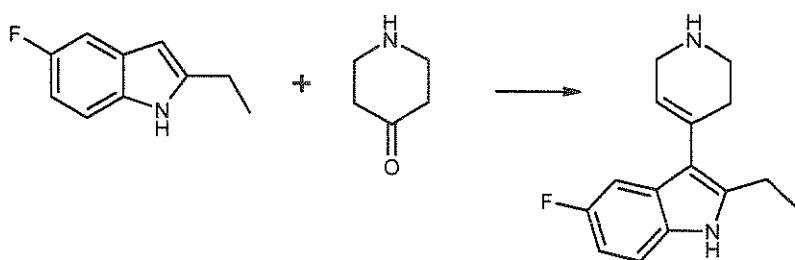
^1H NMR (400 MHz, DMSO): 2.45 (2H, q); 1.18 (3H, t).

10.2 2-ethyl-5-fluoro-1H-indole



Under argon 4.9 g potassium-*tert*-butoxide are suspended in 25 ml N-methyl-2-pyrrolidinone and a suspension of 3.4 g 2-but-1-ynyl-4-fluorophenylamine in 25 ml N-methyl-2-pyrrolidinone is added dropwise thereto. The reaction mixture is stirred for 3 hours at ambient temperature and mixed with water. The product is extracted with diethyl ether and purified by chromatography (silica gel, cyclohexane/ethyl acetate 100/0 – 90/10). 2.83 g product are obtained as a solid. ^1H NMR (400 MHz, DMSO): 2.72 (2H, q); 1.27 (3H, t).

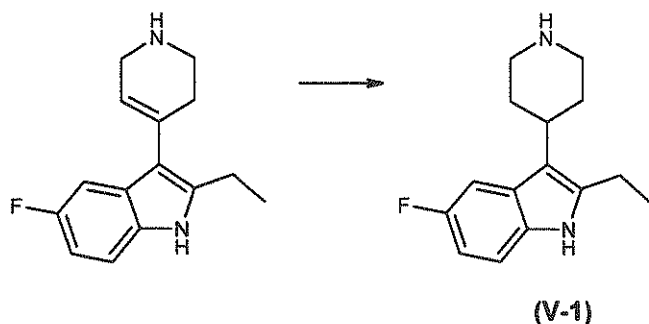
10.3 2-ethyl-5-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1H-indole



2.83 g 2-ethyl-5-fluoro-1H-indole are suspended in 50 ml acetic acid and heated to 90°C. A suspension of 6.66 g 4-piperidone in 15 ml phosphoric acid 2N is added. The reaction mixture is stirred for 3 hours at 90°C, combined with sodium hydroxide solution and the product is extracted with ethyl acetate. 2.85 g product are obtained as a solid.

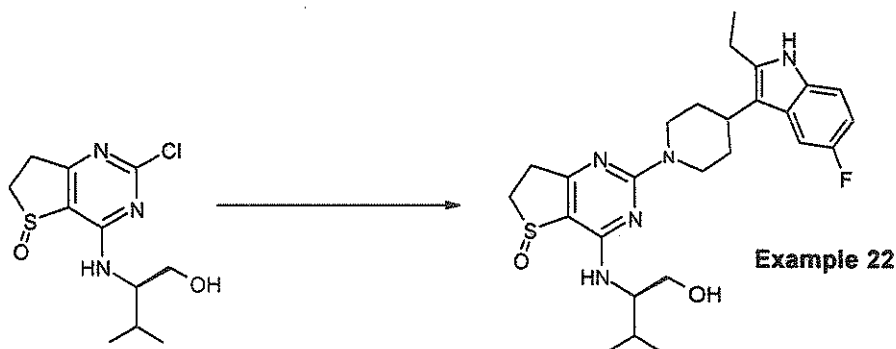
^1H NMR (400 MHz, DMSO): 5.63 (1H, s); 2.73 (2H, q); 1.23 (3H, t).

10.4 2-ethyl-5-fluoro-3-piperidin-4-yl-1H-indole (V-1)



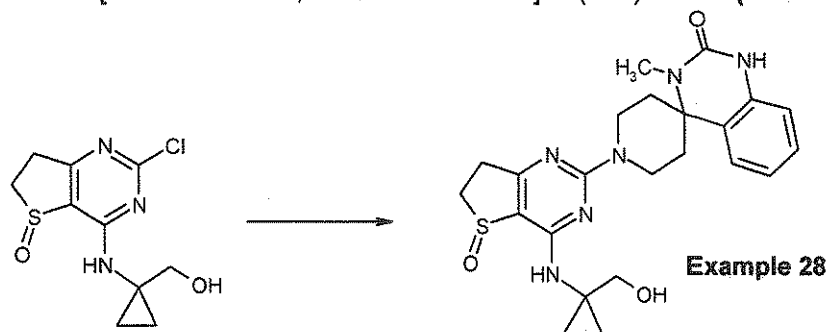
2.83 g 2-ethyl-5-fluoro-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole are suspended in 50 ml of methanol and hydrogenated with 0.3 g Pd/C 10% at normal pressure and ambient temperature. The catalyst is suction filtered and the filtrate is evaporated to dryness. 2.3 g **(V-1)** are obtained as a solid. ¹H NMR (400 MHz, DMSO): 2.70 (2H, q); 1.19 (3H, t).

10.5 (R)-2-{2-[4-(2-ethyl-5-fluoro-1*H*-indol-3-yl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5*H*-5λ⁴-thieno[3,2-*d*]pyrimidin-4-ylamino}-3-methylbutan-1-ol (**Example 22**)



Starting from **(IV-1)** (see 1.2) and **(V-1)** **Example 22** may be prepared and purified analogously to Example 14 (see 7.). Analytical HPLC-MS (method C): RT = 1.83 min.

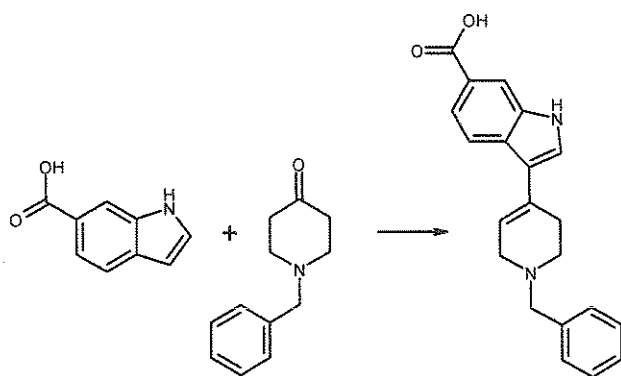
11. SYNTHESIS OF 1-(4-(1-HYDROXYMETHYLCYCLOPROPYLAMINO)-5-OXO-6,7-DIHYDRO-5*H*-5λ⁴-THIENO[3,2-*d*]PYRIMIDIN-2-YL)-3'-METHYL-1'*H*-SPIRO[PIPERIDIN-4,4'-QUINAZOLIN]-2'(3'*H*)-ONE (**EXAMPLE 28**)



Starting from (IV-2) (see 2.4) and 3'-methyl-1'*H*-spiro[piperidin-4,4'-quinazolin]-2'(3'*H*)-one (*Chem. Pharm. Bull.* **1988**, 4659) **Example 28** may be prepared and purified analogously to Example 14 (see 7.). Analytical HPLC-MS (method C): RT = 1.52 min.

12. SYNTHESIS OF ETHYL 3-{1-[4-(1-HYDROXYMETHYLCYCLOPROPYLAMINO)-5-OXO-6,7-DIHYDRO-5*H*-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL]-PIPERIDIN-4-YL}-1*H*-INDOL-6-CARBOXYLATE (**EXAMPLE 29**)

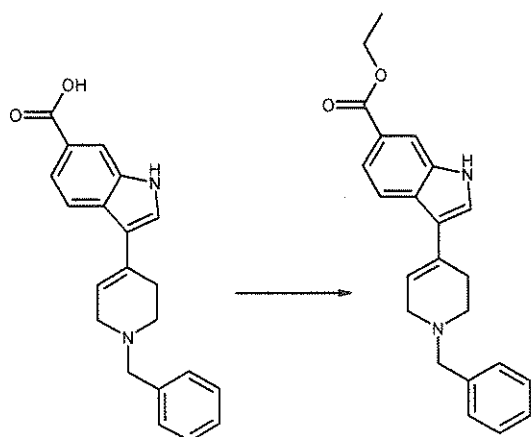
12.1 3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole-6-carboxylic acid



2.6 g potassium hydroxide are suspended in 25 ml of methanol and 2.5 g 1*H*-indole-6-carboxylic acid and 5.5 g 1-benzyl-piperidin-4-one are added. The reaction mixture is stirred for 15 hours at reflux temperature and then evaporated to dryness. The residue is combined with hydrochloric acid (1 M) and evaporated to dryness. The residue is treated with methanol and diethyl ether and the solid is suction filtered. 12.4 g product are obtained as a solid.

¹H NMR (400 MHz, DMSO): 6.2 (1H, s).

12.2 ethyl 3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole-6-carboxylate

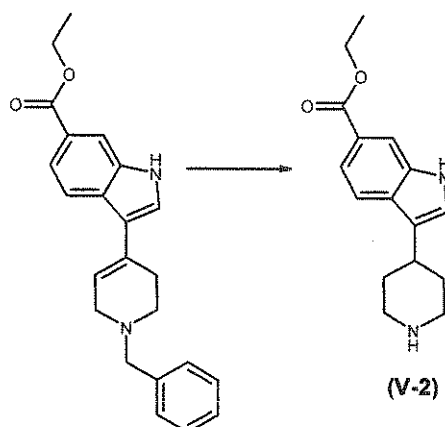


12.4 g 3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole-6-carboxylic acid are suspended

in 80 ml of ethanol and 1.6 ml conc. Sulphuric acid are added. The reaction mixture is stirred for 96 hours at reflux temperature. The solid is suction filtered, dissolved in ethanol and made basic with sodium hydroxide solution. 5.3 g product are obtained as a solid.

¹H NMR (400 MHz, DMSO): 6.2 (1H, s); 4.3 (2H, q); 1.35 (3H, s).

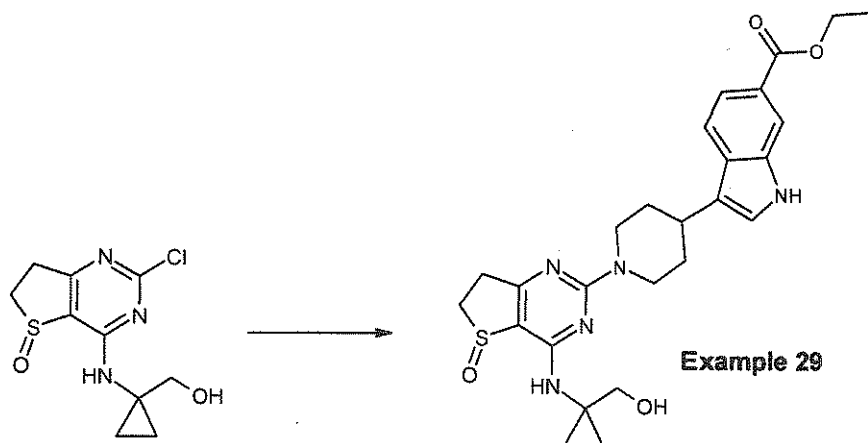
12.3 ethyl 3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole-6-carboxylate (**V-2**)



5 g ethyl 3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole-6-carboxylate and 2.3 g palladium hydroxide are suspended in 180 ml of methanol and hydrogenated at 50 psi for 2 hours at ambient temperature. The catalyst is suction filtered and the mother liquor is evaporated to dryness. 3.6 g (**V-2**) are obtained as a solid.

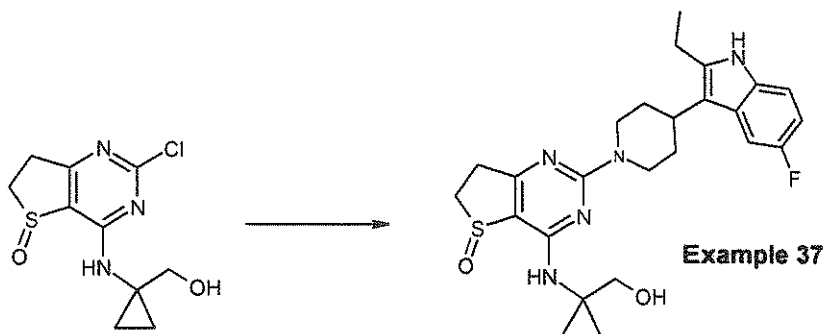
¹H NMR (400 MHz, DMSO): 4.3 (2H, q); 2.95 – 2.80 (1H, m); 1.35 (3H, s).

12.4 ethyl 3-{1-[4-(1-hydroxymethylcyclopropylamino)-5-oxo-6,7-dihydro-5*H*-5λ⁴-thieno[3,2-*d*]pyrimidin-2-yl]-piperidin-4-yl}-1*H*-indole-6-carboxylate (**Example 29**)



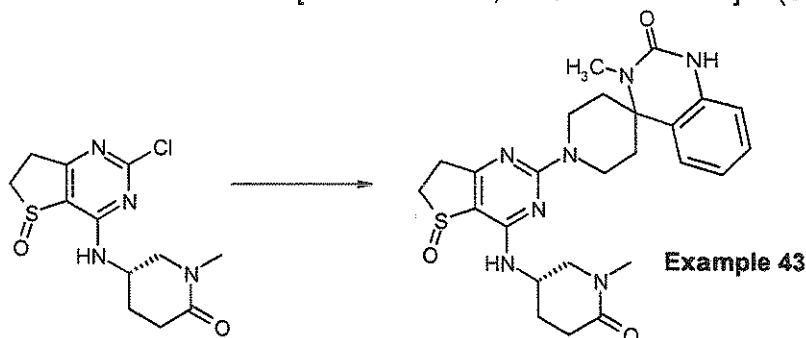
Starting from (IV-2) (see 2.4) and (V-2) (see 12.3) **Example 29** may be prepared and purified analogously to Example 14 (see 7.). Analytical HPLC-MS (method C): RT = 1.77 min.

13. SYNTHESIS OF 1-{2-[4-(2-ETHYL-5-FLUORO-1H-INDOL-3-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-CYCLOPROPYL)-METHANOL (**EXAMPLE 37**)



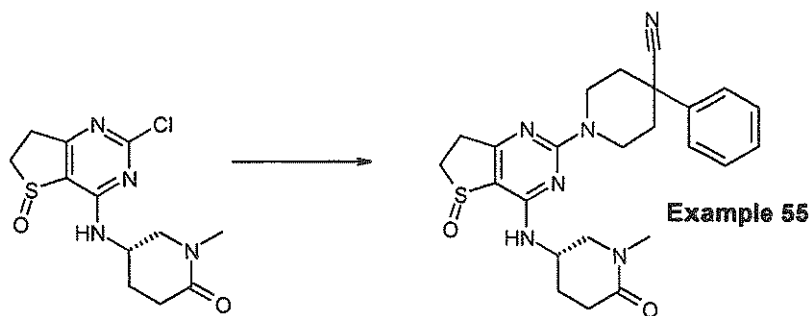
Starting from (IV-2) (see 2.4) and (V-1) (see 10.4) **Example 37** may be prepared and purified analogously to Example 14 (see 7.). Analytical HPLC-MS (method C): RT = 1.78 min.

14. SYNTHESIS OF (S)-3'-METHYL-1-(4-(1-METHYL-6-OXOPIPERIDIN-3-YLAMINO)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL)-3'-METHYL-1'H-SPIRO[PIPERIDIN-4,4'-QUINAZOLIN]-2'(3'*H*)-ONE (**EXAMPLE 43**)



Starting from (IV-5) (see 5.5) and 3'-methyl-1'H-spiro[piperidin-4,4'-quinazolin]-2'(3'*H*)-one (*Chem. Pharm. Bull.* **1988**, 4659) **Example 43** may be prepared and purified analogously to Example 14 (see 7.). Analytical HPLC-MS (method C): RT = 1.49 min.

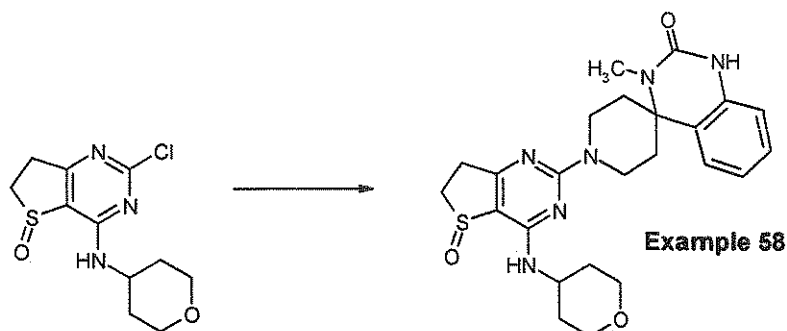
15. SYNTHESIS OF 1-[4-((S)-1-METHYL-6-OXOPIPERIDIN-3-YLAMINO)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDINE -2-YL]-4-PHENYLPYPERIDINE-4-CARBONITRILE (**EXAMPLE 55**)



Starting from (IV-5) (see 5.5) and 4-phenylpiperidine-4-carbonitrile **Example 55** may be prepared and purified analogously to Example 14 (see 7).

Analytical HPLC-MS (method C): RT = 1.71 min.

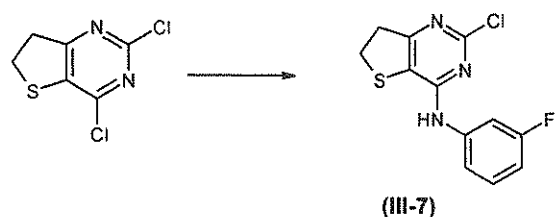
16. SYNTHESIS OF 3'-METHYL-1-(4-(TETRAHYDRO-2H-PYRAN-4-YLAMINO)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL)-1'*H*-SPIRO[PIPERIDIN-4,4'-QUINAZOLIN]-2'(3'*H*)-ONE (**EXAMPLE 58**)



Starting from (IV-6) (see 6.2) and 3'-methyl-1'*H*-spiro[piperidin-4,4'-quinazolin]-2'(3'*H*)-ONE (*Chem. Pharm. Bull.* **1988**, 4659) **Example 58** may be prepared and purified analogously to Example 14 (see 7.). Analytical HPLC-MS (method C): RT = 1.56 min.

17. SYNTHESIS OF 1-(4-(3-FLUOROPHENYLAMINO)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL)-3'-METHYL-1'*H*-SPIRO[PIPERIDIN-4,4'-QUINAZOLIN]-2'(3'*H*)-ONE (**EXAMPLE 73**)

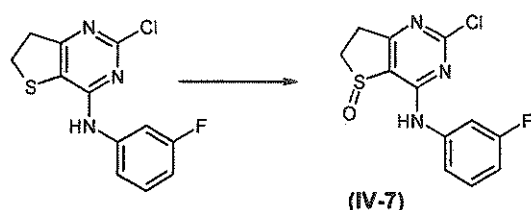
17.1 (2-chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-yl)-(3-fluorophenyl)-amine (III-7):



4 g (II) are placed in 15 ml dimethylformamide, then 4.5 ml diisopropylethylamine and then 2.5 ml 3-fluorophenylamine are added. The reaction mixture is heated to 120°C, until there is no further reaction, and cooled, then evaporated down. The residue is mixed with water. The product is extracted with dichloromethane and purified by chromatography (silica gel, petroleum ether/ethyl acetate 80/20 to 60/40). 2.6 g (III-7) are obtained as a solid.

Analytical HPLC (method A): RT = 3.27 min

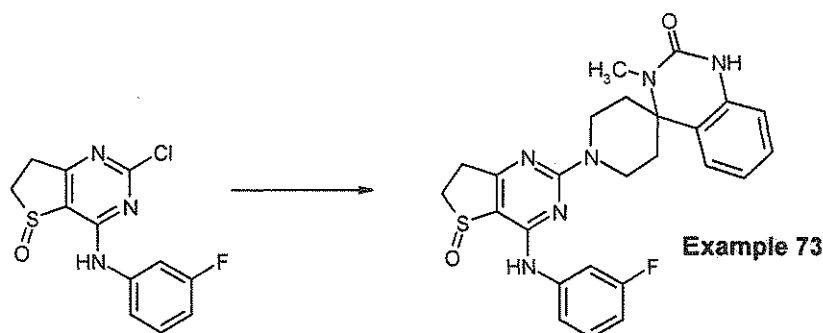
17.2 2-chloro-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-yl)-(3-fluorophenyl)-amine (IV-7):



0.102 g S-(-)-1,1'-bi-2-naphthol are placed in 0.5 ml chloroform under argon, then 0.052 ml titanium(IV)-isopropoxide and 0.064 ml of water are added. The reaction mixture is stirred for 45 minutes at ambient temperature. Then a suspension of 0.5 g (III-7) in 25 ml chloroform is added. The reaction mixture is cooled to -2°/-4°C and after 20 minutes 0.323 ml tert-butylhydroperoxide 5-6 M in decane are added dropwise. The reaction mixture is stirred further at -2°/-4°C, until there is no further reaction, and mixed with water. The product is extracted with dichloromethane and purified by chromatography (silica gel, dichloromethane/methanol 100/0 to 95/5). 0.47 g (IV-7) are obtained as a solid.

Analytical HPLC-MS (method A): RT = 1.15 min.

17.3 1-(4-(3-fluorophenylamino)-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno [3,2-d]pyrimidin-2-yl)-3'-methyl-1'H-spiro[piperidin-4,4'-quinazolin]-2'(3'H)-one (Example 73)

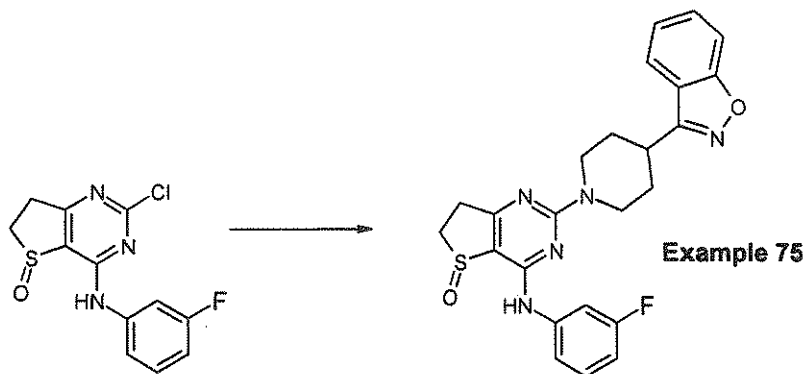


Starting from (IV-7) (see 17.2) and 3'-methyl-1'H-spiro[piperidin-4,4'-quinazolin]-2'(3'H)-one (*Chem. Pharm. Bull.* **1988**, 4659) Example 73 may be prepared and

purified analogously to Example 14 (see 7.). Analytical HPLC-MS (method C): RT = 1.81 min.

18. SYNTHESIS OF [2-(4-BENZO[d]ISOXAZOL-3-YL-PIPERIDIN-1-YL)-5-OXO-6,7,6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YL]-(3-FLUOROPHENYL)-AMINE

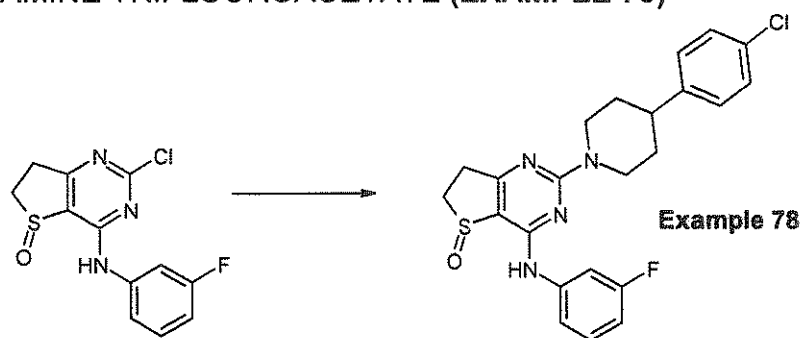
(EXAMPLE 75)



Starting from (IV-7) (see 17.2) and 3-piperidin-4-yl-benzo[d]isoxazole **Example 75** may be prepared and purified analogously to Example 14 (see 7.).

Analytical HPLC-MS (method C): RT = 2.11 min.

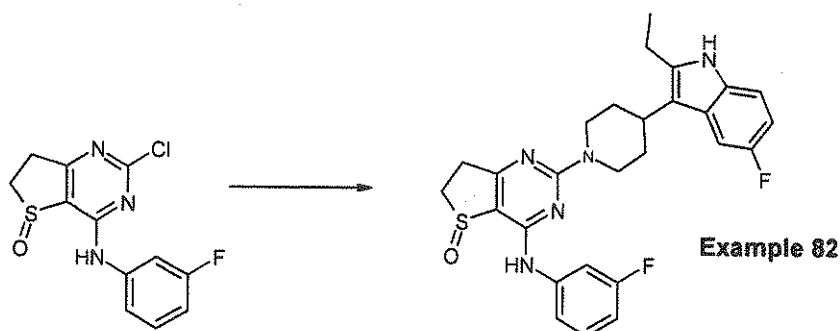
19. SYNTHESIS OF (3-FLUOROPHENYL)-[5-OXO-2-(3,4,5,6-TETRAHYDRO-2H-[4,4']BIPYRIDINYL-1-YL)-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YL]-AMINE TRIFLUOROACETATE (**EXAMPLE 78**)



Starting from (IV-7) (see 17.2) and 4-(4-chlorophenyl)-piperidine **Example 78** may be prepared and purified as the trifluoroacetate analogously to Example 14 (see 7.).

Analytical HPLC-MS (method C): RT = 1.55 min.

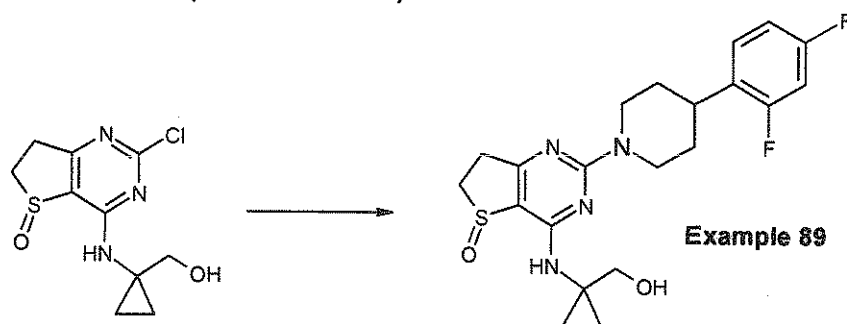
20. SYNTHESIS OF {2-[4-(2-ETHYL-5-FLUORO-1H-INDOL-3-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YL}-(3-FLUOROPHENYL)-AMINE (**EXAMPLE 82**)



Starting from (IV-7) (see 17.2) and (V-1) (see 10.4) **Example 82** may be prepared and purified analogously to Example 14 (see 7.).

Analytical HPLC-MS (method C): RT = 2.12 min.

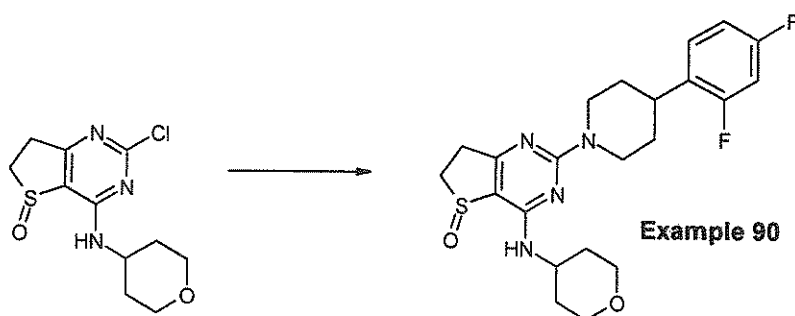
21. SYNTHESIS OF (1-{2-[4-(2,4-DIFLUOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-CYCLOPROPYL)-METHANOL (**EXAMPLE 89**)



Starting from (IV-2) (see 2.4) and 4-(2,4-difluorophenyl)-piperidine **Example 89** may be prepared analogously to Example 14 (see 7.). The product may be purified by chromatography (preparative HPLC, method B).

Analytical HPLC-MS (method D): RT = 1.18 min.

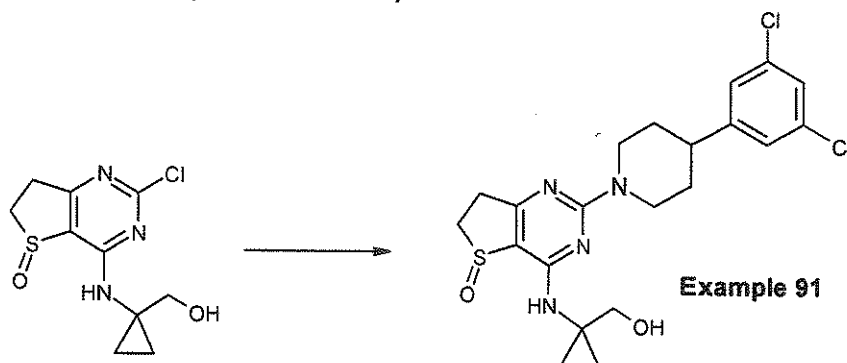
22. SYNTHESIS OF {2-[4-(2,4-DIFLUOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YL}-(TETRAHYDROPYRAN-4-YL)-AMINE (**EXAMPLE 90**)



Starting from (IV-6) (see 6.2) and 4-(2,4-difluorophenyl)-piperidine **Example 90** may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method D): RT = 1.23 min.

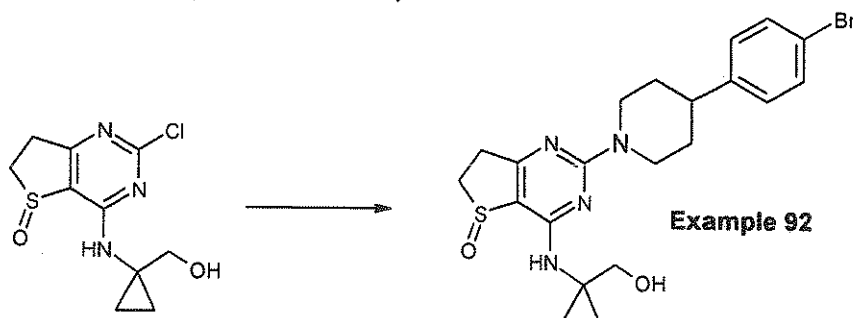
23. SYNTHESIS OF (1-{2-[4-(3,5-DICHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-CYCLOPROPYL)-METHANOL (**EXAMPLE 91**)



Starting from (IV-2) (see 2.4) and 4-(3,5-dichlorophenyl)-piperidine **Example 91** may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method D): RT = 1.30 min.

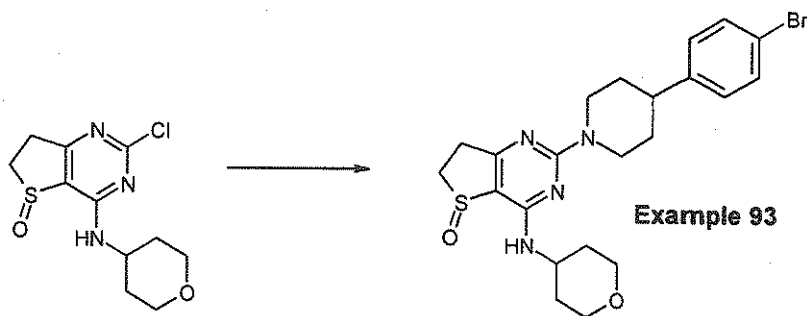
24. SYNTHESIS OF (1-{2-[4-(4-BROMOPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-CYCLOPROPYL)-METHANOL (**EXAMPLE 92**)



Starting from (IV-2) (see 2.4) and 4-(4-bromophenyl)-piperidine **Example 92** may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method D): RT = 1.23 min.

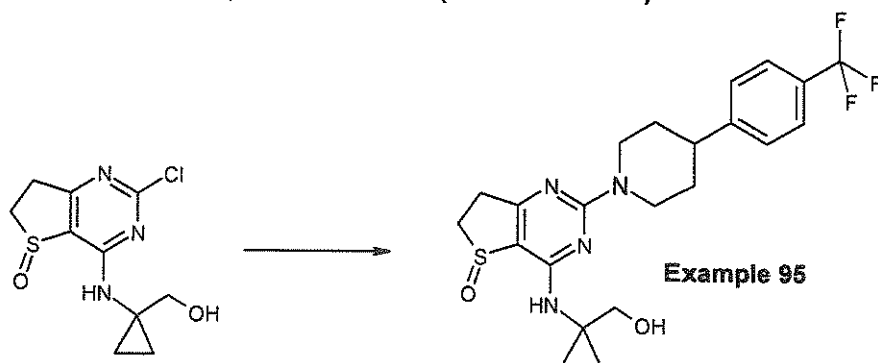
25. SYNTHESIS OF {2-[4-(4-BROMOPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDINE-4-YL}-[TETRAHYDROPYRAN-4-YL]-AMINE (**EXAMPLE 93**)



Starting from (IV-6) (see 6.2) and 4-(4-bromophenyl)-piperidine **Example 93** may be prepared and purified analogously to Example 89 (see 21).

Analytical HPLC-MS (method D): RT = 1.28 min.

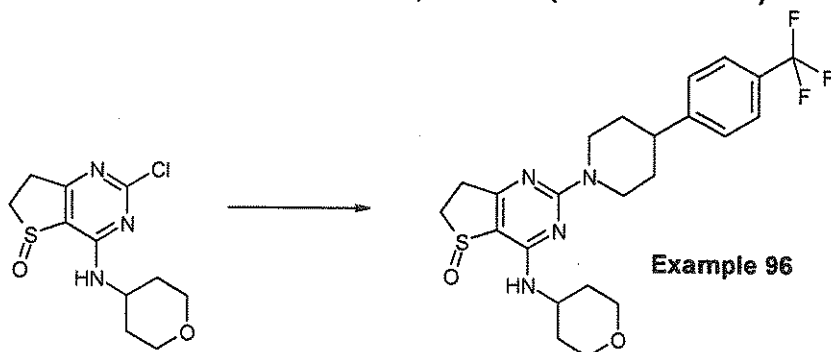
26. SYNTHESIS OF (1-{5-OXO-2-[4-(4-TRIFLUOROMETHYLPHENYL)-PIPERIDIN-1-YL]-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-CYCLOPROPYL)-METHANOL (**EXAMPLE 95**)



Starting from (IV-2) (see 2.4) and 4-(4-(trifluoromethyl)phenyl)-piperidine **Example 95** may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method D): RT = 1.25 min.

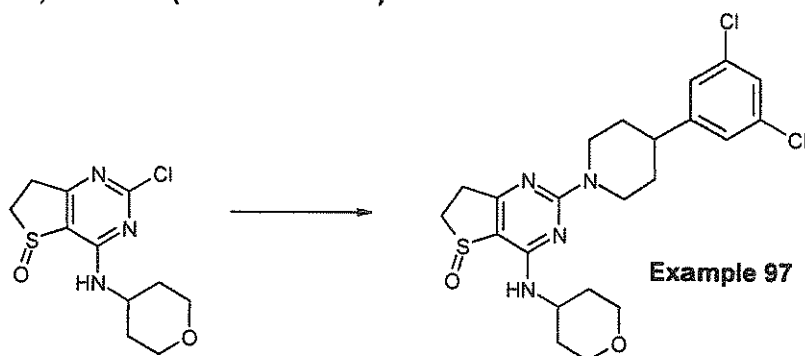
27. SYNTHESIS OF {5-OXO-2-[4-(4-TRIFLUOROMETHYLPHENYL)-PIPERIDIN-1-YL]-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YL}-(TETRAHYDROPYRAN-4-YL)-AMINE (**EXAMPLE 96**)



Starting from (IV-6) (see 6.2) and 4-(4-trifluoromethylphenyl)-piperidine **Example 96** may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method D): RT = 1.29 min.

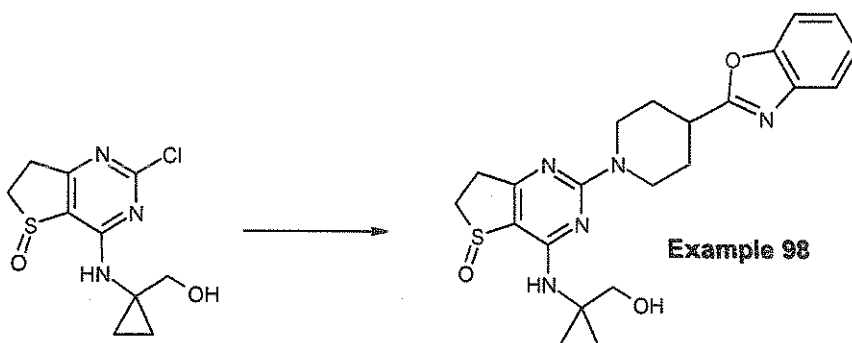
28. SYNTHESIS OF {2-[4-(3,5-DICHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YL}-(TETRAHYDROPYRAN-4-YL)-AMINE (**EXAMPLE 97**)



Starting from (IV-6) (see 6.2) and 4-(3,5-dichlorophenyl)-piperidine **Example 97** may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method A): RT = 1.29 min.

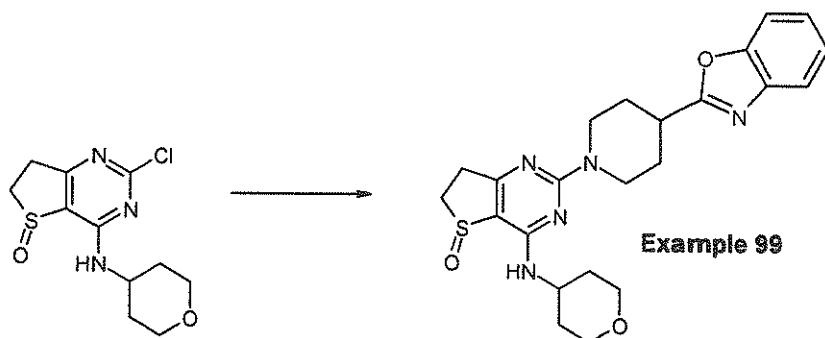
29. SYNTHESIS OF {1-[2-(4-BENZOXAZOL-2-YL-PIPERIDIN-1-YL)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YLAMINO]-CYCLOPROPYL}-METHANOL (**EXAMPLE 98**)



Starting from (IV-2) (see 2.4) and 2-piperidin-4-yl-benzoxazole **Example 98** may be prepared and purified analogously to Example 89 (see 21).

Analytical HPLC-MS (method B): RT = 1.22 min.

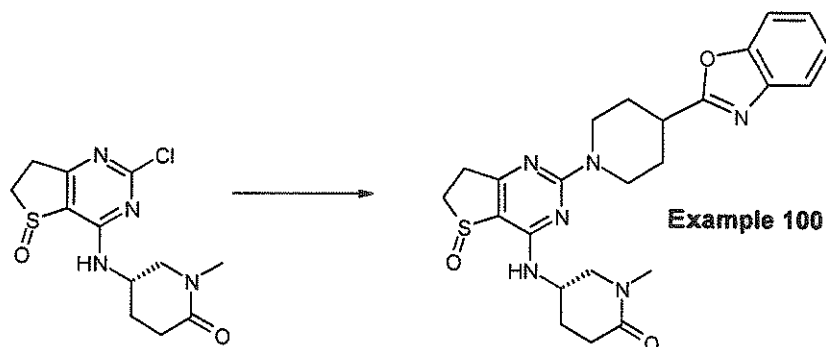
30. SYNTHESIS OF [2-(4-BENZOXAZOL-2-YL-PIPERIDIN-1-YL)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YL}-(TETRAHYDROPYRAN-4-YL)-AMINE (**EXAMPLE 99**)



Starting from (IV-6) (see 6.2) and 2-piperidin-4-yl-benzoxazole **Example 99** may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method B): RT = 1.23 min.

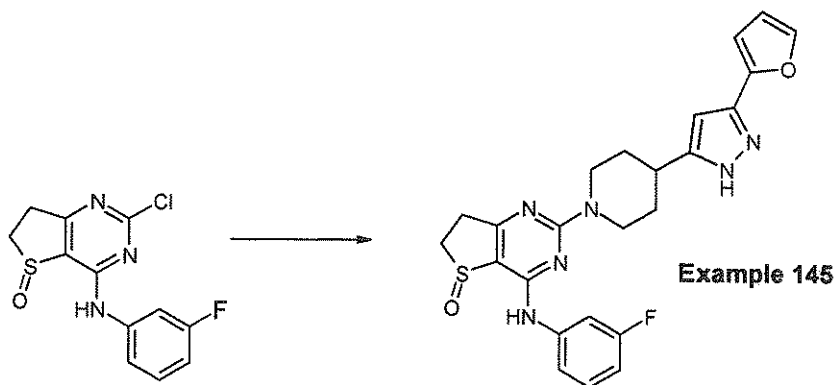
31. SYNTHESIS OF (S)-5-[2-(4-BENZOXAZOL-2-YL-PIPERIDIN-1-YL)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO]-1-METHYLPYPERIDIN-2-ONE (**EXAMPLE 100**)



Starting from (IV-5) (see 5.5) and 2-piperidin-4-yl-benzoxazole **Example 100** may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method B): RT = 1.18 min.

32. SYNTHESIS OF (3-FLUOROPHENYL)-{2-[4-(5-FURAN-2-YL-2*H*-PYRAZOL-3-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YL}-AMINE TRIFLUORACETAT (**EXAMPLE 145**)

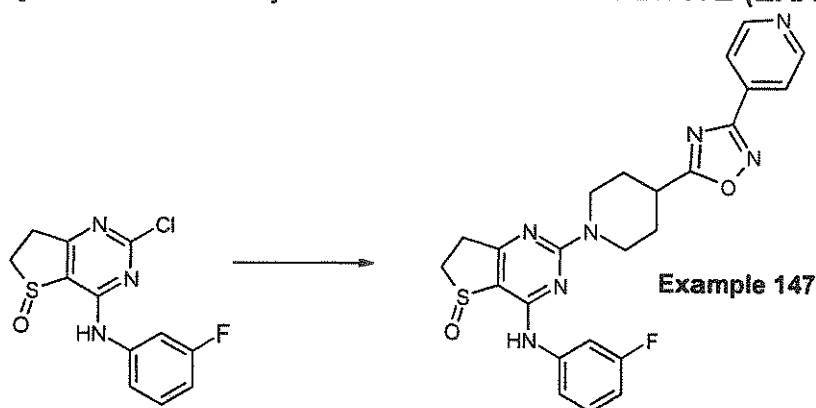


Starting from (IV-7) (see 17.2) and 4-(5-furan-2-yl-2*H*-pyrazol-3-yl)-piperidine

Example 145

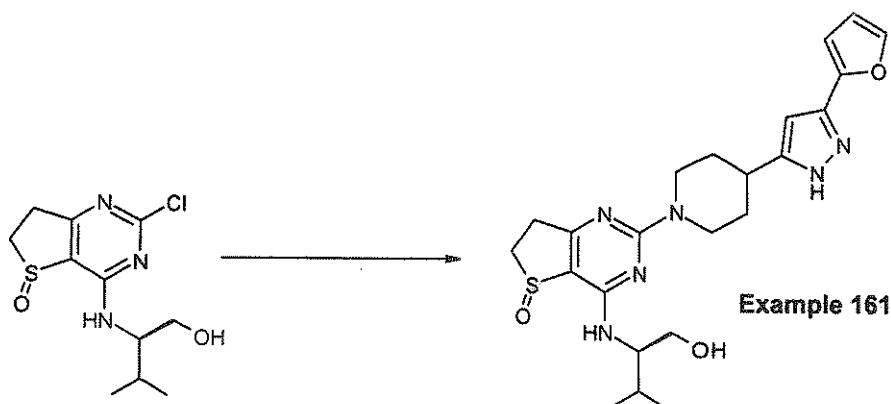
may be prepared and purified as the trifluoroacetate analogously to Example 14 (see 7.). Analytical HPLC-MS (method C): RT = 1.89 min.

33. SYNTHESIS OF (3-FLUOROPHENYL)-{5-OXO-2-[4-(3-PYRIDIN-4-YL-[1,2,4]OXADIAZOL-5-YL)-PIPERIDIN-1-YL]-6,7-DIHYDRO-5*H*-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YL}-AMINE TRIFLUOROACETATE (**EXAMPLE 147**)



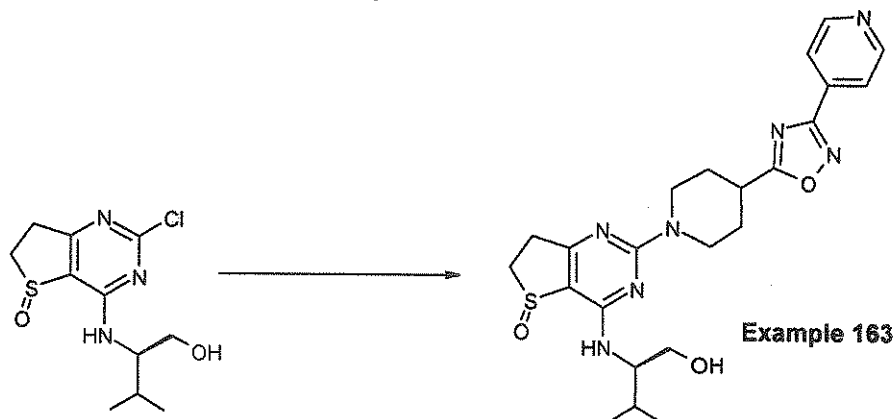
Starting from (IV-7) (see 17.2) and 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)-pyridine **Example 147** may be prepared and purified as the trifluoroacetate analogously to Example 14 (see 7.). Analytical HPLC-MS (method C): RT = 1.72 min.

34. SYNTHESIS OF (R)-2-{2-[4-(5-FURAN-2-YL-2*H*-PYRAZOL-3-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5*H*-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-3-METHYLBUTAN-1-OL TRIFLUOROACETATE (**EXAMPLE 161**)



Starting from (IV-1) (see 1.2) and 4-(5-furan-2-yl-2*H*-pyrazol-3-yl)-piperidine **Example 161** may be prepared and purified as the trifluoroacetate analogously to Example 14 (see 7.). Analytical HPLC-MS (method C): RT = 1.67 min.

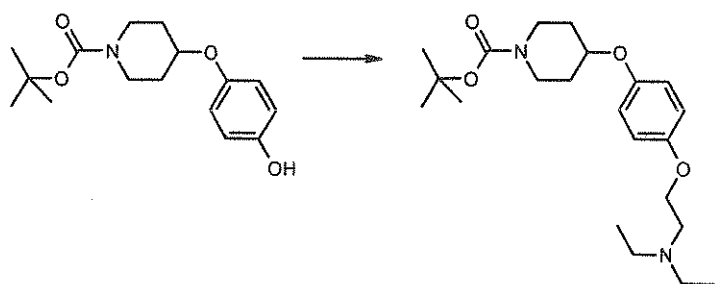
35. SYNTHESIS OF (R)-3-METHYL-2-{5-OXO-2-[4-(3-PYRIDIN-4-YL-[1,2,4]OXADIAZOL-5-YL)-PIPERIDIN-1-YL]-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-BUTAN-1-OL TRIFLUOROACETATE (**EXAMPLE 163**)



Starting from (**IV-1**) (see 1.2) and 4-(5-piperidin-4-yl-[1,2,4]oxadiazol-3-yl)-pyridine **Example 163** may be prepared and purified as the trifluoroacetate analogously to Example 14 (see 7.). Analytical HPLC-MS (method C): RT = 1.48 min.

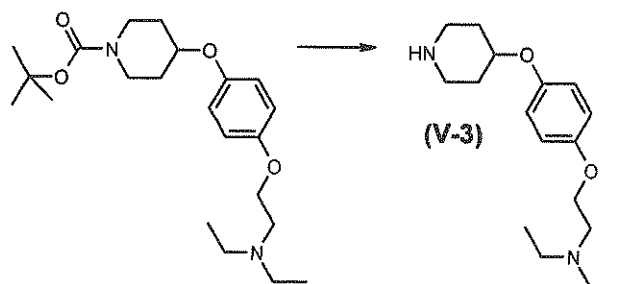
36. SYNTHESIS OF: (2-{4-[4-(2-DIETHYLAMINOETHOXY)-PHENOXY]-PIPERIDIN-1-YL}-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YL)-(TETRAHYDRO PYRAN-4-YL)-AMINE (**EXAMPLE 178**)

36.1 tert-butyl 4-[4-(2-diethylaminoethoxy)-phenoxy]-piperidine-1-carboxylate:



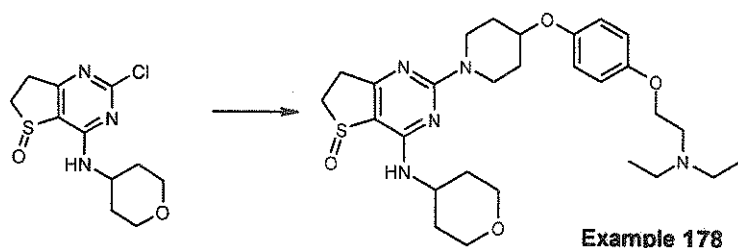
7.9 g tert-butyl 4-(4-hydroxyphenoxy)-piperidine-1-carboxylate (see WO2006/64218), 5.2 g (2-chloroethyl)-diethylamine hydrochloride and 16.6 g potassium carbonate are placed in 250 ml acetone. The reaction mixture is stirred at reflux temperature. After 4 hours the inorganic salts are suction filtered and the mixture is evaporated to dryness. The residue is combined with ethyl acetate. The organic phase is washed with a saturated NaHCO₃ solution, dried and evaporated to dryness. 10.1 g of the product are obtained as an oil.

36.2 diethyl-{2-[4-(piperidin-4-yloxy)-phenoxy]-ethyl}-amine (**V-3**):



10.1 g tert-butyl 4-[4-(2-diethylaminoethoxy)-phenoxy]-piperidine-1-carboxylate are placed in 20 ml dichloromethane and combined with 30 ml trifluoroacetic acid while being cooled. The reaction mixture is stirred at ambient temperature. After 2 hours the reaction mixture is evaporated to dryness. The residue is combined with an NaOH solution (1M) and the product is extracted with dichloromethane. 5.6 g (**V-3**) are obtained.

36.3 (2-{4-[4-(2-diethylaminoethoxy)-phenoxy]-piperidin-1-yl}-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-4-yl)-(tetrahydropyran-4-yl)-amine (**Example 178**)

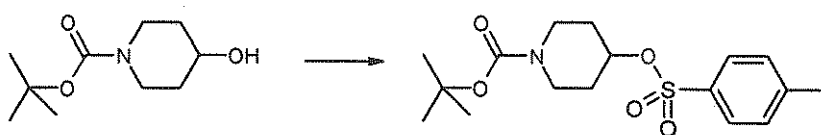


Example 178

Starting from (**IV-6**) (see 6.2) and (**V-3**) **Example 178** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method A): RT = 1.01 min.

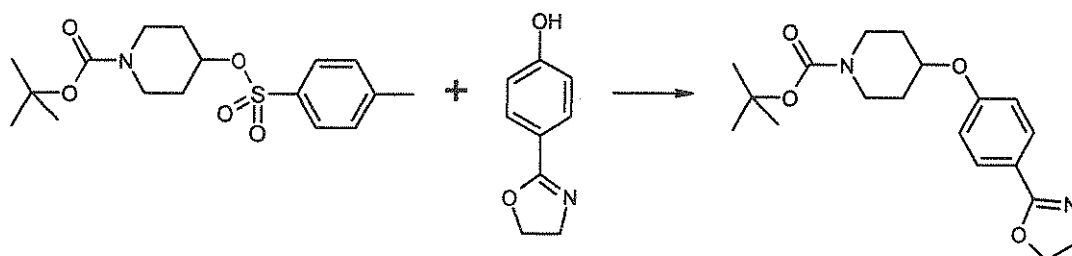
37. SYNTHESIS OF: (2-{4-[4-(4,5-DIHYDROXAZOL-2-YL)-PHENOXY]-PIPERIDIN-1-YL}-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YL)-(TETRAHYDRO PYRAN-4-YL)-AMINE (**EXAMPLE 180**)

37.1 tert-butyl 4-(toluene-4-sulphonyloxy)-piperidine-1-carboxylate:



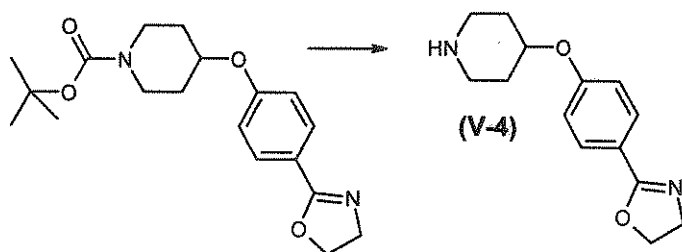
5 g tert-butyl 4-hydroxypiperidine-1-carboxylate are placed in 15 ml of pyridine, then 4.7 g *p*-toluenesulphonyl chloride are added batchwise. The reaction mixture is stirred at ambient temperature, after 12 hours it is poured onto ice water and the mixture obtained is stirred for a further hour at ambient temperature. The precipitated solid is suction filtered and dried. 7.5 g product are obtained.

37.2 tert-butyl 4-[4-(4,5-dihydroxazol-2-yl)-phenoxy]-piperidine-1-carboxylate:



2.0 g 4-(4,5-dihydroxazol-2-yl)-phenol (see US5491201) are placed in 30 ml dimethylformamide, then 3.3 g potassium carbonate and 4.2 g tert-butyl 4-(toluene-4-sulphonyloxy)-piperidine-1-carboxylate are added. The reaction mixture is stirred at 75°C, after 12 hours it is mixed with water and the precipitated solid is suction filtered and dried. 2.8 g product are obtained.

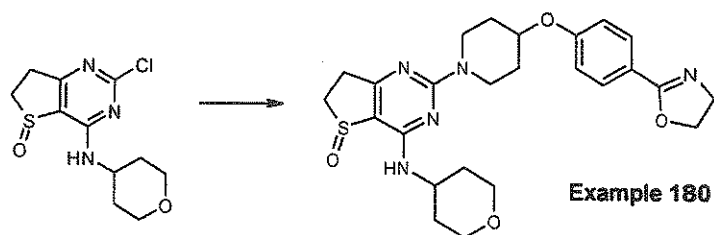
37.3 4-[4-(4,5-dihydroxazol-2-yl)-phenoxy]-piperidine (V-4):



50 mg tert-butyl 4-[4-(4,5-dihydroxazol-2-yl)-phenoxy]-piperidine-1-carboxylate are taken and combined with 6 ml of a (5/1) dichloromethane/trifluoroacetic acid mixture. The reaction mixture is stirred at ambient temperature and after 15 min it is carefully

combined with a saturated NaHCO_3 solution. The organic phase is dried and evaporated to dryness. 20 mg (**V-4**) are obtained.

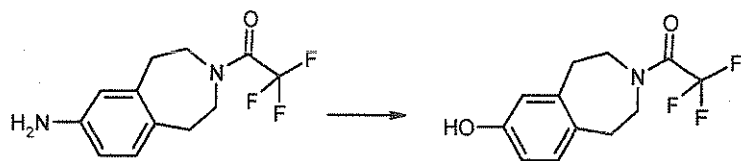
37.4 (2-{4-[4-(4,5-dihydroxazol-2-yl)-phenoxy]-piperidin-1-yl}-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-yl)-(tetrahydropyran-4-yl)-amine (**Example 180**)



Starting from (**IV-6**) (see 6.2) and (**V-4**) **Example 180** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method A): RT = 0.99 min.

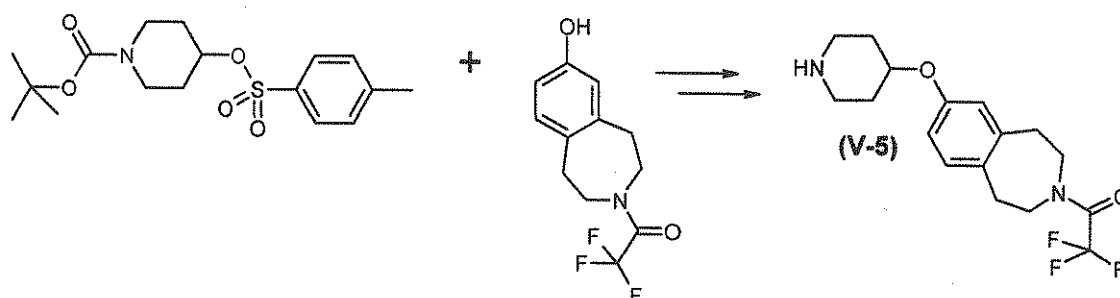
38. SYNTHESIS OF: 2,2,2-TRIFLUORO-1-(7-{1-[5-OXO-4-(TETRAHYDROPYRAN-4-YLAMINO)-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-2-YL]-PIPERIDIN-4-YLOXY}-1,2,4,5-TETRAHYDROBENZO[d]AZEPIN-3-YL)-ETHANONE (**EXAMPLE 182**)

38.1 2,2,2-trifluoro-1-(7-hydroxy-1,2,4,5-tetrahydrobenzo[d]azepin-3-yl)-ethanone:



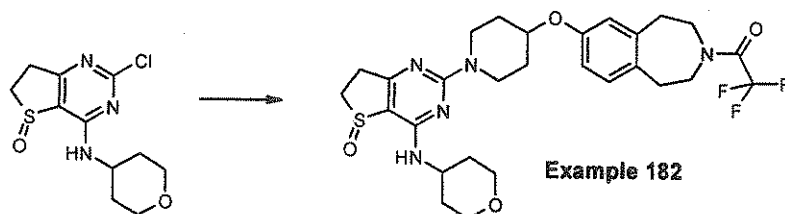
80 g 1-(7-amino-1,2,4,5-tetrahydrobenzo[d]azepin-3-yl)-2,2,2-trifluoro-ethanone (see US2005/137186) and 80 ml conc. Sulphuric acid are placed in 672 ml of water. The reaction mixture is cooled to 0°C, then a mixture of 21.6 g sodium nitrite in 128 ml of water is added dropwise within 10 min.. The reaction mixture is stirred for 10 min. At 0°, then for 2 hours at reflux temperature, cooled and poured onto 4 litres of ice water. The precipitated solid is suction filtered and dried. 71.9 g product are obtained.

38.2 2,2,2-trifluoro-1-[7-(piperidin-4-yloxy)-1,2,4,5-tetrahydrobenzo[d]azepin-3-yl]-ethanone (**V-5**):



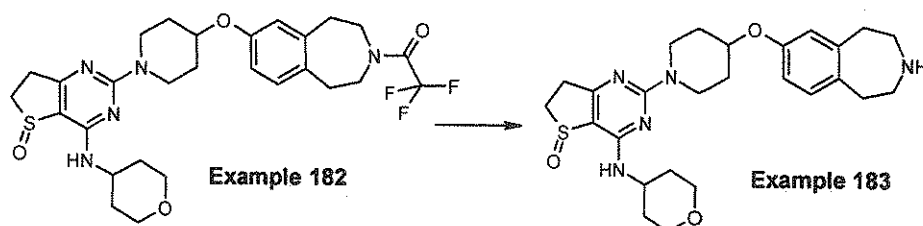
Starting from tert-butyl 4-(toluene-4-sulphonyloxy)-piperidine-1-carboxylate (see 37.1) and 2,2,2-trifluoro-1-(7-hydroxy-1,2,4,5-tetrahydrobenzo[d]azepin-3-yl)-ethanone (see 38.1) (**V-5**) may be prepared analogously to (V-4) (see 37.2 and 37.3).

38.3 (2-{4-[4-(4,5-dihydroxazol-2-yl)-phenoxy]-piperidin-1-yl}-5-oxo-6,7-dihydro-5H-5λ⁴-thieno[3,2-d]pyrimidin-4-yl)-(tetrahydropyran-4-yl)-amine (**Example 182**)



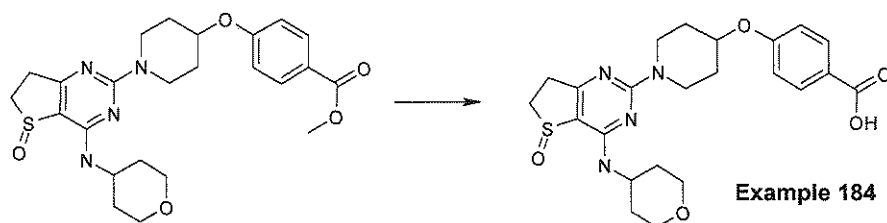
Starting from (IV-6) (see 6.2) and (**V-5**) **Example 182** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method A): RT = 1.27 min.

39. SYNTHESIS OF: {5-OXO-2-[4-(2,3,4,5-TETRAHYDRO-1H-BENZO[D]AZEPIN-7-YLOXY)-PIPERIDIN-1-YL]-6,7-DIHYDRO-5H-5λ⁴-THIENO[3,2-d]PYRIMIDIN-4-YL}-(TETRAHYDROPYRAN-4-YL)-AMINE (**EXAMPLE 183**)



160 mg of **Example 182** (see 38.3) are placed in 5 ml of methanol, then a mixture of 45 mg potassium carbonate in 1 ml of water is added. The reaction mixture is stirred at ambient temperature. After 24 hours the methanol is spun off. The residue is combined with dichloromethane and water. The organic phase is dried and evaporated to dryness. 130 mg **Example 183** are obtained as a solid. Analytical HPLC-MS (method A): RT = 0.99 min.

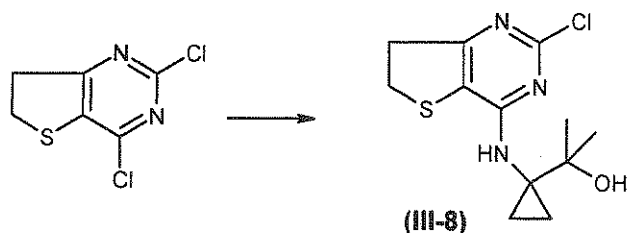
40. SYNTHESIS OF: 4-{1-[5-oxo-4-(tetrahydropyran-4-ylamino)-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-2-yl]-piperidin-4-yloxy}-benzoic acid (**EXAMPLE 184**)



80 mg of **Example 176** (see Table D) are placed in 1.5 ml of methanol, then 560 μ l of a 1N NaOH solution are added. The reaction mixture is stirred at 50°C, until there is no further reaction, then combined with a 1 M HCl solution. The product is extracted with dichloromethane. 77 mg **Example 184** are obtained as a solid. Analytical HPLC-MS (method B): RT = 1.19 min.

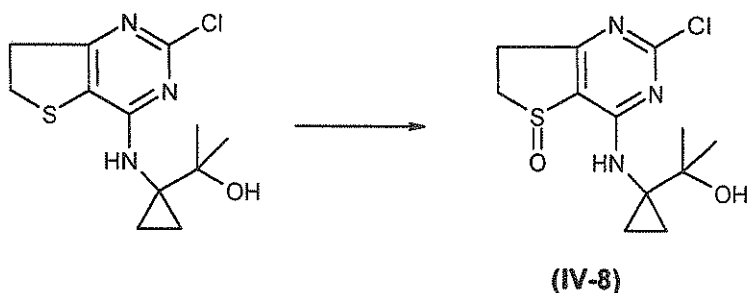
41. SYNTHESIS OF 2-(1-{2-[4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-ylamino}-cyclopropyl)-propan-2-ol (**EXAMPLE 185**)

41.1 2-[1-(2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-ylamino)-cyclopropyl]-propan-2-ol
(III-8):



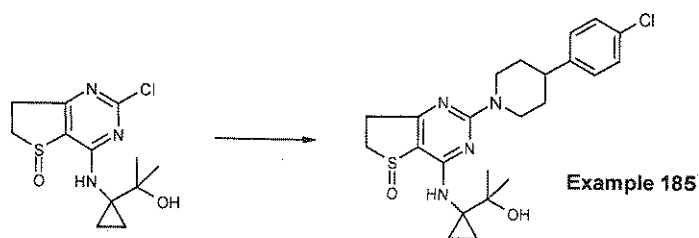
2.7 g (**II**) are placed in 30 ml dioxane, then 6.8 ml diisopropyl-ethylamine and 1.8 g 2-(1-aminocyclopropyl)-propan-2-ol (see *Liebigs Ann. Chem.* **1978**.1194) are added. The reaction mixture is heated to 160°C, until there is no further reaction, and after cooling evaporated to dryness. The residue is combined with ice water. The product is extracted with dichloromethane and purified by chromatography. 125 mg (**III-8**) are obtained as a solid. Analytical HPLC-MS (method A): RT = 1.08 min.

41.2 2-[1-(2-chloro-5-oxo-6,7-dihydro-5H- λ^4 -thieno[3,2-*d*]pyrimidin-4-ylamino)-cyclopropyl]-propan-2-ol (**IV-8**):



21.6 mg S-(-)-1,1'-bi-2-naphthol are placed in 1 ml chloroform under argon, then 11 μ l titanium(IV)-isopropoxide and 14 μ l water are added. The reaction mixture is stirred for 1 hour at ambient temperature. Then a mixture of 120 mg (**III-8**) in 4 ml dichloromethane is added. The reaction mixture is cooled to -5°C and after 30 minutes 69.5 μ l *tert*-butylhydroperoxide 5-6 M in decane are added dropwise. The reaction mixture is stirred at -5°C. After 2 days are the same amounts again of S-(-)-1,1'-bi-2-naphthol, titanium(IV)-isopropoxide, water and *tert*-butylhydroperoxide are added. The reaction mixture is stirred further at -5°C to 5°C until there is no further reaction, mixed with water and made basic with NH₄OH. The organic phase is evaporated to dryness and the product is purified by chromatography (preparative HPLC, method B). 105 mg (**IV-8**) are obtained. Analytical HPLC-MS (method A): RT = 0.96 min.

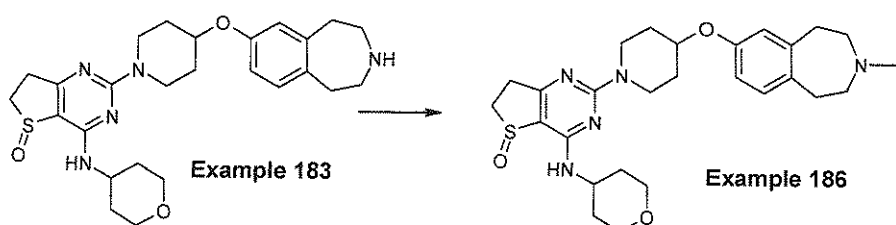
41.3 2-(1-{2-[4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-4-ylamino}-cyclopropyl)-propan-2-ol (**Example 185**)



Starting from (**IV-8**) and 4-(4-chlorophenyl)-piperidine hydrochloride **Example 185** may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method B): RT = 1.37 min.

42. SYNTHESIS OF: {2-[4-(3-METHYL-2,3,4,5-TETRAHYDRO-1H-BENZO[d]AZEPIN-7-YLOXY)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YL}-(TETRAHYDROPYRAN-4-YL)-AMINE (**EXAMPLE 186**)



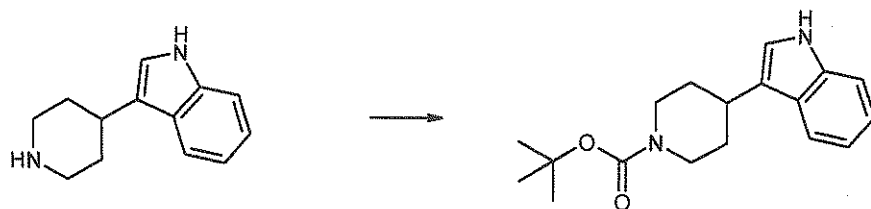
100 mg of **Example 183** (see 39.) are placed in 2 ml of methanol. The pH of the mixture is adjusted to 6 with acetic acid. 34 μ l of an aqueous formalin solution are then added. The reaction mixture is stirred for 20 min at ambient temperature, then 50 mg sodium triacetoxyborohydride are slowly added. The reaction mixture is stirred for a further hour at ambient temperature, then combined with an NaHCO₃ solution. The product is extracted with dichloromethane and purified by chromatography. 56 mg **Example 186** are obtained. Analytical HPLC-MS (method B): RT = 1.10 min.

43. SYNTHESIS OF: {2-[4-(5-*tert*-BUTYL-1-METHYL-1H-INDOL-3-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YL}-

(TETRAHYDRO

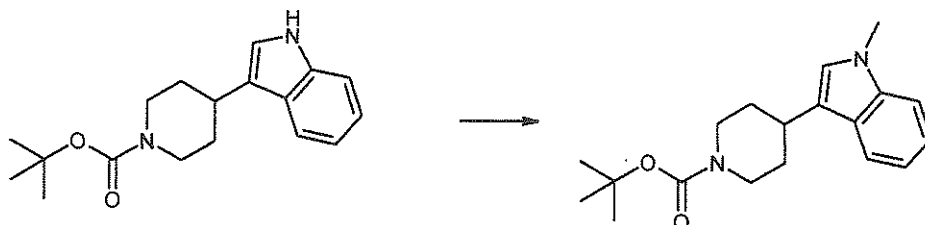
PYRAN-4-YL)-AMINE (EXAMPLE 192)

43.1 tert-butyl 4-(1H-indol-3-yl)-piperidine-1-carboxylate:



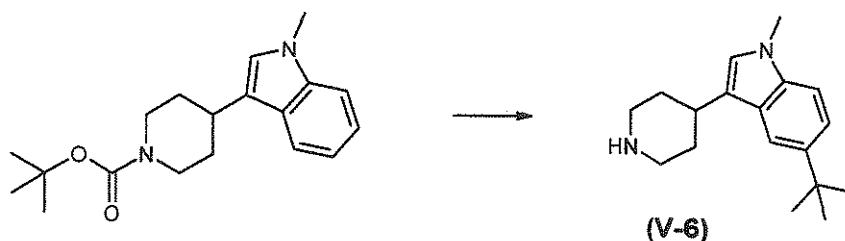
10 g 3-piperidin-4-yl-1H-indole are placed in 300 mL THF and 10.9 g di-*tert*-butyl-dicarbonate are added. The reaction mixture is stirred overnight at ambient temperature and evaporated to dryness. The residue is mixed with water and the product is extracted with diethyl ether and purified by chromatography. 9 g of the product are obtained as a solid.

43.2 tert-butyl 4-(1-methyl-1H-indol-3-yl)-piperidine-1-carboxylate:



500 mg tert-butyl 4-(1H-indol-3-yl)-piperidine-1-carboxylate are placed in 8 ml dimethylformamide and 73.3 mg sodium hydride (60% in mineral oil) are added. After 15 min 175 μ l methyl iodide are added. The reaction mixture is stirred at ambient temperature. After the reaction is complete the product is purified directly by preparative HPLC (method C). 302 mg of the product are obtained as an oil. Analytical HPLC-MS (method A): RT = 1.65 min.

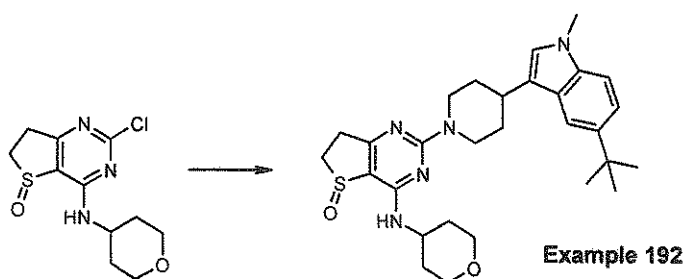
43.3 5-*tert*-butyl-1-methyl-3-piperidin-4-yl-1H-indole (V-6)



365 mg tert-butyl 4-(1-methyl-1H-indol-3-yl)-piperidine-1-carboxylate are placed in 1 ml dichloromethane and combined with 1.03 ml trifluoroacetic acid. The reaction mixture is stirred at ambient temperature. After 12 and 16 h another 1.03 ml trifluoroacetic acid are added. After another 12 h the reaction mixture is evaporated to dryness. The residue is combined with toluene and evaporated to dryness. The residue is triturated with diethyl ether, the precipitate is suction filtered and dried. 154 mg **(V-6)** are obtained as a solid.

Analytical HPLC-MS (method A): RT = 1.34 min.

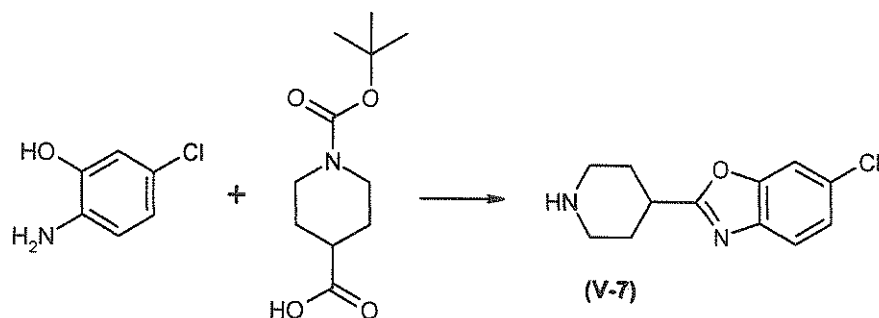
43.4 {2-[4-(5-*tert*-butyl-1-methyl-1H-indol-3-yl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-4-yl}-(tetrahydropyran-4-yl)-amine (**Example 192**)



Starting from **(IV-6)** (see 6.2) and **(V-6)** **Example 192** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.16 min.

44. SYNTHESIS OF: 5-{2-[4-(6-CHLOROBENZOXAZOL-2-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-1-METHYLPYPERIDIN-2-ONE (**EXAMPLE 194**)

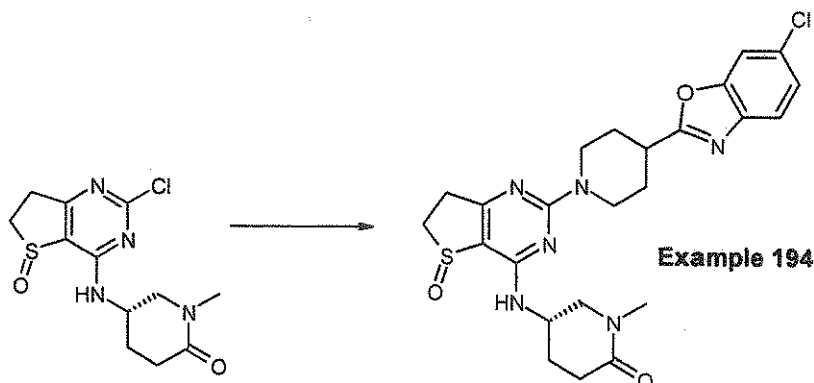
44.1 6-chloro-2-piperidin-4-yl-benzoxazole (**V-7**):



500 mg 2-amino-5-chlorophenol and 800 mg mono-tert-butyl piperidine-1,4-dicarboxylate are heated to 200°C in 4 ml polyphosphoric acid for 4 h. After cooling the reaction mixture is combined with ice water and stirred for 30 min. The precipitate is suction filtered, washed with water and dried. 850 mg product are obtained as the phosphate.

Analytical HPLC-MS (method A): RT = 1.05 min.

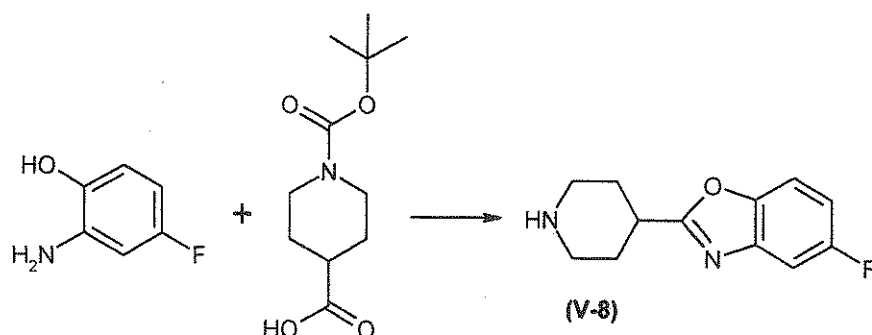
44.2 5-{2-[4-(6-Chlorbenzoxazol-2-yl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5λ⁴-thieno[3,2-d]pyrimidin-4-ylamino}-1-methylpiperidin-2-one (**Example 194**)



Starting from (IV-5) (see 5.5) and (V-7) **Example 194** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.27 min.

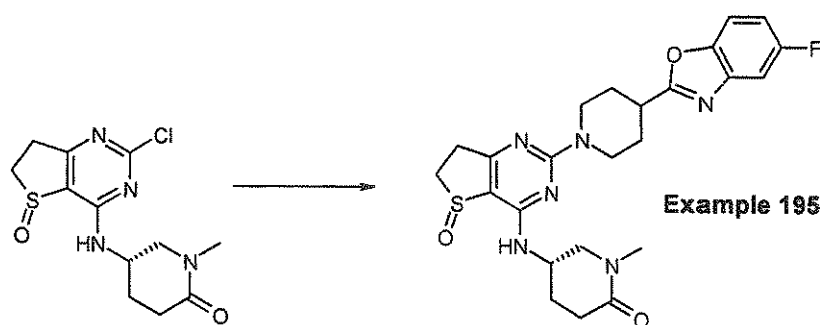
45. SYNTHESIS OF: 5-{2-[4-(5-FLUOROBENZOXAZOL-2-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5λ⁴-THIENO[3,2-d]PYRIMIDIN-4-YLAMINO}-1-METHYLPIPERIDIN-2-ONE (**EXAMPLE 195**)

45.1 5-fluoro-2-piperidin-4-yl-benzoxazole (**V-8**):



500 mg 2-amino-4-fluorophenol and 900 mg mono-tert-butyl piperidine-1,4-dicarboxylate are heated in 5 g polyphosphoric acid at 200°C for 4 h. After cooling the reaction mixture is combined with ice water and made basic with 50% NaOH solution. The precipitate is suction filtered, washed with water and dried. 290 mg (V-8) are obtained as a solid.

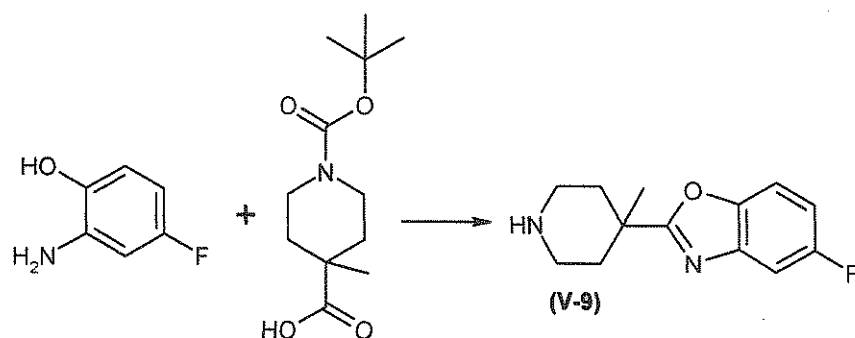
45.2 5-{2-[4-(5-fluorobenzoxazol-2-yl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5λ⁴-thieno[3,2-d]pyrimidin-4-ylamino}-1-methylpiperidin-2-one (**Example 195**)



Starting from (IV-5) (see 5.5) and (V-8) **Example 195** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.21 min.

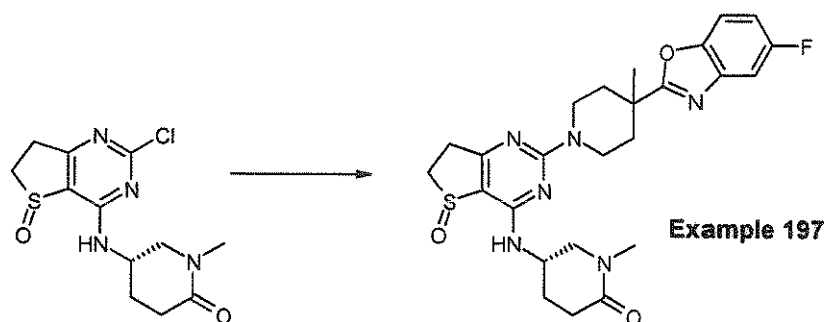
46. SYNTHESIS OF: 5-{2-[4-(5-FLUOROBENZOXAZOL-2-YL)-4-METHYLPIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5λ⁴-THIENO[3,2-d]PYRIMIDIN-4-YLAMINO}-1-METHYLPIPERIDIN-2-ONE (**EXAMPLE 197**)

46.1 5-fluoro-2-(4-methylpiperidin-4-yl)-benzoxazole (V-9):



Starting from 2-amino-4-fluorophenol and mono-tert-butyl 4-methylpiperidine-1,4-dicarboxylate **(V-9)** may be prepared and purified analogously to **(V-8)** (see 45.1).

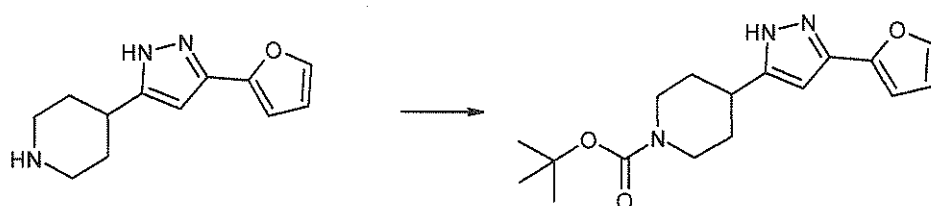
46.2 5-{2-[4-(5-fluorobenzoxazol-2-yl)-4-methylpiperidin-1-yl]-5-oxo-6,7-dihydro-5H-5λ⁴-thieno[3,2-d]pyrimidin-4-ylamino}-1-methylpiperidin-2-one (Example 197)



Starting from **(IV-5)** (see 5.5) and **(V-9)** **Example 197** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.26 min.

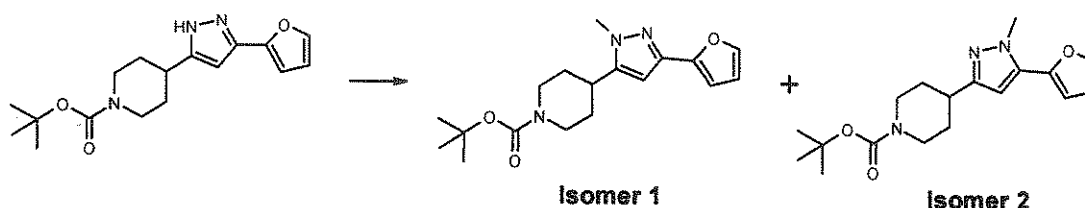
47. SYNTHESIS OF: {2-[4-(5-FURAN-2-YL-1-METHYL-1H-PYRAZOL-3-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5λ⁴-THIENO[3,2-d]PYRIMIDIN-4-YL}-(TETRAHYDROPYRAN-4-YL)-AMINE (EXAMPLE 198)

47.1 tert-butyl 14-(5-furan-2-yl-2H-pyrazol-3-yl)-piperidine-1-carboxylate:



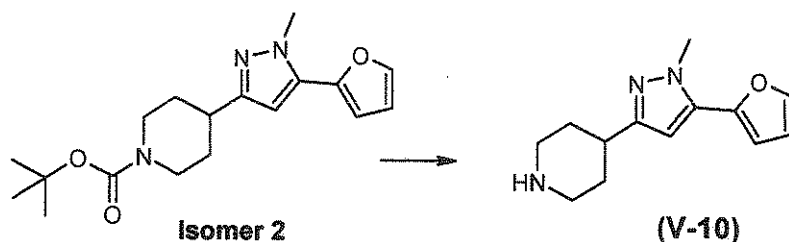
200 mg 4-(5-furan-2-yl-2H-pyrazol-3-yl)-piperidine are placed in 2 ml dioxane. Then 0.34 ml of water and 155 mg sodium carbonate are added. The reaction mixture is stirred at ambient temperature. After 5 min, 204 mg di-tert-butyl-dicarbonate are added. After 3 h the reaction mixture is mixed with water and the product is extracted with dichloromethane. 300 mg product are obtained as an oil. Analytical HPLC-MS (method B): RT = 1.54 min.

47.2 tert-butyl 4-(5-furan-2-yl-2-methyl-2H-pyrazol-3-yl)-piperidine-1-carboxylate
tert-butyl and 4-(5-furan-2-yl-1-methyl-1H-pyrazol-3-yl)-piperidine-1-carboxylate:



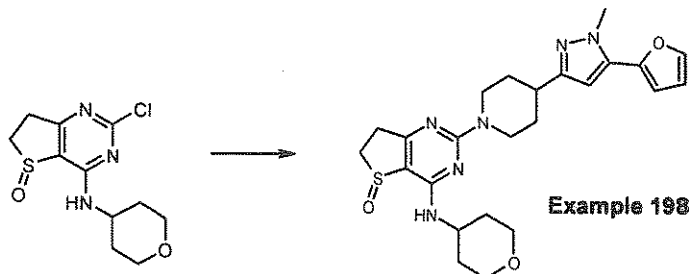
250 mg tert-butyl 4-(5-furan-2-yl-2H-pyrazol-3-yl)-piperidine-1-carboxylate are placed in 1.5 ml dimethylformamide. The reaction mixture is cooled in the ice bath and 40 mg sodium hydride (60% in mineral oil) are added. After 10 min 60 µl methyl iodide are added. The reaction mixture is stirred for 30 min at 5°C and then for 4 h at ambient temperature. The product is then purified directly by preparative HPLC (method D). 90 mg of **isomer 1** and 50 mg of **isomer 2** are obtained as a solid. Analytical HPLC-MS (method D): RT = 1.33 min (isomer 1); RT = 1.28 (isomer 2).

47.3 4-(5-furan-2-yl-1-methyl-1H-pyrazol-3-yl)-piperidine (**V-10**):



47 mg **isomer 2** are placed in 1 ml dichloromethane and 120 µl trifluoroacetic acid are added. The reaction mixture is stirred for 2h at ambient temperature, then evaporated to dryness. The residue is combined with toluene and evaporated to dryness. The residue is mixed with water, made basic with conc. Ammonia and the product is extracted with dichloromethane. 23 mg (**V-10**) are obtained as a solid. Analytical HPLC-MS (method B): RT = 0.85 min

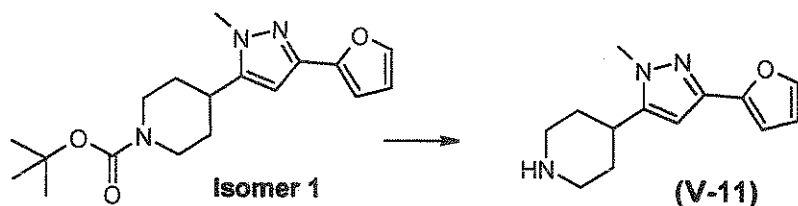
47. 4 {2-[4-(5-furan-2-yl-1-methyl-1H-pyrazol-3-yl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-4-yl}-(tetrahydropyran-4-yl)-amine (**Example 198**)



Starting from (IV-6) (see 6.2) and (V-10) **Example 198** may be prepared and purified analogously to Example 89 (see 21). Analytical HPLC-MS (method B): RT = 1.21 min.

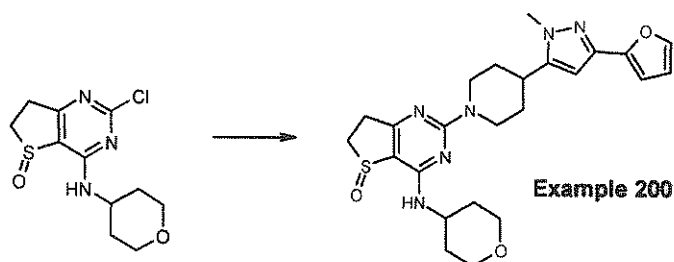
48. SYNTHESIS OF: {2-[4-(5-FURAN-2-YL-2-METHYL-2H-PYRAZOL-3-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YL}-(TETRAHYDROPYRAN-4-YL)-AMINE (**EXAMPLE 200**)

48.1 4-(5-furan-2-yl-2-methyl-2H-pyrazol-3-yl)-piperidine (**V-11**):



Starting from **isomer 1** (see 47.2), (**V-11**) may be prepared analogously to (**V-10**) (see 47.3). Analytical HPLC-MS (method D): RT = 0.89 min.

48. 2 Synthesis of: {2-[4-(5-furan-2-yl-2-methyl-2H-pyrazol-3-yl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-4-yl}-(tetrahydropyran-4-yl)-amine (**Example 200**)



Starting from (IV-6) (see 6.2) and (V-11) **Example 200** may be prepared and purified analogously to Example 89 (see 21). Analytical HPLC-MS (method B): RT = 1.26 min.

49. SYNTHESIS OF 5-{2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-1-PROPYLPYPERIDIN-2-ONE (**EXAMPLE 201**)

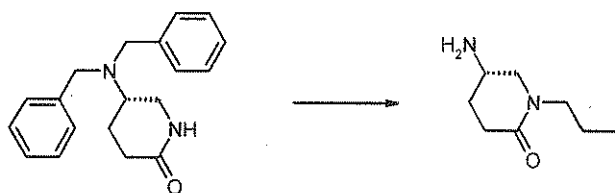
49.1 (S)-5-dibenzylamino-1-propylpiperidin-2-one:



0.51 g (S)-5-dibenzylaminopiperidin-2-one (see 5.1) are placed in 5 ml dimethylformamide. While cooling with the ice bath 120 mg sodium hydride (60% in mineral oil) are added. The reaction mixture is then stirred for 30 minutes at ambient temperature. While cooling with the ice bath 0.289 ml 1-iodopropane are added. The reaction mixture is then stirred overnight at ambient temperature, then combined with a saturated NaCl solution. The product is extracted with ethyl acetate. 0.569 g product are obtained as an oil.

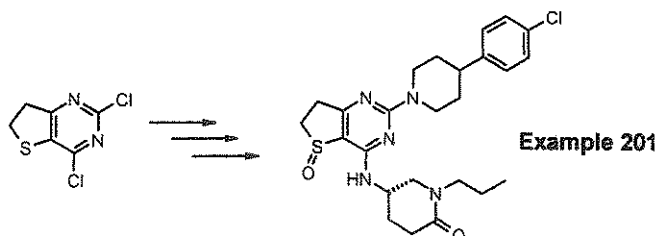
Analytical HPLC-MS (method A): RT = 1.13 min.

49.2 (S)-5-amino-1-propylpiperidin-2-one:



0.569 g (S)-5-dibenzylamino-1-propylpiperidin-2-one are placed in 25 ml of methanol and hydrogenated with 0.150 g Pd/C 10% at a pressure of 3 bar and a temperature of 60°C. After 19 hours the catalyst is suction filtered and the filtrate is evaporated to dryness. 0.217 g of the product are obtained as an oil.

49.3 5-{2-[4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-4-ylamino}-1-propylpiperidin-2-one (**Example 201**)

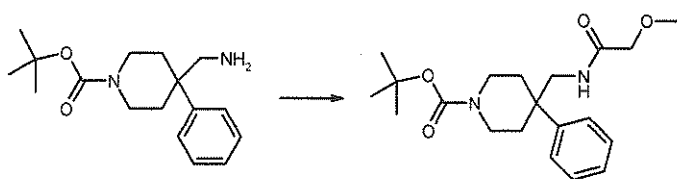


Starting from (II), (S)-5-amino-1-propylpiperidin-2-one (see 49.2) and 4-(4-chlorophenyl)-piperidine hydrochloride **Example 201** may be prepared analogously to Example 5 (see 5.4 to 5.6). The product may be purified by preparative HPLC (method B).

Analytical HPLC-MS (method B): RT = 1.36 min.

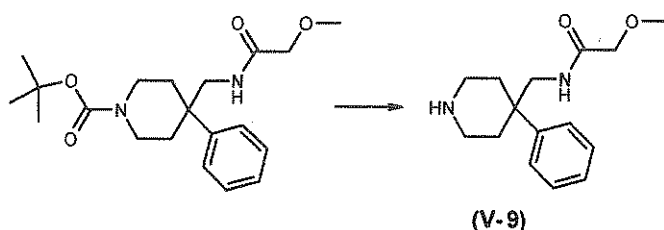
50. SYNTHESIS OF: 2-METHOXY-N-{1-[4-(1-METHYL-6-OXOPIPERIDIN-3-YLAMINO)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL]-4-PHENYL PIPERIDIN-4-YLMETHYL}-ACETAMIDE (**EXAMPLE 202**)

50.1 tert-butyl 4-[(2-methoxyacetylamino)-methyl]-4-phenylpiperidine-1-carboxylate:



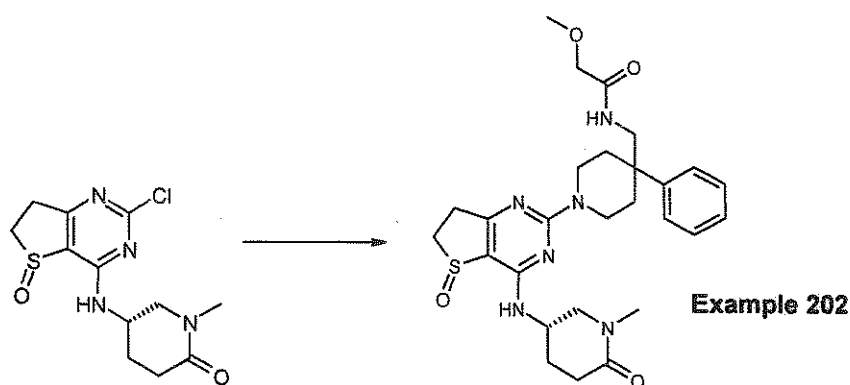
3.7 g of commercial tert-butyl 4-aminomethyl-4-phenyl-piperidine-1-carboxylate and 3 ml diisopropylethylamine are placed in 30 ml dichloromethane. Then 2.25 ml methoxyacetyl chloride are slowly added. The reaction mixture is stirred at ambient temperature, until there is no further reaction, then mixed with water. The organic phase is evaporated to dryness. 4.7 g product are obtained as an oil.

50.2 2-methoxy-N-(4-phenylpiperidin-4-ylmethyl)-acetamide (**V-12**):



1 g tert-butyl 4-[(2-methoxyacetylamino)-methyl]-4-phenylpiperidine-1-carboxylate are placed in 4 ml dichloromethane. Then 1.7 ml trifluoroacetic acid are added and the mixture is stirred overnight at ambient temperature. The reaction mixture is made basic with potassium carbonate and the organic phase is evaporated to dryness. 610 mg (**V-12**) are obtained as an oil.

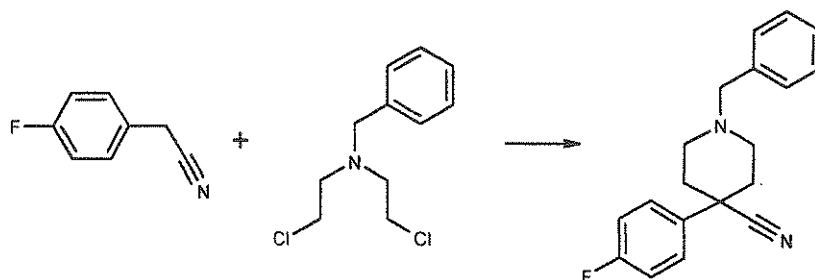
50.3 Synthesis of: 2-methoxy-N-{1-[4-(1-methyl-6-oxopiperidin-3-ylamino)-5-oxo-6,7-dihydro-5H-5λ⁴-thieno[3,2-d]pyrimidin-2-yl]-4-phenylpiperidin-4-ylmethyl}-acetamide (**Example 202**)



Starting from (**IV-5**) (see 5.5) and (**V-12**) **Example 202** may be prepared and purified analogously to **Example 89** (see 21.). Analytical HPLC-MS (method B): RT = 1.16 min.

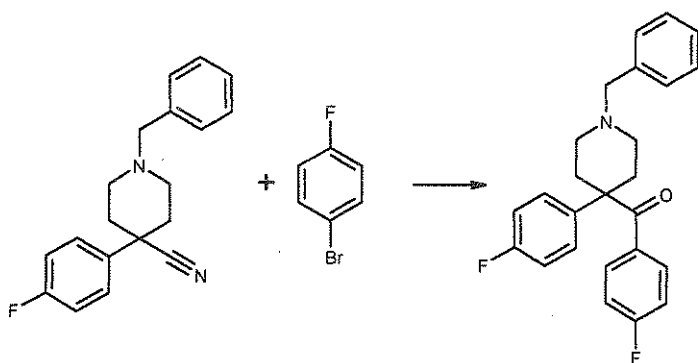
51. SYNTHESIS OF: 5-{2-[4-(4-FLUOROBENZOYL)-4-(4-FLUOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-1-METHYLPYPERIDIN-2-ONE (EXAMPLE 203)

51.1 1-benzyl-4-(4-fluorophenyl)-piperidine-4-carbonitrile:



Under argon 16 ml 4-fluorobenzylcyanide and 35.1 g N-benzyl-N,N-di-(2-chloroethyl)amine hydrochloride are placed in 500 ml NMP and the mixture is cooled to 5°C. Then 18.9 g sodium hydride (55% in mineral oil) are added batchwise within 30 min. The reaction mixture is stirred for 30 min at 5-10°C and for 6 h at ambient temperature and then poured onto ice water. The product is extracted with ethyl acetate and purified by chromatography (silica gel, dichloromethane/ethanol 100:1 to 50:1). 33 g product are obtained as an oil.

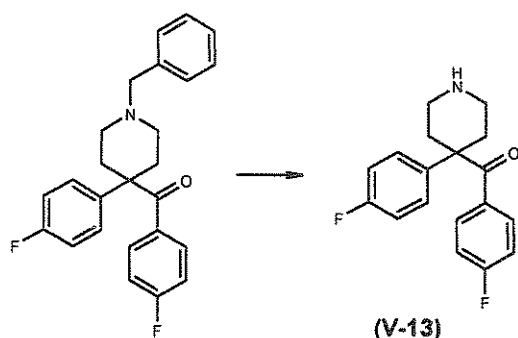
51.2 [1-benzyl-4-(4-fluorophenyl)-piperidin-4-yl]-(4-fluorophenyl)-methanone:



Under argon 11.86 g magnesium chips are placed in 50 ml anhydrous diethyl ether, then a solution of 85.4 g 4-bromofluorobenzene in 200 ml anhydrous diethyl ether is slowly added dropwise. The reaction mixture is stirred for 2 h at reflux temperature and then cooled to ambient temperature. A solution of 45.4 g 1-benzyl-4-(4-fluorophenyl)-piperidine-4-carbonitrile in 100 ml anhydrous toluene is added dropwise. The diethyl ether is distilled off and the remainder of the reaction mixture is stirred

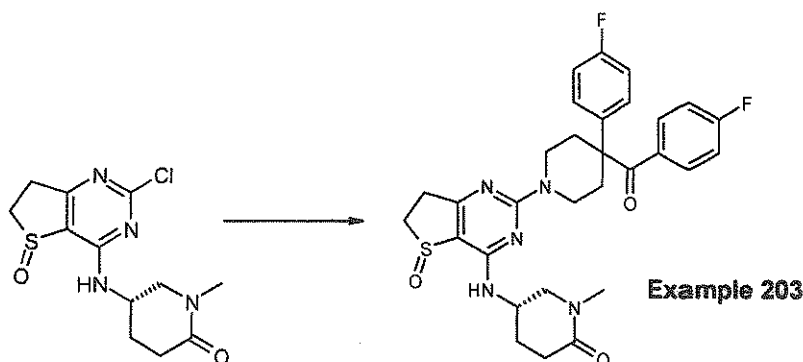
overnight at 80°C. After cooling the reaction mixture is combined with 500 ml ice water and 100 g NH₄Cl and the product is extracted with ethyl acetate. The organic phase is washed with water and sat. NaCl solution, dried and evaporated to dryness. 70 ml glacial acetic acid and 20 ml sulphuric acid 33% are added to the residue. The reaction mixture is heated to 100°C, then cooled, combined with ice water and adjusted to pH ~ 9 with 4N NaOH. Then 250 ml diisopropylether are added. The reaction mixture is then stirred overnight at ambient temperature. The precipitate formed is suction filtered, washed with diisopropylether and water and dried. 42.7 g product are obtained as a solid. M.p: 136-138.5°C.

51.3 (4-fluorophenyl)-[4-(4-fluorophenyl)-piperidin-4-yl]-methanone (V-13):



42.6 g [1-benzyl-4-(4-fluoro-phenyl)-piperidin-4-yl]-(4-fluoro-phenyl)-methanone are placed in 400 ml of methanol and 15 ml ethereal hydrochloric acid 10 mol/l and hydrogenated overnight with 8 g Pd/C 5% at 30°C and 50 psi hydrogen pressure. The catalyst is filtered off and the filtrate is evaporated to dryness. The residue is stirred with *tert*-butylmethylether, the solid is suction filtered, washed with *tert*-butylmethylether and dried. 35.08 g (V-13) are obtained as the hydrochloride. M.p: 149-151°C.

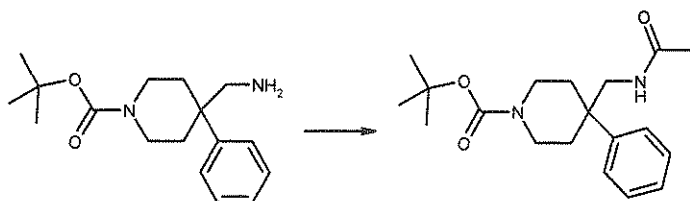
51.4 5-{2-[4-(4-fluorobenzoyl)-4-(4-fluorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5λ⁴-thieno[3,2-*d*]pyrimidin-4-ylamino}-1-methylpiperidin-2-one (Example 203)



Starting from (IV-5) (see 5.5) and (V-13) **Example 203** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.38 min.

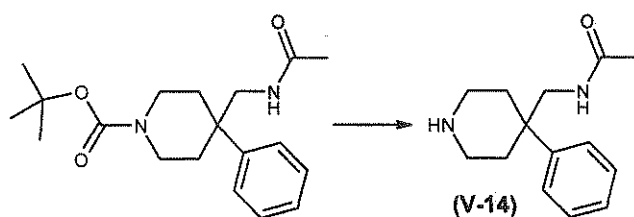
52. SYNTHESIS OF: N-{1-[4-(1-METHYL-6-OXOPIPERIDIN-3-YLAMINO)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-2-YL]-4-PHENYLPYPERIDIN-4-YLMETHYL}-ACETAMIDE (**Example 204**)

52.1 tert-butyl 4-(acetylaminomethyl)-4-phenylpiperidine-1-carboxylate:



8 g tert-butyl 4-aminomethyl-4-phenylpiperidine-1-carboxylate and 2.9 ml acetic anhydride are stirred in 80 ml of ethanol overnight at ambient temperature and then evaporated to dryness. 10.4 g product are obtained.

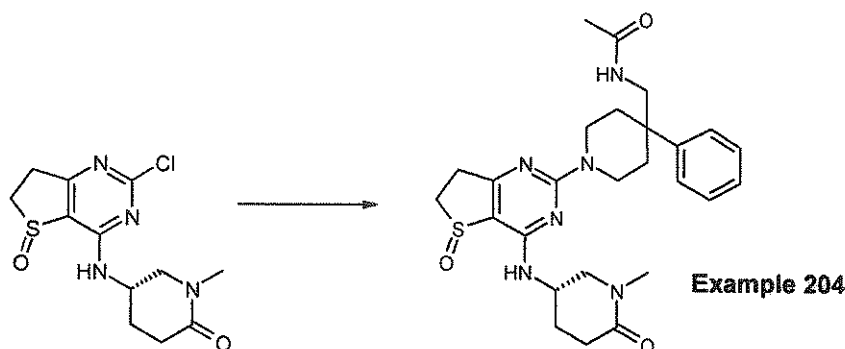
52.2 N-(4-phenylpiperidin-4-ylmethyl)-acetamide (**V-14**):



11.5 g tert-butyl 4-(acetylaminomethyl)-4-phenylpiperidine-1-carboxylate and 25 ml trifluoroacetic acid are stirred in 200 ml dichloromethane overnight at ambient

temperature. The reaction mixture is evaporated to dryness and the residue is triturated with diethyl ether/diisopropylether. The precipitated solid is suction filtered and washed with diethyl ether. 10 g (**V-14**) are obtained as the trifluoroacetate.

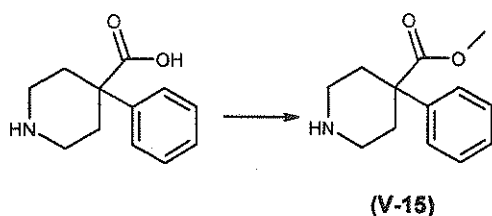
52.3 N-{1-[4-(1-methyl-6-oxopiperidin-3-ylamino)-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-2-yl]-4-phenylpiperidin-4-ylmethyl}-acetamide (**Example 204**)



Starting from (**IV-5**) (see 5.5) and (**V-14**) **Example 204** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.11 min.

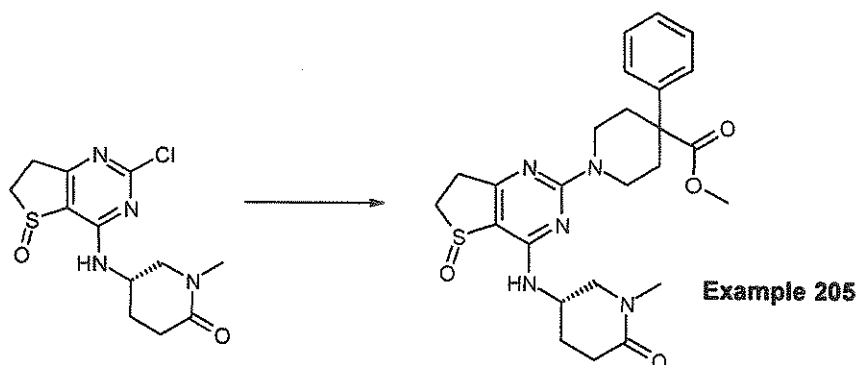
53. SYNTHESIS OF: METHYL 1-[4-(1-METHYL-6-OXOPIPERIDIN-3-YLAMINO)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-2-YL]-4-PHENYLPYPERIDINE-4-CARBOXYLATE (**EXAMPLE 205**)

53.1 methyl 4-phenylpiperidine-4-carboxylate (**V-15**):



270 ml of methanol are taken. 10.6 ml sulphuric acid and 25 g 4-phenyl-4-piperidine-carboxylic acid *p*-toluenesulphonic acid are added with stirring. The reaction mixture is refluxed for 9 h, cooled and carefully poured onto a mixture of ice water and 10 M NaOH. The precipitated solid is suction filtered, washed with water and dried. 11.2 g (**V-15**) are obtained as a solid.

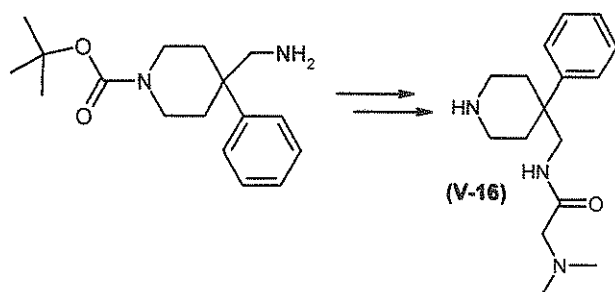
53.2 methyl 1-[4-(1-methyl-6-oxopiperidin-3-ylamino)-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-2-yl]-4-phenylpiperidine-4-carboxylate (**Example 205**)



Starting from (**IV-5**) (see 5.5) and (**V-15**) **Example 205** may be prepared and purified analogously to **Example 89** (see 21.). Analytical HPLC-MS (method B): RT = 1.23 min.

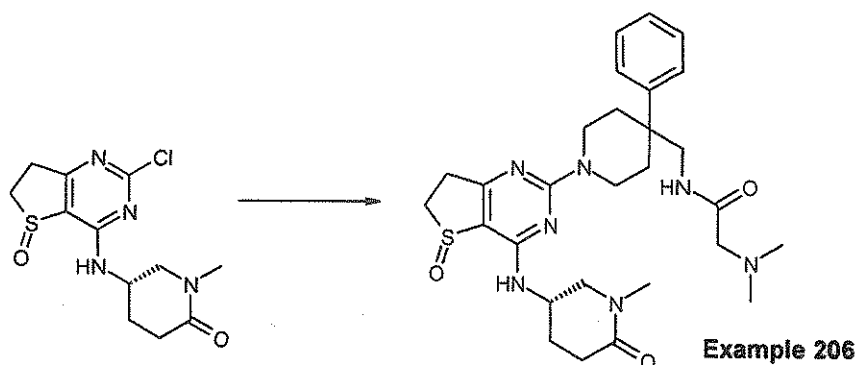
54. SYNTHESIS OF: 2-DIMETHYLAMINO-N-{1-[4-(1-METHYL-6-OXOPIPERIDIN-3-YLAMINO)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL]-4-PHENYL PIPERIDIN-4-YLMETHYL}-ACETAMIDE (**EXAMPLE 206**)

54.1 2-dimethylamino-N-[4-(1-propenylbuta-1,3-dienyl)-piperidin-4-ylmethyl]-acetamide (**V-16**):



Starting from commercial tert-butyl 4-aminomethyl-4-phenylpiperidine-1-carboxylate and dimethylaminoacetyl chloride hydrochloride (**V-16**) may be prepared analogously to (**V-12**) (see 50.1 and 50.2).

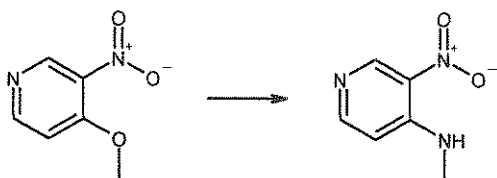
48.2 2-dimethylamino-N-{1-[4-(1-methyl-6-oxopiperidin-3-ylamino)-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-2-yl]-4-phenylpiperidin-4-ylmethyl}-acetamide
(**Example 206**)



Starting from (**IV-5**) (see 5.5) and (**V-16**) **Example 206** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.08 min.

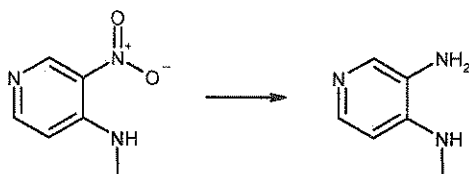
55. SYNTHESIS OF: {2-[4-(1-METHYL-1H-IMIDAZO[4,5-*c*]PYRIDIN-2-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YL}-(TETRAHYDRO PYRAN-4-YL)-AMINE (**EXAMPLE 210**)

55.1 methyl-(3-nitropyridin-4-yl)-amine:



2.36 g 4-methoxy-3-nitro-pyridine and 2.33 ml methylamine (40% in water) are refluxed in 25 ml of ethanol for 3 h. Then the reaction mixture is evaporated to dryness. 2.3 g product are obtained as a solid.

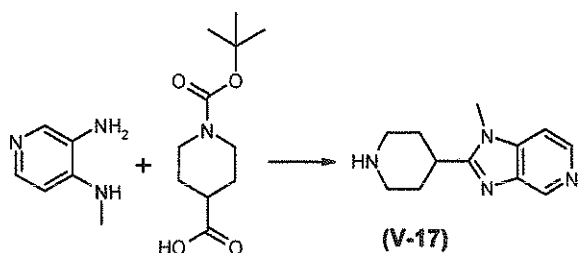
55.2 *N*⁴-methylpyridin-3,4-diamine:



2.3 g methyl-(3-nitropyridin-4-yl)-amine are hydrogenated in 50 ml of methanol for and with 0.8 g Raney nickel for 2.5 h at 50°C and 50 psi hydrogen pressure. The catalyst is filtered off and the filtrate is evaporated to dryness. The product is purified by chromatography (Alox, dichloromethane/methanol from 99/1 to 19/1). 1.55 g product are obtained as a solid.

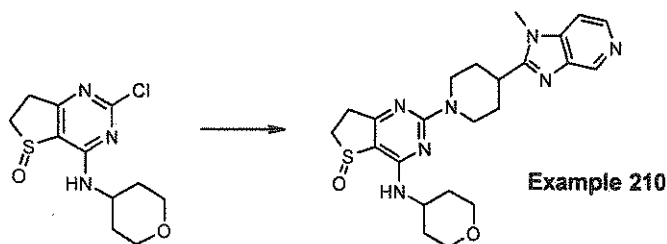
M.p: 163-165°C.

55.3 1-methyl-2-piperidin-4-yl-1H-imidazo[4,5-c]pyridine (V-17):



450 mg *N*⁴-methylpyridin-3,4-diamine and 838 mg mono-*tert*-butyl piperidine-1,4-dicarboxylate are heated for 4 h in 8.6 g polyphosphoric acid at 200°C. After cooling the mixture is made basic with 4 N NaOH and acidified with trifluoroacetic acid. The mixture is purified by preparative HPLC (method C). 3.37 g (50%) (V-17) are obtained as the trifluoroacetate. Analytical HPLC-MS (method B): RT = 0.30 min.

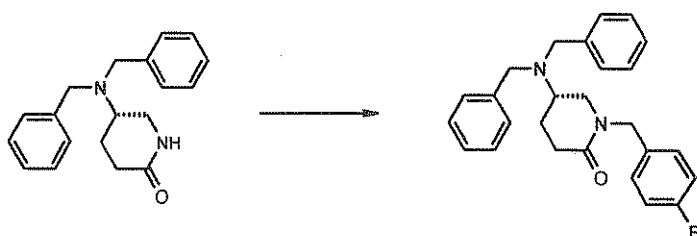
55.4 {2-[4-(1-methyl-1H-imidazo[4,5-c]pyridin-2-yl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5λ⁴-thieno[3,2-*d*]pyrimidin-4-yl}-(tetrahydropyran-4-yl)-amine (Example 210)



Starting from (IV-6) (see 6.2) and (V-17) **Example 210** may be prepared and purified analogously to Example 89 (see 21). Analytical HPLC-MS (method D): RT = 0.86 min.

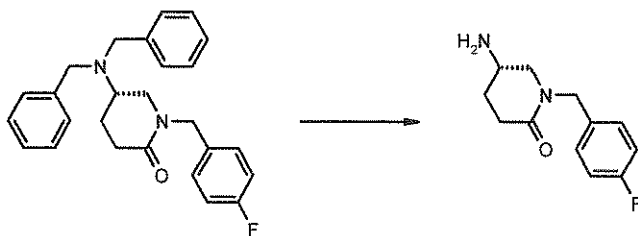
56. SYNTHESIS OF 5-{2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-1-(4-FLUOROBENZYL)-PIPERIDIN-2-ONE (**EXAMPLE 211**)

56.1 (S)-5-dibenzylamino-1-(4-fluorobenzyl)-piperidin-2-one:



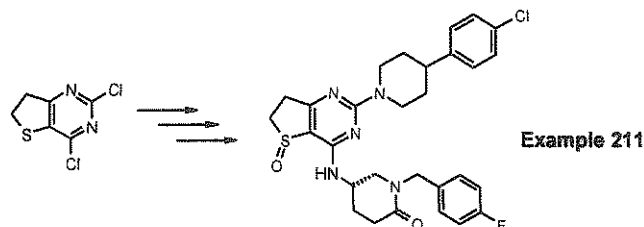
0.8 g (S)-5-dibenzylaminopiperidin-2-one (see 5.1) are placed in 8 ml dimethylformamide, then 200 mg sodium hydride (60% in mineral oil) and 0.4 ml 4-fluorobenzylbromide are added. The reaction mixture is stirred overnight at 70°C and then combined with ice water. The precipitate is filtered off and washed with water. The product is purified by chromatography (silica gel, petroleum ether/ethyl acetate and ethyl acetate/methanol). 0.5 g product are obtained as an oil. Analytical HPLC-MS (method A): RT = 1.21 min.

56.2 (S)-5-amino-1-(4-fluoro-benzyl)-piperidin-2-one:



0.5 g (S)-5-dibenzylamino-1-(4-fluorobenzyl)-piperidin-2-one are placed in 20 ml of methanol and hydrogenated with 0.150 g Pd/C 10% at a pressure of 3 bar and a temperature of 60°C. After 5 hours the catalyst is suction filtered and the filtrate is evaporated to dryness. 0.21 g of the product are obtained as an oil. Analytical HPLC-MS (method A): RT = 0.68 min.

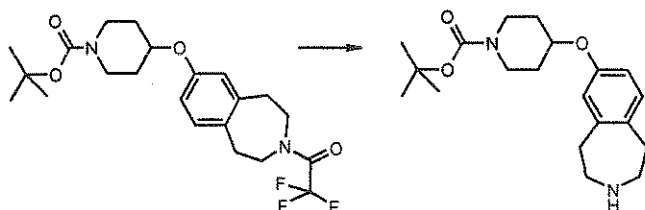
56.3 5-{2-[4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H- λ^4 -thieno[3,2-*d*]pyrimidin-4-ylamino}-1-(4-fluorobenzyl)-piperidin-2-one (**Example 211**)



Starting from (II), (S)-5-amino-1-(4-fluorobenzyl)-piperidin-2-one (see 56.2) and 4-(4-chlorophenyl)-piperidine hydrochloride **Example 211** may be prepared analogously to Example 5 (see 5.4 to 5.6). The product may be purified by preparative HPLC (method A). Analytical HPLC-MS (method B): RT = 1.45 min.

57. SYNTHESIS OF: CYCLOPROPYL-(7-{1-[5-OXO-4-(TETRAHYDROPYRAN-4-YLAMINO)-6,7-DIHYDRO-5H- λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL]-PIPERIDIN-4-YLOXY}-1,2,4,5-TETRAHYDROBENZO[d]AZEPIN-3-YL)-METHANONE (**EXAMPLE 214**)

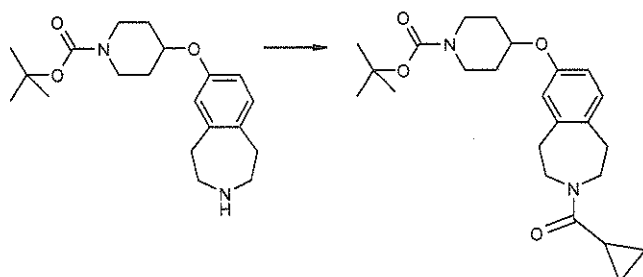
57.1 tert-butyl 4-(2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidine-1-carboxylate:



400 mg tert-butyl 4-[3-(2,2,2-trifluoroacetyl)-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy]-piperidine-1-carboxylate (see 38.2) are placed in 17 ml of methanol, then a mixture of 151.2 mg potassium carbonate in 3.3 ml of water is added. The reaction mixture is stirred at ambient temperature, until there is no further reaction. The methanol is then spun off. The residue is combined with dichloromethane and water. The organic phase is dried and evaporated to dryness. 310 mg are obtained as an oil.

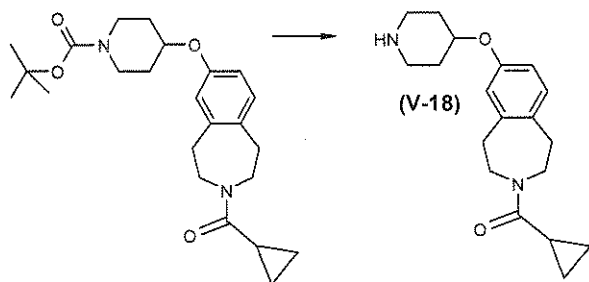
Analytical HPLC-MS (method D): RT = 1.25 min.

57.2 tert-butyl 4-(3-cyclopropanecarbonyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidine-1-carboxylate:



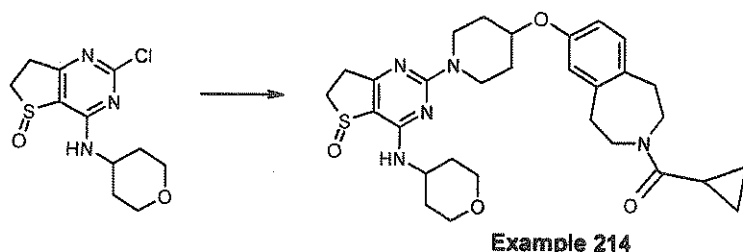
16 μ l cyclopropylcarboxylic acid are placed in 3 ml dimethylformamide, then 174 μ l diisopropylethylamine and 93.1 mg O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) are added. After 15 min 77.5 mg tert-butyl 4-(2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidine-1-carboxylate are added. The reaction mixture is stirred at ambient temperature until there is no further reaction and the product is purified directly by preparative HPLC (method B). 70 mg of the product are obtained as a solid. Analytical HPLC-MS (method D): RT = 1.37 min.

57.3 cyclopropyl-[7-(piperidin-4-yloxy)-1,2,4,5-tetrahydro-benzo[d]azepin-3-yl]-methanone (**V-18**):



70 mg tert-butyl 4-(3-cyclopropanecarbonyl-2,3,4,5-tetrahydro-1H-benzo[d]azepin-7-yloxy)-piperidine-1-carboxylate are placed in 1.4 ml dichloromethane and combined with 224 μ l trifluoroacetic acid. The reaction mixture is stirred for 3 hours at ambient temperature, then evaporated to dryness. The residue is combined with toluene and evaporated to dryness. 77 mg (**V-18**) are obtained as an oil. Analytical HPLC-MS (method B): RT = 1.18 min.

57.4 cyclopropyl-(7-{1-[5-oxo-4-(tetrahydropyran-4-ylamino)-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-2-yl]-piperidin-4-yloxy}-1,2,4,5-tetrahydrobenzo[d]azepin-3-yl)-methanone (**Example 214**)



Starting from (IV-6) (see 6.2) and (V-18) **Example 214** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method D): RT = 1.10 min.

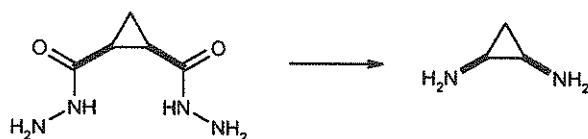
58. SYNTHESIS OF *tert*-BUTYL (2-{2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-CYCLOPROPYL)-CARBAMIDATE (**EXAMPLE 222**)

58.1 dihydrazide *cis*-1,2-cyclopropanedicarboxylic acid:



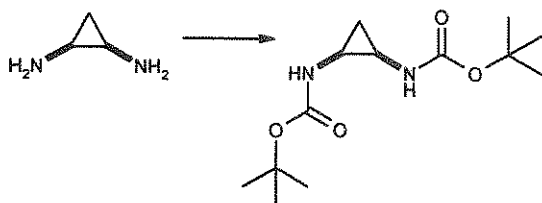
10 g dimethyl *cis*-1,2-cyclopropanedicarboxylate are placed in 100 ml of ethanol and 12.7 ml hydrazine monohydrate are added. The reaction mixture is stirred for 12 h at reflux temperature. After cooling the precipitated solid is filtered, washed with petroleum ether and diethyl ether and dried. 8 g (80%) product are obtained as a solid.

58.2 *cis*-1,2-cyclopropanediamine:



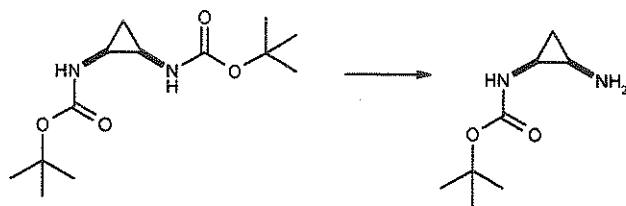
2 g dihydrazide *cis*-1,2-cyclopropanedicarboxylic acid are placed in 35 ml diethyl ether, then 14.2 ml conc. Hydrochloric acid in 28 g ice are added. The reaction mixture is cooled to 0-5°C and then a solution of 5.45 g sodium nitrite in water is slowly added dropwise. After 20 min the organic phase is separated off and dried. 50 ml of toluene are added and the ether is distilled off. The toluene solution remaining is heated at 80-90°C until the development of nitrogen ceases. The hot toluene solution is carefully poured onto hot (60°C) conc. Hydrochloric acid and the toluene is distilled off. Anhydrous ethanol is added and distilled off again until a solid is obtained. The solid is combined with cold ethanol and filtered off. 1.25 g product are obtained as the dihydrochloride. M.p: 225°C (decomposition).

58.3 *tert*-butyl *cis*-(2-*tert*-butoxycarbonylamino)cyclopropyl)-carbamidate:



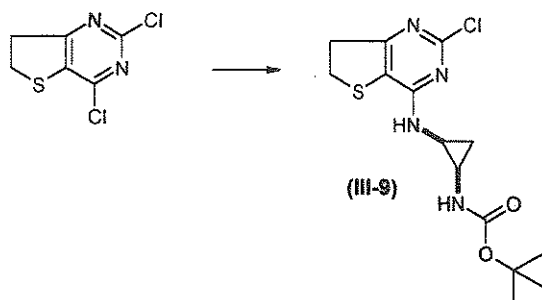
5 g *cis*-1,2-cyclopropanediamine dihydrochloride is placed in 50 ml dioxane, cooled to 0°C and then combined with 13.8 g 5 N sodium hydroxide solution and 22.55 g di-*tert*-butyl-dicarbonate. The reaction mixture is stirred for 3 h at ambient temperature and the product is extracted with dichloromethane. 6.3 g product are obtained as a solid. M.p: 131-132°C.

58.4 *cis*-N-*tert*-butoxycarbonyl-1,2-cyclopropanediamine:



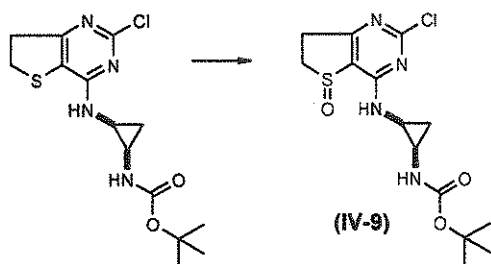
5 g *tert*-butyl *cis*-(2-*tert*-butoxycarbonylamino)cyclopropyl)-carbamidate are placed in 50 ml of ethyl acetate and cooled to 0°C. A solution of 0.87 g hydrochloric acid in 9.5 ml of ethyl acetate is added dropwise. Then the reaction mixture is stirred overnight at ambient temperature. The precipitated solid is filtered off and washed with ethyl acetate. 0.76 g product are obtained as the hydrochloride. M.p: 208-209°C.

58.5 tert-butyl [2-(2-chloro-6,7-dihydrothieno[3,2-d]pyrimidin-4-ylamino)-cyclopropyl]-carbamate (**III-9**):



0.55 g (**II**) are placed in 9 ml dioxane, then 1.4 ml diisopropyl ethylamine and 0.6 g *cis*-N-*tert*-butyloxycarbonyl-1,2-cyclopropanediamin hydrochloride (see 58.4) are added. The reaction mixture is heated in the microwave at 110°C until there is no further reaction and after cooling it is evaporated to dryness. The residue is treated with water in the ultrasound bath, the precipitate is suction filtered and washed with water. The solid is treated with 10 ml petroleum ether/ethyl acetate = 7/3 and suction filtered. 520 mg (**III-9**) are obtained as a solid. Analytical HPLC-MS (method B): RT = 1.42 min.

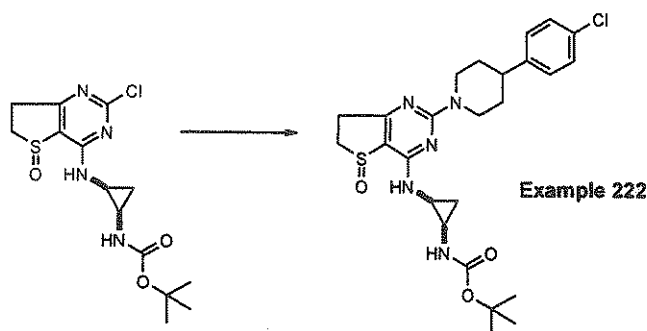
58.6 tert-butyl [2-(2-chloro-5-oxo-6,7-dihydro-5*H*-5λ⁴-thieno[3,2-d]pyrimidin-4-ylamino)-cyclopropyl]-carbamate (**IV-9**):



73 mg S-(-)-1,1'-bi-2-naphthol are placed in 2 ml chloroform under argon, then 38 µl titanium(IV)-isopropoxide and 47 µl water are added. The reaction mixture is stirred for 1 hour at ambient temperature. Then a mixture of 480 mg (**III-9**) in 6 ml chloroform is added. The reaction mixture is cooled to -5°C and after 60 minutes 232 µl *tert*-butylhydroperoxide 5-6 M in decane are added dropwise. The reaction mixture is stirred for 24 h at -5°C and then combined with water and made basic with NH₄OH. The organic phase is evaporated to dryness and the product is purified by chromatography (silica gel, ethyl acetate/methanol + 1% NH₄OH). 460 mg (**IV-9**) are obtained as a mixture of diastereomers.

Analytical HPLC-MS (method B): RT = 1.23 and 1.24 min.

58.7 Synthesis of tert-butyl (2-{2-[4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-ylamino}-cyclopropyl)-carbamate (**Example 222**)

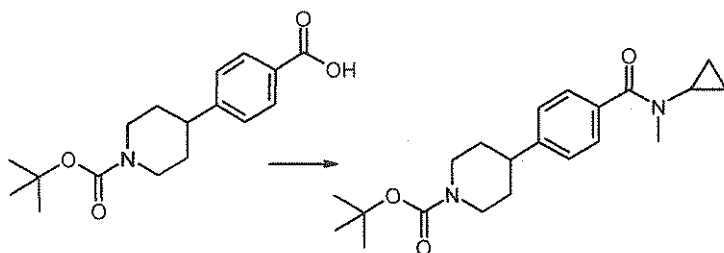


380 mg (**IV-9**) and 266 mg 4-(4-chlorophenyl)-piperidine hydrochloride are placed in 3 ml dioxane, combined with 570 μ l diisopropylethylamine and heated in the microwave for 25 min at 120°C. The reaction mixture is combined with ice water and the product is extracted with dichloromethane. The organic phase is evaporated to dryness and the residue is treated with water in the ultrasound bath. The precipitated solid is suction filtered, washed with water and dried. 485 mg product are obtained as a mixture of diastereomers.

Analytical HPLC-MS (method B): RT = 1.46 min. Chiral HPLC (column: Diacel ADS-H, 250 x 4.6 mm, 5 μ m, eluant: (hexane+diethylamine (0.2%)/isopropanol (75/25), 10°C, flow rate: 1 ml/min): RT = 11.5 min and RT = 13.7 min.

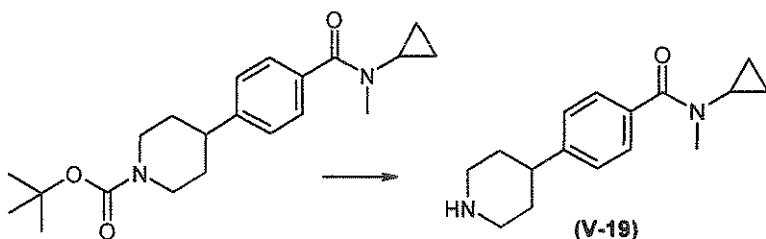
59. SYNTHESIS OF: N-CYCLOPROPYL-N-METHYL-4-{1-[5-OXO-4-(TETRAHYDRO PYRAN-4-YLAMINO)-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-2-YL]-PIPERIDIN-4-YL}-BENZAMIDE (**EXAMPLE 229**)

59.1 tert-butyl 4-[4-(cyclopropylmethylcarbamoyl)-phenyl]-piperidine-1-carboxylate:



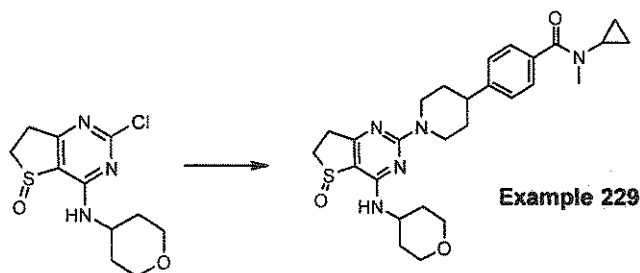
500 mg tert-butyl 4-(4-carboxyphenyl)-piperidine-1-carboxylate are placed in 28 ml dimethylformamide, then 1.14 ml diisopropylethylamine and 747 mg HATU are added. The reaction mixture is stirred for 15 min at ambient temperature, then 194 mg cyclopropylmethylamin hydrochloride are added. The reaction mixture is stirred overnight at ambient temperature. Then the product is purified by preparative HPLC (method A). 480 mg product are obtained as an oil. Analytical HPLC-MS (method B): RT = 1.64 min.

59.2 N-cyclopropyl-N-methyl-4-piperidin-4-yl-benzamide (**V-19**):



480 mg tert-butyl 4-[4-(cyclopropylmethylcarbamoyl)-phenyl]-piperidine-1-carboxylate are placed in 7.8 ml dichloromethane and combined with 1.09 ml trifluoroacetic acid. The reaction mixture is stirred for 1.5 h at ambient temperature and then evaporated to dryness. The residue is combined with toluene and evaporated to dryness again. 444 mg (**V-19**) are obtained as the trifluoroacetate. Analytical HPLC-MS (method B): RT = 1.11 min.

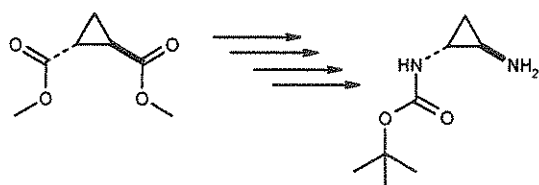
59.3 N-cyclopropyl-N-methyl-4-{1-[5-oxo-4-(tetrahydropyran-4-ylamino)-6,7-dihydro-5H-5λ⁴-thieno[3,2-d]pyrimidin-2-yl]-piperidin-4-yl}-benzamide (**Example 229**)



Starting from (IV-6) (see 6.2) and (V-19) **Example 229** may be prepared and purified analogously to **Example 89** (see 21). Analytical HPLC-MS (method D): RT = 1.05 min.

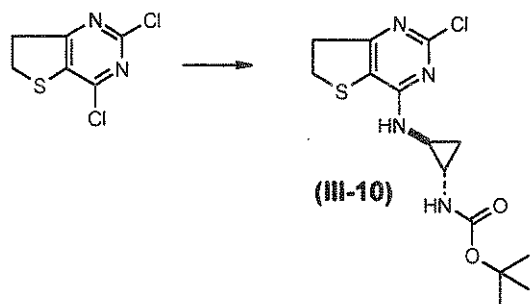
60. SYNTHESIS OF *tert*-BUTYL (2-{2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5λ⁴-THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-CYCLOPROPYL)-CARBAMIDATE (**EXAMPLE 231**)

60.1 *trans*-N-*tert*-butyloxycarbonyl-1,2-cyclopropanediamine:



Starting from dimethyl *trans*-1,2-cyclopropanedicarboxylate, *trans*-N-*tert*-butyloxycarbonyl-1,2-cyclopropanediamin hydrochloride may be prepared and purified analogously to *cis*-N-*tert*-butyloxycarbonyl-1,2-cyclopropanediamin hydrochloride (see 58.4). M.p: 200-202°C.

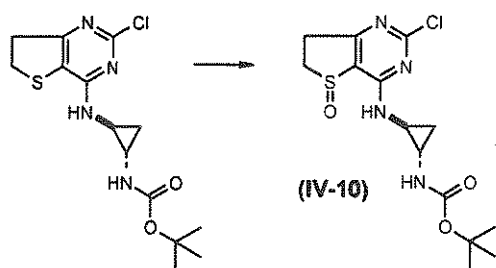
60.2 *tert*-butyl [2-(2-chloro-6,7-dihydrothieno[3,2-*d*]pyrimidin-4-ylamino)-cyclopropyl]-carbamidate (**III-10**):



Starting from (II) and *trans*-N-*tert*-butyloxycarbonyl-1,2-cyclopropanediamin hydrochloride (**III-10**) may be prepared and purified analogously to **Example (III-9)** (see 58.5).

Analytical HPLC-MS (method B): RT = 1.46 min.

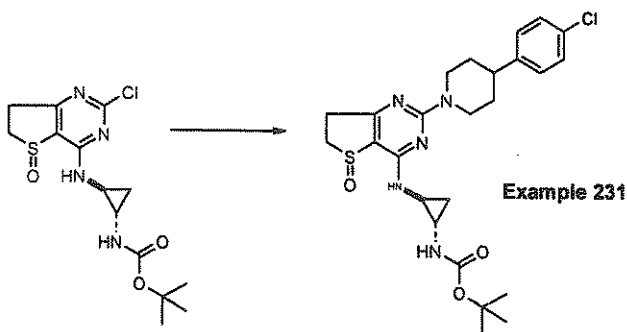
60.3 tert-butyl 2-(2-chloro-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-ylamino)-cyclopropyl]-carbamate (**IV-10**):



Starting from (**III-10**) (**IV-10**) is prepared and purified as a mixture of diastereomers analogously to Example (**IV-9**).

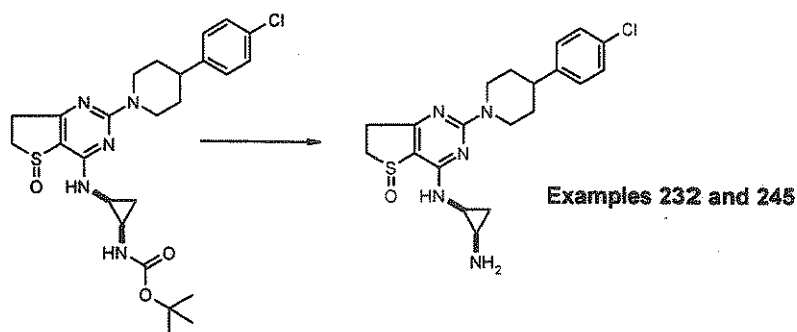
Analytical HPLC-MS (method B): RT = 1.27 min. Chiral HPLC (column: Diacel ADS-H, 250 x 4.6 mm, 5 μ m, eluant: ((9/1) hexane+diethylamine (0.2%)/methanol/ethanol (1/1), 10°C, flow rate: 1 ml/min): RT = 6.7 min and RT = 8.3 min.

60.4 tert-butyl (2-{2-[4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-ylamino}-cyclopropyl)-carbamate (**Example 231**)



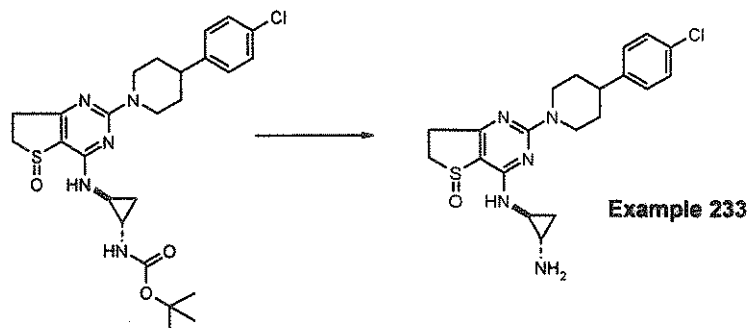
Starting from (**IV-10**) **Example 231** is prepared and purified as a mixture of diastereoisomers analogously to **Example 222** (see 58.7). Analytical HPLC-MS (method B): RT = 1.48 min. Chiral HPLC (column: Diacel ADS-H, 250 x 4.6 mm, 5 μ m, eluant: (hexane+diethylamine (0.2%)/isopropanol (8/2), 10°C, flow rate: 1 ml/min): RT = 15.17 min and RT = 18.1 min.

61. SYNTHESIS OF: N-{2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YL}-CYCLOPROPAN-1,2-DIAMINE (**EXAMPLEE 232 AND 245**)



150 mg of **Example 222** (see 58.7) are placed in 0.5 ml dichloromethane and 0.25 ml trifluoroacetic acid are added. The reaction mixture is stirred for 1 h in the ice bath and 2 h at ambient temperature, then cooled in the ice bath, mixed with water and made basic with conc. Ammonia. The product is extracted with dichloromethane and purified by chromatography (preparative HPLC, method B). 57 mg of **Example 232** and 27 mg of **Example 245** are obtained. Analytical HPLC-MS (method E): RT = 2.73 min (**Example 232**); RT = 2.85 min (**Example 245**).

62. SYNTHESIS OF: N-{2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5λ⁴-THIENO[3,2-d]PYRIMIDIN-4-YL}-CYCLOPROPAN-1,2-DIAMINE

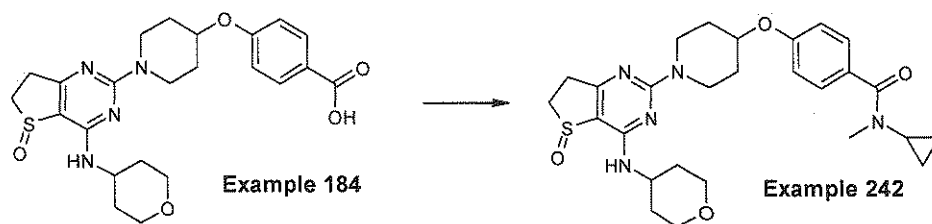


(EXAMPLE 233)

Starting from **Example 231** (see 60.4) **Example 233** is prepared and purified as a mixture of diastereomers analogously to **Examples 232/245** (see 61.).

Analytical HPLC-MS (method B): RT = 1.24 min.

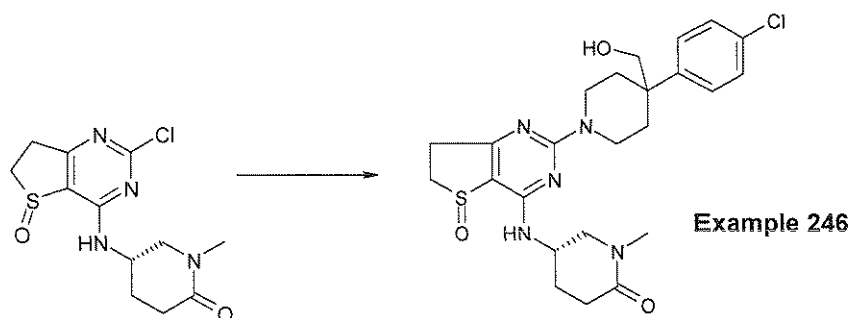
62. SYNTHESIS OF: N-CYCLOPROPYL-N-METHYL-4-{1-[5-OXO-4-(TETRAHYDROPYRAN-4-YLAMINO)-6,7-DIHYDRO-5H-5λ⁴-THIENO[3,2-d]PYRIMIDIN-2-YL]-PIPERIDIN-4-YLOXY}-BENZAMIDE (**EXAMPLE 242**)



55 mg of **Example 184** (see 40.) are placed in 2 ml dimethylformamide, then 81 μ l diisopropylethylamine and 53.1 mg O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) are added. After 15 min 13.8 mg cyclopropylmethylamine hydrochloride are added. The reaction mixture is stirred at ambient temperature until there is no further reaction and the product is purified directly by preparative HPLC (method B). 30 mg of **Example 242** are obtained as a solid.

Analytical HPLC-MS (method D): RT = 1.03 min.

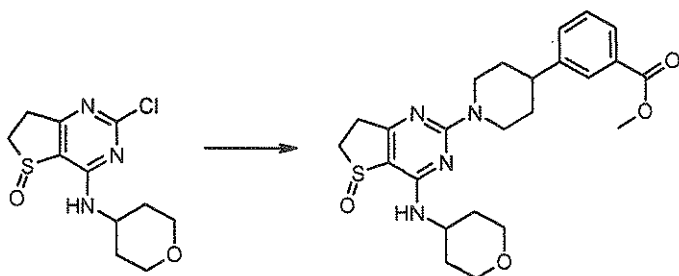
63. SYNTHESIS OF: 5-{2-[4-(4-CHLOROPHENYL)-4-HYDROXYMETHYLPIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-1-METHYLPIPERIDIN-2-ONE (**EXAMPLE 246**)



Starting from (**IV-5**) (see 5.5) and [4-(4-chlorophenyl)-piperidin-4-yl]-methanol (see *J. Med. Chem.* **2004**, 497) **Example 246** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.21 min.

64. SYNTHESIS OF: N-CYCLOPROPYL-N-METHYL-3-{1-[5-OXO-4-(TETRAHYDRO PYRAN-4-YLAMINO)-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL]-PIPERIDIN-4-YL}-BENZAMIDE (**EXAMPLE 249**)

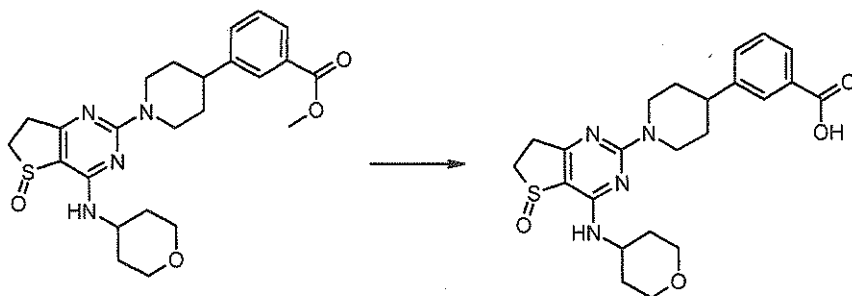
64.1 methyl 3-{1-[5-oxo-4-(tetrahydropyran-4-ylamino)-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-2-yl]-piperidin-4-yl}-benzoate:



Starting from (IV-6) (see 6.2) and methyl 3-piperidin-4-yl-benzoate hydrochloride the product may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method D): RT = 1.15 min.

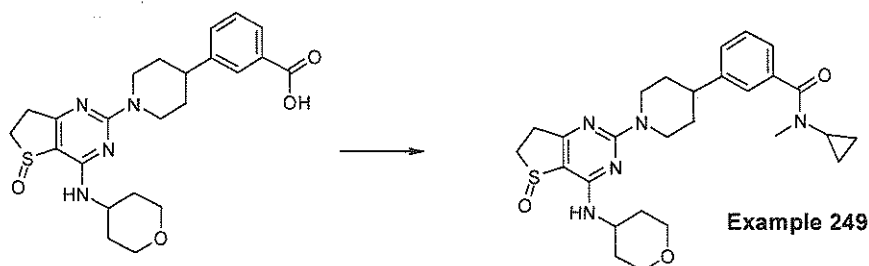
64.2 3-{1-[5-oxo-4-(tetrahydropyran-4-ylamino)-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-2-yl]-piperidin-4-yl}-benzoic acid:



1.3 g methyl 3-{1-[5-oxo-4-(tetrahydropyran-4-ylamino)-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-2-yl]-piperidin-4-yl}-benzoate are placed in 24.6 ml of methanol, then 9.2 ml of a 1 N NaOH solution are added. The reaction mixture is stirred at ambient temperature until there is no further reaction, then combined with a 1 N HCl solution. The methanol is spun off and the precipitated solid is suction filtered. The product is purified by preparative HPLC (method B). 760 mg product are obtained as a solid.

Analytical HPLC-MS (method D): RT = 0.80 min.

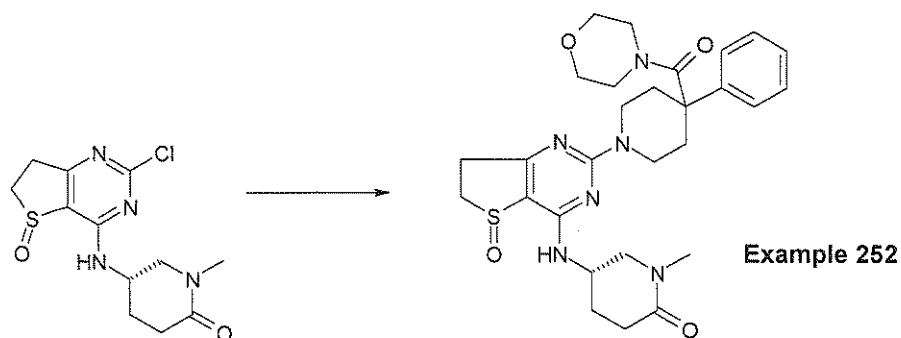
64.3 N-cyclopropyl-N-methyl-3-{1-[5-oxo-4-(tetrahydropyran-4-ylamino)-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-2-yl]-piperidin-4-yl}-benzamide (**Example 249**)



59.8 mg 3-{1-[5-oxo-4-(tetrahydropyran-4-ylamino)-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-2-yl]-piperidin-4-yl}-benzoic acid are placed in 2.3 ml dimethylformamide, then 91 μ l diisopropylethylamine and 60 mg O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) are added. After 15 min a mixture of 15.5 mg cyclopropylmethylamine hydrochloride in 300 μ l dimethylformamide is added. The reaction mixture is stirred at ambient temperature until there is no further reaction, and the product is purified directly by preparative HPLC (method B). 50 mg **Example 249** are obtained as a solid. Analytical HPLC-MS (method D): RT = 1.05 min.

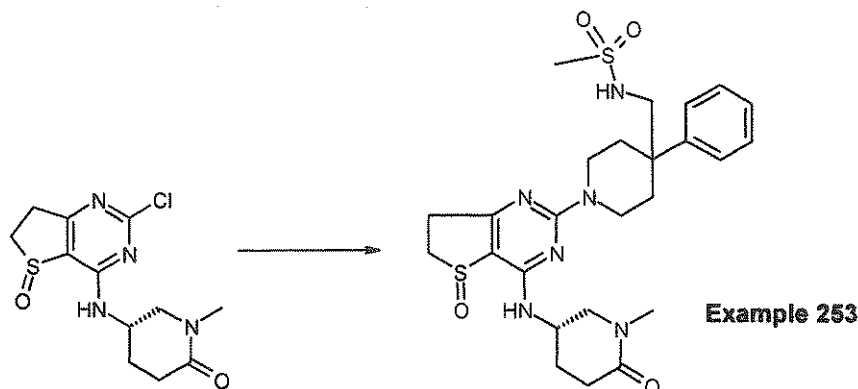
65. SYNTHESIS OF: 1-METHYL-5-{2-[4-(MORPHOLINE-4-CARBONYL)-4-PHENYL

PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-PIPERIDIN-2-ONE (**EXAMPLE 252**)



Starting from (**IV-5**) (see 5.5) and morpholin-4-yl-(4-phenylpiperidin-4-yl)-methanone (see *bioorg. Med. Chem. Lett.* **1997**, 2531) **Example 252** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.18 min.

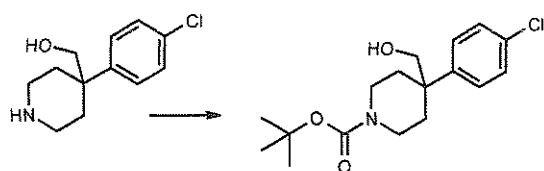
66. SYNTHESIS OF: N-{1-[4-(1-METHYL-6-OXO-PIPERIDIN-3-YLAMINO)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL]-4-PHENYLPYPERIDIN-4-YLMETHYL}-METHANESULPHONAMIDE (**EXAMPLE 253**)



Starting from (IV-5) (see 5.5) and N-(4-phenylpiperidin-4-ylmethyl)-methanesulphonamide (see *Bioorg. Med. Chem. Lett.*, **1998**, 1851) **Example 253** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.15 min.

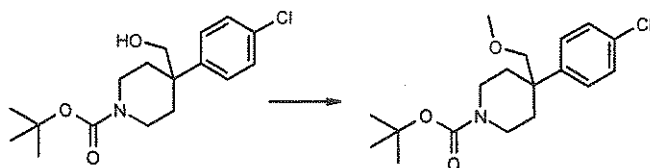
67. SYNTHESIS OF: 5-{2-[4-(4-CHLOROPHENYL)-4-METHOXYMETHYLPYPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-1-METHYLPYPERIDIN-2-ONE (**EXAMPLE 260**)

67.1 tert-butyl 4-(4-chlorophenyl)-4-hydroxymethylpiperidine-1-carboxylate:



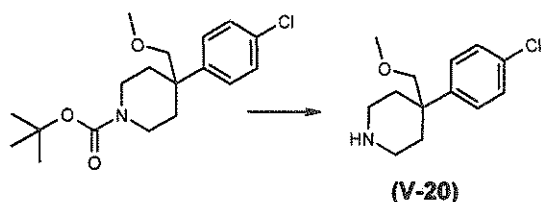
300 mg [4-(4-chlorophenyl)-piperidin-4-yl]-methanol (see *J. Med. Chem.* **2004**, 497) are placed in 3 ml dioxane, then 0.5 ml of water and 0.224 g sodium carbonate are added. After 5 min 300 mg di-tert-butyl-dicarbonate are added. The reaction mixture is stirred for 3 h at ambient temperature, then mixed with water and the product is extracted with dichloromethane.. 440 mg product are obtained as an oil. Analytical HPLC-MS (method B): RT = 1.65 min.

67.2 tert-butyl 4-(4-chlorophenyl)-4-methoxymethylpiperidine-1-carboxylate:



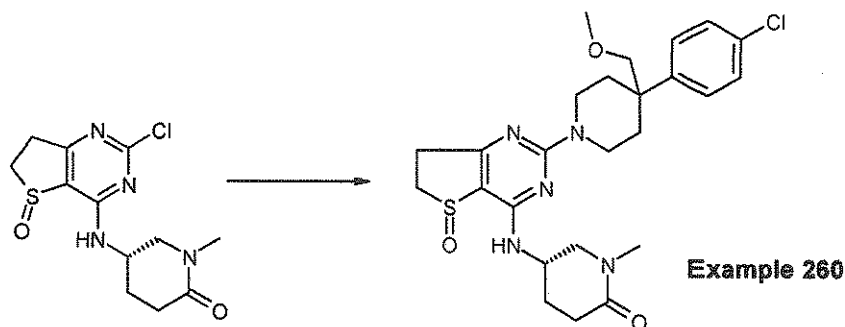
440 mg tert-butyl 4-(4-chlorophenyl)-4-hydroxymethylpiperidine-1-carboxylate are placed in 2.5 ml dimethylformamide and 92 mg sodium hydride (60% in mineral oil) are added. The reaction mixture is stirred for 30 min at ambient temperature, then 95 μ l methyl iodide are added. After 1 h the reaction mixture is poured onto ice and the product is extracted with diethyl ether. 370 mg product are obtained as an oil.

Analytical HPLC-MS (method B): RT = 1.87 min.

67.3 4-(4-chlorophenyl)-4-methoxymethylpiperidine (**V-20**):

370 mg tert-butyl 4-(4-chlorophenyl)-4-methoxymethylpiperidine-1-carboxylate are placed in 1.5 ml dichloromethane, then 0.8 ml trifluoroacetic acid are added. The reaction mixture is stirred overnight at ambient temperature and evaporated to dryness. The residue is combined with toluene and evaporated to dryness again. The residue is triturated with diethyl ether and the solid is suction filtered. 284 mg (**V-20**) are obtained as the trifluoroacetate. Analytical HPLC-MS (method B): RT = 1.23 min.

67.4 5-{2-[4-(4-chlorophenyl)-4-methoxymethylpiperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-ylamino}-1-methylpiperidin-2-one (**Example 260**)



Starting from (IV-5) (see 5.5) and (V-20) **Example 260** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.30 min.

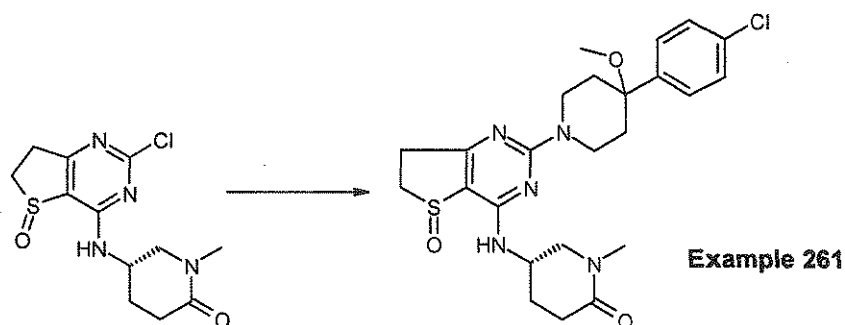
68. SYNTHESIS OF: 5-{2-[4-(4-CHLOROPHENYL)-4-METHOXYPIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-1-METHYLPYPERIDIN-2-ONE (**EXAMPLE 261**)

68.1 4-(4-chlorophenyl)-4-methoxypiperidine (**V-21**):



Starting from 4-(4-chlorophenyl)-piperidin-4-ol (**V-21**) may be prepared analogously to (V-20) (see 67.1 to 67.3). Analytical HPLC-MS (method B): RT = 1.22 min.

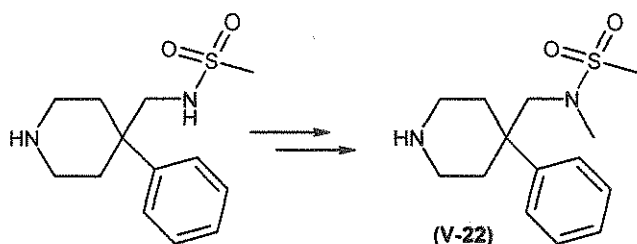
68.2 5-{2-[4-(4-chlorophenyl)-4-methoxypiperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-4-ylamino}-1-methylpiperidin-2-one (**Example 261**)



Starting from (IV-5) (see 5.5) and (V-21) **Example 261** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.30 min.

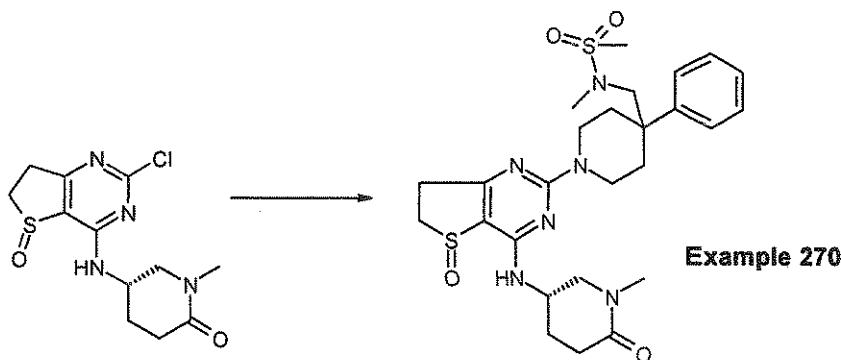
69. SYNTHESIS OF: N-METHYL-N-{1-[4-(1-METHYL-6-OXO-PIPERIDIN-3-YLAMINO)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL]-4-PHENYLPYPERIDIN-4-YLMETHYL}-METHANESULPHONAMIDE (**EXAMPLE 270**)

69.1 N-methyl-N-(4-phenylpiperidin-4-ylmethyl)-methanesulphonamide (**V-22**):



Starting from N-(4-phenylpiperidin-4-ylmethyl)-methanesulphonamide (see *Bioorg. Med. Chem. Lett.*, **1998**, 1851) (**V-22**) may be prepared analogously to (**V-20**) (see 67.1 to 67.3). Analytical HPLC-MS (method B): RT = 1.10 min.

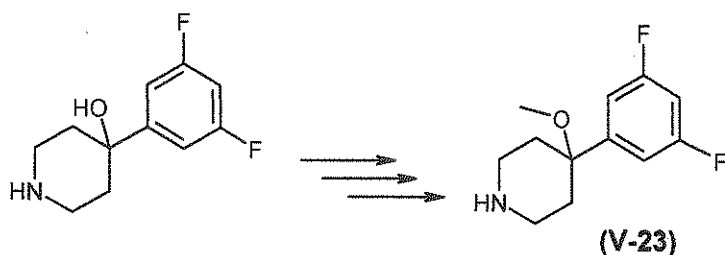
69.2 N-methyl-N-{1-[4-(1-methyl-6-oxo-piperidin-3-ylamino)-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-2-yl]-4-phenylpiperidin-4-ylmethyl}-methanesulphonamide (**Example 270**)



Starting from (IV-5) (see 5.5) and (**V-22**) **Example 270** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.21 min.

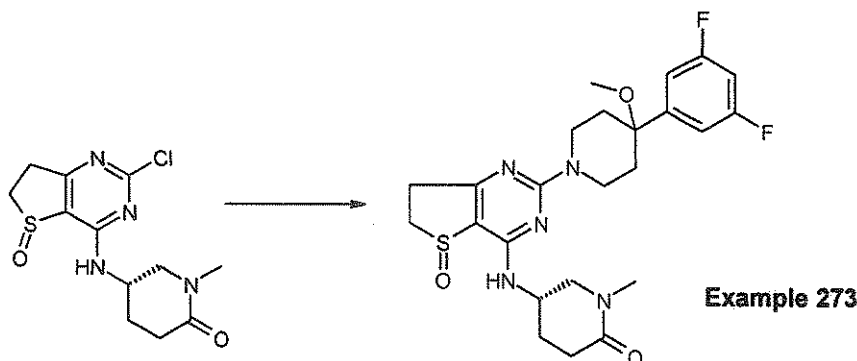
70. SYNTHESIS OF: 5-{2-[4-(3,5-DIFLUOROPHENYL)-4-METHOXYPIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-1-METHYL PIPERIDIN-2-ONE (EXAMPLE 273)

70.1 4-(3,5-difluorophenyl)-4-methoxypiperidine (V-23):



Starting from 4-(3,5-difluorophenyl)-piperidin-4-ol hydrochloride (V-23) may be prepared analogously to (V-20) (see 67.1 to 67.3). Analytical HPLC-MS (method B): RT = 1.10 min.

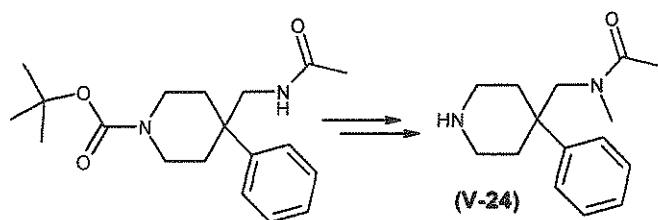
70.2 5-{2-[4-(3,5-difluorophenyl)-4-methoxypiperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-4-ylamino}-1-methylpiperidin-2-one (Example 273)



Starting from (IV-5) (see 5.5) and (V-23) Example 273 may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.23 min.

71. SYNTHESIS OF: N-METHYL-N-{1-[4-(1-METHYL-6-OXO-PIPERIDIN-3-YLAMINO)-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL]-4-PHENYLPYPERIDIN-4-YLMETHYL}-ACETAMIDE (EXAMPLE 274)

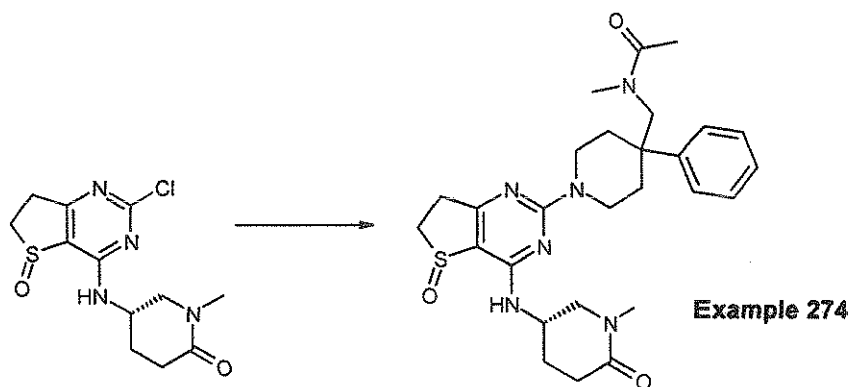
71.1 N-methyl-N-(4-phenylpiperidin-4-ylmethyl)-acetamide (V-24):



Starting from tert-butyl 4-(acetylaminoethyl)-4-phenylpiperidine-1-carboxylate (see 52.1) **(V-24)** may be prepared analogously to **(V-20)** (see 67.2 and 67.3).

Analytical HPLC-MS (method B): RT = 1.12 min.

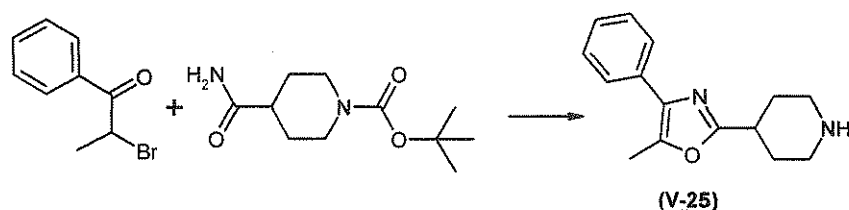
71.2 N-methyl-N-{1-[4-(1-methyl-6-oxo-piperidin-3-ylamino)-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-2-yl]-4-phenylpiperidin-4-ylmethyl}-acetamide (**EXAMPLE 274**)



Starting from **(IV-5)** (see 5.5) and **(V-24)** **Example 274** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method D): RT = 1.19 min.

72. SYNTHESIS OF: 1-METHYL-5-{2-[4-(5-METHYL-4-PHENYL-OXAZOL-2-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YLAMINO}-PIPERIDIN-2-ONE (**EXAMPLE 275**)

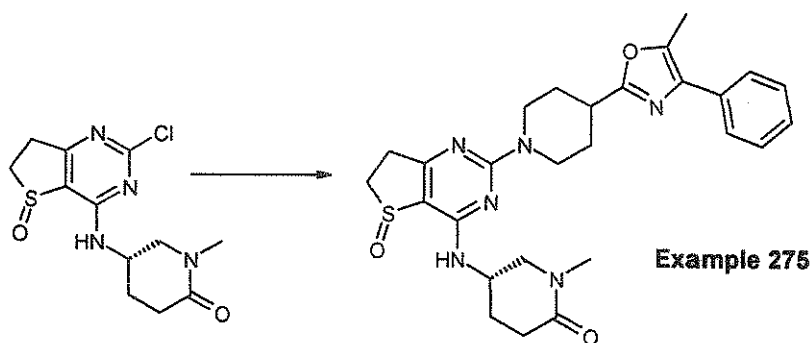
72.1 4-(5-methyl-4-phenyloxazol-2-yl)-piperidine **(V-25)**:



1.75 g 2-bromo-1-phenylpropan-1-one and 1.87 g tert-butyl 4-carbamoylpiperidine-1-carboxylate are placed in 0.5 ml NMP. The reaction mixture is heated to 160°C for 20 min in the microwave and for 35 min in the oil bath, then after cooling it is taken up in methanol and evaporated to dryness. The residue is mixed with water, treated in the ultrasound bath and the insoluble oil is suction filtered. The mother liquor is purified by preparative HPLC (method C). 160 mg (**V-25**) are obtained as the trifluoroacetate.

Analytical HPLC-MS (method B): RT = 1.24 min.

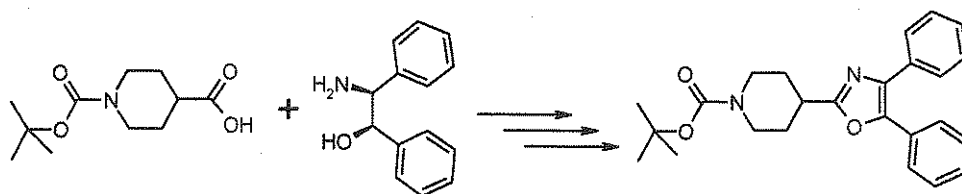
72.2 1-methyl-5-{2-[4-(5-methyl-4-phenyloxazol-2-yl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-d]pyrimidin-4-ylamino}-piperidin-2-one (**Example 275**)



Starting from (**IV-5**) (see 5.5) and (**V-21**) **Example 275** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method D): RT = 1.08 min.

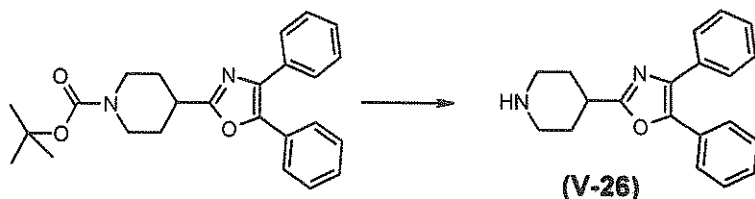
73. SYNTHESIS OF: 5-{2-[4-(4,5-DIPHENYLOXAZOL-2-YL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-d]PYRIMIDIN-4-YLAMINO}-1-METHYLPYPERIDIN-2-ONE (**EXAMPLE 278**)

73.1 tert-butyl 4-(4,5-diphenyloxazol-2-yl)-piperidine-1-carboxylate



Starting from 1.08 g mono-tert-butyl piperidine-1,4-dicarboxylate and 1 g 2-amino-1,2-diphenyl-ethanol the product may be obtained as described in the literature (see *Tet.* **2001**, 4867). The product is purified by chromatography (method B). 560 mg are obtained as an oil. Analytical HPLC-MS (method A): RT = 1.72 min.

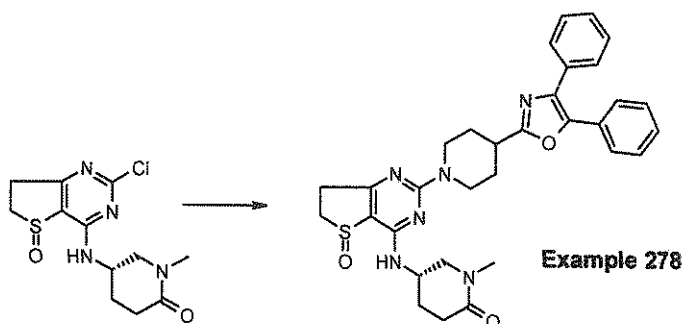
73.2 4-(4,5-diphenyloxazol-2-yl)-piperidine (**V-26**)



560 mg tert-butyl 4-(4,5-diphenyloxazol-2-yl)-piperidine-1-carboxylate are placed in 2 ml dichloromethane, then 1.1 ml trifluoroacetic acid are added. The reaction mixture is stirred for 15 hours at ambient temperature, then evaporated to dryness. The residue is combined with toluene and evaporated to dryness again. The residue is combined with diethyl ether and the precipitated solid is suction filtered and dried. 510 mg **(V-26)** are obtained.

Analytical HPLC-MS (method B): RT = 1.38 min.

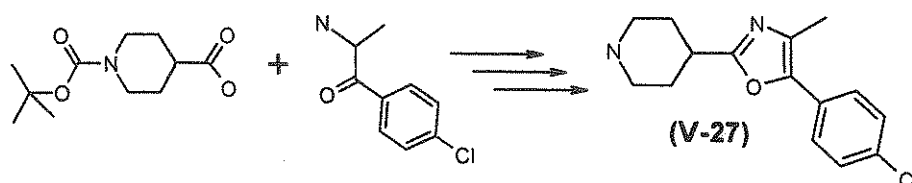
73.3 5-{2-[4-(4,5-diphenyloxazol-2-yl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5λ⁴-thieno[3,2-d]pyrimidin-4-ylamino}-1-methylpiperidin-2-one (**Example 278**)



Starting from **(IV-5)** (see 5.5) and **(V-26)** **Example 278** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.40 min.

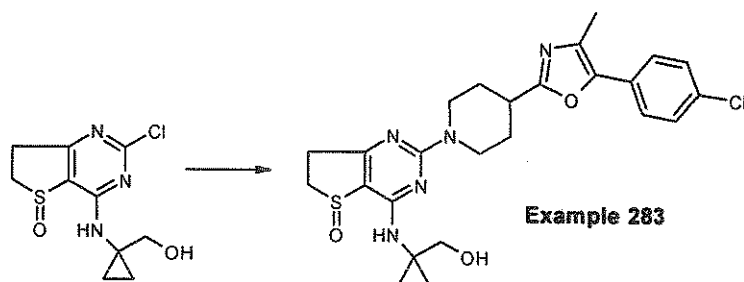
74. SYNTHESIS OF: [1-(2-{4-[5-(4-CHLOROPHENYL)-4-METHYLOXAZOL-2-YL]-PIPERIDIN-1-YL}-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO)-CYCLOPROPYL]-METHANOL (**EXAMPLE 283**)

74.1 4-[5-(4-chlorophenyl)-4-methyloxazol-2-yl]-piperidine (**V-27**):



Starting from mono-tert-butyl piperidine-1,4-dicarboxylate and 2-amino-1-(4-chlorophenyl)-propane-1-one (see *J. Med. Chem.* **1974**, 416) (**V-27**) may be prepared analogously to (V-26) (see 73.1 and 73.2). Analytical HPLC-MS (method B): RT = 1.30 min.

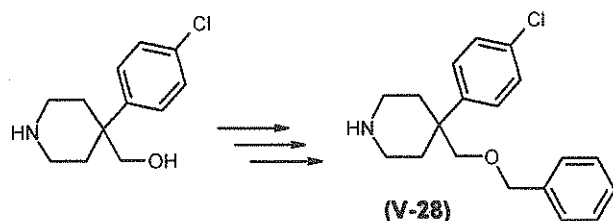
74.2 [1-(2-{4-[5-(4-chlorophenyl)-4-methyloxazol-2-yl]-piperidin-1-yl}-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-4-ylamino)-cyclopropyl]-methanol (**Example 283**)



Starting from (IV-2) (see 2.4) and (V-27) **Example 283** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.37 min.

75. SYNTHESIS OF: {2-[4-BENZYLOXYMETHYL-4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5-OXO-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YL}-(3-FLUOROPHENYL)-AMINE (**EXAMPLE 306**)

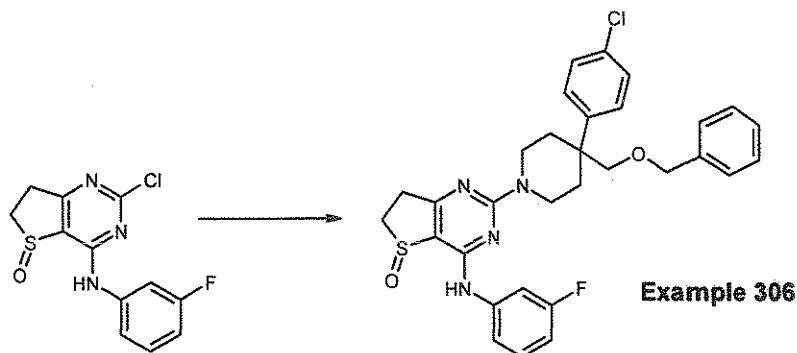
75.1 4-benzyloxymethyl-4-(4-chlorophenyl)-piperidine (**V-28**):



Starting from [4-(4-chlorophenyl)-piperidin-4-yl]-methanol (see *J. Med. Chem.* **2004**, 497) **(V-28)** may be prepared analogously to **(V-20)** (see 67.1 to 67.3).

Analytical HPLC-MS (method B): RT = 1.43 min

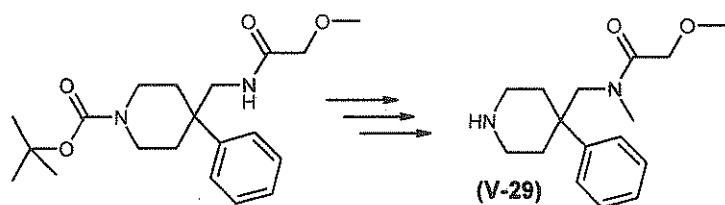
75.2 {2-[4-benzyloxymethyl-4-(4-chlorophenyl)-piperidin-1-yl]-5-oxo-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-4-yl}-(3-fluorophenyl)-amine (**Example 306**)



Starting from **(IV-7)** (see 17.2) and **(V-28)** **Example 306** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.75 min.

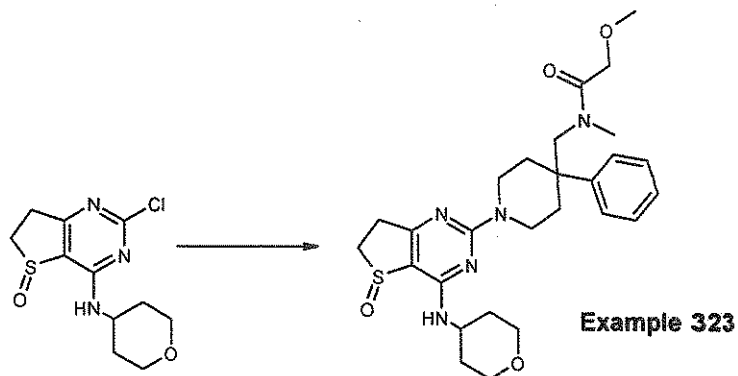
76. SYNTHESIS OF: 2-METHOXY-N-METHYL-N-{1-[5-OXO-4-(TETRAHYDROPYRAN-4-YLAMINO)-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-2-YL]-4-PHENYLPYPERIDIN-4-YLMETHYL}-ACETAMIDE (**EXAMPLE 323**)

76.1 4-benzyloxymethyl-4-(4-chlorophenyl)-piperidine **(V-29)**:



Starting from tert-butyl 4-[(2-methoxyacetyl-amino)-methyl]-4-phenylpiperidine-1-carboxylate (see 50.1) (**V-28**) may be prepared analogously to (**V-20**) (see 67.2 to 67.3).

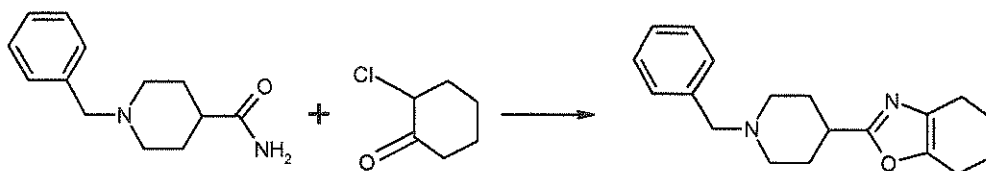
76.2 2-methoxy-N-methyl-N-{1-[5-oxo-4-(tetrahydropyran-4-ylamino)-6,7-dihydro-5H-5 λ^4 -thieno[3,2-*d*]pyrimidin-2-yl]-4-phenylpiperidin-4-ylmethyl}-acetamide
(**Example 323**)



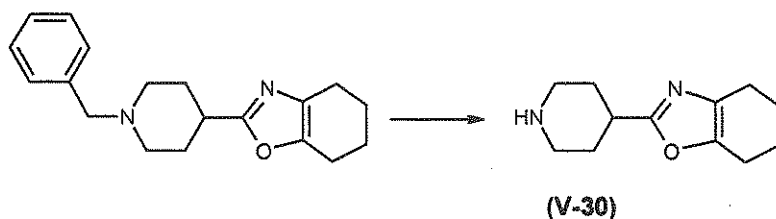
Starting from (**IV-6**) (see 6.2) and (**V-29**) **Example 323** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.24 min.

77. SYNTHESIS OF: 5-OXO-2-[4-(4,5,6,7-TETRAHYDROBENZOXAZOL-2-YL)-PIPERIDIN-1-YL]-6,7-DIHYDRO-5H-5 λ^4 -THIENO[3,2-*d*]PYRIMIDIN-4-YL}-
(TETRAHYDRO
PYRAN-4-YL)-AMINE (**EXAMPLE 329**)

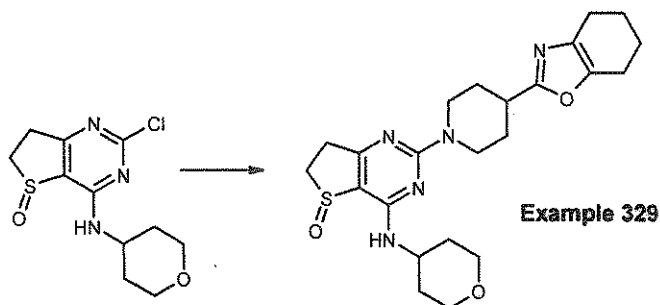
77.1 2-(1-benzylpiperidin-4-yl)-4,5,6,7-tetrahydrobenzoxazole:



A mixture of 2.43 g 2-chlorocyclohexanone and 1g 1-benzylpiperidine-4-carboxylic acid amide (see WO2005/61483) is heated to 160°C in the microwave until there is no further reaction. The product is purified by chromatography. 963 mg of the product are obtained. Analytical HPLC-MS (method B): RT = 1.28 min.

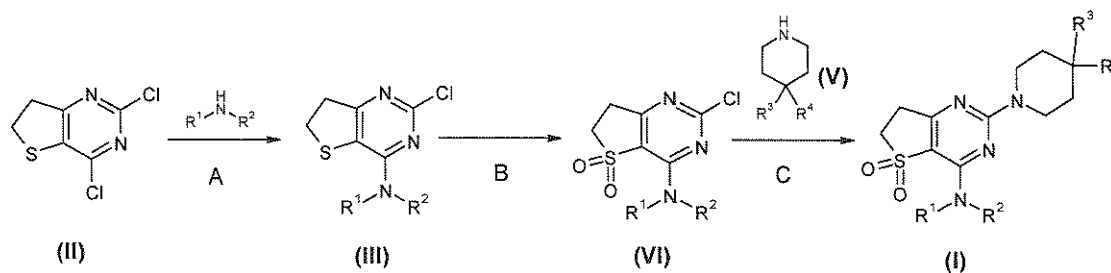
77.2 2-(1-benzyl-piperidin-4-yl)-4,5,6,7-tetrahydrobenzoxazole (**V-30**):

903 mg 2-(1-benzyl-piperidin-4-yl)-4,5,6,7-tetrahydrobenzoxazole are placed in 20 ml of methanol and hydrogenated with 450 mg Pd/C 10% at a pressure of 3 bar and at ambient temperature. After 12 hours the catalyst is suction filtered and the filtrate is evaporated to dryness. The product is purified by chromatography. 469 mg **(V-30)** are obtained as the trifluoroacetate. Analytical HPLC-MS (method B): RT = 1.09 min.

77.3 5-oxo-2-[4-(4,5,6,7-tetrahydrobenzoxazol-2-yl)-piperidin-1-yl]-6,7-dihydro-5H-5λ⁴-thieno[3,2-d]pyrimidin-4-yl)-(tetrahydropyran-4-yl)-amine (**Example 329**)

Starting from **(IV-2)** (see 2.4) and **(V-30)** **Example 329** may be prepared and purified analogously to Example 89 (see 21.). Analytical HPLC-MS (method B): RT = 1.23 min.

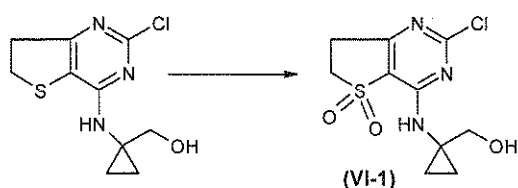
Synthesis Scheme 2



For the preparation of
(II) see WO06111549

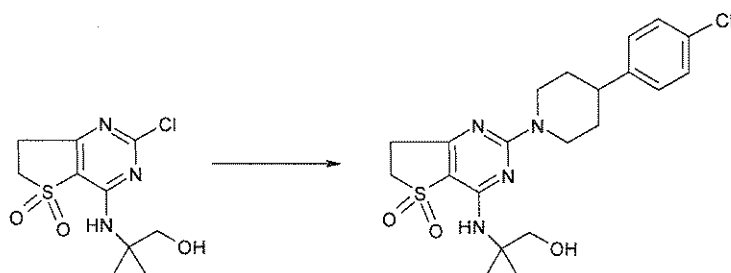
78. SYNTHESIS OF: (1-{2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5.5-DIOXO-6,7-DIHYDRO-5H-5 λ^6 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-CYCLOPROPYL)-METHANOL (**Example 333**)

78.1 [1-(2-chloro-5.5-dioxo-6,7-dihydro-5H-5 λ^6 -thieno[3,2-*d*]pyrimidin-4-ylamino)-cyclopropyl]-methanol (**VI-1**):



200 mg (**III-2**) (see 2.2) are placed in 3 ml trifluoroacetic acid, then 180 μ l hydrogen peroxide (35%) are slowly added dropwise. An exothermic reaction takes place. The reaction mixture is stirred for 12 hours at ambient temperature, then combined with ice water and made basic with NH_4OH . The precipitated solid is suction filtered and dried. 80 mg (**VI-1**) are obtained. Analytical HPLC-MS (method B): RT = 1.1 min.

78.2 (1-{2-[4-(4-chlorophenyl)-piperidin-1-yl]-5.5-dioxo-6,7-dihydro-5H-5 λ^6 -thieno[3,2-*d*]pyrimidin-4-ylamino}-cyclopropyl)-methanol (**Example 333**)

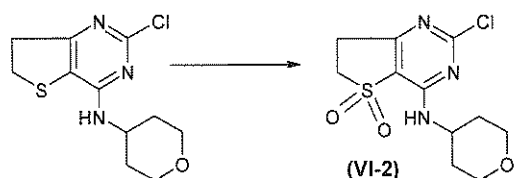


Starting from (VI-1) and 4-(4-chlorophenyl)-piperidine hydrochloride **Example 333** may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method B): RT = 1.49 min.

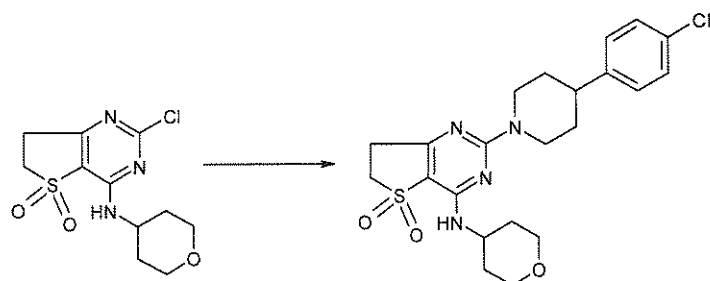
79. SYNTHESIS OF: {2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5,5-DIOXO-6,7-DIHYDRO-5H-5 λ^6 -THIENO[3,2-*d*]PYRIMIDINE -4-YL}-(TETRAHYDROPYRAN-4-YL)-AMINE (**Example 334**)

79.1 (2-chloro-5,5-dioxo-6,7-dihydro-5H-5 λ^6 -thieno[3,2-*d*]pyrimidin-4-yl)-(tetrahydropyran-4-yl)-amine (**VI-2**):



200 mg (**III-2**) (see 2.2) are placed in 3 ml trifluoroacetic acid, then 180 μ l hydrogen peroxide (35%) is slowly added dropwise. An exothermic reaction takes place. The reaction mixture is stirred for 12 hours at ambient temperature, then combined with ice water and made basic with NH₄OH. The precipitated solid is suction filtered and dried. 170 mg (**VI-2**) are obtained as a solid.

79.2 {2-[4-(4-chlorophenyl)-piperidin-1-yl]-5,5-dioxo-6,7-dihydro-5H-5 λ^6 -thieno[3,2-*d*]pyrimidin-4-yl}-(tetrahydropyran-4-yl)-amine (**Example 334**)

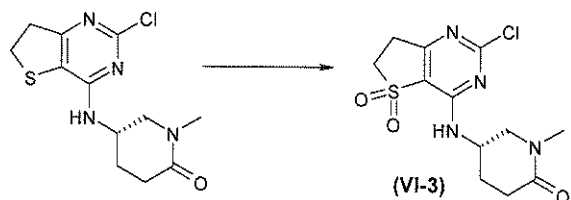


Starting from (**VI-2**) and 4-(4-chlorophenyl)-piperidine hydrochloride **Example 334** may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method B): RT = 1.55 min.

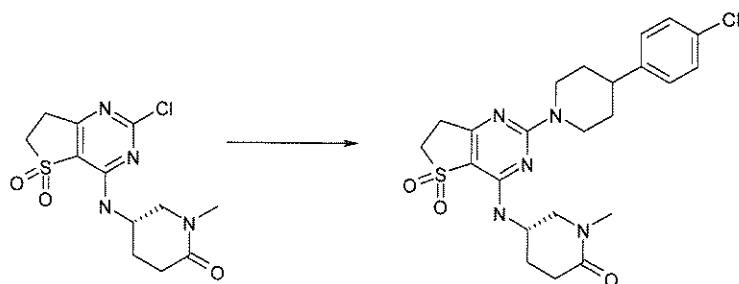
80. SYNTHESIS OF: 5-{2-[4-(4-CHLOROPHENYL)-PIPERIDIN-1-YL]-5,5-DIOXO-6,7-DIHYDRO-5H-5 λ^6 -THIENO[3,2-*d*]PYRIMIDIN-4-YLAMINO}-1-METHYLPYPERIDIN-2-ONE (**Example 335**)

80.1 5-(2-chloro-5,5-dioxo-6,7-dihydro-5H-5 λ^6 -thieno[3,2-*d*]pyrimidin-4-ylamino)-1-methylpiperidin-2-one (**VI-3**):



200 mg (**III-5**) (see 5.4) are placed in 3 ml trifluoroacetic acid, then 165 μ l hydrogen peroxide (35%) are slowly added dropwise. An exothermic reaction takes place. The reaction mixture is stirred for 12 hours at ambient temperature, then combined with ice water and made basic with NH_4OH . The product is extracted with dichloromethane. 150 mg (**VI-3**) are obtained as a solid.

80.2 5-{2-[4-(4-chlorophenyl)-piperidin-1-yl]-5,5-dioxo-6,7-dihydro-5H-5 λ^6 -thieno[3,2-*d*]pyrimidin-4-ylamino}-1-methylpiperidin-2-one (**Example 335**)



Starting from (**VI-3**) and 4-(4-chlorophenyl)-piperidine hydrochloride **Example 335** may be prepared and purified analogously to Example 89 (see 21.).

Analytical HPLC-MS (method B): RT = 1.48 min.

CHROMATOGRAPHICAL METHODS

The Example compounds prepared by the synthesis schemes shown hereinbefore were characterised by the following chromatographical methods, which, if carried out, are shown specifically in Tables B, D and E.

Analytical HPLC-MS, method A

Waters ZMD Mass spectrometer (positive ionisation (ESI+)), Alliance 2690/2695 HPLC (diode array detector, wavelength range: 210 to 500 nm), Waters 2700 Autosampler, Waters 996/2996.

A: water with 0.10% TFA

B: acetonitrile with 0.10% TFA

time in min	%A	%B	flow rate in ml/min
0.00	95	5	2.50
0.20	95	5	2.50
1.50	2	98	2.50
1.70	2	98	2.50
1.90	95	5	2.50
2.20	95	5	2.50

The stationary phase used is a Merck Chromolith™ Flash RP-18e column, 4.6 mm x 25 mm (column temperature: constant at 25°C).

Analytical HPLC-MS, method B

Waters ZMD mass spectrometer (positive ionisation (ESI+)), Alliance 2690/2695 HPLC (diode array detector, wavelength range: 210 to 500 nm), Waters 2700 Autosampler, Waters 996/2996.

A: water with 0.10% TFA

B: acetonitrile with 0.10% TFA

time in min	%A	%B	flow rate in ml/min
0.00	95	5	2.80
0.30	95	5	2.80
1.60	2	98	2.80
1.90	2	98	2.80
2.00	95	5	2.50

The stationary phase used is a Merck Chromolith™ Flash RP-18e column, 3 mm x 100 mm (column temperature: constant at 25°C).

Analytical HPLC-MS, method C

Waters ZQ2000 mass spectrometer (positive ionisation (ESI+)), HP1100 HPLC (DAD, wavelength range: 210 to 500 nm), and Gilson 215 Autosampler.

A: water with 0.10% TFA

B: acetonitrile with 0.10% TFA

time in min	%A	%B	flow rate in ml/min
0.00	95	5	1.50
2.00	0	100	1.50
2.50	0	100	1.50

2.60 95 5 1.50

The stationary phase used is a Sunfire C18 column, 4.6 X 50mm, 3.5 µm, column temperature 40°C.

Analytical HPLC-MS, method D

Waters ZMD mass spectrometer (positive ionisation (ESI+)), Alliance 2690/2695 HPLC (diode array detector, wavelength range: 210 to 500 nm), Waters 2700 Autosampler, Waters 996/2996.

A: water with 0.10% NH₃

B: acetonitrile with 0.10% NH₃

time in min	%A	%B	flow rate in ml/min
0.00	95	5	3.00
0.20	95	5	3.00
1.50	2	98	3.00
1.90	2	98	3.00
2.00	2	98	3.00

The stationary phase used is Waters, X-Bridge, C18, 3.5 nm, 4.6 X 20 mm. Ambient temperature.

Analytical HPLC-MS, method E

Waters ZMD mass spectrometer (positive ionisation (ESI+)), Alliance 2690/2695 HPLC (diode array detector, wavelength range: 210 to 500 nm), Waters 2700 Autosampler, Waters 996/2996.

A: water with 0.10% TFA

B: acetonitrile with 0.10% TFA

time in min	%A	%B	flow rate in ml/min
0.00	95	5	1.20
0.30	95	5	1.20
9.00	2	98	1.20
9.40	2	98	1.20
9.50	95	5	2.80
9.90	95	5	2.80
10.00	95	5	0.20

The stationary phase used is a Merck Chromolith™ Flash RP-18e column, 4.6 mm x 25 mm (column temperature: constant at 25°C).

Analytical HPLC, method A

Agilent 1100 (diode array detection, wavelength range: 210-380 nm).

A: water with 0.10% TFA

B: acetonitrile with 0.13% TFA

time in min	%A	%B	flow rate in ml/min
0.00	95	5	1.50
0.60	95	5	1.50
3.40	2	98	1.50
3.90	2	98	1.50
4.20	95	5	1.50
4.90	95	5	1.50

The stationary phase used is a Varian Microsorb column, RP C18, 3 μ m, 100 Å, ambient temperature.

Preparative HPLC-MS, method A

Waters ZQ2000 mass spectrometer (positive ionisation (ESI+)), HP1100 HPLC (DAD, wavelength range: 210 - 500 nm), and Gilson 215 Autosampler.

A: water with 0.10% TFA

B: acetonitrile

time in min	%A	%B	flow rate in ml/min
0.00	90	10	50
1.50	90	10	50
8.00	40	60	50
10.00	40	60	50
11.00	90	10	50

The stationary phase used is a Sunfire C18 column, 30 X 100 mm, 5 μ m, ambient temperature.

Preparative HPLC, method A

Gilson HPLC with Gilson UV-VIS-155 detector, Sampling injector 231 XL.

The wavelength given is the substance-specific UV maximum.

A: water with 0.13% TFA

B: acetonitrile with 0.1% TFA

time in min	%A	%B	flow rate in ml/min
0.00	95	5	165
1.30	95	5	165
8.90	2	98	165
10.00	2	98	165
10.50	95	5	165
11.60	95	5	165

The stationary phase used is a Microsorb RP 18 column, 8 μ m, 50 X 65 mm, ambient temperature.

Preparative HPLC, method B

Gilson HPLC with Gilson UV-VIS-155 detector, Sampling injector 231 XL.

The wavelength given is the substance-specific UV maximum.

A: water with 0.1% ammonia 35%

B: acetonitrile

time in min	%A	%B	flow rate in ml/min
0.00	95	5	180
1.40	95	5	180
17.00	2	98	180
18.50	2	98	180
18.70	95	5	180
20.-50	95	5	180

The stationary phase used is a Pursuit XRS RP 18 column, 10 μ m, 50 X 150 mm, ambient temperature.

Preparative HPLC, method C

Gilson HPLC with Gilson UV-VIS-155 detector, sampling injector 231 XL.

The wavelength given is the substance-specific UV maximum.

A: water with 0.13% TFA

B: acetonitrile with 0.1% TFA

time in min	%A	%B	flow rate in ml/min
0.00	95	5	180
1.40	95	5	180
17.00	2	98	180
18.50	2	98	180
18.70	95	5	180
20.50	95	5	180

The stationary phase used is a Microsorb RP 18 column, 8 μ m, 50 X 150 mm, ambient temperature.

Preparative HPLC, method D

Gilson HPLC with Gilson UV-VIS-155 detector, sampling injector 231 XL.

The wavelength given is the substance-specific UV maximum.

A: water with 0.1% ammonia 35%

B: acetonitrile

time in min	%A	%B	flow rate in ml/min
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WO2009/050248

PCT/EP2008/063999

0.00	95	5	180
1.10	95	5	180
9.00	2	98	180
10.00	2	98	180
10.50	95	5	180
12.00	95	5	180

The stationary phase used is an X-Bridge C18 column, 5 μ m, 50 X 65 mm, ambient temperature.

EXAMPLES

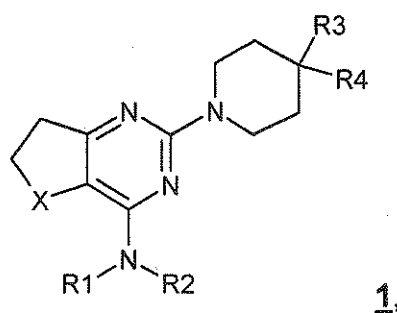
The following Examples were prepared analogously to the methods of synthesis described hereinbefore (as indicated in the Table). These compounds are suitable for use as PDE4-inhibitors and have IC_{50} values of less than or equal to $1\text{ }\mu\text{mol}$. The inhibitions (in %) at $1\text{ }\mu\text{M}$ of the individual Example substances are given in the following Table of Examples and were determined as follows:

The Scintillation Proximity Assay (SPA) (GE Healthcare, No. TRKQ7090) was carried out by using the different affinities of cyclic 3'-5'-adenosinemonophosphate (cAMP, low affinity) and linear 5'-adenosinemonophosphate (AMP, high affinity) for yttrium silicate scintillator beads. The cAMP specific phosphodiesterase (PDE) PDE4B cleaves the 3'-phosphoester bond of tritium-labelled [H3]-cAMP to form [H3]-5'-AMP. This [H3]-AMP accumulates on the scintillator beads because of its higher affinity for them and causes scintillation events (flashes of light) which are measured in a *Wallac Microbeta Scintillation Counter*.

The experiment starts with a one-hour incubation of [H3]-cAMP with the PDE4B enzyme in assay buffer at 30°C , in each case once with the Example substance to be tested (in a concentration of $1\text{ }\mu\text{M}$) and once without the Example substance to be tested.

After this incubation, the reaction is stopped by the addition of the beads. The beads have an opportunity to settle in the next 45 minutes, then the measurement is carried out in the Scintillation Counter. If the substance is capable of inhibiting the enzymatic activity of the PDE4B, less [H3]-AMP is produced during the incubation phase and fewer scintillation events can be measured. These results are expressed as the percentage inhibition at a concentration of the test substance of $1\text{ }\mu\text{M}$.

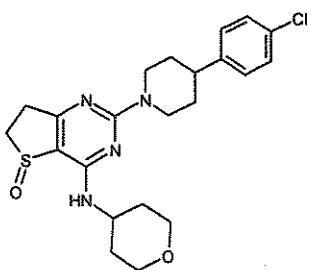
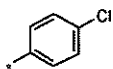
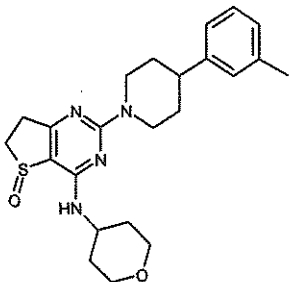
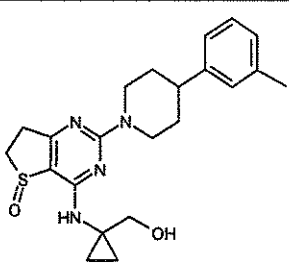
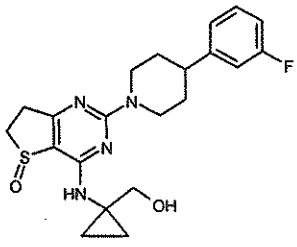
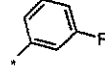
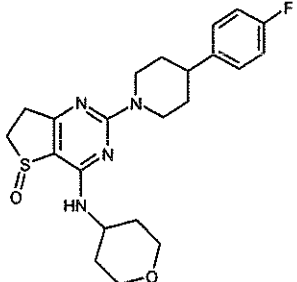
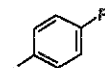
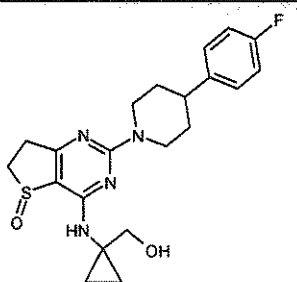
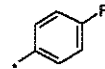
The Examples relate to compounds of the following formula 1,

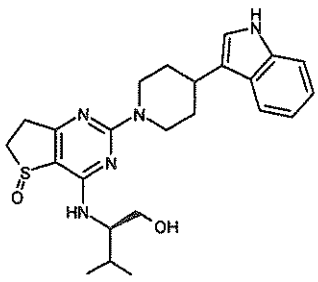
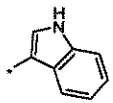
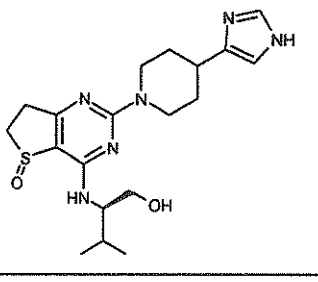
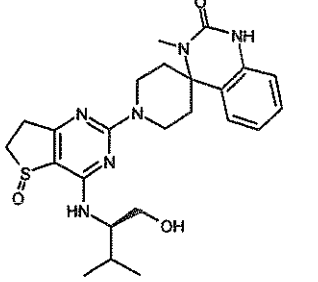
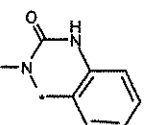
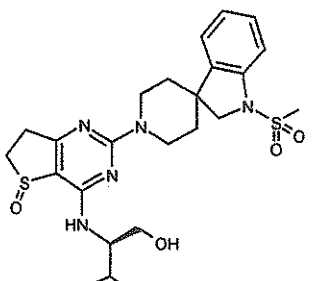
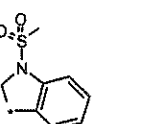
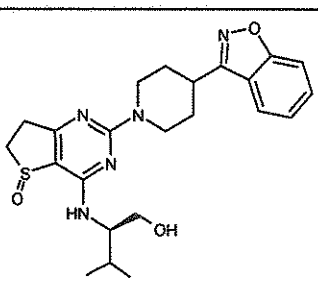
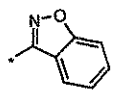
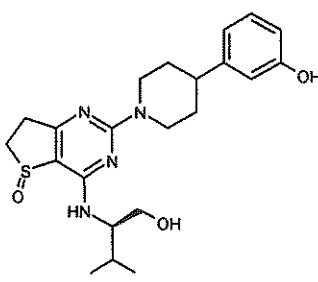
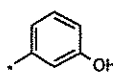


having the properties indicated in Tables A and B hereinafter:

Table A: Chemical structures of the Example substances 1 - 163

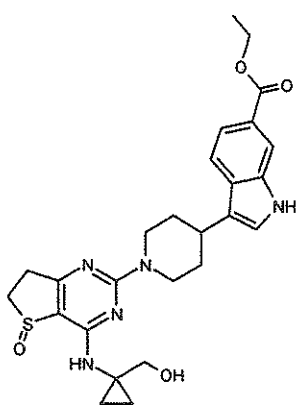
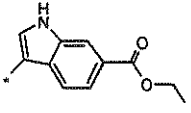
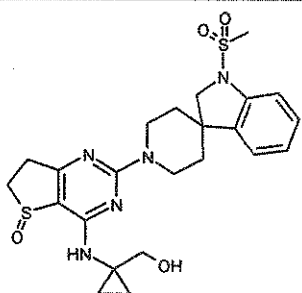
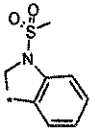
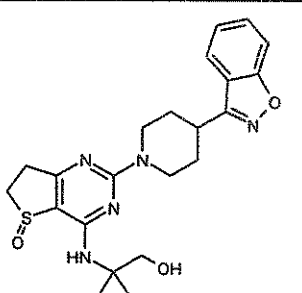
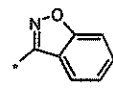
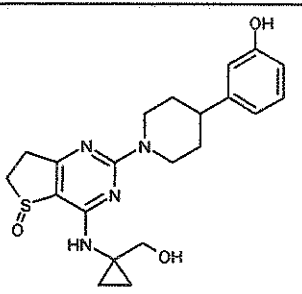
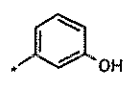
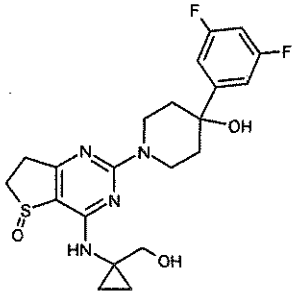
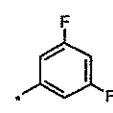
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4		H			H	91
5		H			H	94

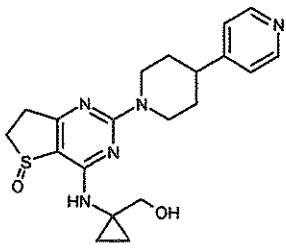
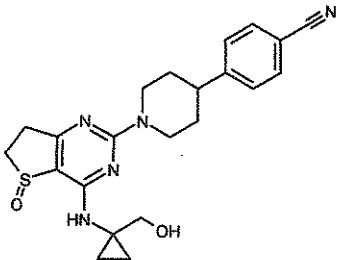
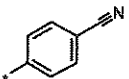
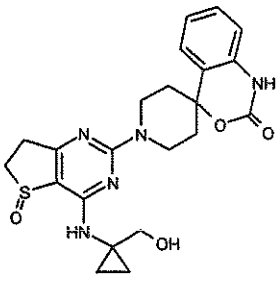
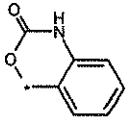
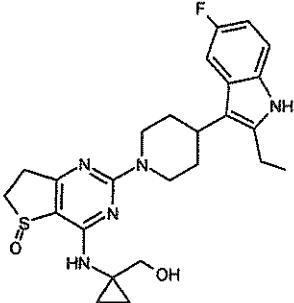
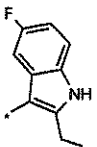
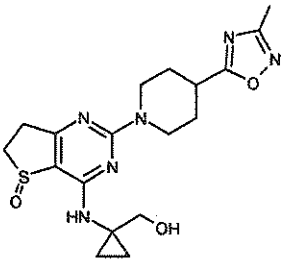
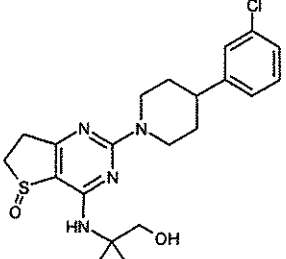
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10		H			H	93
11		H			H	94

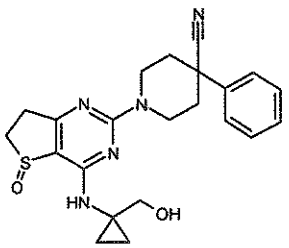
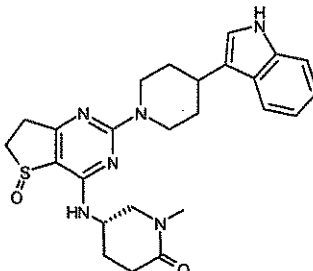
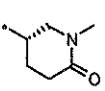
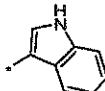
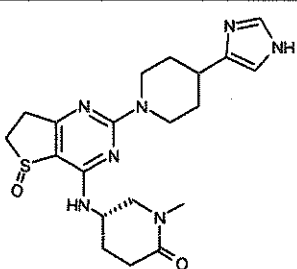
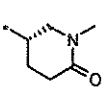
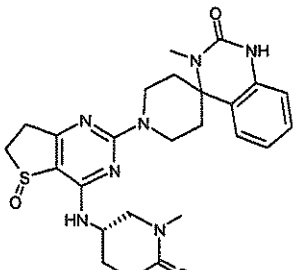
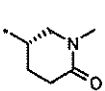
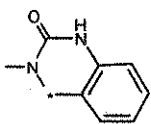
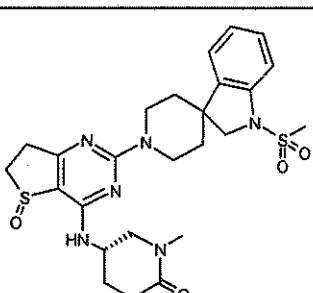
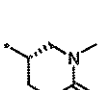
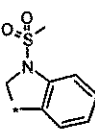
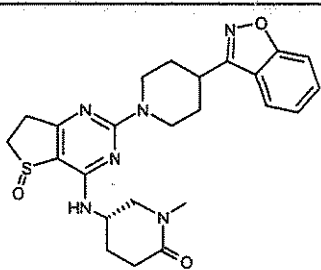
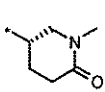
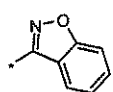
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
12		H			H	94
13		H			H	71
14		H				60
15		H				67
16		H			H	96
17		H			H	93

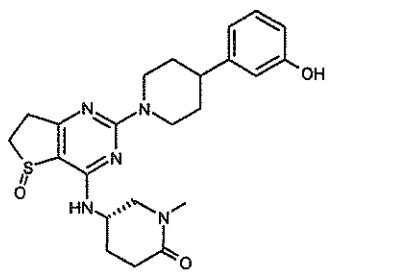
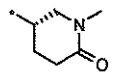
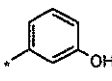
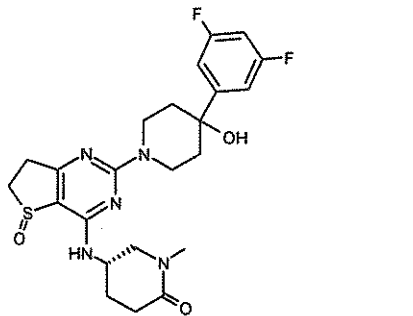
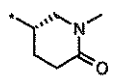
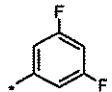
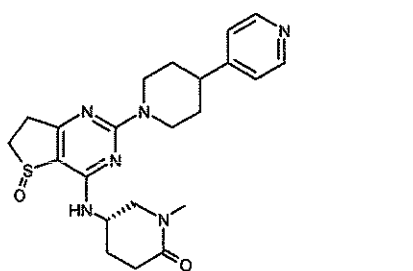
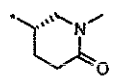
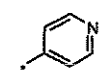
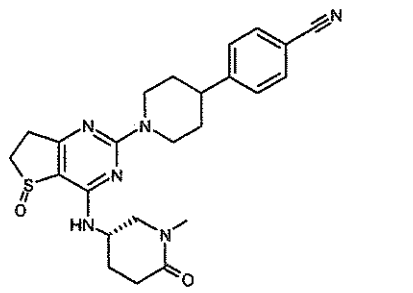
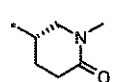
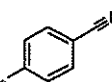
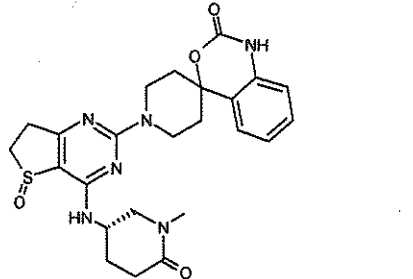
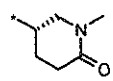
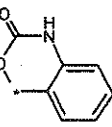
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
18		H			OH	92
19		H			H	83
20		H			H	94
21		H				83
22		H			H	86

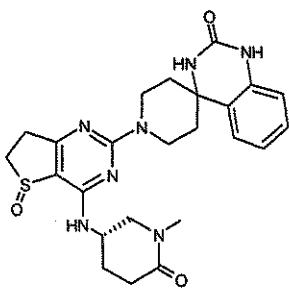
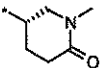
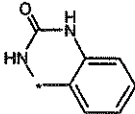
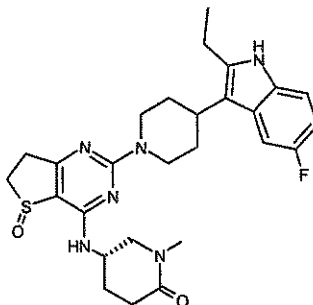
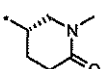
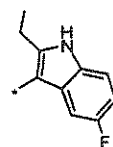
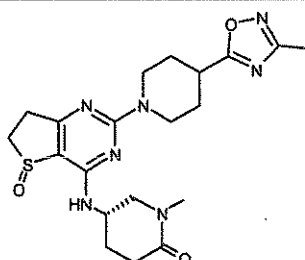
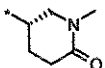
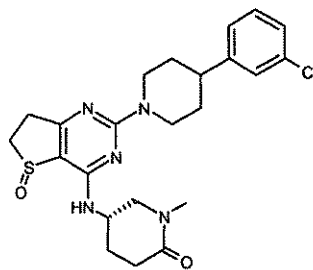
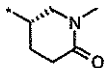
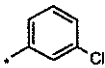
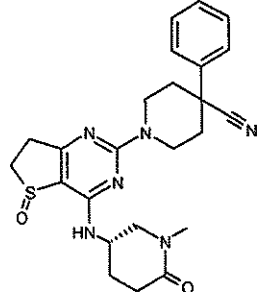
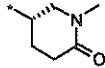
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
23		H			H	85
24		H			H	94
25		H			CN	90
26		H			H	96
27		H			H	87
28		H				85

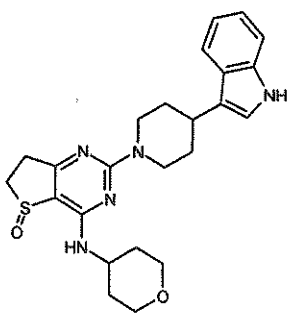
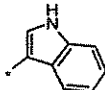
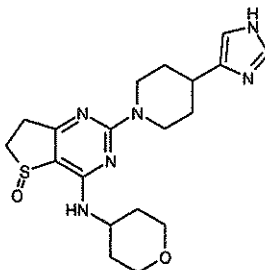
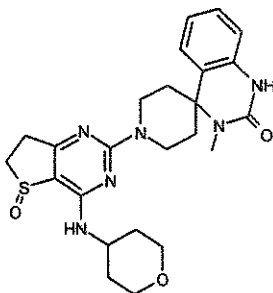
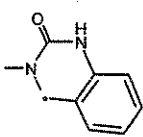
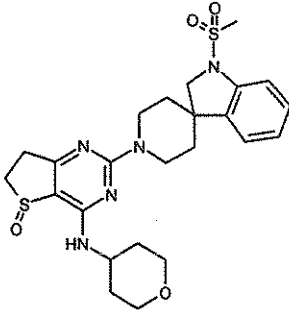
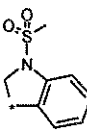
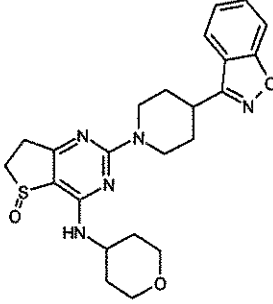
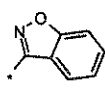
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
29		H			H	97
30		H				89
31		H			H	97
32		H			H	96
33		H			OH	95

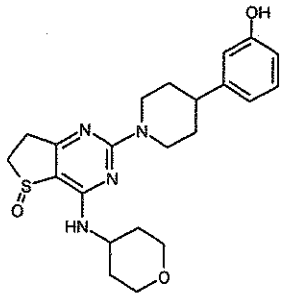
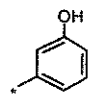
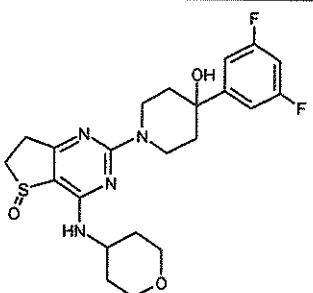
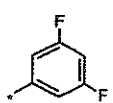
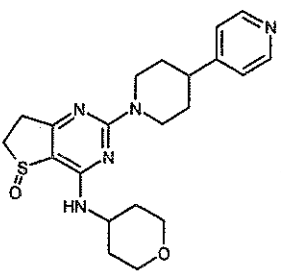
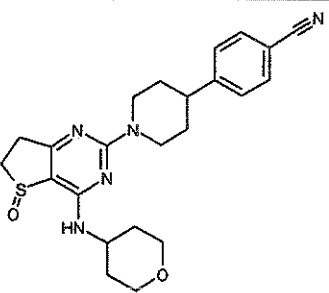
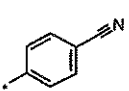
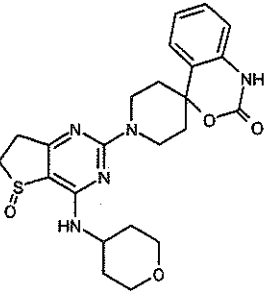
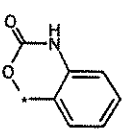
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
34		H			H	92
35		H			H	95
36		H				92
37		H			H	92
38		H			H	92
39		H			H	96

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
40		H			CN	94
41		H			H	97
42		H			H	95
43		H				95
44		H				95
45		H			H	97

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
46		H			H	97
47		H			OH	97
48		H			H	96
49		H			H	96
50		H				95

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
51		H				83
52		H			H	96
53		H			H	96
54		H			H	97
55		H			CN	96

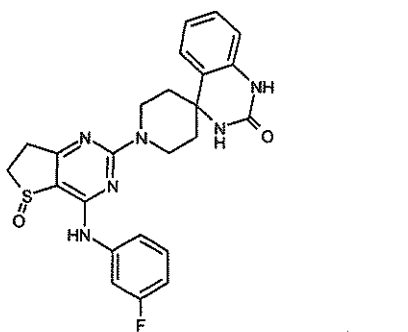
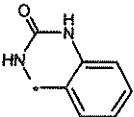
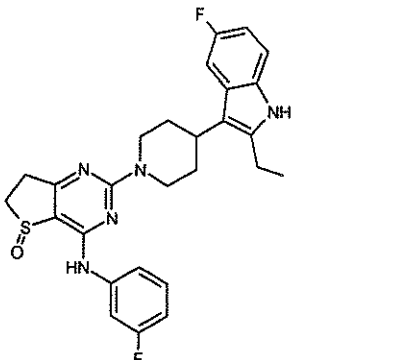
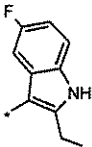
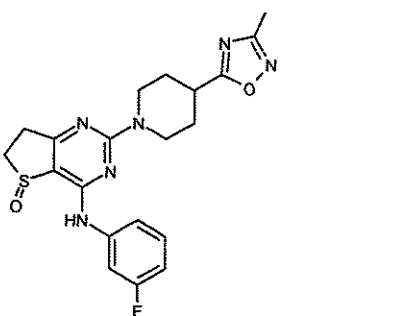
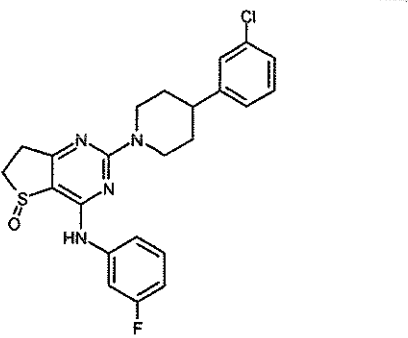
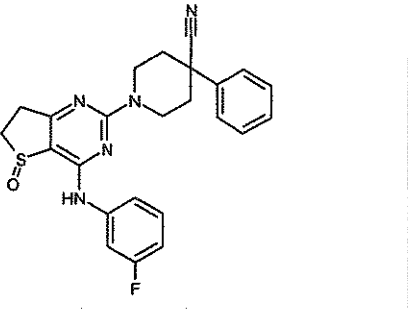
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
56		H			H	96
57		H			H	86
58		H				88
59		H				90
60		H			H	97

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
61		H			H	95
62		H			OH	96
63		H			H	92
64		H			H	96
65		H				94

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
66		H				62
67		H			H	93
68		H			H	93
69		H			H	93
70		H			CN	95

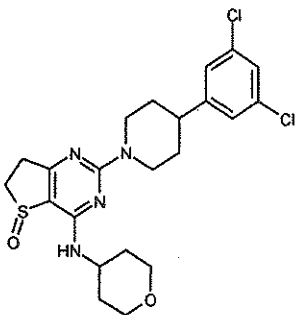
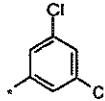
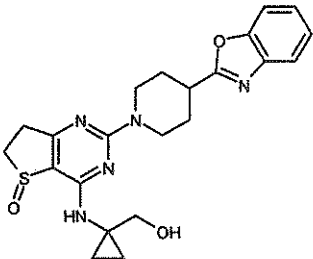
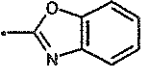
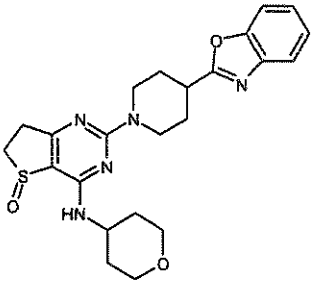
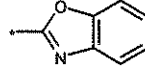
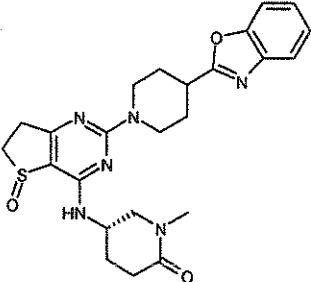
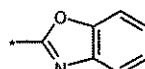
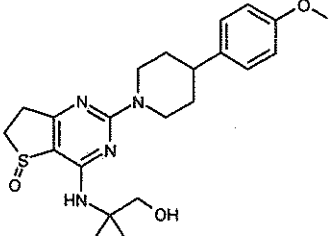
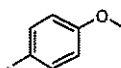
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
71		H			H	96
72		H			H	95
73		H				94
74		H				95
75		H			H	97

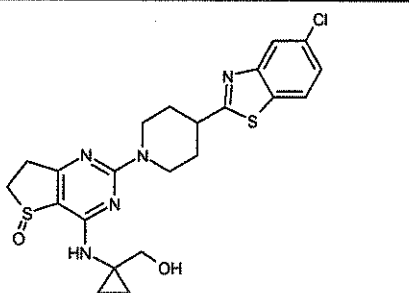
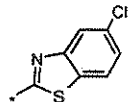
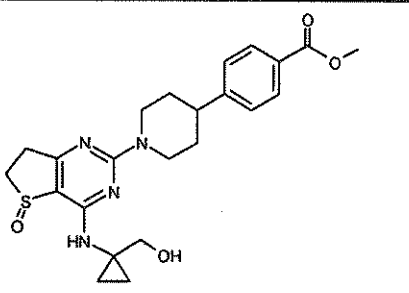
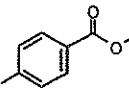
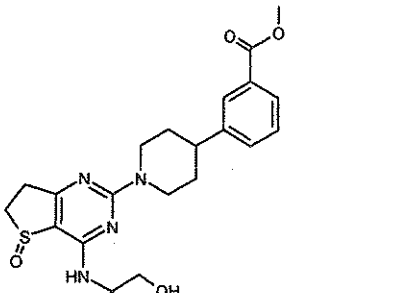
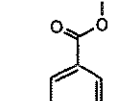
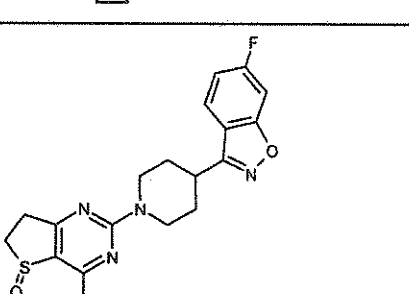
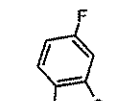
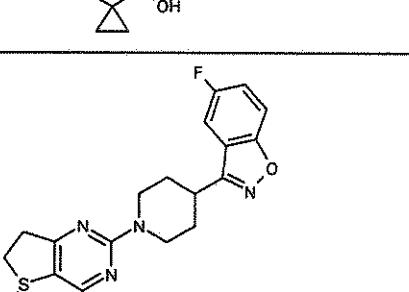
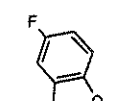
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
76		H			H	97
77		H			OH	96
78		H			H	96
79		H			H	96
80		H				94

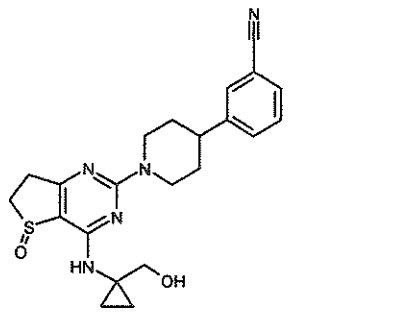
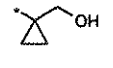
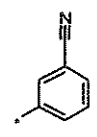
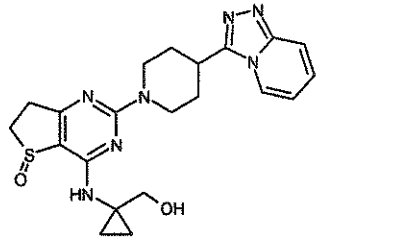
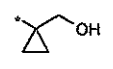
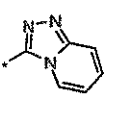
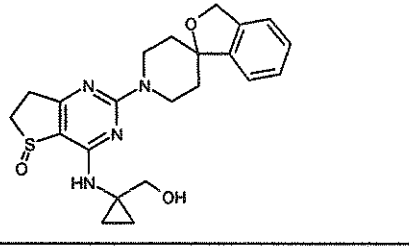
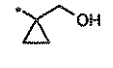
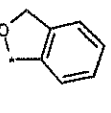
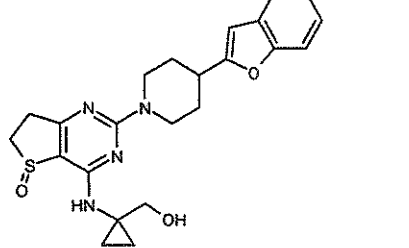
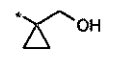
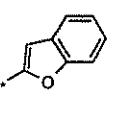
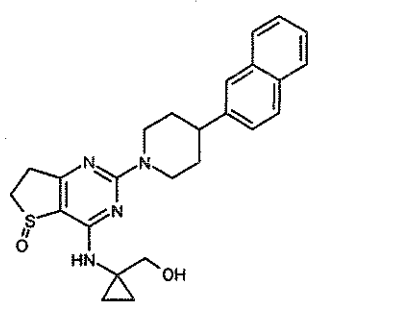
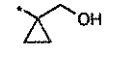
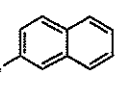
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
81		H				83
82		H			H	92
83		H			H	96
84		H			H	95
85		H			CN	96

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μM
86		H			H	94
87		H			H	92
88		H			H	92
89		H			H	93
90		H			H	92

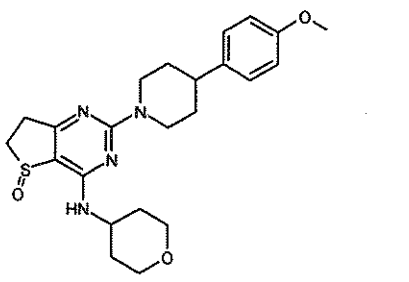
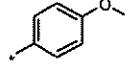
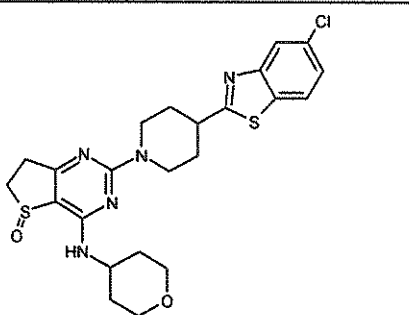
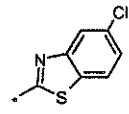
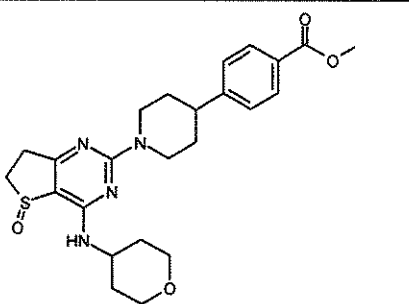
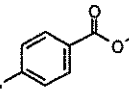
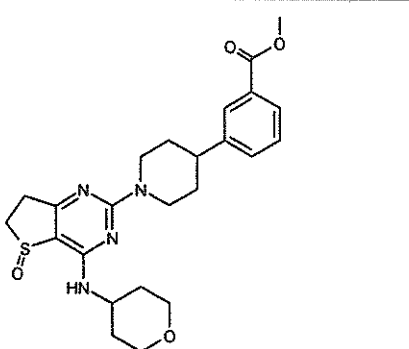
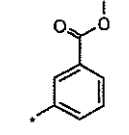
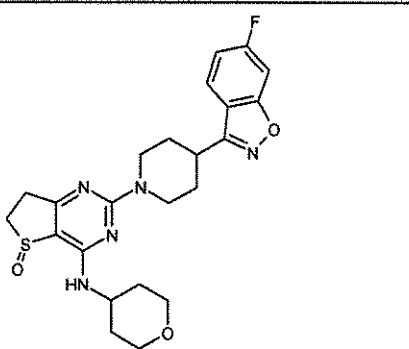
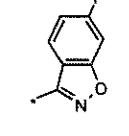
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μM
91		H			H	94
92		H			H	94
93		H			H	94
94		H			H	94
95		H			H	93
96		H			H	94

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
97		H			H	93
98		H			H	97
99		H			H	97
100		H			H	97
101		H			H	94

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
102		H			H	95
103		H			H	95
104		H			H	95
105		H			H	95
106		H			H	95

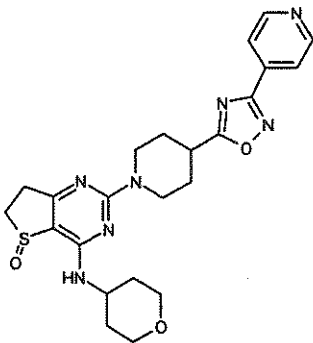
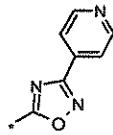
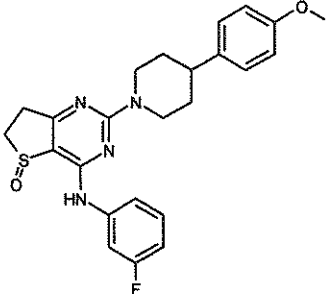
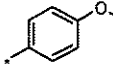
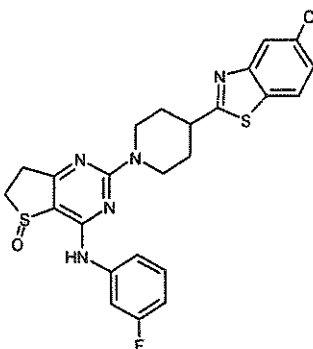
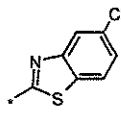
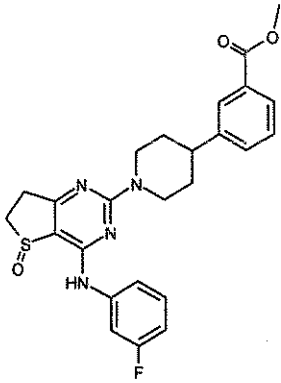
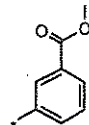
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μM
107		H			H	94
108		H			H	88
109		H			H	75
110		H			H	97
111		H			H	96

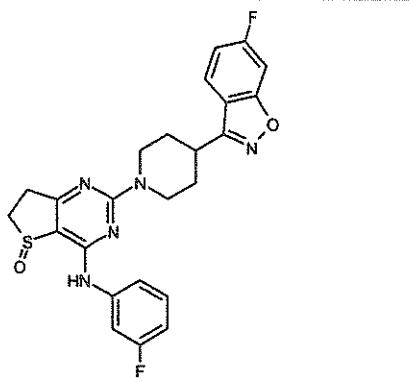
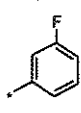
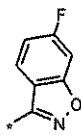
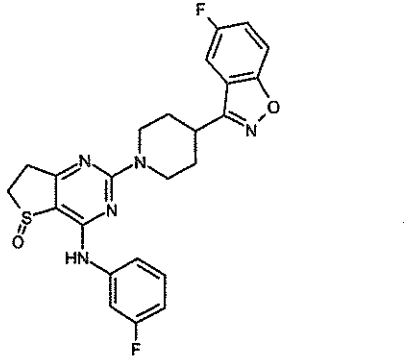
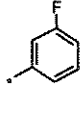
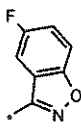
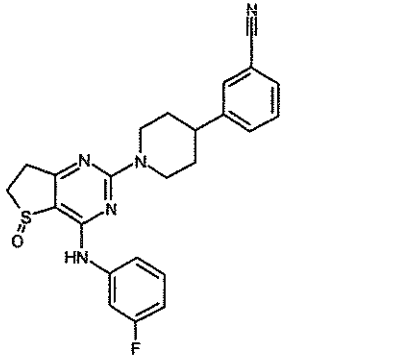
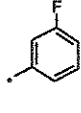
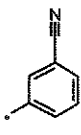
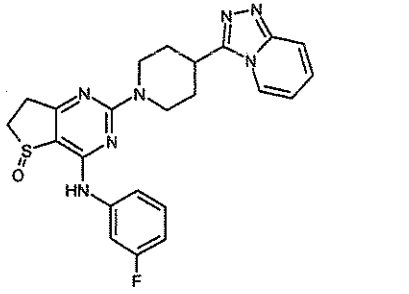
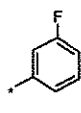
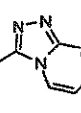
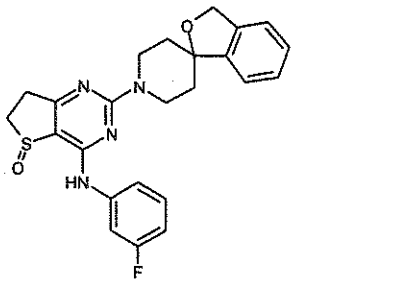
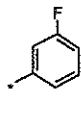
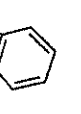
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
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113		H			H	92
114		H			H	96
115		H			H	94
116		H			H	94

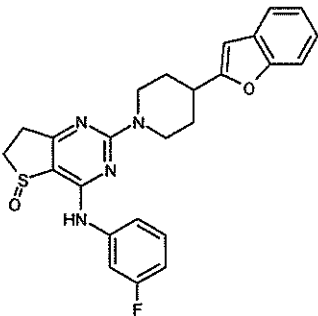
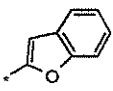
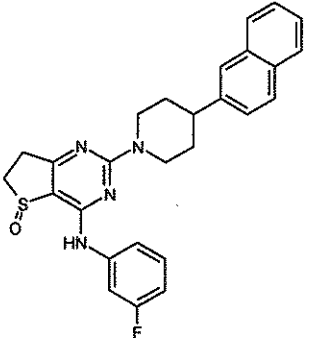
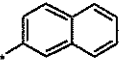
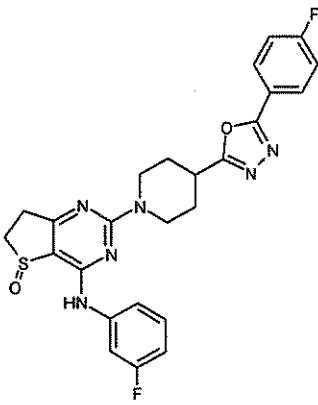
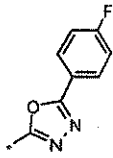
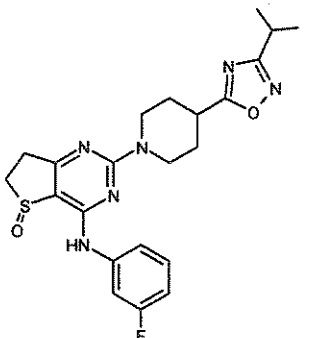
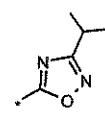
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
117		H			H	94
118		H			H	96
119		H			H	95
120		H			H	95
121		H			H	96

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
122		H			H	96
123		H			H	94
124		H			H	89
125		H			H	74
126		H			H	96

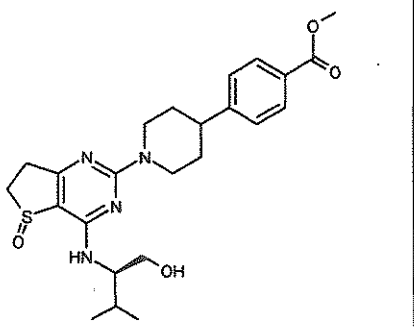
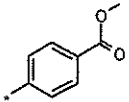
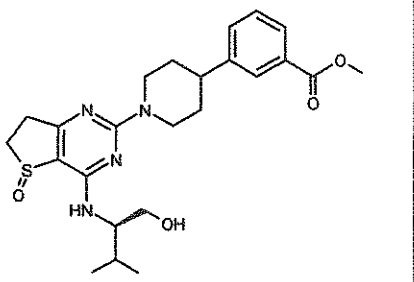
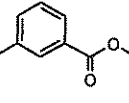
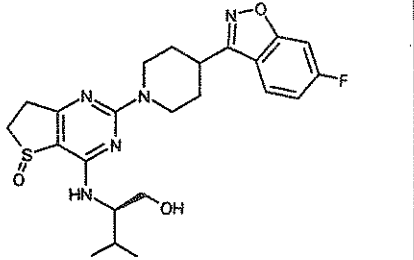
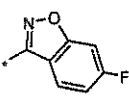
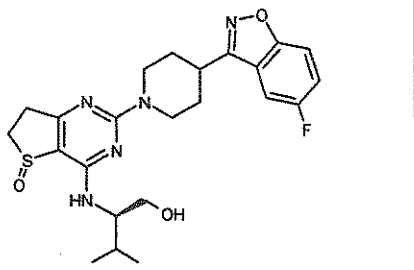
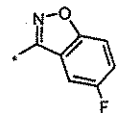
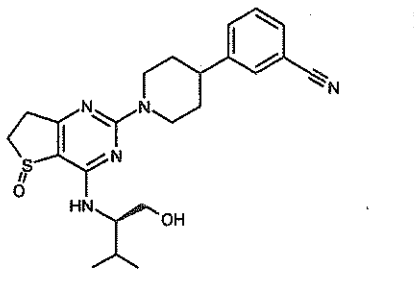
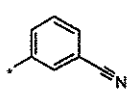
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
127		H			H	96
128		H			H	95
129		H			H	93
130		H			H	96
131		H			H	94

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
132		H			H	95
133		H			H	95
134		H			H	95
135		H			H	96

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
136		H			H	95
137		H			H	95
138		H			H	96
139		H			H	94
140		H				83

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μM
141		H				97
142		H				94
143		H			H	95
144		H			H	94

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
145		H			H	96
146		H			H	96
147		H			H	95
148		H			H	93
149		H			H	94

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
150		H			H	94
151		H			H	94
152		H			H	95
153		H			H	95
154		H			H	92

#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
155		H			H	83
156		H				64
157		H			H	96
158		H			H	94
159		H			H	94

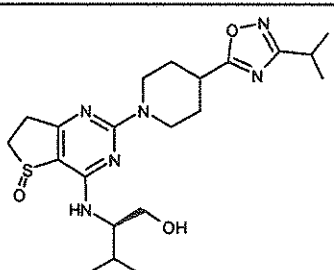
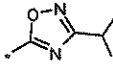
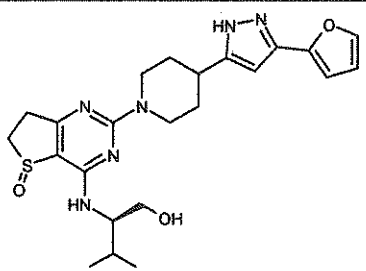
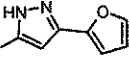
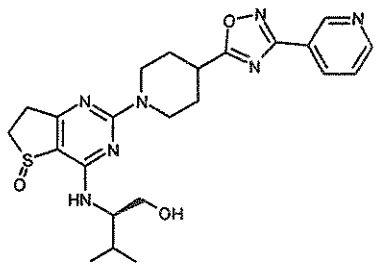
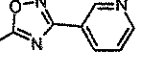
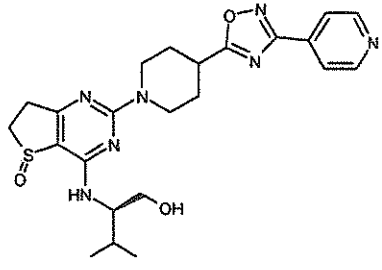
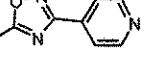
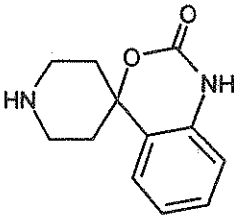
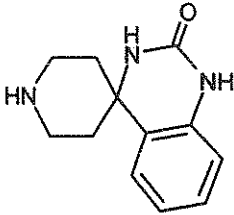
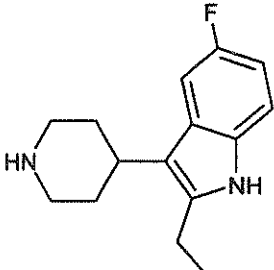
#	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
160		H			H	86
161		H			H	94
162		H			H	92
163		H			H	92

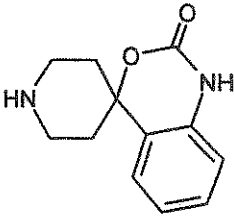
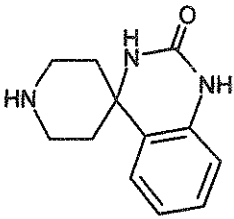
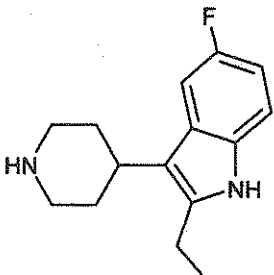
Table B that follows gives detailed information on the chemical syntheses and the analysis of the individual Example substances 1-163.

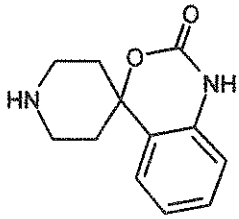
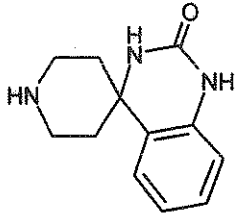
Table B: Detailed information on the preparatio of the individual Example substances 1-163

#	Prepared analogously to #*	non-commercial arylpiperidine component (V)	literature on the preparation of the non-commercial arylpiperidine component (V)	analytical HPLC-MS, RT [min], method
1	see experim. Section			1.24 method A
2	see experim. Section			1.32 method B
3	see experim. Section			1.29 method A
4	see experim. Section			1.36 method A
5	see experim. Section			1.18 method A
6	see experim. Section			1.24 method A
7	6			1.25 method A
8	2			1.21 method A
9	2			1.15 method D
10	6			1.20 method D
11	2			1.14 method D
12	14			1.77 method C
13	14			1.32 method C
14	see experim. Section			1.58 method C
15	14			1.74 method C
16	see experim. Section			1.74 method C
17	14			1.65 method C
18	14			1.64 method C
19	see experim. Section			1.33 method C
20	14			1.73 method C

#	Prepared analogously to #*	non-commercial arylpiperidine component (V)	literature on the preparation of the non-commercial arylpiperidine component (V)	analytical HPLC-MS, RT [min], method
21	14		<i>J. Med. Chem.</i> 1983 , 657	1.6 method C
22	see experim. Section			1.83 method C
23	14			1.55 method C
24	14			1.87 method C
25	14			1.78 method C
26	28			1.72 method C
27	28			0.55 method C
28	see experim. Section			1.52 method C
29	see experim. Section			1.77 method C
30	28			1.69 method C
31	28			1.7 method C
32	28			1.59 method C
33	28			1.58 method C
34	28			0.56 method C
35	28			1.68 method C
36	28		<i>J. Med. Chem.</i> 1983 , 657	1.54 method C
37	see experim. Section			1.78 method C
38	28			1.48 method C

#	Prepared analogously to #*	non-commercial arylpiperidine component (V)	literature on the preparation of the non-commercial arylpiperidine component (V)	analytical HPLC-MS, RT [min], method
39	28			1.21 method D
40	28			1.74 method C
41	43			1.68 method C
42	43			0.55 method C
43	see experim. Section			1.49 method C
44	43			1.66 method C
45	43			1.66 method C
46	43			1.55 method C
47	43			1.54 method C
48	43			0.56 method C
49	43			1.64 method C
50	43		<i>J. Med. Chem.</i> 1983 , 657	1.5 method C
51	43		WO2003/104236	1.49 method C
52	43		see experim. Section § 10.4, component (V-1)	1.73 method C
53	43			1.45 method C

#	Prepared analogously to #*	non-commercial arylpiperidine component (V)	literature on the preparation of the non-commercial arylpiperidine component (V)	analytical HPLC-MS, RT [min], method
54	43			1.77 method C
55	see experim. Section			1.71 method C
56	58			1.76 method C
57	58			1.3 method C
58	see experim. Section			1.56 method C
59	58			1.72 method C
60	58			1.73 method C
61	58			1.63 method C
62	58			1.61 method C
63	58			1.3 method C
64	58			1.71 method C
65	58		<i>J. Med. Chem.</i> 1983 , 657	1.56 method C
66	58		WO2003/104236	1.55 method C
67	58		see experim. Section § 10.4, component (V-1)	1.81 method C
68	58			1.52 method C

#	Prepared analogously to #*	non-commercial arylpiperidine component (V)	literature on the preparation of the non-commercial arylpiperidine component (V)	analytical HPLC-MS, RT [min], method
69	58			1.25 method D
70	58			1.78 method C
71	73			2.07 method C
72	73			1.53 method C
73	see experim. Section			1.81 method C
74	73			2.07 method C
75	see experim. Section			2.11 method C
76	73			1.92 method C
77	73			1.91 method C
78	see experim. Section			1.55 method C
79	73			2.09 method C
80	73		<i>J. Med. Chem.</i> 1983 , 657	1.86 method C
81	73		WO2003/104236	1.81 method C
82	see experim. Section			2.12 method C
83	73			1.87 method C
84	73			2.29 method C
85	73			2.24 method C
86	58			1.20 method D

#	Prepared analogously to #*	non-commercial arylpiperidine component (V)	literature on the preparation of the non-commercial arylpiperidine component (V)	analytical HPLC-MS, RT [min], method
87	28			1.15 method D
88	58			1.20 method D
89	see experim. Section			1.18 method D
90	see experim. Section			1.23 method D
91	see experim. Section			1.30 method D
92	see experim. Section			1.23 method D
93	see experim. Section			1.28 method D
94	28			1.22 method D
95	see experim. Section			1.25 method D
96	see experim. Section			1.29 method D
97	see experim. Section			1.29 method A
98	see experim. Section			1.22 method B
99	see experim. Section			1.23 method B
100	see experim. Section			1.18 method B
101	28			1.74 method C
102	28			1.86 method C
103	28			1.73 method C
104	28			1.73 method C
105	28			1.76 method C
106	28			1.74 method C
107	28			1.71 method C
108	28			1.33 method C
109	28			1.71 method C

#	Prepared analogously to #*	non-commercial arylpiperidine component (V)	literature on the preparation of the non-commercial arylpiperidine component (V)	analytical HPLC-MS, RT [min], method
110	28			1.83 method C
111	28			1.89 method C
112	28			1.69 method C
113	28			1.66 method C
114	28			1.61 method C
115	28			1.46 method C
116	28			1.43 method C
117	58			1.77 method C
118	58			1.91 method C
119	58			1.77 method C
120	58			1.78 method C
121	58			1.79 method C
122	58			1.78 method C
123	58			1.74 method C
124	58			1.36 method C
125	58			1.74 method C
126	58			1.88 method C
127	58			1.92 method C
128	58			1.73 method C
129	58			1.69 method C
130	58			1.64 method C
131	58			1.5 method C
132	58			1.45 method C

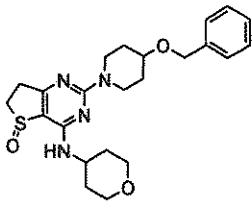
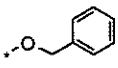
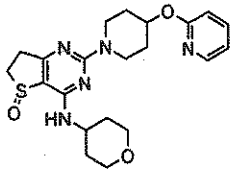
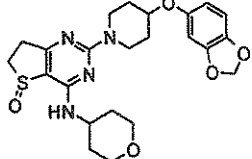
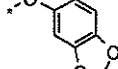
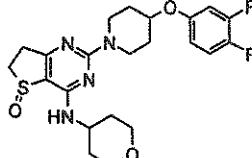
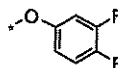
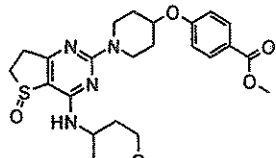
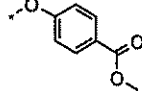
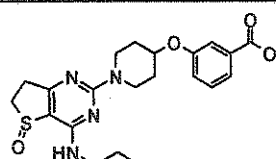
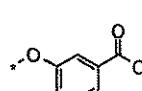
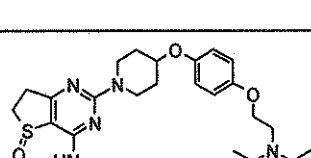
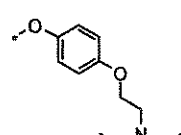
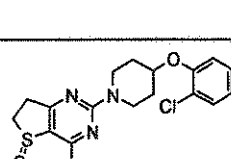
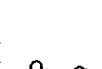
#	Prepared analogously to #*	non-commercial arylpiperidine component (V)	literature on the preparation of the non-commercial arylpiperidine component (V)	analytical HPLC-MS, RT [min], method
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134	73			2.44 method C
135	73			2.14 method C
136	73			2.17 method C
137	73			2.16 method C
138	73			2.09 method C
139	73			1.6 method C
140	73			2.12 method C
141	73			2.31 method C
142	73			2.34 method C
143	73			2.07 method C
144	73			2.08 method C
145	see experim. Section			1.89 method C
146	73			1.79 method C
147	see experim. Section			1.72 method C
148	14			1.8 method C
149	14			1.9 method C
150	14			1.78 method C
151	14			1.79 method C
152	14			1.81 method C
153	14			1.8 method C
154	14			1.76 method C
155	14			1.39 method C

#	Prepared analogously to #*	non-commercial arylpiperidine component (V)	literature on the preparation of the non-commercial arylpiperidine component (V)	analytical HPLC-MS, RT [min], method
156	14			1.76 method C
157	14			1.88 method C
158	14			1.94 method C
159	14			1.74 method C
160	14			1.71 method C
161	see experim. Section			1.67 method C
162	14			1.52 method C
163	see experim. Section			1.48 method C

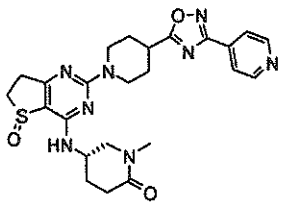
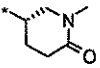
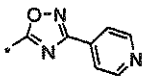
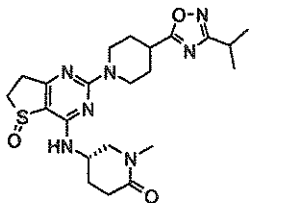
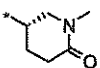
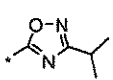
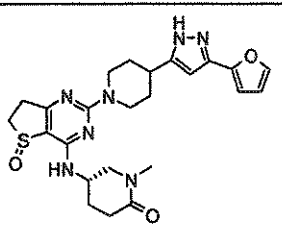
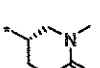
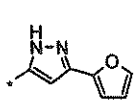
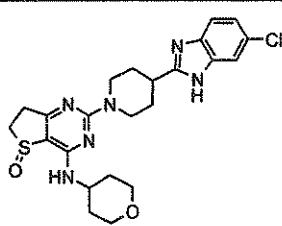
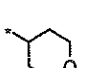
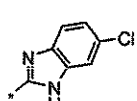
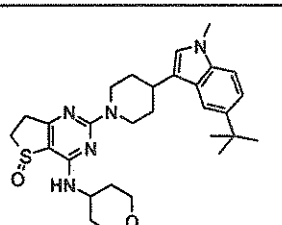
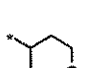
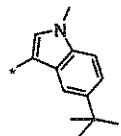
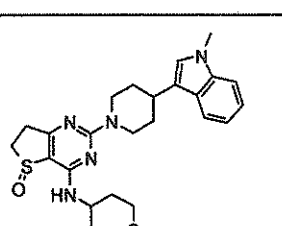
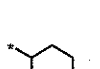
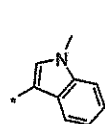
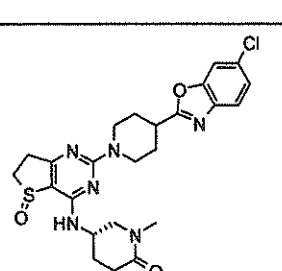
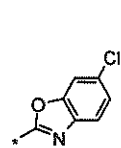
* the Example may be prepared and purified analogously.

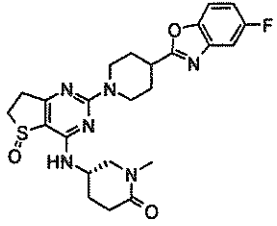
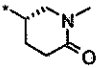
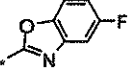
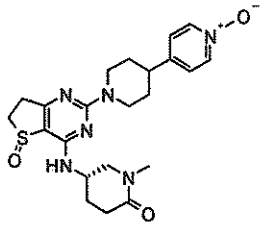
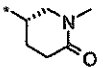
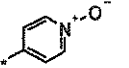
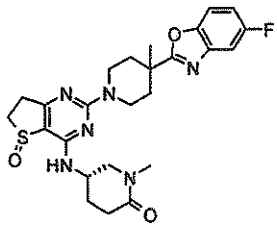
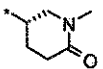
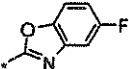
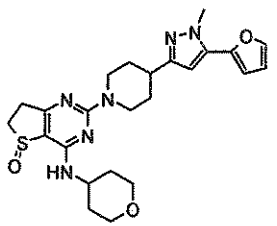
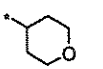
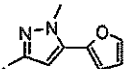
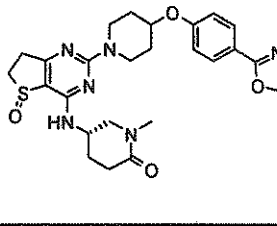
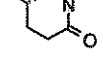
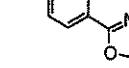
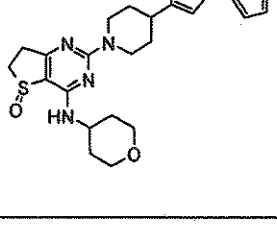
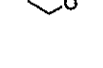
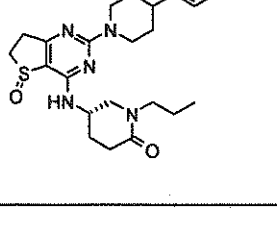
Table C: Chemical structures of the Example substances 164 -332

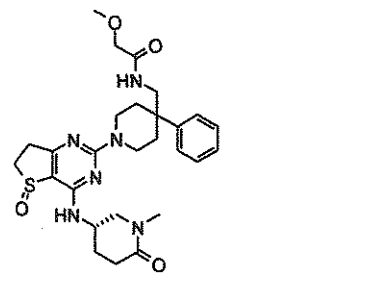
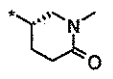
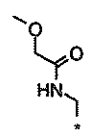
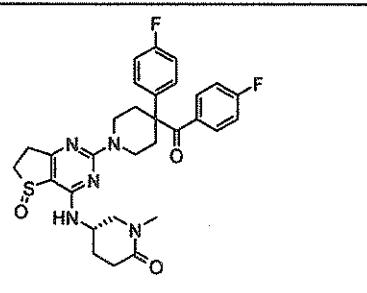
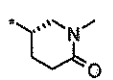
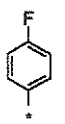
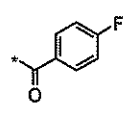
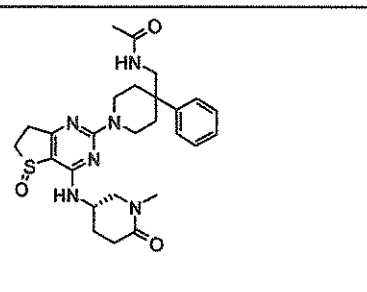
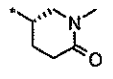
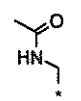
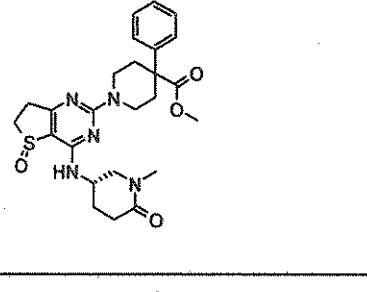
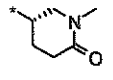
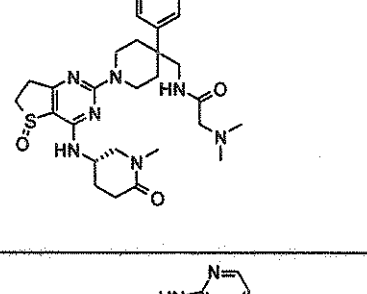
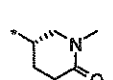
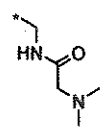
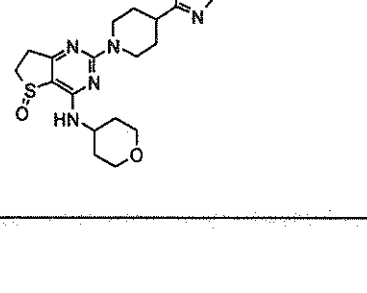
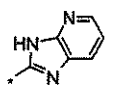
Ex.	Structure	R ¹	R ²	R ³	R ⁴	% Inhibition PDE4B @ 1 μ M
164		H			H	92
165		H			H	92
166		H			H	92
167		H			H	91
168		H			H	89
169		H			H	92
170		H		OCH ₃	H	77

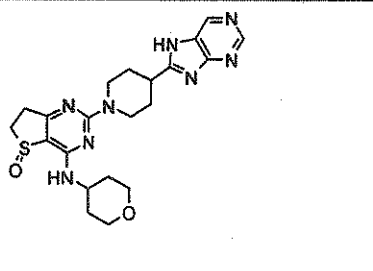
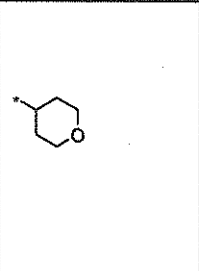
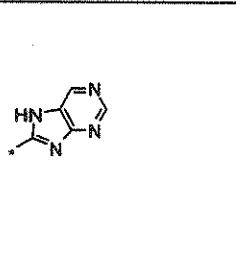
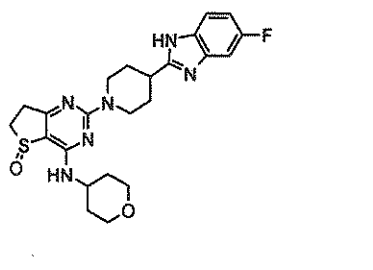
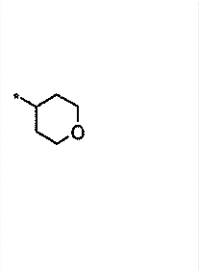
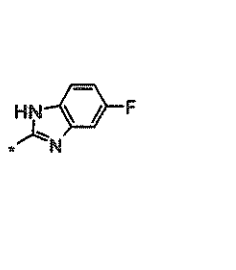
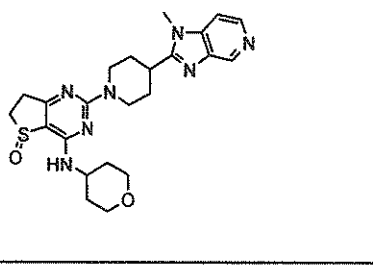
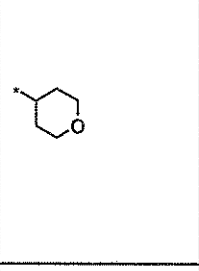
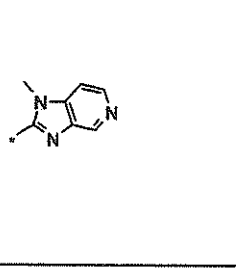
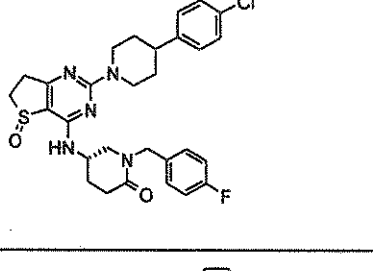
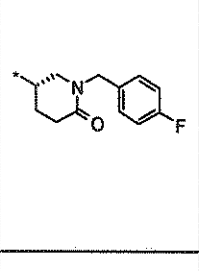
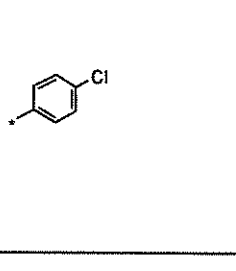
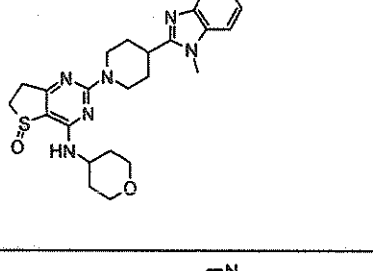
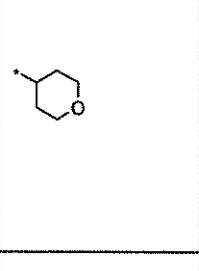
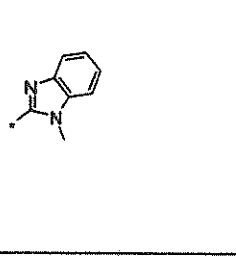
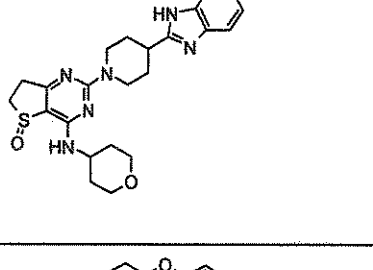
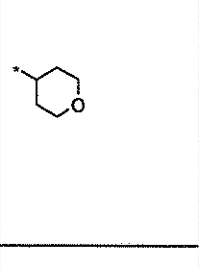
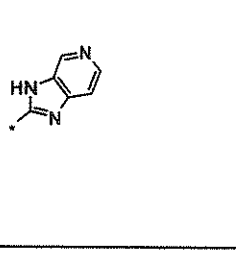
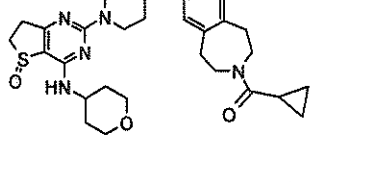
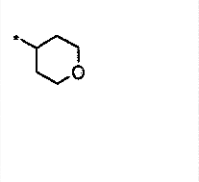
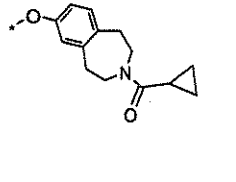
172		H			H	91
173		H			H	95
174		H			H	92
175		H			H	89
176		H			H	93
177		H			H	93
178		H			H	92
179		H			H	75

180		H			H	93
181		H			H	92
182		H			H	82
183		H			H	91
184		H			H	92
185		H			H	94
186		H			H	96
187		H			H	98

188		H			H	97
189		H			H	97
190		H			H	97
191		H			H	96
192		H			H	95
193		H			H	96
194		H			H	97

195		H			H	96
196		H			H	94
197		H			CH ₃	96
198		H			H	94
199		H			H	96
200		H			H	97
201		H			H	95

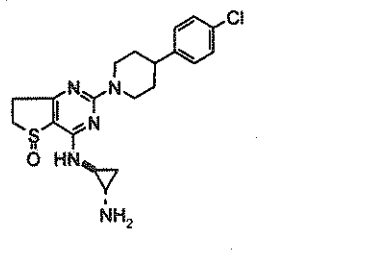
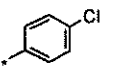
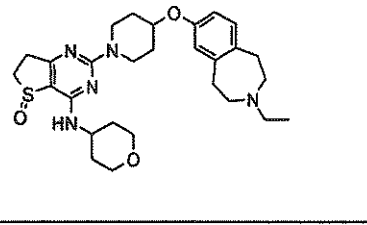
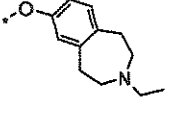
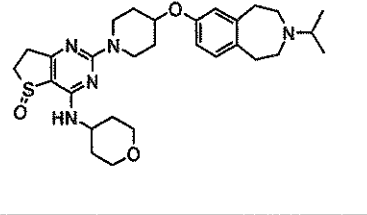
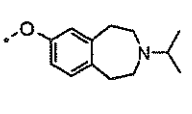
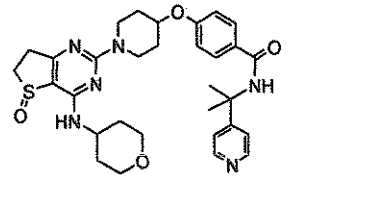
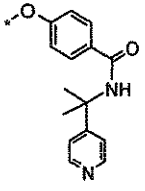
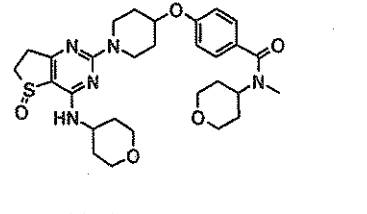
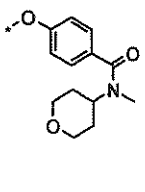
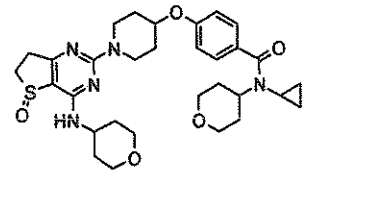
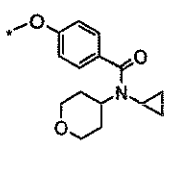
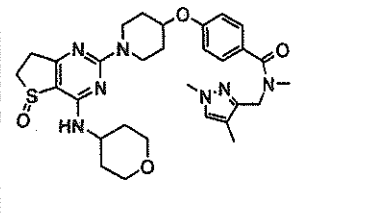
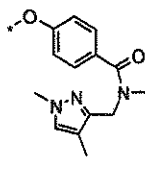
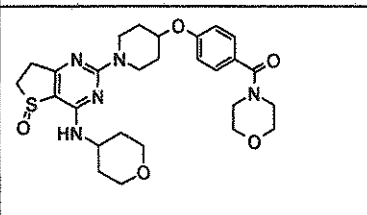
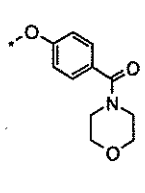
202		H				96
203		H				96
204		H				96
205		H				96
206		H				95
207		H			H	95

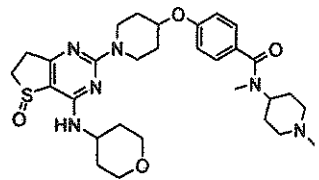
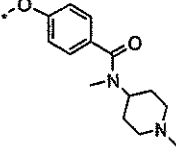
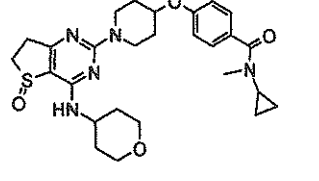
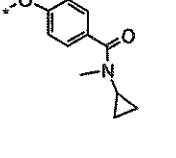
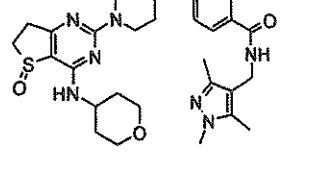
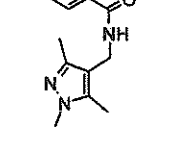
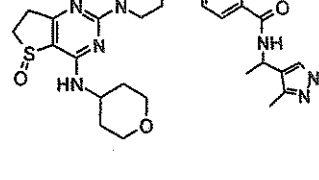
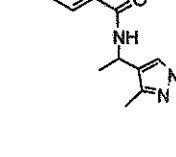
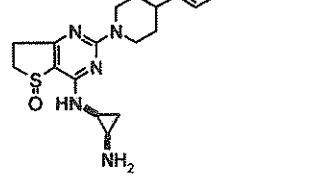
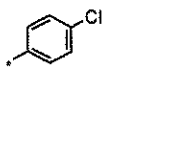
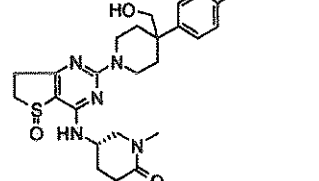
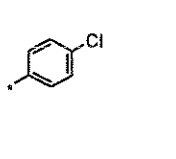
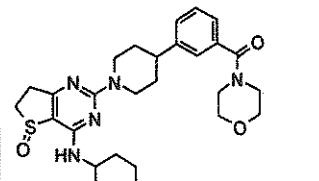
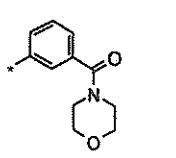
208		H			H	82
209		H			H	95
210		H			H	85
211		H			H	94
212		H			H	93
213		H			H	88
214		H			H	94

215		H			H	79
216		H				80
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218		H			H	94
219		H			H	82
220		H			H	93

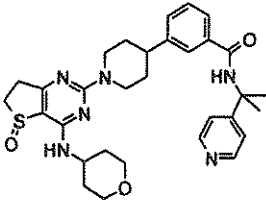
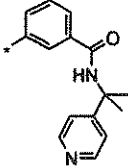
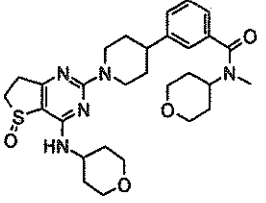
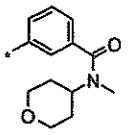
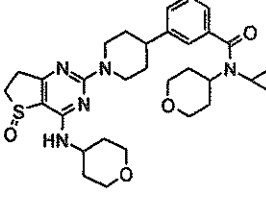
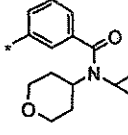
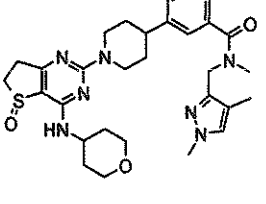
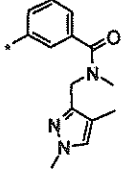
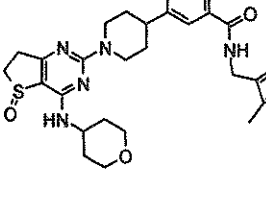
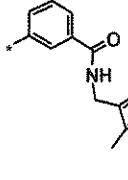
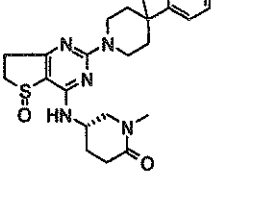
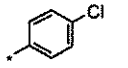
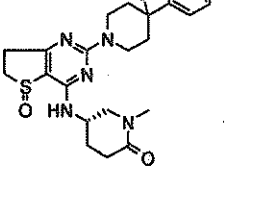
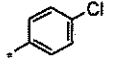
221		H			H	94
222		H			H	89
223		H			H	80
224		H			H	93
225		H			H	89
226		H			H	95

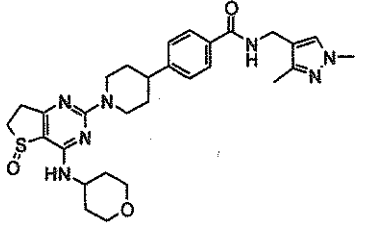
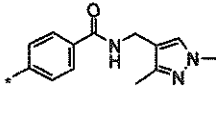
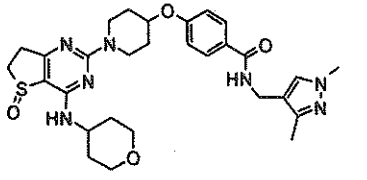
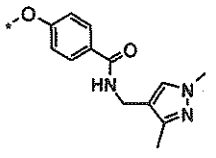
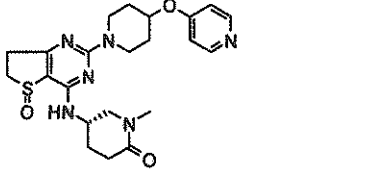
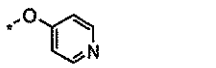
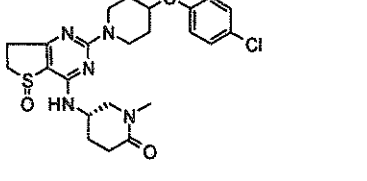
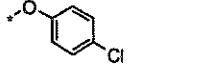
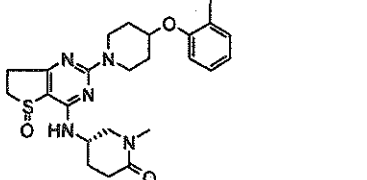
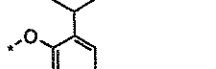
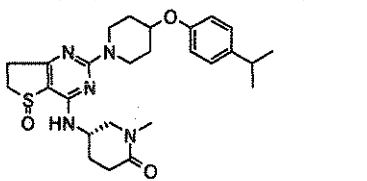
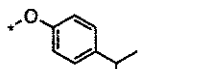
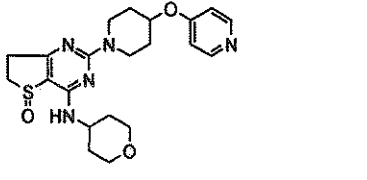
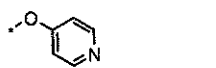
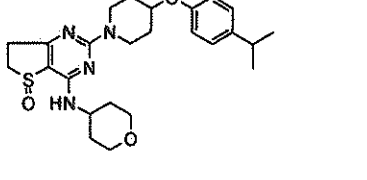
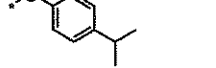
227		H			H	83
228		H			H	94
229		H			H	94
230		H			H	81
231		H			H	94
232 ¹⁾		H			H	84

233		H			H	93
234		H			H	95
235		H			H	87
236		H			H	95
237		H			H	95
238		H			H	95
239		H			H	94
240		H			H	94

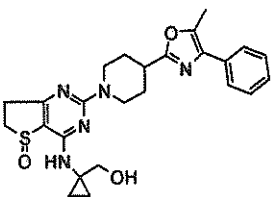
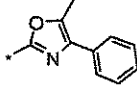
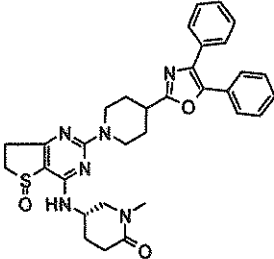
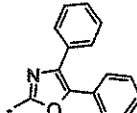
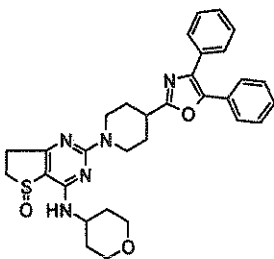
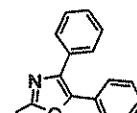
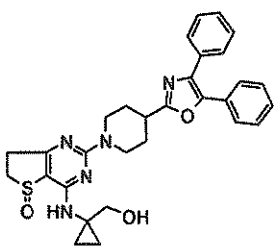
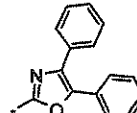
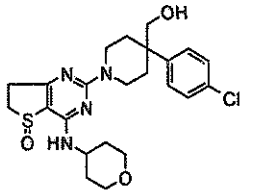
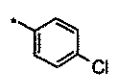
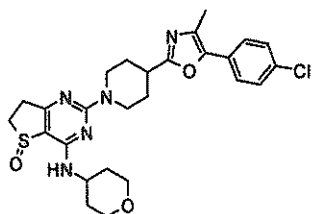
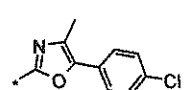
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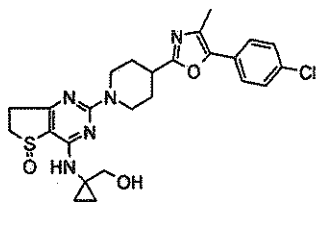
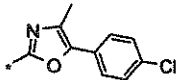
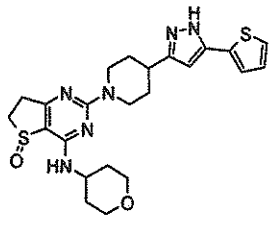
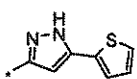
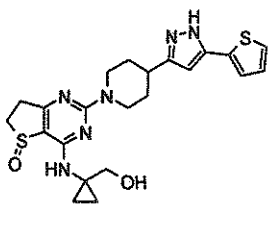
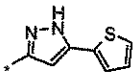
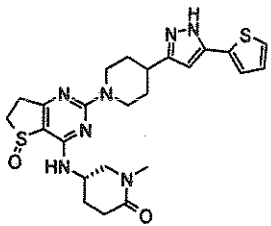
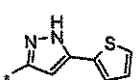
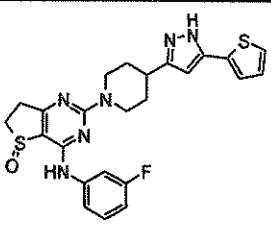
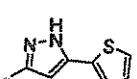
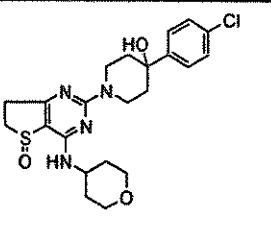
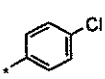
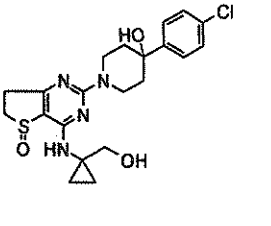
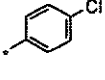
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254		H			OH	92

255		H			H	93
256		H			H	91
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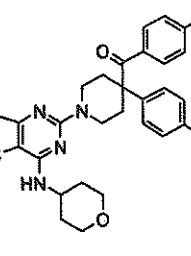
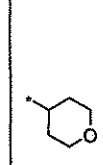
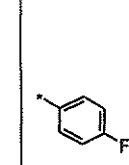
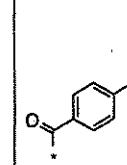
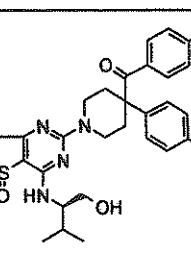
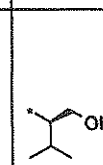
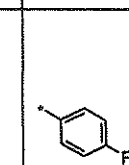
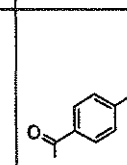
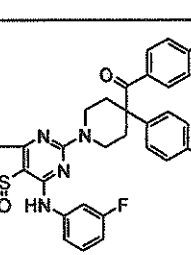
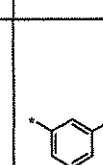
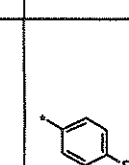
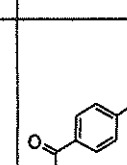
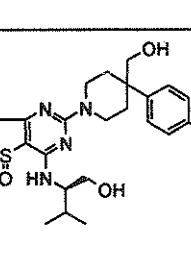
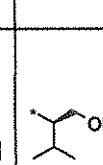
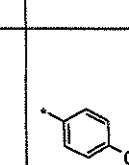
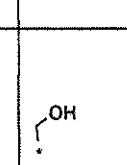
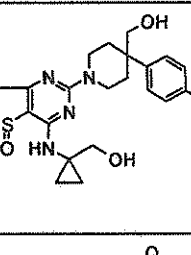
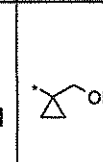
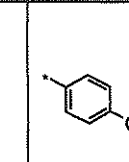
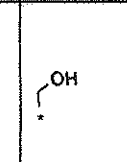
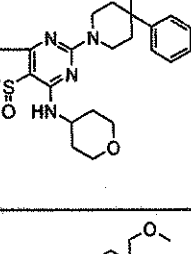
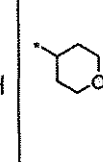
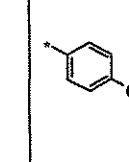
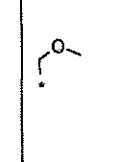
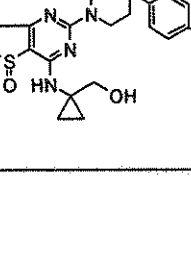
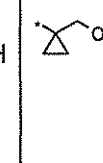
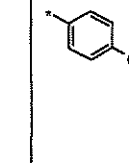
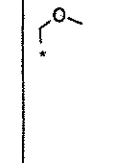
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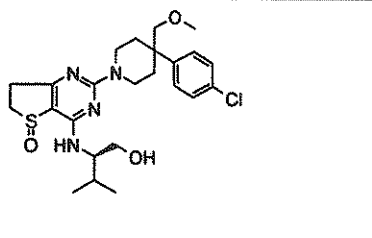
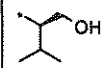
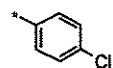
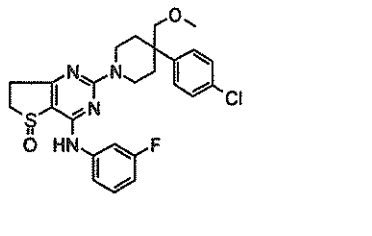
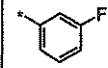
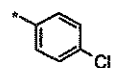
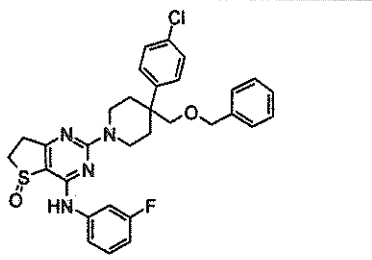
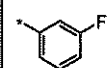
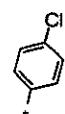
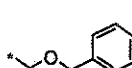
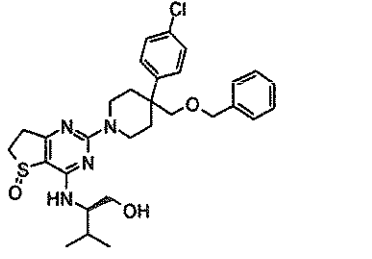
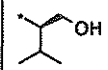
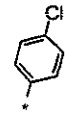
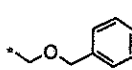
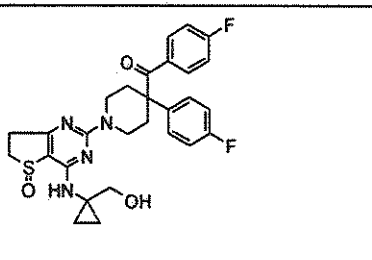
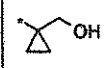
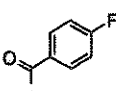
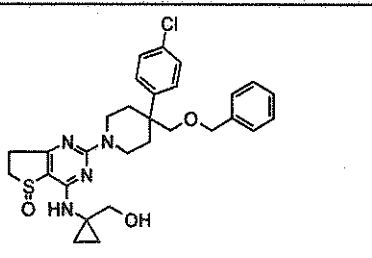
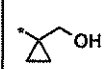
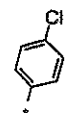
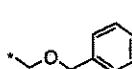
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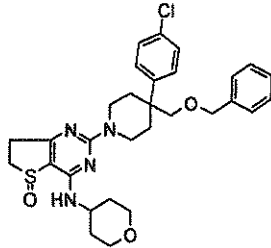
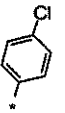
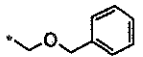
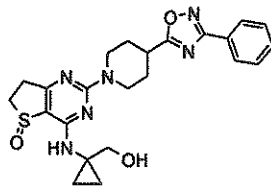
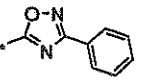
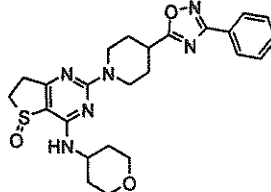
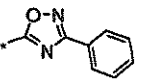
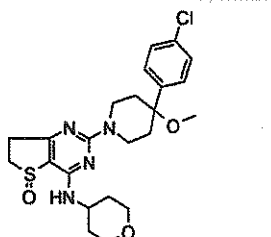
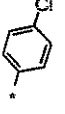
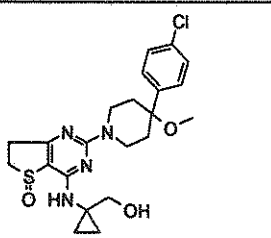
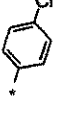
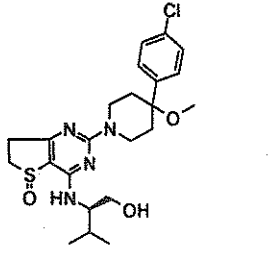
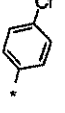
277		H			H	96
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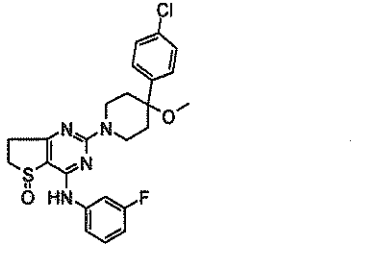
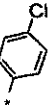
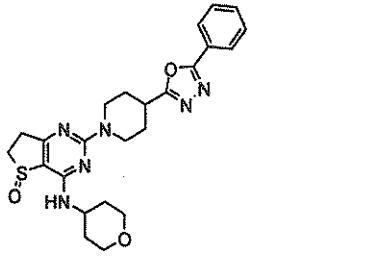
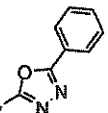
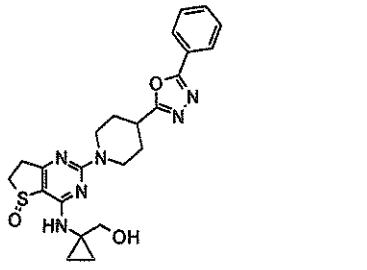
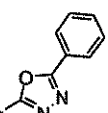
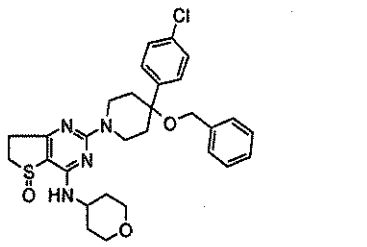
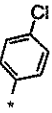
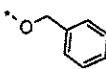
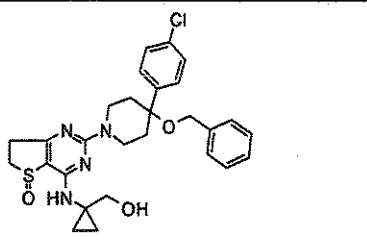
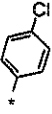
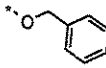
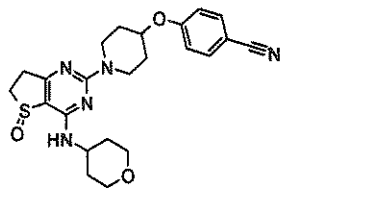
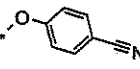
283		H			H	89
284		H			H	83
285		H			H	90
286		H			H	89
287		H			H	89
288		H			OH	89
289		H			OH	81

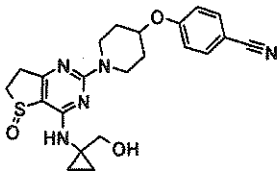
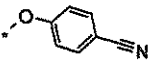
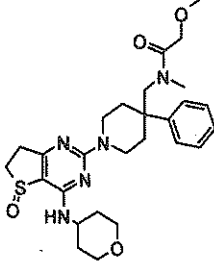
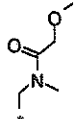
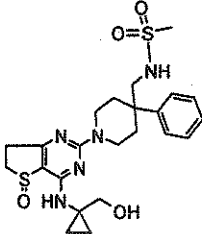
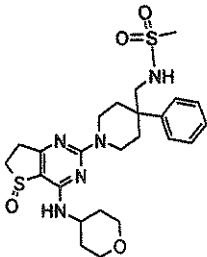
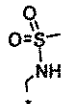
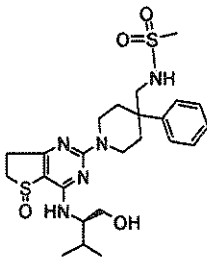
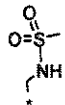
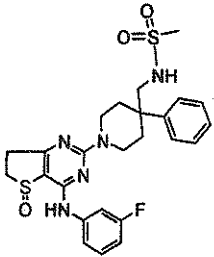
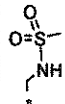
290		H			OH	86
291		H			OH	89
292		H			H	83
293		H			CN	86
294		H			CN	88
295		H			CN	93
296		H			OH	81

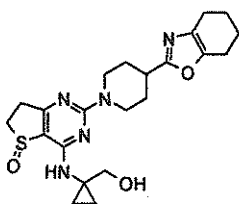
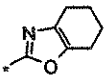
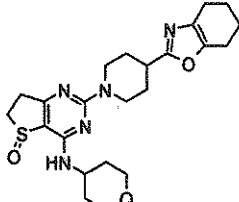
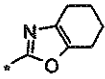
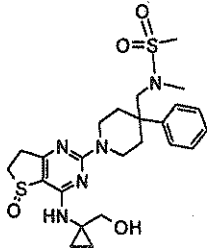
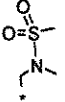
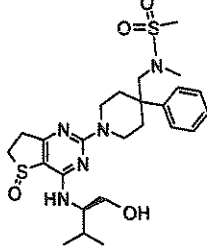
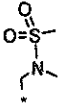
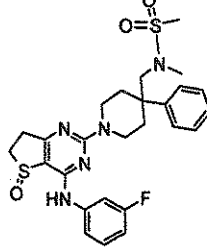
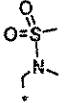
297		H				73
298		H				91
299		H				90
300		H				86
301		H				92
302		H				91
303		H				89

304		H				89
305		H				91
306		H				89
307		H				89
308		H				89
309		H				92

310		H				92
311		H			H	91
312		H			H	92
313		H			OCH ₃	89
314		H			OCH ₃	88
315		H			OCH ₃	89

316		H			OCH ₃	92
317		H			H	95
318		H			H	91
319		H				91
320		H				92
321		H			H	93

322		H			H	91
323		H				94
324		H				89
325		H				87
326		H				88
327		H				83

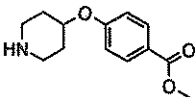
328		H			H	93
329		H			H	95
330		H				92
331		H				85
332		H				93

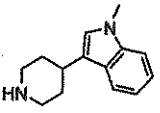
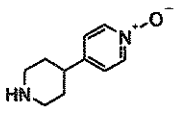
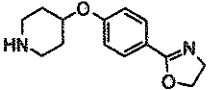
1) This Example is diastereomeric to Example 245 (see experim. Section).

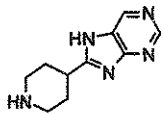
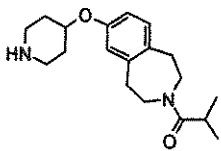
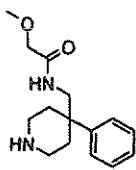
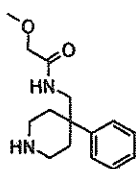
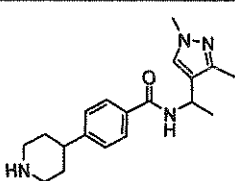
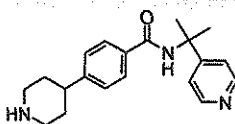
2) This Example is diastereomeric to Example 232 (see experim. Section)

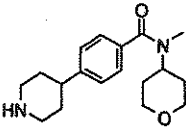
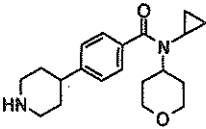
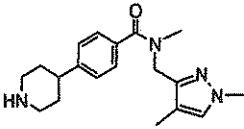
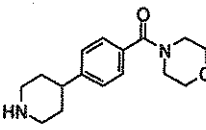
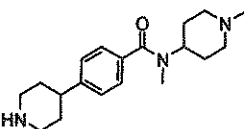
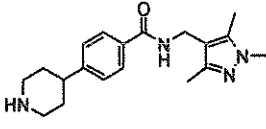
Table D that follows gives detailed information on the chemical syntheses and the analysis of the individual Example substances 164-332.

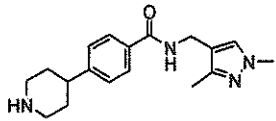
Table D: Detailed information on the preparation of the individual Example substances 164-332

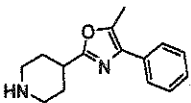
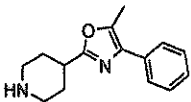
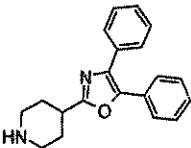
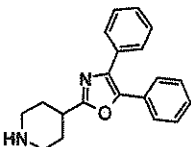
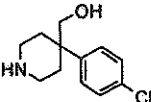
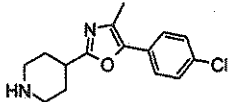
#	Prepared analogously to #*	non-commercial arylpiperidine component (V)	literature on the preparation of component (V)	analytical HPLC-MS, RT [min], method
164	89			1.13 method A
165	73			1.39 method A
166	90			1.20 method A
167	89			1.16 method A
168	14			1.17 method A
169	100			1.15 method A
170	90			0.94 method A
172	90			1.15 method A
173	90			0.97 method A
174	90			1.15 method A
175	90			1.21 method A
176	90		<i>J. Med. Chem.</i> 2002 , 3406	1.17 method A
177	90			1.18 method A
178	see experim. Section			1.01 method A
179	90			1.22 method A
180	see experim. Section			0.99 method A
181	90			1.30 method A
182	see experim. Section			1.27 method A
183	see experim. Section			0.99 method A
184	see experim. Section			1.19 method B

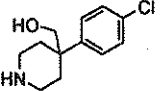
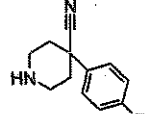
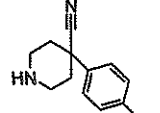
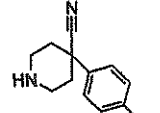
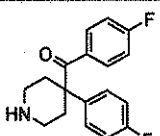
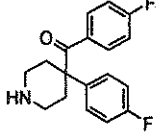
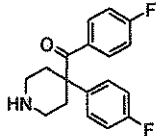
185	see experim. Section			1.37 method B
186	see experim. Section			1.10 method B
187	100			1.33 method B
188	100			1.03 method B
189	100			1.18 method B
190	100			1.14 method B
191	90			1.18 method B
192	see experim. Section			1.16 method B
193	90		WO2004/006922	1.23 method B
194	see experim. Section			1.27 method B
195	see experim. Section			1.21 method B
196	100		WO03051868	0.96 method B
197	see experim. Section			1.26 method B
198	see experim. Section			1.21 method B
199	100		(V-4) (see experim. Section, 37.3)	1.07 method B
200	see experim. Section			1.26 method B
201	see experim. Section			1.36 method B
202	see experim. Section			1.16 method B
203	see experim. Section			1.38 method B
204	see experim. Section			1.11 method B
205	see experim. Section			1.23 method B
206	see experim. Section			1.08 method B

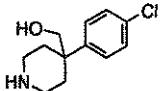
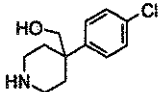
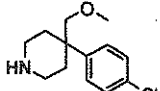
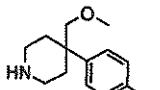
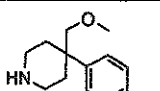
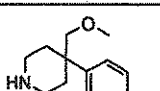
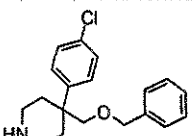
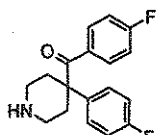
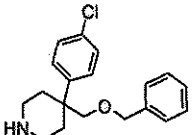
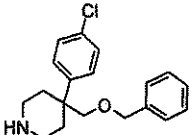
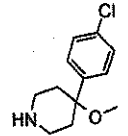
207	90			0.83 method D
208	90		<i>Bioorg. Med. Chem. Lett.</i> 2004 , 695	0.76 method D
209	90			0.95 method D
210	see experim. Section			0.86 method D
211	see experim. Section			1.45 method B
212	90			0.99 method D
213	90			1.00 method B
214	see experim. Section			1.10 method D
215	90		Prepared analogously to (V-18) (see experim. Section 57.3)*	1.11 method D
216	89		(V-12) (see experim. Section 50.2)	1.20 method B
217	90		(V-12) (see experim. Section 50.2)	1.21 method B
218	90		Prepared analogously to (V-19) (see experim. Section 59.2)*	1.17 method B
219	100			1.18 method B
220	89			1.19 method B
221	90			1.22 method B
222	see experim. Section			1.46 method B
223	90		Prepared analogously to (V-19) (see experim. Section 59.2)*	1.03 method D

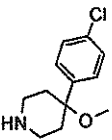
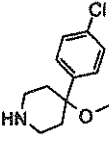
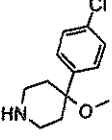
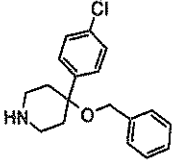
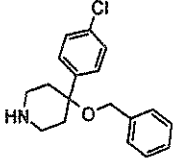
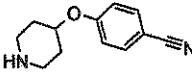
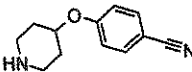
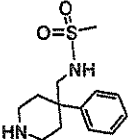
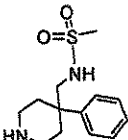
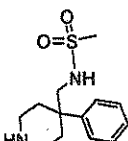
224	90		Prepared analogously to (V-19) (see experim. Section 59.2)*	0.99 method D
225	90		Prepared analogously to (V-19) (see experim. Section 59.2)*	1.06 method D
226	90		Prepared analogously to (V-19) (see experim. Section 59.2)*	0.98 method D
227	90		Prepared analogously to (V-19) (see experim. Section 59.2)*	0.98 method D
228	90		Prepared analogously to (V-19) (see experim. Section 59.2)*	0.96 method D
229	see experim. Section			1.05 method D
230	90		Prepared analogously to (V-19) (see experim. Section 59.2)*	0.99 method D
231	see experim. Section			1.48 method B
232 ¹⁾	see experim. Section			2.73 method E
233	see experim. Section			1.24 method B
234	186			1.14 method D
235	186			1.21 method D
236	242			1.02 method D
237	242			0.98 method D
238	242			1.05 method D
239	242			0.97 method D
240	242			1.23 method B
241	242			1.09 method B

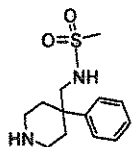
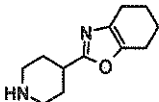
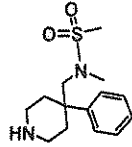
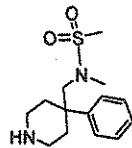
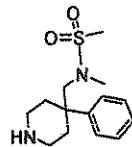
242	see experim. Section			1.03 method D
243	242			0.97 method D
244	242			0.99 method D
245 ²⁾	see experim. Section			2.85 method E
246	see experim. Section			1.21 method B
247	90			1.00 method D
248	90			0.99 method D
249	see experim. Section			1.05 method D
250	249			1.01 method D
251	249			1.14 method D
252	see experim. Section			1.18 method B
253	see experim. Section			1.15 method B
254	100			1.23 method B
255	249			1.04 method D
256	249			1.00 method D
257	249			1.07 method D
258	249			1.00 method D
259	249			0.98 method D
260	see experim. Section			1.30 method B
261	see experim. Section			1.30 method B
262	90		Prepared analogously to (V-19) (see experim. Section 59.2)*	1.15 method B
263	242			1.15 method B
264	100			0.94 method B

265	100			1.32 method B
266	100			1.39 method B
267	100			1.39 method B
268	90			0.99 method B
269	90			1.45 method B
270	see experim. Section			1.21 method B
271	90			1.39 method B
272	90			1.45 method B
273	see experim. Section			1.23 method B
274	see experim. Section			1.19 method D
275	see experim. Section			1.08 method D
276	90		(V-25) (see experim. Section 72.1)	1.18 method D
277	89		(V-25) (see experim. Section 72.1)	1.33 method B
278	see experim. Section			1.40 method B
279	90		(V-26) (see experim. Section 73.2)	1.50 method B
280	89		(V-26) (see experim. Section 73.2)	1.43 method B
281	90		<i>J. Med. Chem.</i> 2004 , 497	1.24 method B
282	90		(V-27) (see experim. Section 74.1)	1.24 method B

283	see experim. Section			1.37 method B
284	90			1.23 method B
285	89			1.0 method D
286	100			1.19 method B
287	73			1.17 method D
288	90			1.25 method B
289	89			1.23 method B
290	73			1.42 method B
291	73		<i>J. Med. Chem.</i> 2004 , 497	1.41 method B
292	14			1.03 method D
293	90		<i>J. Med. Chem.</i> 1999 , 4778	1.11 method D
294	100		<i>J. Med. Chem.</i> 1999 , 4778	1.03 method D
295	89		<i>J. Med. Chem.</i> 1999 , 4778	1.08 method D
296	14			1.27 method B
297	90		(V-13) (see experim. Section 51.3)	1.43 method B
298	14		(V-13) (see experim. Section 51.3)	1.45 method B
299	73		(V-13) (see experim. Section 51.3)	1.66 method B

300	14		<i>J. Med. Chem.</i> 2004 , 497	1.29 method B
301	89		<i>J. Med. Chem.</i> 2004 , 497	1.23 method B
302	90		(V-20) (see experim. Section 67.3)	1.48 method B
303	89		(V-20) (see experim. Section 67.3)	1.32 method B
304	14		(V-20) (see experim. Section 67.3)	1.37 method B
305	73		(V-20) (see experim. Section 67.3)	1.58 method B
306	see experim. Section			1.75 method B
307	14		(V-28) (see experim. Section 75.1)	1.50 method B
308	89		(V-13) (see experim. Section 51.3)	1.40 method B
309	89		(V-28) (see experim. Section 75.1)	1.48 method B
310	90		(V-28) (see experim. Section 75.1)	1.51 method B
311	89			1.29 method B
312	90			1.33 method B
313	90		(V-21) (see experim. Section 68.1)	1.39 method B

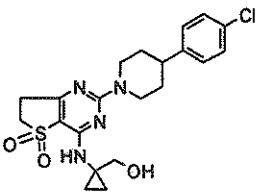
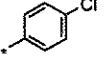
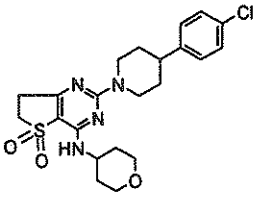
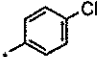
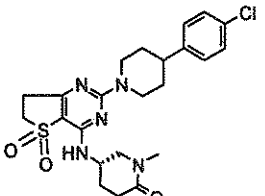
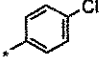
314	89		(V-21) (see experim. Section 68.1)	1.35 method B
315	14		(V-21) (see experim. Section 68.1)	1.39 method B
316	73		(V-21) (see experim. Section 68.1)	1.61 method B
317	90			1.25 method B
318	89			1.22 method B
319	90		(V-28) (see experim. Section 75.1)	1.54 method B
320	89		(V-28) (see experim. Section 75.1)	1.51 method B
321	90		WO2007/106705	1.29 method B
322	89		WO2007/106705	1.24 method B
323	see experim. Section			1.24 method B
324	89		<i>Bioorg. Med. Chem. Lett.</i> 1998 , 1851	1.21 method B
325	90		<i>Bioorg. Med. Chem. Lett.</i> 1998 , 1851	1.21 method B
326	14		<i>Bioorg. Med. Chem. Lett.</i> 1998 , 1851	1.24 method B

327	73		<i>Bioorg. Med. Chem. Lett.</i> 1998 , 1851	1.38 method B
328	89		(V-30) (see experim. Section 77.2)	1.23 method B
329	see experim. Section			1.23 method B
330	89		(V-22) (see experim. Section 69.1)	1.24 method B
331	14		(V-22) (see experim. Section 69.1)	1.30 method B
332	73		(V-22) (see experim. Section 69.1)	1.44 method B

* the Example may be prepared and purified analogously.

- 1) This Example is diastereomeric to Example 245 (see experim. Section).
- 2) This Example is diastereomeric to Example 232 (see experim. Section)

Table E: Chemical structures and preparation of the Example substances 333 -335

#	Structure	R1	R2	R3	R4	preparation	analytical HPLC-MS, RT [min], method	% Inhibition PDE4B @ 1 μM
333		H			H	see experim. Section	1.49 method B	56
334		H			H	see experim. Section	1.55 method B	65
335		H			H	see experim. Section	1.48 method B	85

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 as well as bone tumours such as e.g. osteosarcoma and all kinds of gliomas such as e.g. 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, MRP4-inhibitors, dopamine agonists, H1-antihistamines, PAF-antagonists and PI3-kinase inhibitors or double or triple combinations thereof, such as for example combinations of compounds of formula 1 with one or two compounds selected from among

- betamimetics, corticosteroids, PDE4-inhibitors, EGFR-inhibitors and LTD4-antagonists,
- anticholinergics, betamimetics, corticosteroids, PDE4-inhibitors, EGFR-inhibitors and LTD4-antagonists,
- PDE4-inhibitors, corticosteroids, EGFR-inhibitors and LTD4-antagonists
- EGFR-inhibitors, PDE4-inhibitors and LTD4-antagonists
- EGFR-inhibitors and LTD4-antagonists
- CCR3-inhibitors, iNOS-inhibitors (inducible nitric oxide synthase-inhibitors), (6R)-L-erythro-5,6,7,8-tetrahydrobiopterin (hereinafter referred to as "BH4") and the derivatives thereof as mentioned in WO 2006/120176 and SYK-inhibitors (spleen tyrosine kinase inhibitors)
- anticholinergics, betamimetics, corticosteroids, PDE4-inhibitors and MRP4-inhibitors.

The invention also relates to combinations of three active substances, each chosen 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-{[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-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)-1,1-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 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-fluorene-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, scopolamine 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, CI-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-methylbenzo[s][1.6]naphthyridin-6-yl]-N,N-diisopropylbenzamide, (R)-(+)-1-(4-bromobenzyl)-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, CI-1018, CDC-801, D-22888, YM-58997, Z-15370, N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxy-

benzamide, 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-quinoliny)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methyl)cyclopropane-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-cyclopentylloxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)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-cyclopentylmethoxy-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-cyclopentylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-[[4-(N-cyclopropyl-N-methyl-amino)-1-oxo-2-buten-1-yl]amino]-7-cyclopentylmethoxy-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-acetyl-amino-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-acetyl-amino-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-acetyl-amino-

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-isopropylloxycarbonyl-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-fluorophenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexan-1-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)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-cyclopentylmethoxy-quinazoline, 4-[(3-chloro-4-fluorophenyl)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-fluorophenyl)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-fluorophenyl)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-fluorophenyl)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-cyclopentylmethoxy-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-isopropoxyloxycarbonyl-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-cyclopentylmethoxy-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-acetyl-amino-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-fluorophenyl)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, chlorphenoxamine, 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-beta-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), alpha-naphthyl-beta-D-glucuronide, nitrobenzyl mercaptopurine riboside, probenecid, PSC833, sildenafil, sulfinpyrazone, taurochenodeoxycholate, taurocholate, taurodeoxycholate, tauroolithocholate, tauroolithocholic 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, tauroolithocholate, tauroolithocholic 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.

Compounds which may be used as iNOS inhibitors are compounds selected from among: S-(2-aminoethyl)isothiurea, aminoguanidine, 2-aminomethylpyridine, AMT, L-canavanine, 2-iminopiperidine, S-isopropylisothiurea, S-methylisothiurea, S-

ethylisothiurea, S-methylthiocitrullin, S-ethylthiocitrulline, L-NA (N^{ω} -nitro-L-arginine), L-NAME (N^{ω} -nitro-L-argininemethylester), L-NMMA (N^G -monomethyl-L-arginine), L-NIO (N^{ω} -iminoethyl-L-ornithine), L-NIL (N^{ω} -iminoethyl-lysine), (S)-6-acetimidoylamino-2-amino-hexanoic acid (1*H*-tetrazol-5-yl)-amide (SC-51) (*J. Med. Chem.* 2002, 45, 1686-1689), 1400W, (S)-4-(2-acetimidoylamino-ethylsulphanyl)-2-amino-butyric acid (GW274150) (*Bioorg. Med. Chem. Lett.* 2000, 10, 597-600), 2-[2-(4-methoxy-pyridin-2-yl)-ethyl]-3*H*-imidazo[4,5-*b*]pyridine (BYK191023) (*Mol. Pharmacol.* 2006, 69, 328-337), 2-((R)-3-amino-1-phenyl-propoxy)-4-chloro-5-fluorobenzonitrile (WO 01/62704), 2-((1*R*,3*S*)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-6-trifluoromethyl-nicotinonitrile (WO 2004/041794), 2-((1*R*,3*S*)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-4-chloro-benzonitrile (WO 2004/041794), 2-((1*R*,3*S*)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-5-chloro-benzonitrile (WO 2004/041794), (2*S*,4*R*)-2-amino-4-(2-chloro-5-trifluoromethyl-phenylsulphanyl)-4-thiazol-5-yl-butan-1-ol (WO 2004/041794), 2-((1*R*,3*S*)-3-amino-4-hydroxy-1-thiazol-5-yl-butylsulphanyl)-5-chloro-nicotinonitrile (WO 2004/041794), 4-((S)-3-amino-4-hydroxy-1-phenyl-butylsulphanyl)-6-methoxy-nicotinonitrile (WO 02/090332), substituted 3-phenyl-3,4-dihydro-1-isoquinolinamine such as e.g. AR-C102222 (*J. Med. Chem.* 2003, 46, 913-916), (1*S*,5*S*,6*R*)-7-chloro-5-methyl-2-azabicyclo[4.1.0]hept-2-en-3-ylamine (ONO-1714) (*Biochem. Biophys. Res. Commun.* 2000, 270, 663-667), (4*R*,5*R*)-5-ethyl-4-methyl-thiazolidin-2-ylideneamine (*Bioorg. Med. Chem.* 2004, 12, 4101), (4*R*,5*R*)-5-ethyl-4-methyl-selenazolidin-2-ylideneamine (*Bioorg. Med. Chem. Lett.* 2005, 15, 1361), 4-aminotetrahydrobiopterine (*Curr. Drug Metabol.* 2002, 3, 119-121), (E)-3-(4-chloro-phenyl)-*N*-(1-{2-oxo-2-[4-(6-trifluoromethyl-pyrimidin-4-yloxy)-piperidin-1-yl]-ethylcarbamoyl}-2-pyridin-2-yl-ethyl)-acrylamide (FR260330) (*Eur. J. Pharmacol.* 2005, 509, 71-76), 3-(2,4-difluorophenyl)-6-[2-(4-imidazol-1-ylmethyl-phenoxy)-ethoxy]-2-phenyl-pyridine (PPA250) (*J. Pharmacol. Exp. Ther.* 2002, 303, 52-57), methyl 3-[[[(benzo[1,3]dioxol-5-ylmethyl)-carbamoyl]-methyl]-4-(2-imidazol-1-yl-pyrimidin-4-yl)-piperazine-1-carboxylate (BBS-1) (*Drugs Future* 2004, 29, 45-52), (R)-1-(2-imidazol-1-yl-6-methyl-pyrimidin-4-yl)-pyrrolidine-2-carboxylic acid (2-benzo[1,3]dioxol-5-yl-ethyl)-amide (BBS-2) (*Drugs Future* 2004, 29, 45-52) and the pharmaceutical salts, prodrugs or solvates thereof.

Examples of iNOS-inhibitors within the scope of the present invention may also include antisense oligonucleotides, particularly those antisense oligonucleotides which bind iNOS-coding nucleic acids. For example, WO 01/52902 describes antisense oligonucleotides, particularly antisense oligonucleotides, which bind iNOS coding nucleic acids, for modulating the expression of iNOS. iNOS-antisense oligonucleotides as described particularly in WO 01/52902 may therefore also be

combined with the PDE4-inhibitors of the present invention on account of their similar effect to the iNOS-inhibitors.

Compounds which may be used as SYK-inhibitors are preferably compounds selected from among:

2-[(2-aminoethyl)amino]-4-[(3-bromophenyl)amino]-5-pyrimidinecarboxamide;
2-[[7-(3,4-dimethoxyphenyl)imidazo[1,2-c]pyrimidin-5-yl]amino]-3-pyridinecarboxamide;
6-[[5-fluoro-2-[3,4,5-trimethoxyphenyl)amino]-4-pyrimidinyl]amino]-2,2-dimethyl-2H-pyrido[3,2-b]-1,4-oxazin-3(4H)-one;
N-[3-bromo-7-(4-methoxyphenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine
7-(4-methoxyphenyl)-N-methyl-1,6-naphthyridin-5-amine;
N-[7-(4-methoxyphenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(2-thienyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-1,2-ethanediamine;
N-[7-(4-methoxyphenyl)-2-(trifluoromethyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(4-methoxyphenyl)-3-phenyl-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-(7-phenyl-1,6-naphthyridin-5-yl)-1,3-propanediamine;
N-[7-(3-fluorophenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(3-chlorophenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[3-(trifluoromethoxy)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(4-fluorophenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(4-fluorophenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(4-chlorophenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(4'-methyl[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-(diethylamino)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-(4-morpholinyl)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-[[2-(dimethylamino)ethyl]methylamino]phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(4-bromophenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(4-methylphenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-(methylthio)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-(1-methylethyl)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
7-[4-(dimethylamino)phenyl]-N-methyl-1,6-naphthyridin-5-amine;
7-[4-(dimethylamino)phenyl]-N,N-dimethyl-1,6-naphthyridin-5-amine;
N-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-1,4-butanediamine;
N-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-1,5-pentanediamine;

3-[[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]oxy]-1-propanol;
4-[5-(4-aminobutoxy)-1,6-naphthyridin-7-yl]-N,N-dimethyl-benzenamine;
4-[[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]amino]-1-butanol;
N-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-N-methyl-1,3-propanediamine;
N-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-N'-methyl-1,3-propanediamine;
N-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-N,N'-dimethyl-1,3-propanediamine;
1-amino-3-[[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]amino]-2-propanol;
N-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-2,2-dimethyl-1,3-propanediamine;
7-[4-(dimethylamino)phenyl]-N-(3-pyridinylmethyl)-1,6-naphthyridin-5-amine;
N-[(2-aminophenyl)methyl]-7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-amine;
N-[7-[6-(dimethylamino)[1,1'-biphenyl]-3-yl]-1,6-naphthyridin-5-yl]-1,3-propanediamine, ;
N-[7-[3-chloro-4-(diethylamino)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-(dimethylamino)-3-methoxyphenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-(diethylamino)phenyl]-3-methyl-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(3'-fluoro[1,1'-biphenyl]-3-yl)-1,6-naphthyridin-5-yl]-1,2-ethanediamine,
N-[7-(4-methoxyphenyl)-1,6-naphthyridin-5-yl]-1,6-naphthyridine-1,3-propanediamine;
N,N'-bis(3-aminopropyl)-7-(4-methoxyphenyl)-2,5-diamine;
N-[7-(4-methoxyphenyl)-2-(phenylmethoxy)-1,6-naphthyridin-5-yl]-1,6-naphthyridine-1,3-propanediamine;
N5-(3-aminopropyl)-7-(4-methoxyphenyl)-N2-(phenylmethyl)-2,5-diamine;
N-[7-(2-naphthalenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(2'-fluoro[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(3,4,5-trimethoxyphenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(3,4-dimethylphenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
1-amino-3-[[7-(2-naphthalenyl)-1,6-naphthyridin-5-yl]amino]-2-propanol;
1-amino-3-[[7-(2'-fluoro[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-5-yl]amino]-2-propanol;
1-amino-3-[[7-(4'-methoxy[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-5-yl]amino]-2-propanol;
1-amino-3-[[7-(3,4,5-trimethoxyphenyl)-1,6-naphthyridin-5-yl]amino]-2-propanol;
1-amino-3-[[7-(4-bromophenyl)-1,6-naphthyridin-5-yl]amino]-2-propanol;
N-[7-(4'-methoxy[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-5-yl]-2,2-dimethyl-1,3-propanediamine;
1-[[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]amino]-2-propanol;
2-[[2-[[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]amino]ethyl]thio]-ethanol;
7-[4-(dimethylamino)phenyl]-N-(3-methyl-5-isoxazolyl)-1,6-naphthyridin-5-amine;

7-[4-(dimethylamino)phenyl]-N-4-pyrimidinyl-1,6-naphthyridin-5-amine;
N-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-1,3-cyclohexanediamine;
N,N-dimethyl-4-[5-(1-piperazinyl)-1,6-naphthyridin-7-yl]-benzenamine;
4-[5-(2-methoxyethoxy)-1,6-naphthyridin-7-yl]-N,N-dimethyl-benzenamine;
1-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-4-piperidinol;
1-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-3-pyrrolidinol;
7-[4-(dimethylamino)phenyl]-N-(2-furanylmethyl)-1,6-naphthyridin-5-amine;
7-[4-(dimethylamino)phenyl]-N-[3-(1H-imidazol-1-yl)propyl]-1,6-naphthyridin-5-amine;
1-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-4-piperidinecarboxamide;
1-[3-[[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]amino]propyl]-2-pyrrolidinone;
N-[3'-[5-[(3-aminopropyl)amino]-1,6-naphthyridin-7-yl][1,1'-biphenyl]-3-yl]-acetamide;
N-[7-(4'-fluoro[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[4'-[5-[(3-aminopropyl)amino]-1,6-naphthyridin-7-yl][1,1'-biphenyl]-3-yl]-acetamide;
N-[7-[4-(1,3-benzodioxol-5-yl)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-(2-thienyl)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-fluoro-3-(trifluoromethyl)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-(3-pyridinyl)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(1,3-benzodioxol-5-yl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(6-methoxy-2-naphthalenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
7-[4-(dimethylamino)phenyl]-N-(4-pyridinylmethyl)-1,6-naphthyridin-5-amine;
3-[[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]methylamino]-propanenitrile;
7-[4-(dimethylamino)phenyl]-N-[1-(phenylmethyl)-4-piperidinyl]-1,6-naphthyridin-5-amine;
N-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-1,2-cyclohexanediamine, (1R,2S)-rel-;
N-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-1,2-benzenedimethanamine;
N-[7-[4-(diethylamino)phenyl]-1,6-naphthyridin-5-yl]-1,4-butanediamine;
N-[7-[3',5'-bis(trifluoromethyl)[1,1'-biphenyl]-4-yl]-1,6-naphthyridin-5-yl]-3-propanediamine;
N-[7-(3'-methoxy[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(3'-fluoro[1,1'-biphenyl]-4-yl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
4-[[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]oxy]-1-butanol;
N-[7-[4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-1,4-cyclohexanediamine;
7-[4-(dimethylamino)phenyl]-N-(2,2,6,6-tetramethyl-4-piperidinyl)-1,6-naphthyridin-5-amine;
N-[7-[3-bromo-4-(dimethylamino)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(1-methyl-1H-indol-5-yl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[3-(trifluoromethyl)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;

N-[7-[4-(trifluoromethyl)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-(3-bromo-4-methoxyphenyl)-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N-[7-[4-[[3-(dimethylamino)propyl]methylamino]phenyl]-1,6-naphthyridin-5-yl]-1,4-cyclohexanediamine;
N-[7-[4-[[2-(dimethylamino)ethyl]methylamino]phenyl]-1,6-naphthyridin-5-yl]-1,4-cyclohexanediamine;
N-[7-[4-(dimethylamino)-3-methoxyphenyl]-1,6-naphthyridin-5-yl]-1,4-cyclohexanediamine;
N-[7-[4-(4-morpholinyl)phenyl]-1,6-naphthyridin-5-yl]-1,4-cyclohexanediamine;
N-[7-[3-bromo-4-(4-morpholinyl)phenyl]-1,6-naphthyridin-5-yl]-1,4-cyclohexanediamine;
4-[[7-[4-[[2-(dimethylamino)ethyl]methylamino]phenyl]-1,6-naphthyridin-5-yl]oxy]-cyclohexanol;
N-[7-[3-bromo-4-(4-morpholinyl)phenyl]-1,6-naphthyridin-5-yl]-1,3-propanediamine;
N,N-dimethyl-4-[5-(4-methyl-1-piperazinyl)-1,6-naphthyridin-7-yl]-benzenamine;
4-[[7-[4-[[3-(dimethylamino)propyl]methylamino]phenyl]-1,6-naphthyridin-5-yl]oxy]-cyclohexanol;
N-[7-[4-[[2-(dimethylamino)ethyl]methylamino]phenyl]-1,6-naphthyridin-5-yl]-1,4-butanediamine;
1,1-dimethylethyl [3-[[5-[(3-aminopropyl)amino]-7-(4-methoxyphenyl)-1,6-naphthyridin-2-yl]amino]propyl]-carbamate.

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 tableting 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 the compounds of formula 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.

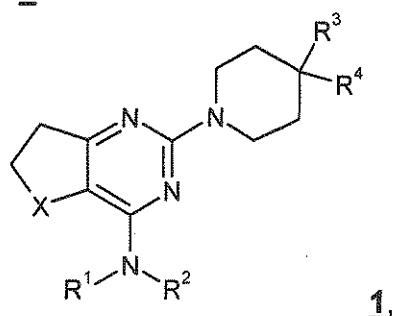
Co-solvents and/or other excipients may be added to the propellant-free inhalable solutions used for the purpose according to the invention. Preferred co-solvents are those which contain hydroxyl groups or other polar groups, e.g. Alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol,

polyethyleneglycol, polypropyleneglycol, glycoether, 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, together with dihydrothienopyrimidine and one or more combination partners selected from those described above.

Patent Claims

1. Compounds of formula 1



wherein

X denotes SO or SO₂,

R¹ denotes H, C₁₋₆-alkyl,

R² is H or a group selected from among C₁₋₁₀-alkyl and C₂₋₆-alkenyl, which may optionally be substituted by one or more groups selected from halogen and C₁₋₃-fluoroalkyl or which may optionally be substituted by one or more groups selected from among OR^{2.1}, COOR^{2.1}, CONR^{2.2}R^{2.3}, SR^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, C₆₋₁₀-aryl, -het, hetaryl, a mono- or bicyclic -C₃₋₁₀-cycloalkyl, CH₂-NR^{2.2}R^{2.3} and NR^{2.2}R^{2.3},

which in turn may optionally be substituted by one or more groups selected from among OH, halogen, OR^{2.1}, oxo, CF₃, CHF₂, CH₂F, C₁₋₆-alkyl, C₁₋₆-alkanol, C₆₋₁₀-aryl, COOR^{2.1}, CH₂-NR^{2.2}R^{2.3} and NR^{2.2}R^{2.3},

wherein

het denotes a three- to eleven-membered, mono- or bicyclic, saturated or partially saturated, optionally anellated or optionally bridged heterocycle is, which contains 1, 2, 3 or 4 heteroatoms selected independently of one another from among N, S or O contains,
and wherein

hetaryl is a five- to ten-membered, mono- or bicyclic, optionally anellated heteroaryl, which contains 1, 2, 3 or 4 heteroatoms selected independently of one another from among N, S or O,

and wherein

cycloalkyl may be saturated or partially saturated,

wherein $R^{2.1}$ is H or is a group selected from among C_{1-6} -alkyl, C_{1-6} -alkanol, C_{1-3} -haloalkyl, mono- or bicyclic, $-C_{3-10}$ -cycloalkyl, C_{6-10} -aryl- C_{1-6} -alkylene, hetaryl- C_{1-6} -alkylene, het- C_{1-6} -alkylene, C_{3-10} -cycloalkyl- C_{1-6} -alkylene, a mono- or bicyclic C_{6-10} -aryl, heteroaryl and a -het, which may optionally be substituted by one or more groups selected from among OH, O- $(C_{1-3}$ -alkyl), halogen, C_{1-6} -alkyl and C_{6-10} -aryl,

wherein $R^{2.2}$ and $R^{2.3}$ independently of one another denote H or a group selected from among C_{1-6} -alkyl, mono- or bicyclic C_{3-10} cycloalkyl, C_{6-10} -aryl- C_{1-6} -alkylene, hetaryl- C_{1-6} -alkylene, mono- or bicyclic C_{6-10} -aryl, het, hetaryl, CO-NH₂, CO-NHCH₃, -CO-N(CH₃)₂, SO₂-(C_{1-2} -alkyl), CO- $R^{2.1}$ and COOR^{2.1}, which may optionally be substituted by one or more groups selected from among OH, halogen, C_{1-6} -alkyl, C_{6-10} -aryl and COOR^{2.1},

or

R^2 denotes a mono- or polycyclic C_{3-10} cycloalkyl, which may optionally be bridged one or more times via C_{1-3} -alkyl groups and which may optionally be substituted by a group selected from among branched or unbranched C_{1-6} -alkanol, C_{1-3} -fluoroalkyl, C_{1-3} -alkylene-OR^{2.1}, OR^{2.1}, COOR^{2.1}, -SO₂-NR^{2.2}R^{2.3}, het, -NH-CO-O- $(C_{1-6}$ -alkyl), -NH-CO- $(C_{1-6}$ -alkyl), -NH-CO-O- $(C_{6-10}$ -aryl), -NH-CO- $(C_{6-10}$ -aryl), -NH-CO-O-hetaryl, -NH-CO-hetaryl, -NH-CO-O- $(C_{1-3}$ -alkylene)- $(C_{6-10}$ -aryl), -NH-CO- $(C_{1-3}$ -alkylene)- $(C_{6-10}$ -aryl), -N(C_{1-3} -alkyl)-CO- $(C_{1-6}$ -alkyl), -N(C_{1-3} -alkyl)-CO-O- $(C_{6-10}$ -aryl), -N(C_{1-3} -alkyl)-CO- $(C_{6-10}$ -aryl), -N(C_{1-3} -alkyl)-CO-O-hetaryl, -N(C_{1-3} -alkyl)-CO-hetaryl, -N(C_{1-3} -alkyl)-CO-O- $(C_{1-3}$ -alkylene)- $(C_{6-10}$ -aryl), -N(C_{1-3} -alkyl)-CO- $(C_{1-3}$ -alkylene)- $(C_{6-10}$ -aryl), C_{6-10} -aryl, C_{1-6} -alkyl, C_{6-10} -aryl- C_{1-6} -alkylene, hetaryl- C_{1-6} -alkylene, mono- or bicyclic C_{3-10} cycloalkyl and NR^{2.2}R^{2.3},

which may optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, halogen, CF₃, CHF₂, CH₂F, C_{1-6} -alkyl, C_{6-10} -aryl and NR^{2.2}R^{2.3},

or

R^2 denotes a mono- or polycyclic C_{6-10} -aryl, which may optionally be substituted by OH, SH or halogen or by one or more groups selected from among OR^{2.1}, COOR^{2.1}, NR^{2.2}R^{2.3}, CH₂-NR^{2.2}R^{2.3}, C_{3-10} -cycloalkyl, het, C_{1-6} -alkyl, C_{1-3} -fluoroalkyl, CF₃, CHF₂, CH₂F, C_{6-10} -aryl- C_{1-6} -alkylene, het- C_{1-6} -alkylene, hetaryl- C_{1-6} -alkylene, C_{6-10} -aryl, SO₂-CH₃, SO₂-CH₂CH₃ and SO₂-NR^{2.2}R^{2.3},

which may in turn optionally be substituted by one or more groups selected from among OH, OR^{2.1}, CF₃, CHF₂, CH₂F, oxo, halogen, CF₃, CHF₂, CH₂F, C₁₋₆-alkyl, C₆₋₁₀-aryl and NR^{2.2}R^{2.3},

or

R² denotes a group selected from among het and hetaryl, which may optionally be substituted by one or more groups selected from among halogen, OH, oxo, CF₃, CHF₂ and CH₂F or by one or more groups selected from among OR^{2.1}, C₁₋₃-alkylene-OR^{2.1}, SR^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, COOR^{2.1}, COR^{2.1}, C₁₋₆-alkanol, mono- or bicyclic C₃₋₁₀-cycloalkyl, C₆₋₁₀-aryl, C₁₋₆-alkyl, C₆₋₁₀-aryl-C₁₋₆-alkylene, hetaryl-C₁₋₆-alkylene, het, hetaryl, C₁₋₃-alkylene-OR^{2.1} and NR^{2.2}R^{2.3}, which may in turn optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, halogen, CF₃, CHF₂, CH₂F, C₁₋₆-alkyl, C₆₋₁₀-aryl and NR^{2.2}R^{2.3},

or wherein

NR¹R² together denotes a heterocyclic C₄₋₇ ring, which may optionally be bridged, which contains 1, 2 or 3 heteroatoms selected from among N, O and S and which may optionally be substituted by one or more groups selected from among OH, OR^{2.1}, C₁₋₃-alkylene-OR^{2.1}, oxo, halogen, C₁₋₆-alkyl, C₆₋₁₀-aryl, COOR^{2.1}, CH₂-NR^{2.2}-COO-R^{2.1}, CH₂-NR^{2.2}-CO-R^{2.1}, CH₂-NR^{2.2}-CO-CH₂-NR^{2.2}R^{2.3}, CH₂-NR^{2.2}-SO₂-C₁₋₃-alkyl, CH₂-NR^{2.2}-SO₂-NR^{2.2}R^{2.3}, CH₂-NR^{2.2}-CO-NR^{2.2}R^{2.3}, CO-NR^{2.2}R^{2.3}, CH₂-NR^{2.2}R^{2.3} and NR^{2.2}R^{2.3},

and wherein

R³ is a C₆₋₁₀-aryl, which may optionally be substituted by in the ortho, para or meta position by one, two or three groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, C₁₋₆-alkyl, C₁₋₃-fluoroalkyl, -C₁₋₃-alkylene-OR^{2.1}, -C₁₋₃-alkylene-NR^{2.2}R^{2.3}, -NR^{2.2}R^{2.3}, O-R^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, COOR^{2.1}, -CO-NH-(C₁₋₆-alkylene)-hetaryl, -CO-NH-hetaryl, -CO-N(CH₃)-het, -CO-N(CH₃)-(C₁₋₃-alkylene)-het, -CO-N(CH₃)-(C₁₋₃-alkylene)-hetaryl, -CO-N(C₃₋₇-cycloalkyl)-het, -CO-NR^{2.2}R^{2.3}, -CO-NH-(C₁₋₆-alkylene)-het, NR^{2.2}-CO-R^{2.1}, C₆₋₁₀-aryl, C₆₋₁₀-aryl-C₁₋₂-alkylene, het-C₁₋₂-alkylene, -het, -CO-het, , CO-N(CH₃)-C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₂-alkylene, hetaryl-C₁₋₂-alkylene and hetaryl,

while this groups may optionally be substituted by one or more groups selected from among OH, halogen, -C₁₋₃-fluoroalkyl, oxo, methyl and phenyl,

or wherein

R³ is a group selected from among het and hetaryl, which may optionally be substituted by one or more groups selected from among halogen, C₁₋₃-fluoroalkyl, CN, OH, oxo, -C₁₋₆-alkyl, -C₁₋₃-alkylene-NR^{2.2}R^{2.3}, -NR^{2.2}R^{2.3}, SO-R^{2.1}, SO₂-R^{2.1}, -O-R^{2.1}, -COOR^{2.1}, SO₂-(CH₃), SO₂-(CH₂-CH₃), C₆₋₁₀-aryl, het, C₃₋₇-cycloalkyl and hetaryl, which may in turn optionally be substituted by one or more groups selected from among OH, halogen, -C₁₋₃-fluoroalkyl, C₁₋₆-alkyl, C₆₋₁₀-aryl, -COO(C₁₋₃-alkyl) and O-(C₁₋₃-alkyl),

or wherein

R³ denotes -O-R^{3.1},

wherein **R^{3.1}** is a group selected from among -C₁₋₆-alkyl, -C₆₋₁₀-aryl, -C₁₋₃-alkylene-C₆₋₁₀-aryl, hetaryl and het, which may optionally be substituted in the ortho, para or meta position by one, two or three groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, C₁₋₆-alkyl, C₁₋₃-fluoroalkyl, CO-(C₁₋₅-alkyl), -CO-(C₁₋₃-fluoroalkyl), -CO-NH-(C₁₋₆-alkylene)-hetaryl, -CO-N(C₁₋₃-alkyl)-(C₁₋₆-alkylene)-hetaryl, -CO-N(C₁₋₃-alkyl)-het, -CO-N(C₃₋₇-cycloalkyl)-het, -C₁₋₃-alkylene-OR^{2.1}, -C₁₋₃-alkylene-NR^{2.2}R^{2.3}, -NR^{2.2}R^{2.3}, O-R^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, COOH, COO-(C₁₋₄-alkyl), -O-C₁₋₃-alkylene-N(C₁₋₃-alkyl)₂, CO-NR^{2.2}R^{2.3}, NR^{2.2}-CO-R^{2.1}, C₆₋₁₀-aryl, C₆₋₁₀-aryl-C₁₋₂-alkylene, het-C₁₋₂-alkylene, -CO-het, het, -CO-C₃₋₇-cycloalkyl, -CO-N(C₁₋₃-alkyl)-C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₂-alkylene, hetaryl-C₁₋₂-alkylene and hetaryl,

which may in turn optionally be substituted by 1, 2, 3 or 4 groups selected independently of one another from among F, Cl, Br, methyl, O-methyl, ethyl, O-ethyl, OH, oxo and CF₃.

and wherein

R⁴ denotes H, CN, OH, CF₃, CHF₂, CH₂F, F, methyl, ethyl, -O-(C₁₋₃-alkyl), -C₁₋₃-alkylene-OH, -COO(C₁₋₃-alkyl), -CO-het, -(C₁₋₂-alkylene)-NH-SO₂-(C₁₋₂-alkyl), -(C₁₋₂-alkylene)-N(C₁₋₃-alkyl)-SO₂-(C₁₋₂-alkyl), -(C₁₋₂-alkylene)-O-(C₁₋₂-alkylene)-C₆₋₁₀-aryl, -C₁₋₃-alkylene-O-C₁₋₃-alkyl, -(C₁₋₂-alkylene)-N(C₁₋₃-alkyl)-CO-(C₁₋₂-alkyl), -NH-CO-(C₁₋₃-alkylene)-O-(C₁₋₃-alkyl), -C₁₋₃-alkylene-NH-CO-(C₁₋₃-alkyl), -C₁₋₃-alkylene-NH-CO-(C₁₋₃-alkylene)-N(C₁₋₃-alkyl)₂, -O-(C₁₋₂-alkylene)-(C₆₋₁₀-aryl), -C₁₋₃-alkylene-NH-CO-(C₁₋₃-alkylene)-O-(C₁₋₃-alkyl), -CO-(C₆₋₁₀-aryl), -(C₁₋₂-alkylene)-N(C₁₋₃-alkyl)-CO-(C₁₋₂-alkylene)-O-(C₁₋₃-alkyl),

wherein the aryl in the above groups may in turn optionally be substituted by one or more other groups selected from among F, Cl, Br, methyl, ethyl, propyl,

isopropyl, cyclopropyl, -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -O-cyclopropyl, -OH and CF₃

or wherein

R³ and R⁴ together form a mono- or bicyclic, unsaturated, saturated or partially saturated heterocycle, which contains 1, 2 or 3 heteroatoms selected from among N, O and S contains and which may optionally be substituted by one or more groups selected from among halogen, OH, oxo, C₁₋₃-fluoroalkyl, CN, C₁₋₆-alkyl, -O-R^{2.1}, -COOR^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, -C₁₋₃-alkylene-NR^{2.2}R^{2.3}, -NR^{2.2}R^{2.3}, C₆₋₁₀-aryl, C₃₋₇- cycloalkyl, het and hetaryl,

as well as pharmacologically acceptable salts thereof.

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

X denotes SO or SO₂,

R¹ denotes H

R² denotes H or C₁₋₁₀-alkyl, which may optionally be substituted by one or more groups selected from halogen and C₁₋₃-fluoroalkyl or which may optionally be substituted by one or more groups selected from among OR^{2.1}, COOR^{2.1}, CONR^{2.2}R^{2.3}, SR^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, phenyl, het, hetaryl, a monocyclic C₃₋₇-cycloalkyl, CH₂-NR^{2.2}R^{2.3} and NR^{2.2}R^{2.3}, which in turn may optionally be substituted by one or more groups selected from among OH, F, Cl, Br, OR^{2.1}, oxo, CF₃, CHF₂, CH₂F, C₁₋₆-alkyl, C₁₋₆-alkanol, phenyl, COOR^{2.1}, CH₂-NR^{2.2}R^{2.3} and NR^{2.2}R^{2.3},

wherein

het is a three- to seven-membered, monocyclic, saturated or partially saturated heterocycle or a seven- to eleven-membered, bicyclic, saturated or partially saturated heterocycle, which contains 1, 2, 3 or 4 heteroatoms selected independently of one another from among N, S or O, and wherein

hetaryl is a five- to six-membered, monocyclic, aromatic heteroaryl or a seven- to eleven-membered, bicyclic, aromatic heteroaryl, which contains in each case 1, 2, 3 or 4 heteroatoms selected independently of one another from among N, S or O,

and wherein

cycloalkyl may be saturated or partially saturated,

wherein $R^{2.1}$ is H or a group selected from among C_{1-6} -alkyl, C_{1-6} -alkanol, C_{1-3} -haloalkyl, monocyclic C_{3-7} cycloalkyl, phenyl- C_{1-6} -alkylene, hetaryl- C_{1-6} -alkylene, het- C_{1-6} -alkylene, - C_{3-7} -cycloalkyl- C_{1-6} -alkylene, phenyl, hetaryl and a het, which may optionally be substituted by one or more groups selected from among OH, F, Cl, C_{1-6} -alkyl, -O-(C_{1-3} -alkyl) and phenyl,

wherein $R^{2.2}$ and $R^{2.3}$ independently of one another denote H or a group selected from among C_{1-6} -alkyl, monocyclic C_{3-7} cycloalkyl, phenyl- C_{1-3} -alkylene, hetaryl- C_{1-3} -alkylene, phenyl, het, hetaryl, CO-NH₂, -CO-NHCH₃, -CON(CH₃)₂, SO₂-(C_{1-2} -alkyl), CO- $R^{2.1}$ and COOR^{2.1},

which may optionally be substituted by one or more groups selected from among OH, F, Cl, C_{1-6} -alkyl, phenyl and COOR^{2.1},

or

R^2 denotes a monocyclic C_{3-7} cycloalkyl, which may optionally be substituted by a group selected from among branched or unbranched C_{1-6} -alkanol, C_{1-3} -fluoroalkyl, OR^{2.1}, C_{1-3} -alkylene-OR^{2.1}, OR^{2.1}, COOR^{2.1}, SO₂-NR^{2.2}R^{2.3}, -het, -NH-CO-O-(phenyl), phenyl, C_{1-6} -alkyl, phenyl- C_{1-6} -alkylene, -hetaryl- C_{1-6} -alkylene, monocyclic C_{3-7} cycloalkyl and NR^{2.2}R^{2.3},

which may optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, F, Cl, CF₃, CHF₂, CH₂F, C_{1-6} -alkyl, phenyl and -NR^{2.2}R^{2.3},

or

R^2 denotes a phenyl, which may optionally be substituted by OH, SH or halogen or by one or more groups selected from among OR^{2.1}, COOR^{2.1}, NR^{2.2}R^{2.3}, CH₂-NR^{2.2}R^{2.3}, C_{3-7} -cycloalkyl, C_{3-7} heterocycle, C_{1-6} -alkyl, C_{1-3} -fluoroalkyl, phenyl- C_{1-6} -alkylene, -het- C_{1-6} -alkylene, -hetaryl- C_{1-6} -alkylene, phenyl, SO₂-CH₃, SO₂-CH₂CH₃ and SO₂-NR^{2.2}R^{2.3},

which may in turn optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, F, Cl, CF₃, CHF₂, CH₂F, C_{1-6} -alkyl, phenyl and NR^{2.2}R^{2.3},

or

R^2 denotes a group selected from among het and hetaryl, which may optionally be substituted by one or more groups selected from among F, Cl, OH, oxo, CF₃, CHF₂ and CH₂F or by one or more groups selected from among OR^{2.1}, -

C₁₋₃-alkylene-OR^{2.1}, SR^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, COOR^{2.1}, COR^{2.1}, C₁₋₆-alkanol, monocyclic C₃₋₇-cycloalkyl, phenyl, C₁₋₆-alkyl, phenyl-C₁₋₆-alkylene, -hetaryl-C₁₋₆-alkylene, -het, -hetaryl, and NR^{2.2}R^{2.3}, which may in turn optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, F, Cl, CF₃, CHF₂, CH₂F, C₁₋₆-alkyl, phenyl and NR^{2.2}R^{2.3},

or wherein

NR¹R² together denotes a heterocyclic C₄₋₇ ring which may optionally be bridged, which contains 1, 2 or 3 heteroatoms selected from among N, O and S and which may optionally be substituted by one or more groups selected from among OH, OR^{2.1}, C₁₋₃-alkylene-OR^{2.1}, oxo, F, Cl, C₁₋₆-alkyl, phenyl, COOR^{2.1}, CH₂-NR^{2.2}-COO-R^{2.1}, CH₂-NR^{2.2}-CO-R^{2.1}, CH₂-NR^{2.2}-CO-CH₂-NR^{2.2}R^{2.3}, CH₂-NR^{2.2}-SO₂-C₁₋₃-alkyl, CH₂-NR^{2.2}-SO₂-NR^{2.2}R^{2.3}, CH₂-NR^{2.2}-CO-NR^{2.2}R^{2.3}, CO-NR^{2.2}R^{2.3}, CH₂-NR^{2.2}R^{2.3} and NR^{2.2}R^{2.3},

and wherein

R³ is a naphthalene or phenyl, which may optionally be substituted in the ortho, para or meta position by one or two groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, C₁₋₆-alkyl, C₁₋₃-fluoroalkyl, -C₁₋₃-alkylene-OR^{2.1}, -C₁₋₃-alkylene-NR^{2.2}R^{2.3}, -NR^{2.2}R^{2.3}, O-R^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, COOR^{2.1}, -CO-NH-(C₁₋₆-alkylene)-hetaryl, -CO-NH-hetaryl, -CO-N(CH₃)-het, -CO-N(CH₃)-(C₁₋₃-alkylene)-het, -CO-N(CH₃)-(C₁₋₃-alkylene)-hetaryl, -CO-N(C₃₋₇-cycloalkyl)-het, CO-NR^{2.2}R^{2.3}, -CO-NH-(C₁₋₆-alkylene)-het, -NR^{2.2}-CO-R^{2.1}, phenyl, phenyl-C₁₋₂-alkylene, -het-C₁₋₂-alkylene, -het, -CO-het, -CO-N(CH₃)-het, CO-N(CH₃)-C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₂-alkylene, -hetaryl-C₁₋₂-alkylene and -hetaryl, while these groups may optionally be substituted by one or more groups selected from among OH, F, Cl, -C₁₋₃-fluoroalkyl, oxo, methyl and phenyl,

or wherein

R³ denotes a group selected from among het and hetaryl, which may optionally be substituted by one or more groups selected from among F, Cl, Br, C₁₋₃-fluoroalkyl, CN, OH, oxo, -C₁₋₆-alkyl, -C₁₋₃-alkylene-NR^{2.2}R^{2.3}, -NR^{2.2}R^{2.3}, SO-R^{2.1}, SO₂-R^{2.1}, -O-R^{2.1}, -COOR^{2.1}, SO₂-(CH₃), SO₂-(CH₂-CH₃), phenyl, het, C₃₋₇-cycloalkyl and hetaryl,

which may in turn optionally be substituted by one or more groups selected from among OH, F, Cl, Br, -C₁₋₃-fluoroalkyl, C₁₋₆-alkyl, phenyl, -COO(C₁₋₃-alkyl) and O-(C₁₋₃-alkyl),

or wherein

R³ denotes -O-R^{3.1},

wherein **R^{3.1}** is a group selected from among -C₁₋₆-alkyl, -phenyl, -C₁₋₃-alkylene-phenyl, hetaryl and het,

which is optionally substituted in the ortho, para or meta position by one, two or three groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, C₁₋₆-alkyl, C₁₋₃-fluoroalkyl, CO-(C₁₋₅-alkyl), -CO-(C₁₋₃-fluoroalkyl), -CO-NH-(C₁₋₆-alkylene)-hetaryl, -CO-N(CH₃)-(C₁₋₆-alkylene)-hetaryl, -CO-N(CH₃)-het, -CO-N(C₃₋₇-cycloalkyl)-het, -C₁₋₃-alkylene-OR^{2.1}, -C₁₋₃-alkylene-NR^{2.2}R^{2.3}, -NR^{2.2}R^{2.3}, O-R^{2.1}; SO-R^{2.1}, SO₂-R^{2.1}, COOH, COO-(C₁₋₄-alkyl), -O-C₁₋₃-alkylene-N(C₁₋₃-alkyl)₂, CO-NR^{2.2}R^{2.3}, NR^{2.2}-CO-R^{2.1}, phenyl, phenyl-C₁₋₂-alkylene, het-C₁₋₂-alkylene, -CO-het, het, -CO-C₃₋₇-cycloalkyl, -CO-N(CH₃)-C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl, C₃₋₇-cycloalkyl-C₁₋₂-alkylene, hetaryl-C₁₋₂-alkylene and hetaryl, which may in turn optionally be substituted by 1, 2, 3 or 4 groups selected independently of one another from among F, Cl, Br, methyl, O-methyl, ethyl, O-ethyl, OH, oxo and CF₃,

and wherein

R⁴ denotes H, CN, OH, CF₃, CHF₂, CH₂F, F, methyl, ethyl, O-methyl, O-ethyl, O-propyl, O-isopropyl, -C₁₋₃-alkylene-OH, -COO(C₁₋₃-alkyl), -CO-het, -(C₁₋₂-alkylene)-NH-SO₂-(C₁₋₂-alkyl), -(C₁₋₂-alkylene)-N(CH₃)-SO₂-(C₁₋₂-alkyl), -(C₁₋₂-alkylene)-O-(C₁₋₂-alkylene)-phenyl, -C₁₋₃-alkylene-O-C₁₋₃-alkyl, -(C₁₋₂-alkylene)-N(CH₃)-CO-(C₁₋₂-alkyl), -NH-CO-(C₁₋₃-alkylene)-O-(C₁₋₃-alkyl), -C₁₋₃-alkylene-NH-CO-(C₁₋₃-alkyl), -C₁₋₃-alkylene-NH-CO-(C₁₋₃-alkylene)-N(C₁₋₃-alkyl)₂, -O-(C₁₋₂-alkylene)-phenyl, -C₁₋₃-alkylene-NH-CO-(C₁₋₃-alkylene)-O-(C₁₋₃-alkyl), -CO-phenyl, -(C₁₋₂-alkylene)-N(CH₃)-CO-(C₁₋₂-alkylene)-O-(C₁₋₃-alkyl), wherein the phenyl in the above groups may optionally be substituted by one or more other groups selected from among F, Cl, Br, methyl, ethyl, propyl, -O-methyl, -O-ethyl, -O-propyl, -OH and CF₃

or wherein

R³ and R⁴ together form a mono- or bicyclic, unsaturated, saturated or partially saturated heterocycle, which contains 1, 2 or 3 heteroatoms selected from among N, O and S contains and which may optionally be substituted by one or more groups selected from among F, Cl, Br, OH, oxo, C₁₋₃-fluoroalkyl, CN, C₁₋₆-alkyl, -O- R^{2.1}, -COOR^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, -C₁₋₃-alkylene-NR^{2.2}R^{2.3}, -NR^{2.2}R^{2.3}, phenyl, C₃₋₇-cycloalkyl, het and hetaryl,

as well as pharmacologically acceptable salts thereof.

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

X denotes SO,

R¹ denotes H

R² denotes H or C₁₋₆-alkyl, which may optionally be substituted by one or more groups selected from F, Cl, CF₃, CHF₂ or CH₂F or which may optionally be substituted by one or more groups selected from among OR^{2.1}, COOR^{2.1}, CONR^{2.2}R^{2.3}, SR^{2.1}, SO-R^{2.1}, SO₂-R^{2.1}, phenyl, het, hetaryl, a monocyclic C₃₋₇-cycloalkyl, CH₂-NR^{2.2}R^{2.3} and NR^{2.2}R^{2.3}, which in turn may optionally be substituted by one or more groups selected from among OH, F, Cl, Br, CF₃, CHF₂, CH₂F, OR^{2.1}, oxo, methyl, ethyl, propyl, isopropyl, methanol, ethanol, phenyl, COOR^{2.1}, CH₂-NR^{2.2}R^{2.3} and NR^{2.2}R^{2.3},

wherein

het is a three- to seven-membered, monocyclic, saturated or partially saturated heterocycle, which contains 1, 2 or 3 heteroatoms selected independently of one another from among N, S or O,

and wherein

hetaryl is a five- to six-membered, monocyclic, aromatic heteroaryl which contains 1, 2 or 3 heteroatoms selected independently of one another from among N, S or O,

and wherein

cycloalkyl may be saturated or partially saturated,

wherein **R^{2.1}** is H or a group selected from among methyl, ethyl, propyl, isopropyl, methanol, ethanol, monocyclic C₃₋₇ cycloalkyl, phenyl-C₁₋₂-alkylene, -

hetaryl-C₁₋₂-alkylene, -het-C₁₋₂-alkylene, C₃₋₇-cycloalkyl-C₁₋₂-alkylene, phenyl, hetaryl and a het,

which may optionally be substituted by one or more groups selected from among OH, F, Cl, methyl, ethyl, propyl, isopropyl, O-methyl, O-ethyl, O-propyl, O-isopropyl and phenyl,

wherein R^{2.2} and R^{2.3} independently of one another denote H or a group selected from among methyl, ethyl, propyl, isopropyl, monocyclic C₃₋₇ cycloalkyl, phenyl-C₁₋₃-alkylene, hetaryl-C₁₋₃-alkylene, phenyl, -het, -hetaryl, CO-NH₂, CO-NHCH₃, CON(CH₃)₂, SO₂-(C₁₋₂-alkyl), CO-R^{2.1} and COOR^{2.1},

which may optionally be substituted by one or more groups selected from among OH, F, Cl, methyl, ethyl, propyl, isopropyl, phenyl and COOR^{2.1},

or

R² denotes a monocyclic C₃₋₇ cycloalkyl, which may optionally be substituted by a group selected from among C₁₋₂-alkanol, C₁₋₃-fluoroalkyl, C₁₋₃-alkylene-OR^{2.1}, OR^{2.1}, COOR^{2.1}, SO₂-NR^{2.2}R^{2.3}, -het, -NH-CO-O-(phenyl), methyl, ethyl, propyl, isopropyl, phenyl, phenyl-C₁₋₂-alkylene, -hetaryl-C₁₋₂-alkylene, monocyclic C₃₋₇ cycloalkyl and NR^{2.2}R^{2.3},

which may optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, F, Cl, CF₃, CHF₂, CH₂F, methyl, ethyl, propyl, isopropyl, phenyl and NR^{2.2}R^{2.3},

or

R² denotes a phenyl, which may optionally be substituted by OH, SH, F, Cl or Br or by one or more groups selected from among OR^{2.1}, COOR^{2.1}, NR^{2.2}R^{2.3}, CH₂-NR^{2.2}R^{2.3}, monocyclic C₃₋₇-cycloalkyl, -het, methyl, ethyl, propyl, isopropyl, CF₃, CHF₂, CH₂F, phenyl-C₁₋₂-alkylene, het-C₁₋₂-alkylene, hetaryl-C₁₋₂-alkylene, phenyl, SO₂-CH₃, SO₂-CH₂CH₃ and SO₂-NR^{2.2}R^{2.3},

which may in turn optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, F, Cl, CF₃, CHF₂, CH₂F, methyl, ethyl, propyl, isopropyl, phenyl and NR^{2.2}R^{2.3},

or

R² denotes a group selected from among het and hetaryl, which may optionally be substituted by one or more groups selected from among F, Cl, OH, oxo, CF₃, CHF₂ and CH₂F or by one or more groups

selected from among $OR^{2.1}$, C_{1-3} -alkylene- $OR^{2.1}$, $SR^{2.1}$, $SO-R^{2.1}$, $SO_2-R^{2.1}$, $COOR^{2.1}$, $COR^{2.1}$, methanol, ethanol, monocyclic C_{3-7} -cycloalkyl, phenyl, methyl, ethyl, propyl, isopropyl, phenyl- C_{1-2} -alkylene, hetaryl- C_{1-2} -alkylene, -het, -hetaryl and $NR^{2.2}R^{2.3}$,

which may in turn optionally be substituted by one or more groups selected from among OH, $OR^{2.1}$, oxo, F, Cl, CF_3 , CHF_2 , CH_2F , methyl, ethyl, propyl, isopropyl, butyl, isobutyl, phenyl and $NR^{2.2}R^{2.3}$,

and wherein

R^3 is a naphthalene or phenyl,

which may optionally be substituted in the ortho, para or meta position by one or two groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, methyl, ethyl, propyl, isopropyl, cyclopropyl, CF_3 , CHF_2 , CH_2F , -OCH₃, OCH₂CH₃; SO₂-CH₃, SO-CH₃, COOCH₃, COOCH₂CH₃, -CO-NH-(methylene)-hetaryl, -CO-NH-(ethylene)-hetaryl, -CO-NH-hetaryl, -CO-N(CH₃)-het, -CO-N(CH₃)-(methylene)-het, -CO-N(CH₃)-(ethylene)-het, -CO-N(CH₃)-(methylene)-hetaryl, -CO-N(CH₃)-(ethylene)-hetaryl, -CO-N(cyclopropyl)-het, CO-NH₂, CONH(CH₃), CON(CH₃)₂, -CO-NH-(methylene)-het, -CO-NH-(ethylene)-het, -NH-CO-methyl, NCH₃-CO-methyl, -NH-CO-ethyl, NCH₃-CO-ethyl, -NH-CO-propyl, NCH₃-CO-propyl, -NH-CO-isopropyl, NCH₃-CO-isopropyl, phenyl, phenyl-methylene, phenyl-ethylene, het-methylene, het-ethylene, -het, -CO-het, -CO-N(CH₃)-het, CO-N(CH₃)-cyclopropyl, C_{3-7} -cycloalkyl, C_{3-7} -cycloalkyl-methylene, C_{3-7} -cycloalkyl-ethylene, hetaryl-methylene, hetaryl-ethylene, -hetaryl, CH₂-NH₂, CH₂-NH(CH₃), CH₂-N(CH₃)₂, -NH₂, -NH(CH₃) and -N(CH₃)₂, while these groups may optionally be substituted by one or more groups selected from among OH, F, Cl, -CF₃, CHF_2 , CH_2F , oxo, methyl and phenyl

or wherein

R^3 denotes a group selected from among a het and hetaryl, which may optionally be substituted by one or more groups selected from among F, Cl, Br, CF_3 , CHF_2 , CH_2F , CN, OH, oxo, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclopropyl, -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -COO-methyl, -COO-ethyl, -COO-propyl, -COO-isopropyl, SO-(CH₃), SO-(CH₂-CH₃), SO₂-(CH₃), SO₂-(CH₂-CH₃), phenyl, CH₂-NH₂, CH₂-NH(CH₃), CH₂-N(CH₃)₂, -NH₂, -NH(CH₃), -N(CH₃)₂, het and hetaryl,

which may in turn optionally be substituted by one or more groups selected from among OH, F, Cl, CF_3 , CHF_2 , CH_2F , methyl, ethyl, propyl, isopropyl, phenyl, -COO-methyl, -COO-ethyl and O-methyl, O-ethyl,

or wherein

R^3 denotes $-O-R^{3.1}$,

wherein $R^{3.1}$ denotes a group selected from among $-C_{1-3}$ -alkyl, -phenyl, $-C_{1-3}$ -alkylene-phenyl, hetaryl and het,

which may optionally be substituted in the ortho, para or meta position by one, two or three groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, CF_3 , CHF_2 , CH_2F , CO -(methyl), CO -(ethyl), CO -(propyl), CO -(isopropyl), $-CO$ -(CF_3), $-CO-NH$ -(methylene)-hetaryl, $-CO-NH$ -(ethylene)-hetaryl, $-CO-N(CH_3)$ -(methylene)-hetaryl, $-CO-N(CH_3)$ -(ethylene)-hetaryl, $-CO-N(CH_3)$ -(propylene)-hetaryl, $-CO-N(CH_3)$ -(isopropylene)-hetaryl, $-CO-N(CH_3)$ -het, $-CO-N$ (cyclopropyl)-het, $-CO-N$ (C_{5-7} -cycloalkyl)-het, $-methylene-O$ -methyl, $-ethylene-O$ -methyl, $-propylene-O$ -methyl, $-methylene-O$ -ethyl, $-ethylene-O$ -ethyl, $-propylene-O$ -ethyl, $-methylene-NH_2$, $-methylene-NHCH_3$, $-methylene-N(CH_3)_2$, $-ethylene-NH_2$, $-ethylene-NHCH_3$, $-ethylene-N(CH_3)_2$, NH_2 , $N(CH_3)_2$, $NHCH_3$, $-O$ -methyl, O -ethyl, O -propyl, O -isopropyl, O -butyl, O -isobutyl, $-SO-CH_3$, SO -ethyl, $-SO$ -propyl, $-SO$ -isopropyl, SO_2 -methyl, $-SO_2$ -ethyl, SO_2 -propyl, SO_2 -isopropyl, $COOH$, COO -(methyl), COO -(ethyl), COO -(propyl), COO -(isopropyl), $-O$ -methylene- N (methyl) $_2$, $-O$ -ethylene- N (methyl) $_2$, $-O$ -methylene- N (ethyl) $_2$, $-O$ -ethylene- N (ethyl) $_2$, $CO-NH_2$, $CO-NH(CH_3)$, $CO-N(CH_3)_2$, $-NH-CO$ -methyl, $-NCH_3-CO$ -methyl, $-NH-CO$ -ethyl, NCH_3-CO -ethyl, phenyl, phenyl-methylene, phenyl-ethylene, het-methylene, het-ethylene, $-CO$ -het, het, $-CO-C_{5-7}$ -cycloalkyl, $-CO$ -cyclopropyl, $-CO-N(CH_3)-C_{5-7}$ -cycloalkyl, $-CO-N(CH_3)$ -cyclopropyl, C_{5-7} -cycloalkyl, cyclopropyl, C_{5-7} -cycloalkyl-methylene, C_{5-7} -cycloalkyl-ethylene, cyclopropyl-methylene, cyclopropyl-ethylene, hetaryl-methylene, hetaryl-ethylene and hetaryl, which may in turn optionally be substituted by 1, 2, 3 or 4 groups selected independently of one another from among F, Cl, Br, methyl, O -methyl, ethyl, O -ethyl, OH, oxo and CF_3 ,

and wherein

R^4 denotes H, CN, OH, CF_3 , CHF_2 , CH_2F , F, methyl, ethyl, O -methyl or O -ethyl, $-methylene-OH$, $-ethylene-OH$, $-propylene-OH$, $isopropylene-OH$, $-COO$ (methyl), $-COO$ (ethyl), $-COO$ (propyl), $-COO$ (isopropyl), $-CO$ -het, $-(methylene)-NH-SO_2$ -(methyl), $-(methylene)-NH-SO_2$ -(ethyl), $-(ethylene)-NH-SO_2$ -(methyl), $-(ethylene)-NH-SO_2$ -(ethyl), $-(methylene)-N(CH_3)-SO_2$ -(methyl), $-(methylene)-N(CH_3)-SO_2$ -(ethyl),

-(ethylene)-N(CH₃)-SO₂-(methyl), -(ethylene)-N(CH₃)-SO₂-(ethyl),
 -(methylene)-O-(methylene)-phenyl, -(methylene)-O-(ethylene)-phenyl,
 -(ethylene)-O-(methylene)-phenyl, -(ethylene)-O-(ethylene)-phenyl,
 -methylene-O-methyl, -methylene-O-ethyl, -ethylene-O-methyl
 -ethylene-O-ethyl,
 -(methylene)-N(CH₃)-CO-(methyl), -(methylene)-N(CH₃)-CO-(ethyl)
 -(ethylene)-N(CH₃)-CO-(methyl), -(ethylene)-N(CH₃)-CO-(ethyl),
 -NH-CO-(methylene)-O-(methyl), -NH-CO-(methylene)-O-(ethyl),
 -NH-CO-(ethylene)-O-(methyl), -NH-CO-(ethylene)-O-(ethyl),
 -methylene-NH-CO-(methyl), -methylene-NH-CO-(ethyl),
 -ethylene-NH-CO-(methyl), -ethylene-NH-CO-(ethyl),
 -methylene-NH-CO-(methylene)-N(methyl)₂,
 -methylene-NH-CO-(ethylene)-N(methyl)₂,
 -ethylene-NH-CO-(methylene)-N(methyl)₂,
 -ethylene-NH-CO-(ethylene)-N(methyl)₂,
 -methylene-NH-CO-(methylene)-O-(methyl),
 -methylene-NH-CO-(ethylene)-O-(methyl),
 -ethylene-NH-CO-(methylene)-O-(methyl),
 -methylene-NH-CO-(methylene)-O-(ethyl),
 -methylene-NH-CO-(ethylene)-O-(ethyl),
 -ethylene-NH-CO-(methylene)-O-(ethyl),
 -(methylene)-N(CH₃)-CO-(methylene)-O-(methyl),
 -(methylene)-N(CH₃)-CO-(ethylene)-O-(methyl),
 -(ethylene)-N(CH₃)-CO-(methylene)-O-(methyl),
 -(methylene)-N(CH₃)-CO-(methylene)-O-(ethyl),
 -(methylene)-N(CH₃)-CO-(ethylene)-O-(ethyl),
 -(ethylene)-N(CH₃)-CO-(methylene)-O-(ethyl),
 -O-(methylene)-phenyl, -O-(ethylene)-phenyl,
 -CO-phenyl,

wherein the phenyl in the above groups may optionally be substituted by one
 or more other groups selected from among F, Cl, Br, methyl, ethyl, propyl, -O-
 methyl, -O-ethyl, -O-propyl, -OH and CF₃

or wherein

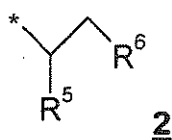
R³ and R⁴ together form a mono- or bicyclic, unsaturated, saturated or partially
 saturated heterocycle, which contains 1, 2 or 3 heteroatoms selected from
 among N, O and S and which may optionally be substituted by one or more
 groups selected from among F, Cl, Br, OH, oxo, CF₃, CHF₂, CH₂F, CN, methyl,
 ethyl, propyl, isopropyl, cyclopropyl, COO-methyl, -COO-ethyl, O-methyl, O-

ethyl, $\text{SO}_2\text{-(CH}_3\text{)}$, $\text{SO}_2\text{-(CH}_2\text{CH}_3\text{)}$, $\text{SO-(CH}_3\text{)}$, $\text{SO-(CH}_2\text{CH}_3\text{)}$, $\text{CH}_2\text{-NH}_2$, $\text{CH}_2\text{-NH(CH}_3\text{)}$, $\text{CH}_2\text{-N(CH}_3\text{)}_2$, -NH_2 , $\text{-NH(CH}_3\text{)}$, $\text{-N(CH}_3\text{)}_2$, phenyl, $\text{C}_{5-7}\text{-cycloalkyl}$, het and hetaryl,

as well as pharmacologically acceptable salts thereof.

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

R^2 denotes a group according to formula 2



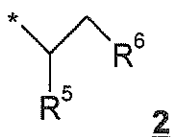
wherein R^6 is OH or NH_2 and

wherein R^5 is a group selected from among $\text{C}_{1-4}\text{-alkyl}$, a five- to six-membered heteroaryl with 1, 2 or 3 heteroatoms selected from among S, O and N and phenyl, which may optionally be substituted by one or more groups selected from among OH , F, Br, $\text{OR}^{2.1}$, oxo, methyl, ethyl, methanol, ethanol, phenyl, $\text{COOR}^{2.1}$, $\text{CH}_2\text{-NR}^{2.2}\text{R}^{2.3}$ and $\text{NR}^{2.2}\text{R}^{2.3}$,

as well as pharmacologically acceptable salts thereof.

5. Compounds of formula 1 according to claim 4, wherein

R^2 denotes a group according to formula 2



wherein R^6 is OH or NH_2 and

wherein R^5 is methyl, ethyl, propyl, isopropyl

as well as pharmacologically acceptable salts thereof.

6. Compounds of formula 1 according to one of Claims 1 to 3, wherein

R^2 is a monocyclic three-, four-, five-, six- or seven-membered cycloalkyl ring which may optionally be substituted in the spiro position by a group selected from among $-CH_2-OR^{2.1}$, branched or unbranched C_{2-6} -alkylene- $OR^{2.1}$, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclopropyl, $-CF_3$, CHF_2 , CH_2F and C_{2-4} -fluoroalkyl, wherein

$R^{2.1}$ is selected from among methyl, ethyl, propyl, isopropyl, butyl, isobutyl,

as well as pharmacologically acceptable salts thereof.

7. Compounds of formula 1 according to one of Claims 1, 2 or 3, wherein

R^2 is a cyclopropyl which may optionally be substituted by another group selected from among $-NH_2$, CH_2-NH_2 , $-NH(CH_3)$, $-N(CH_3)_2$, methyl, ethyl, propyl, isopropyl, $-NH-CO-(tert-butyl)$, $-NH-CO-O-(tert-butyl)$, $-N(CH_3)-CO-(tert-butyl)$, $-N(CH_3)-CO-O-(tert-butyl)$, $-CF_3$, $-CHF_2$, CH_2F , F, Cl and Br,

as well as pharmacologically acceptable salts thereof.

8. Compounds of formula 1 according to one of Claims 1 to 3, wherein

R^2 denotes a phenyl which may optionally be substituted in one or both meta positions by one or more groups selected from among methyl, ethyl, propyl, isopropyl, cyclopropyl, F, Cl, Br, OH, $OR^{2.1}$, $COOR^{2.1}$, CF_3 , CHF_2 , CH_2F , NH_2 , $NH(CH_3)$ and $N(CH_3)_2$, wherein $R^{2.1}$ may be H, methyl or ethyl,

as well as pharmacologically acceptable salts thereof.

9. Compounds of formula 1 according to one of Claims 1 to 3, wherein

R^2 is a group selected from among monocyclic, saturated three-, four-, five-, six- or seven-membered heterocycles with 1, 2 or 3 heteroatoms selected in each case from among N, O and S, which may optionally be substituted by one or more groups selected from among fluorine, chlorine, bromine, CF_3 , CHF_2 , CH_2F , OH and oxo or by one or more groups selected from among $OR^{2.1}$, C_{1-3} -alkylene- $OR^{2.1}$, $SR^{2.1}$, $SO-R^{2.1}$, $SO_2-R^{2.1}$, $COOR^{2.1}$, $COR^{2.1}$, C_{1-6} -alkanol, C_{3-10} -cycloalkyl, phenyl, C_{1-6} -alkyl, phenyl- C_{1-6} -alkylene, C_{5-10} -heteroaryl- C_{1-6} -alkylene, C_{5-10} heterocycle, C_{5-10} -heteroaryl and $NR^{2.2}R^{2.3}$, which may in turn

optionally be substituted by one or more groups selected from among OH, OR^{2.1}, oxo, F, Cl, CF₃, CHF₂, CH₂F, C₁₋₆-alkyl, phenyl and NR^{2.2}R^{2.3},

wherein R^{2.1}, R^{2.2} and R^{2.3} are defined as in claim 1,

as well as pharmacologically acceptable salts thereof.

10. Compounds of formula 1 according to claim 9, wherein

R² denotes a group selected from among a monocyclic, saturated six-membered heterocycle with a heteroatom selected from among N, O and S, which may optionally be substituted by one or more groups selected from among F, Cl, Br, CF₃, CHF₂, CH₂F, OH, oxo, NH₂, NHCH₃ and N(CH₃)₂, methyl, ethyl, propyl, isopropyl, cyclopropyl, methoxy and ethoxy,

as well as pharmacologically acceptable salts thereof.

11. Compounds of formula 1 according to claim 9 or 10, wherein

R² denotes a group selected from among piperidine or tetrahydropyran, which may optionally be substituted by one or more groups selected from among F, Cl, Br, OH, CF₃, CHF₂, CH₂F, NH₂, NHCH₃, N(CH₃)₂, oxo, methyl and methoxy,

as well as pharmacologically acceptable salts thereof.

12. Compounds of formula 1 according to one of Claims 1 to 3, wherein

R³ is a naphthalene or phenyl, which may optionally be substituted in any position by one, two or three groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, methyl, ethyl, propyl, isopropyl, cyclopropyl, CF₃, CHF₂, CH₂F, -OCH₃, OCH₂CH₃; SO₂-CH₃, SO₂-CH₂CH₃, COOCH₃ and CO-O-CH₂CH₃,

as well as pharmacologically acceptable salts thereof.

13. Compounds of formula 1 according to one of Claims 1 or 2, wherein

R³ denotes a group selected from among het and hetaryl, which may optionally be substituted by one or more groups selected from among F, Cl, Br, CF₃, CHF₂, CH₂F, CN, OH, oxo, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclopropyl, C₅₋₇-cycloalkyl, -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -COO-methyl, -COO-ethyl, -COO-propyl, -COO-isopropyl, SO₂-(CH₃), SO₂-(CH₂-CH₃), SO-(CH₃), SO-(CH₂-CH₃), phenyl, -CH₂-NH₂, -CH₂-NHCH₃, -CH₂-N(CH₃)₂, NH₂, NHCH₃, N(CH₃)₂, het and hetaryl, which may in turn optionally be substituted by one or more groups selected from among OH, F, Cl, Br, CF₃, CHF₂, CH₂F, methyl, ethyl, propyl, isopropyl, phenyl, -COO-methyl, -COO-ethyl, -COO-propyl, -COO-isopropyl and O-methyl, O-ethyl, O-propyl and O-isopropyl,

and wherein

R⁴ denotes H, CN, OH, CF₃, CHF₂, CH₂F, F, methyl, ethyl, O-methyl or O-ethyl,

wherein

het is a three- to seven-membered, monocyclic, saturated or partially saturated heterocycle or a seven- to eleven-membered, bicyclic, anellated, saturated or partially saturated heterocycle which contains 1, 2 or 3 heteroatoms selected independently of one another from among N, S or O,

and wherein

hetaryl is a five- to six-membered, monocyclic, aromatic heteroaryl or a seven- to eleven-membered, bicyclic, anellated, aromatic heteroaryl, which contains in each case 1, 2 or 3 heteroatoms selected independently of one another from among N, S or O,

and wherein

cycloalkyl may be saturated or partially saturated,

as well as pharmacologically acceptable salts thereof.

14. Compounds of formula 1 according to claim 13, wherein

R³ denotes a group selected from a bicyclic, seven- to eleven-membered, saturated or partially saturated heterocycle or a bicyclic, seven- to eleven-membered heteroaryl, which is selected from among indole, dihydroindole, quinazoline, dihydroquinazoline, tetrahydroquinazoline, benzoisoxazole, dihydrobenzoisoxazole, benzoxazine, dihydrobenzoxazine, benzothiazole, dihydrobenzothiazole, triazolopyridine, dihydrotriazolopyridine, benzofuran, dihydrobenzofuran, isobenzofuran and dihydroisobenzofuran,

which may optionally be substituted by one or more groups selected from among F, Cl, Br, CF₃, CHF₂, CH₂F, CN, OH, oxo, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclopropyl, -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -COO-methyl, -COO-ethyl, -COO-propyl, -COO-isopropyl, SO₂-(CH₃), SO₂-(CH₂-CH₃), SO-(CH₃), SO-(CH₂-CH₃), phenyl, -CH₂-NH₂, -CH₂-NHCH₃, -CH₂-N(CH₃)₂, NH₂, NHCH₃, N(CH₃)₂, furanyl and pyridinyl, which in turn may be substituted by one or more groups selected from among OH, F, Cl, Br, CF₃, CHF₂, CH₂F, methyl, ethyl, propyl, isopropyl, phenyl, -COO-methyl, -COO-ethyl and O-methyl, O-ethyl,

as well as pharmacologically acceptable salts thereof.

15. Compounds of formula 1 according to claim 13, wherein

R³ denotes a group selected from a monocyclic, saturated or partially saturated, three- to seven-membered heterocycle or a monocyclic five- to six-membered heteroaryl,

which is selected from among imidazole, dihydroimidazole, oxadiazole, oxadiazolidine, pyrazole, pyridine and dihydropyrazole,

which may optionally be substituted by one or more groups selected from among F, Cl, Br, CF₃, CHF₂, CH₂F, CN, OH, oxo, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, cyclopropyl, -O-methyl, -O-ethyl, -O-propyl, -O-isopropyl, -COO-methyl, -COO-ethyl, -COO-propyl, -COO-isopropyl, SO₂-(CH₃), SO₂-(CH₂-CH₃), SO-(CH₃), SO-(CH₂-CH₃), phenyl, -CH₂-NH₂, -CH₂-NHCH₃, -CH₂-N(CH₃)₂, NH₂, NHCH₃, N(CH₃)₂, furanyl and pyridinyl, which may in turn optionally be substituted by one or more groups selected from among OH, F, Cl, Br, CF₃, CHF₂, CH₂F, methyl, ethyl, propyl, isopropyl, phenyl, -COO-methyl, -COO-ethyl and O-methyl, O-ethyl,

as well as pharmacologically acceptable salts thereof.

16. Compounds of formula 1 according to one of Claims 1 to 3, wherein

R³ and **R⁴** together form a mono- or bicyclic, unsaturated or partially saturated, three- to eleven-membered heterocycle which contains 1, 2 or 3 heteroatoms selected from among N, O and S and which may optionally be substituted by one or

more groups selected from among F, Cl, Br, OH, oxo, CF₃, CHF₂, CH₂F, CN, methyl, ethyl, propyl, isopropyl, cyclopropyl, COO-methyl, -COO-ethyl, O-methyl, O-ethyl, SO₂-(CH₃), SO₂-(CH₂-CH₃), SO-(CH₃), SO-(CH₂-CH₃), phenyl, -CH₂-NH₂, -CH₂NHCH₃, -CH₂-N(CH₃)₂, NH₂, NHCH₃, N(CH₃)₂, a saturated or partially saturated, five- to six-membered heterocycle and a five- to six-membered heteroaryl,

as well as pharmacologically acceptable salts thereof.

17. Compounds of formula 1 according to claim 16, wherein

R³ and R⁴ together form a bicyclic heterocycle selected from among tetrahydroquinazoline, tetrahydrobenzoxazine and dihydroindole, dihydroisobenzofuran, which may optionally be substituted by one or more groups selected from among F, Cl, Br, OH, oxo, CF₃, CHF₂, CH₂F, CN, methyl, ethyl, propyl, isopropyl, cyclopropyl, COO-methyl, -COO-ethyl, O-methyl, O-ethyl, SO₂-(CH₃), SO₂-(CH₂-CH₃), phenyl, -CH₂-NH₂, -CH₂NHCH₃, -CH₂-N(CH₃)₂, NH₂, NHCH₃, N(CH₃)₂, a saturated or partially saturated, five- to six-membered heterocycle and a five- to six-membered heteroaryl,

as well as pharmacologically acceptable salts thereof.

18. Compounds of formula 1 according to one of Claims 1 or 2,

wherein

R³ is -O-R^{3.1},

wherein R^{3.1} is a group selected from among methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, -phenyl, -methylene-phenyl, -ethylene-phenyl, -propylene-phenyl, -isopropylene-phenyl, hetaryl and het, which may optionally be substituted in the ortho, para or meta position by one, two or three groups selected independently of one another from among fluorine, chlorine, bromine, hydroxy, CN, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, -CF₃, CHF₂, CH₂F, CO-(methyl), CO-(ethyl), CO-(propyl), CO-(isopropyl), CO-(butyl), CO-(isobutyl), -CO-(CF₃), -CO-(CH₂F), -CO-(CHF₂), -CO-NH-(methylene)-hetaryl, -CO-NH-(ethylene)-hetaryl, -CO-NH-(propylene)-hetaryl, -CO-NH-(isopropylene)-hetaryl, -CO-N(CH₃)-(methylene)-hetaryl, -CO-N(CH₃)-(ethylene)-hetaryl, -CO-N(CH₃)-(propylene)-hetaryl, -CO-N(CH₃)-(isopropylene)-hetaryl, -CO-N(CH₃)-het, -CO-N(C₃₋₇-cycloalkyl)-het, -methylene-O-methyl,

-ethylene-O-methyl, -methylene-O-ethyl, -ethylene-O-ethyl, -methylene-NH₂,
 -ethylene-NH₂, -methylene-NHCH₃, -ethylene-NHCH₃, -methylene-N(CH₃)₂,
 -ethylene-N(CH₃)₂, -NH₂, -NHCH₃, -N(CH₃)₂, -O-methyl, -O-ethyl, -O-propyl,
 -O-isopropyl, -SO-CH₃, -SO-(CH₂CH₃), -SO₂-CH₃, -SO₂-(CH₂CH₃), COOH,
 COO-(methyl), COO-(ethyl), COO-(propyl), COO-(isopropyl),
 -O-methylene-N(methyl)₂, -O-ethylene-N(methyl)₂, -O-methylene-N(ethyl)₂,
 -O-ethylene-N(ethyl)₂, CO-NH₂, CO-NHCH₃, CO-N(CH₃)₂, NH-CO-methyl,
 NCH₃-CO-methyl, NH-CO-ethyl, N(CH₃)-CO-ethyl,
 phenyl, phenyl-methylene, phenyl-ethylene, het-methylene, het-ethylene,
 -CO-het, het, -CO-C₄₋₇-cycloalkyl, -CO-cyclopropyl,
 -CO-N(CH₃)-cyclopropyl, -CO-N(CH₃)-C₄₋₇-cycloalkyl,
 C₄₋₇-cycloalkyl, cyclopropyl, C₄₋₇-cycloalkyl-methylene,
 cyclopropyl-methylene, C₄₋₇-cycloalkyl-ethylene, cyclopropyl-ethylene, hetaryl-
 methylene, hetaryl-ethylene and hetaryl,
 which may in turn optionally be substituted by 1, 2, 3 or 4 groups selected
 independently of one another from among F, Cl, Br, methyl, O-methyl, ethyl,
 O-ethyl, OH, oxo and CF₃,

as well as pharmacologically acceptable salts thereof.

19. Compounds of formula 1 according to one of Claims 1, 2 or 3,
 wherein

R⁴ denotes H, CN, OH, CF₃, CHF₂, CH₂F, F, methyl, ethyl, O-methyl or O-ethyl,
 -methylene-OH, -ethylene-OH, -propylene-OH, isopropylene-OH,
 -COO(methyl), -COO(ethyl), -COO(propyl), -COO(isopropyl), -CO-het,
 -(methylene)-NH-SO₂-(methyl), -(methylene)-NH-SO₂-(ethyl),
 -(ethylene)-NH-SO₂-(methyl), -(ethylene)-NH-SO₂-(ethyl),
 -(methylene)-N(CH₃)-SO₂-(methyl), -(methylene)-N(CH₃)-SO₂-(ethyl),
 -(ethylene)-N(CH₃)-SO₂-(methyl), -(ethylene)-N(CH₃)-SO₂-(ethyl),
 -(methylene)-O-(methylene)-phenyl, -(methylene)-O-(ethylene)-phenyl,
 -(ethylene)-O-(methylene)-phenyl, -(ethylene)-O-(ethylene)-phenyl,
 -methylene-O-methyl, -methylene-O-ethyl, -ethylene-O-methyl
 -ethylene-O-ethyl, -(methylene)-N(CH₃)-CO-(methyl), -(methylene)-N(CH₃)-
 CO-(ethyl)
 -(ethylene)-N(CH₃)-CO-(methyl), -(ethylene)-N(CH₃)-CO-(ethyl),
 -NH-CO-(methylene)-O-(methyl), -NH-CO-(methylene)-O-(ethyl),
 -NH-CO-(ethylene)-O-(methyl), -NH-CO-(ethylene)-O-(ethyl),
 -methylene-NH-CO-(methyl), -methylene-NH-CO-(ethyl),
 -ethylene-NH-CO-(methyl), -ethylene-NH-CO-(ethyl),

-methylene-NH-CO-(methylene)-N(methyl)₂,
-methylene-NH-CO-(ethylene)-N(methyl)₂,
-ethylene-NH-CO-(methylene)-N(methyl)₂,
-ethylene-NH-CO-(ethylene)-N(methyl)₂,
-methylene-NH-CO-(methylene)-O-(methyl),
-methylene-NH-CO-(ethylene)-O-(methyl),
-ethylene-NH-CO-(methylene)-O-(methyl),
-methylene-NH-CO-(methylene)-O-(ethyl),
-methylene-NH-CO-(ethylene)-O-(ethyl),
-ethylene-NH-CO-(methylene)-O-(ethyl),
-(methylene)-N(CH₃)-CO-(methylene)-O-(methyl),
-(methylene)-N(CH₃)-CO-(ethylene)-O-(methyl),
-(ethylene)-N(CH₃)-CO-(methylene)-O-(methyl),
-(methylene)-N(CH₃)-CO-(methylene)-O-(ethyl),
-(methylene)-N(CH₃)-CO-(ethylene)-O-(ethyl),
-(ethylene)-N(CH₃)-CO-(methylene)-O-(ethyl),
-O-(methylene)-phenyl, -O-(ethylene)-phenyl,
-CO-phenyl,

while the phenyl in the above groups may optionally be substituted by one or more other groups selected from among F, Cl, Br, methyl, ethyl, propyl, -O-methyl, -O-ethyl, -O-propyl, -OH and CF₃,

as well as pharmacologically acceptable salts thereof.

20. Compounds of formula 1 according to one of Claims 1, 2 or 3, wherein

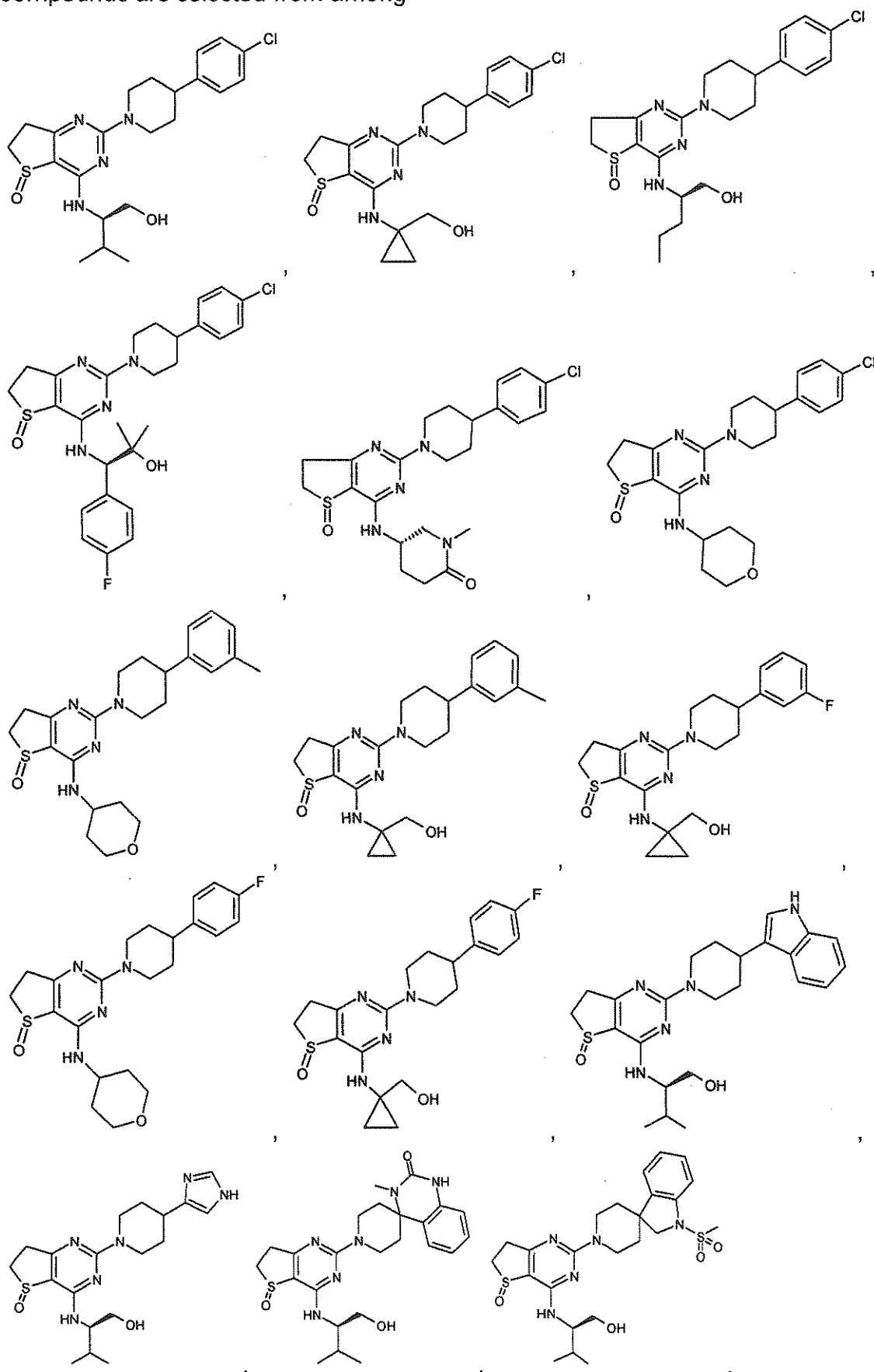
R³ is a group selected from among oxazole, imidazole and thiazole, while these groups may optionally be substituted by one, two or three further groups selected independently of one another from among methyl, ethyl, propyl, isopropyl, O-methyl, O-ethyl, O-propyl, O-isopropyl, OH, F, Cl, Br, CF₃, phenyl, hetaryl and C₃₋₆-cycloalkyl,

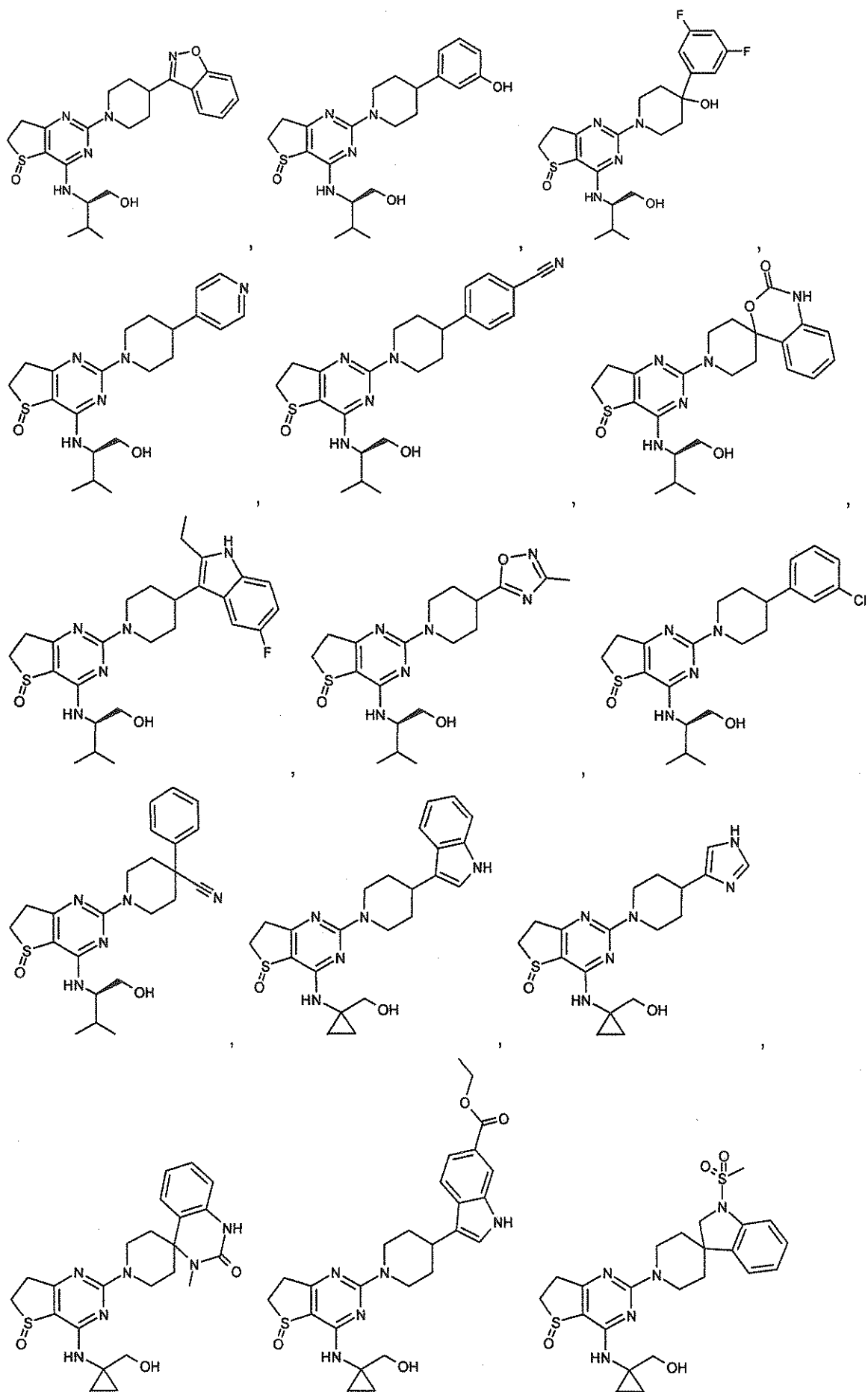
as well as pharmacologically acceptable salts thereof.

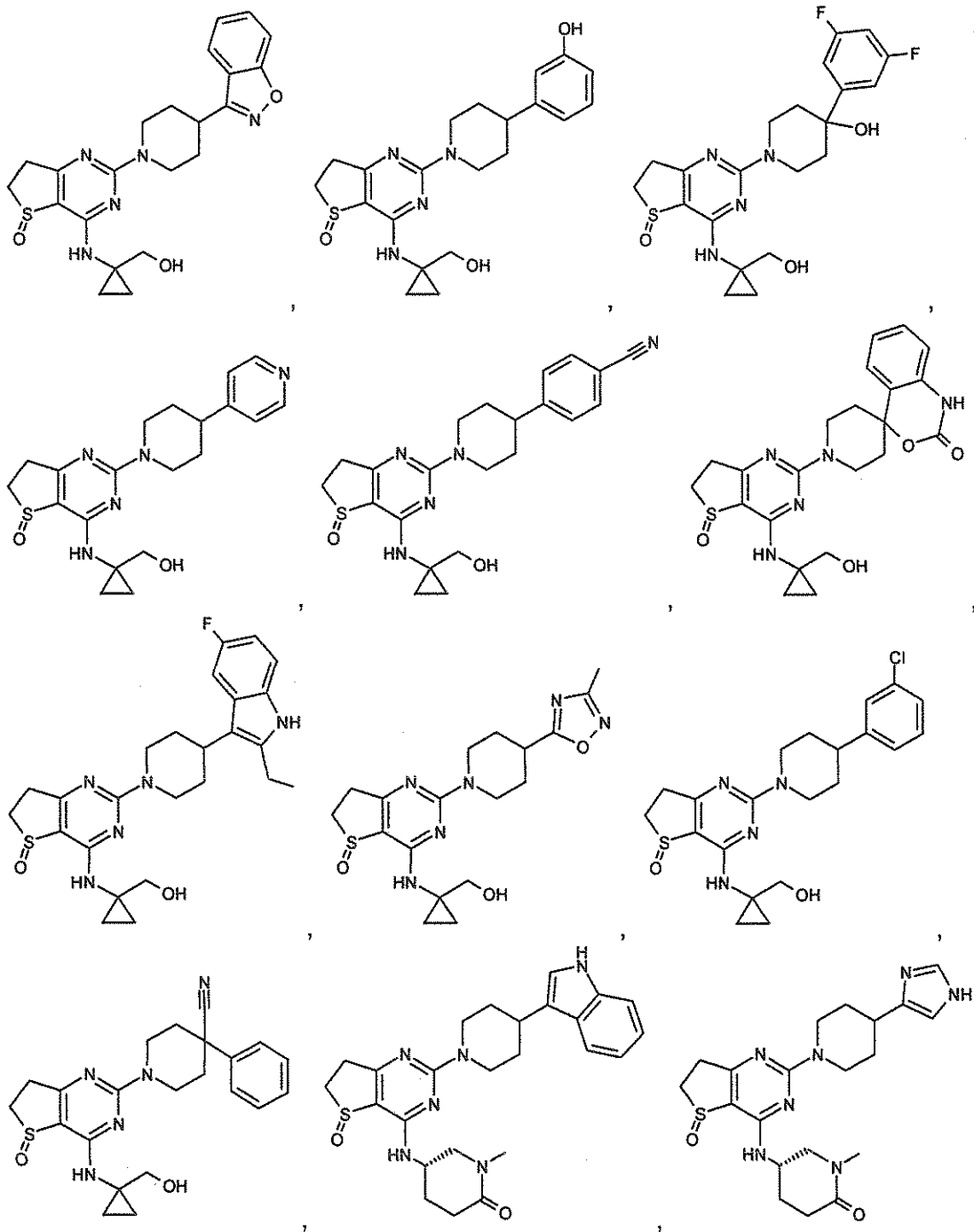
21. Compounds of formula 1 according to one of Claims 1 or 2, wherein X is SO₂,

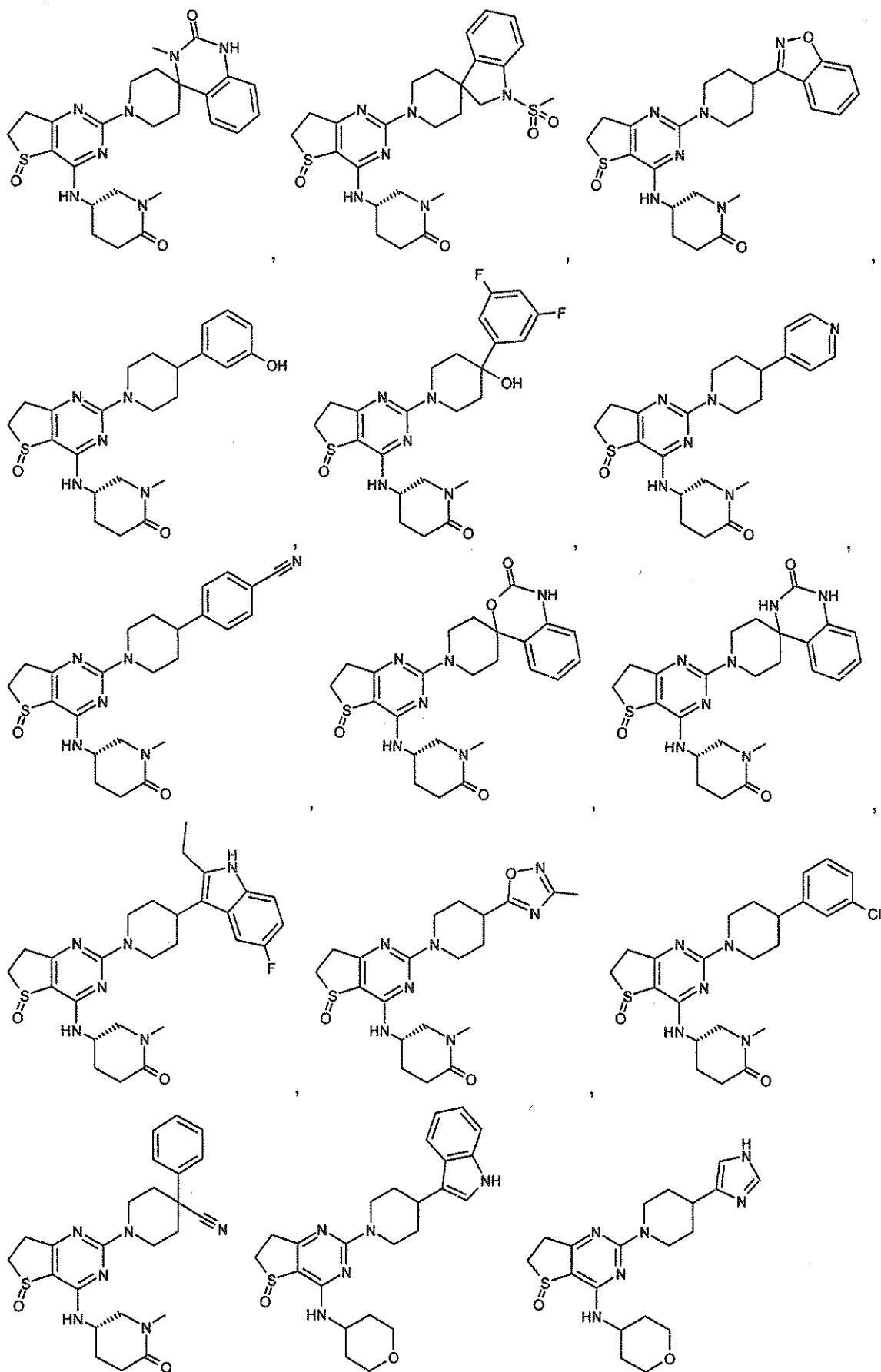
as well as pharmacologically acceptable salts thereof.

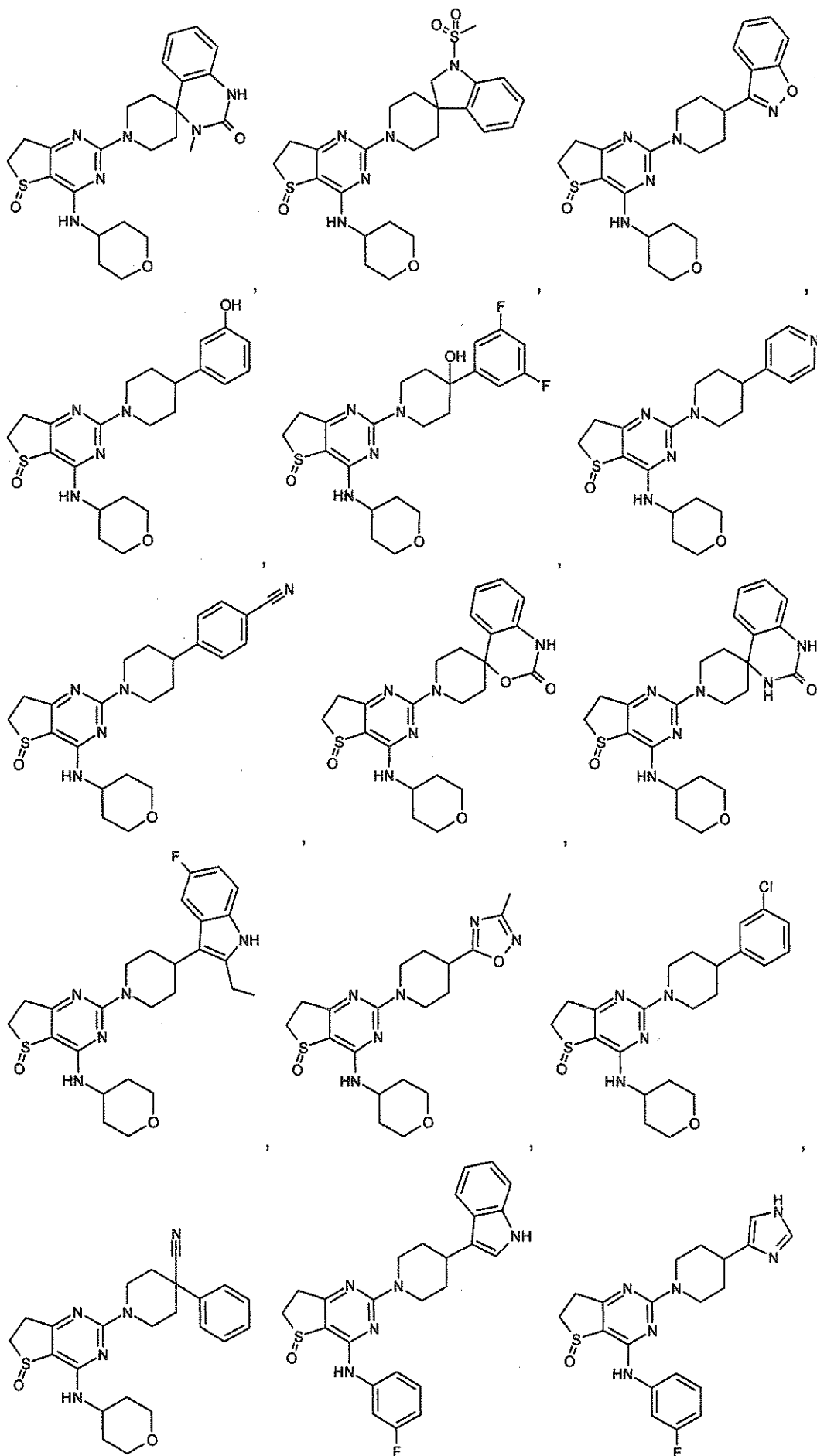
22. Compounds of formula **1** according to one of Claims 1 to 3, wherein the compounds are selected from among

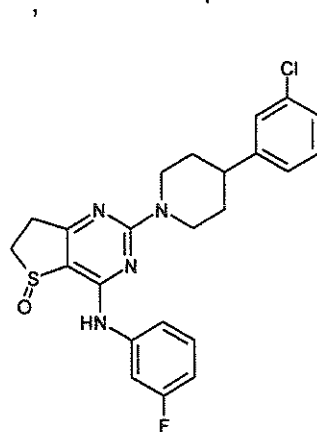
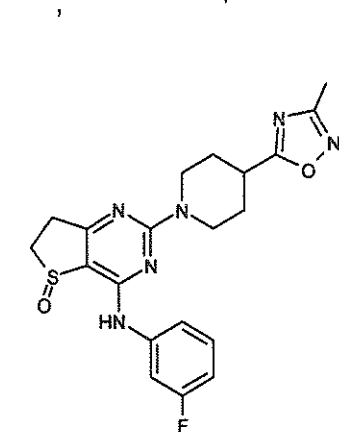
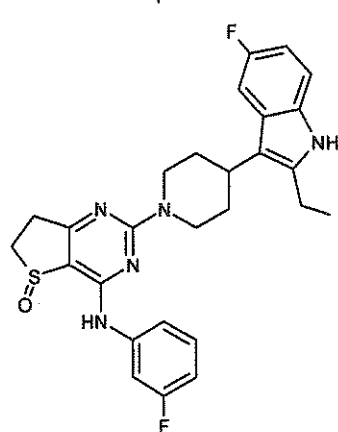
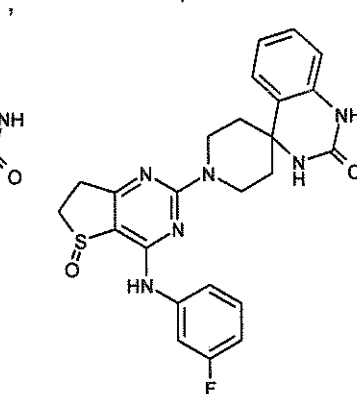
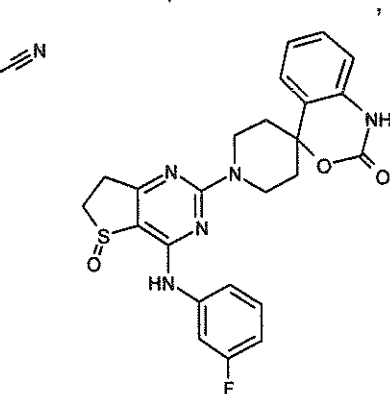
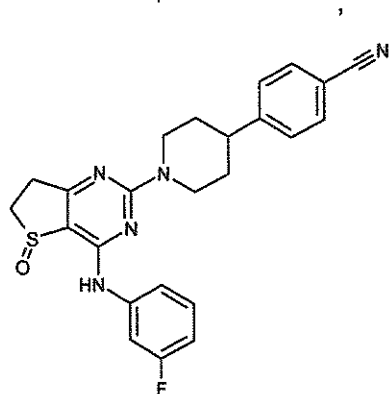
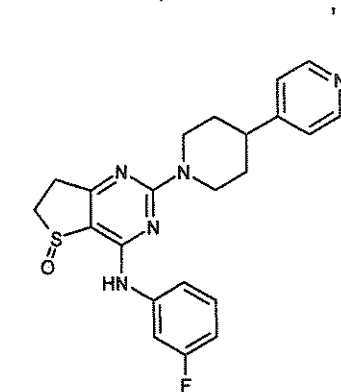
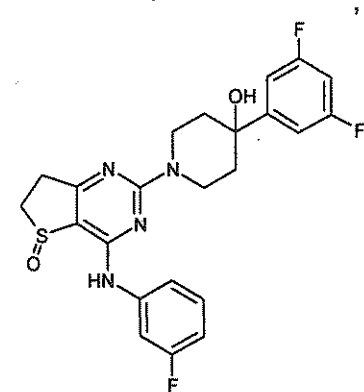
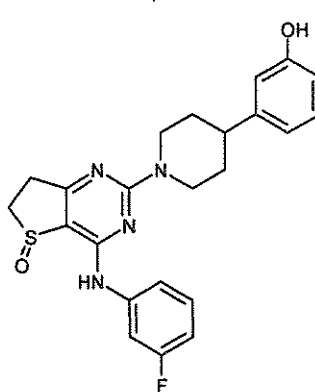
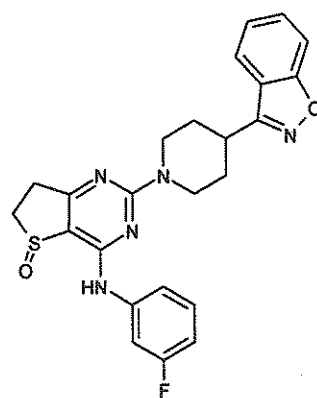
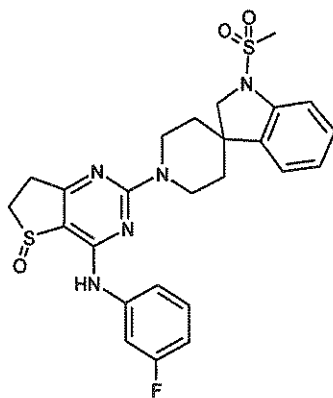
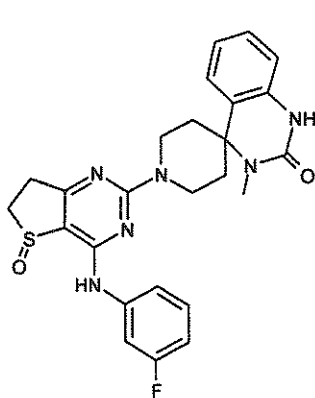


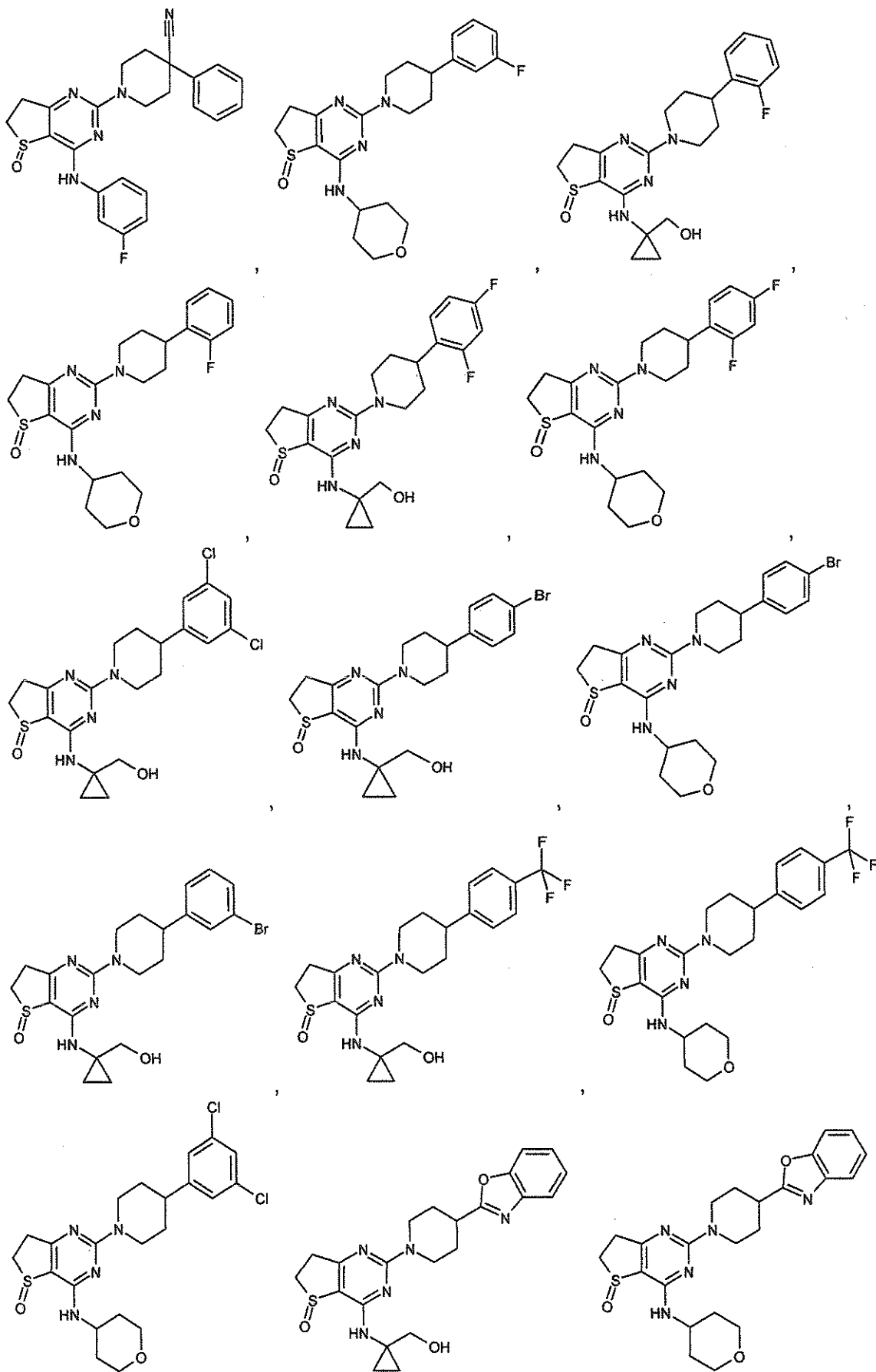


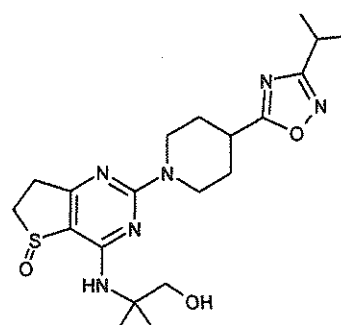
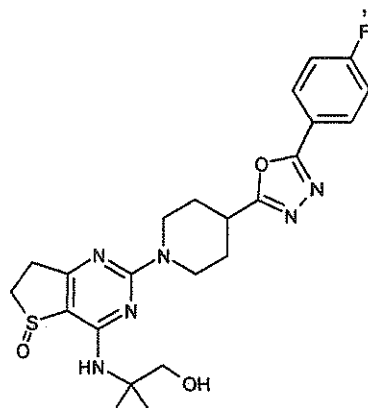
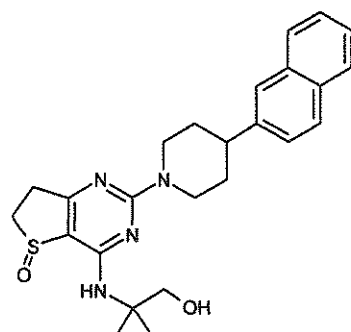
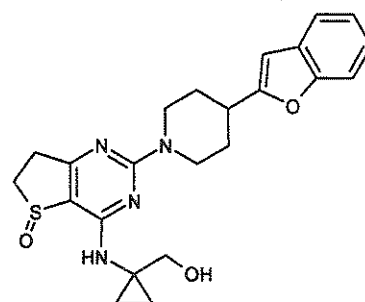
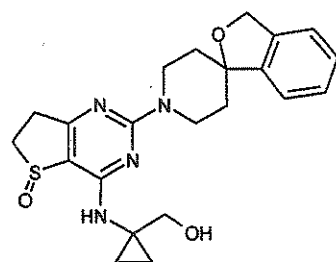
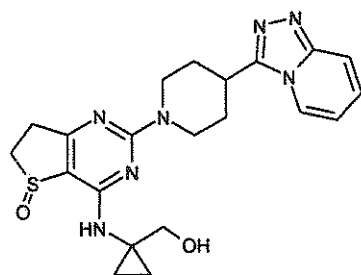
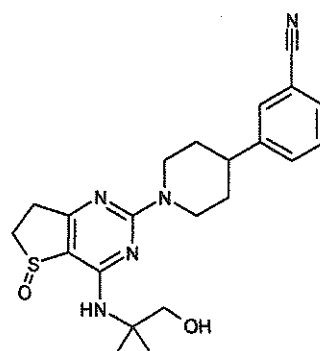
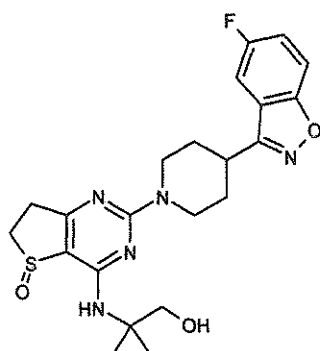
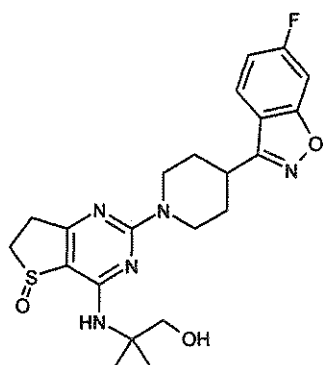
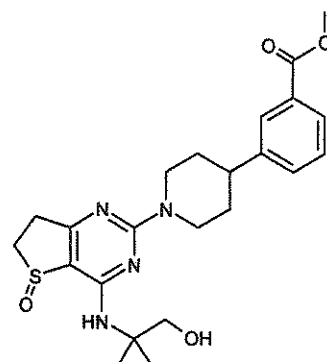
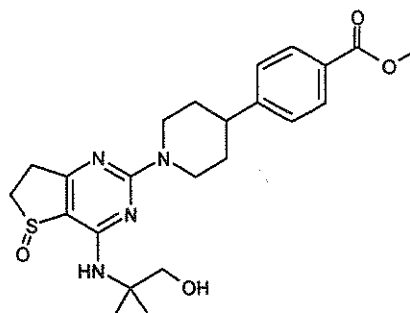
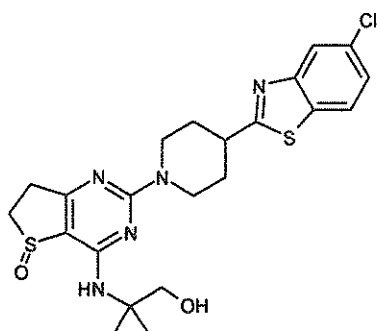
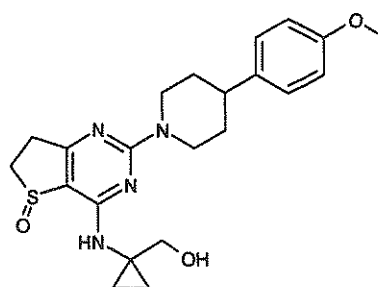
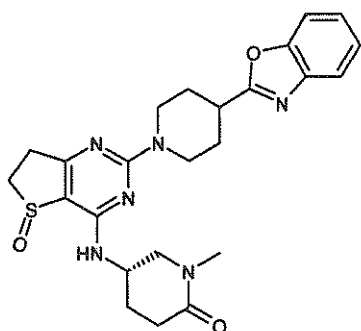


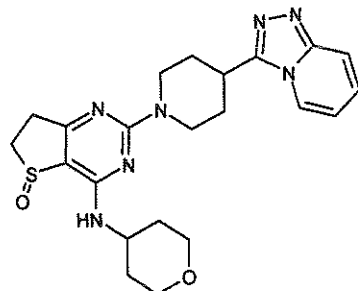
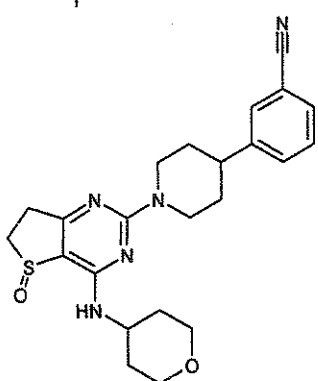
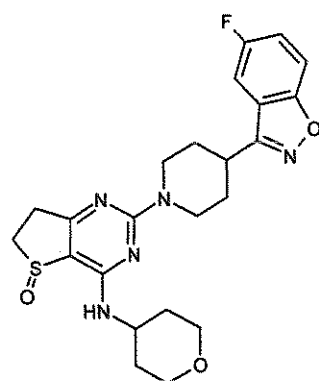
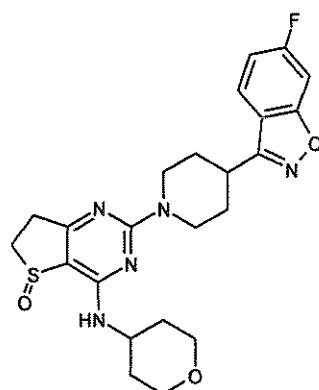
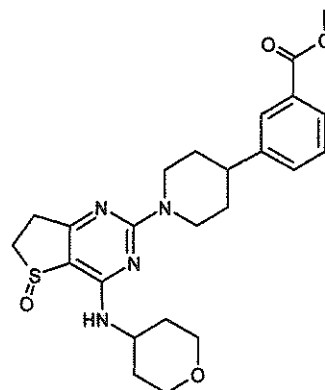
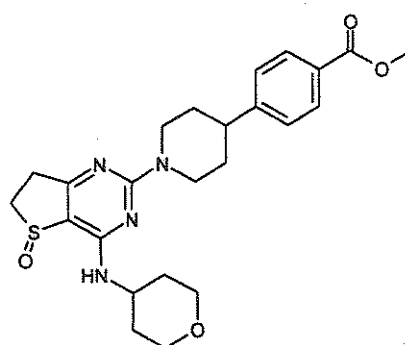
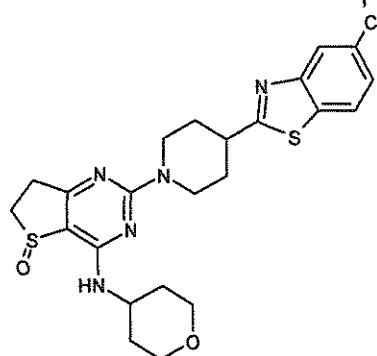
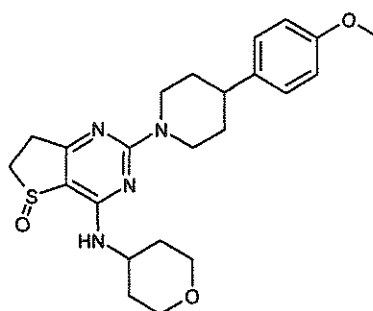
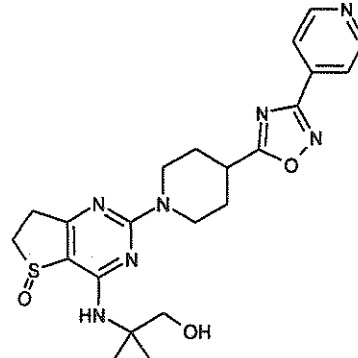
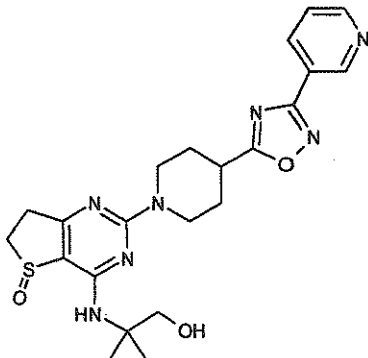
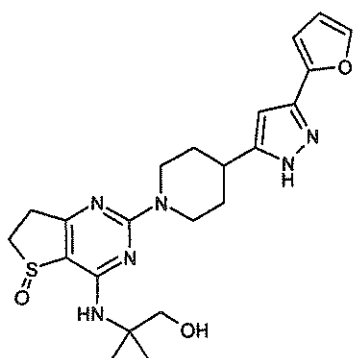


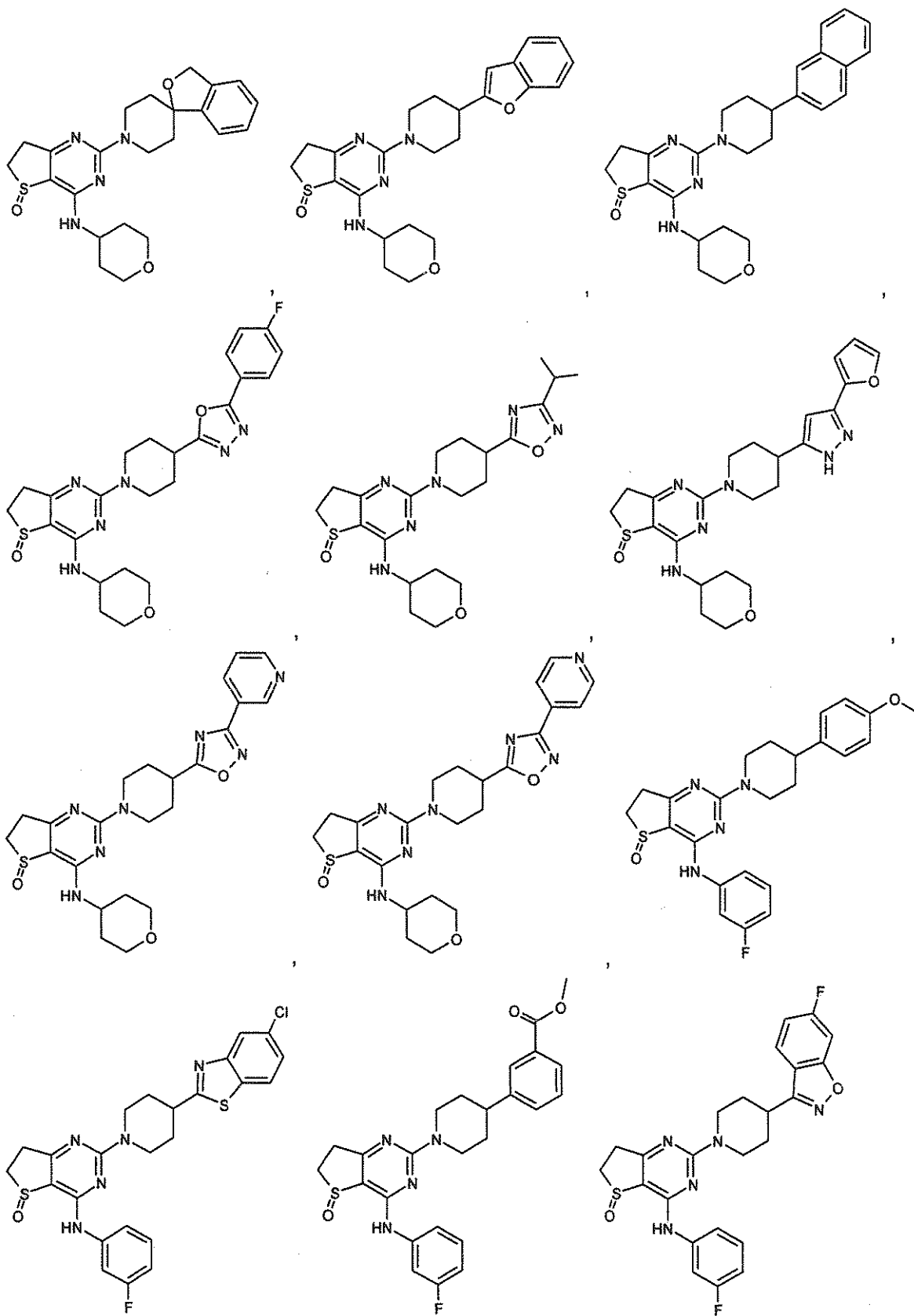


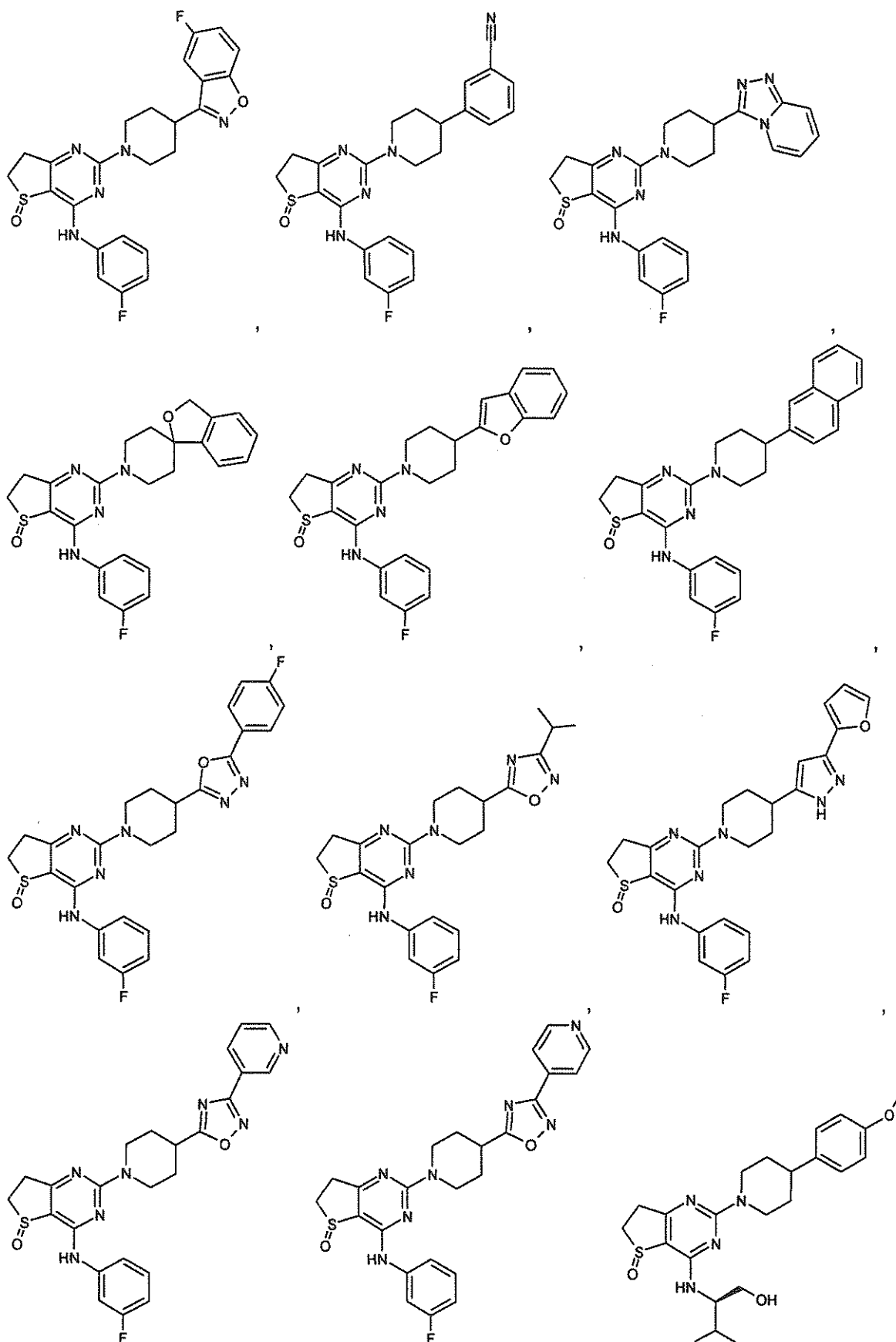


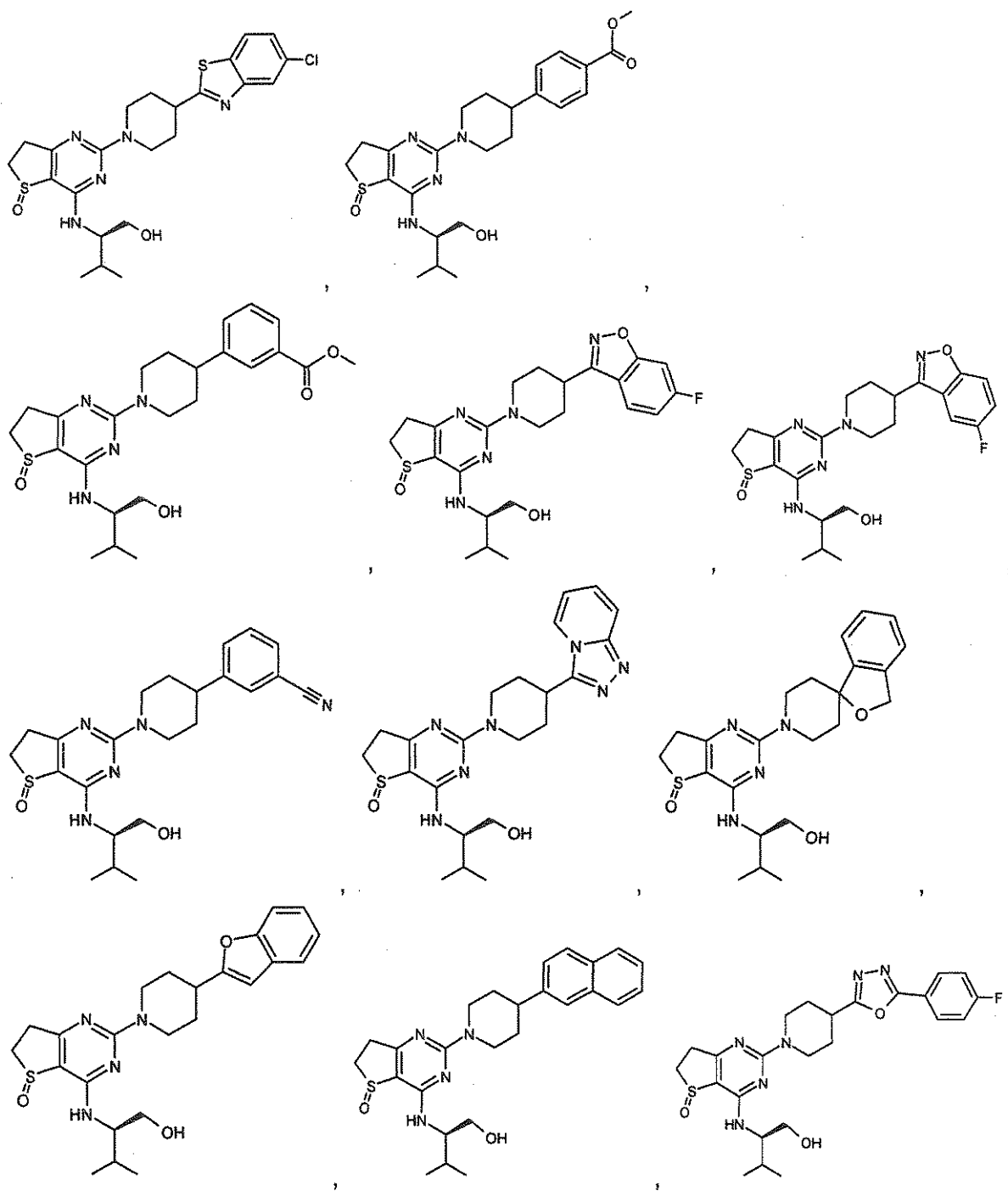


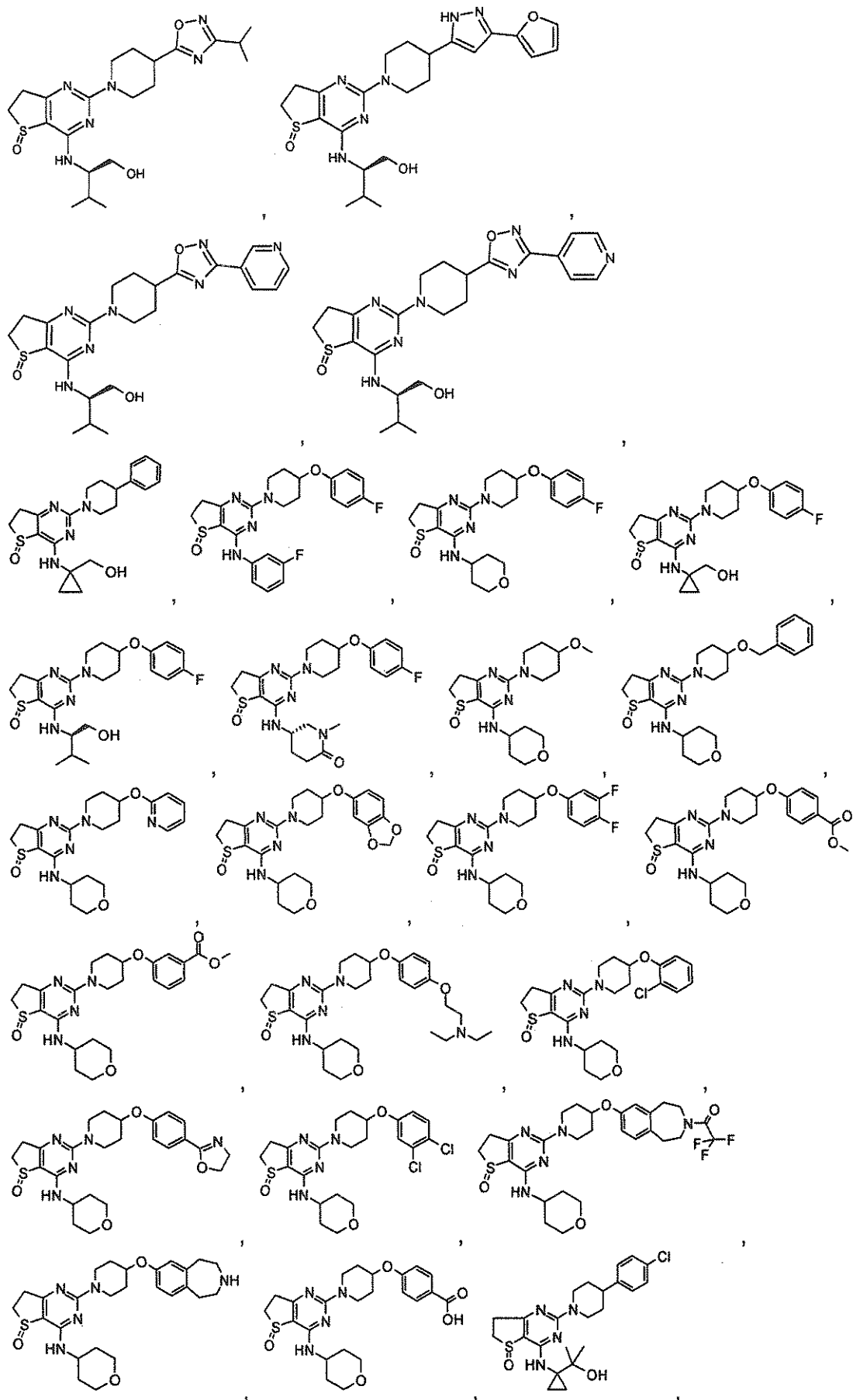


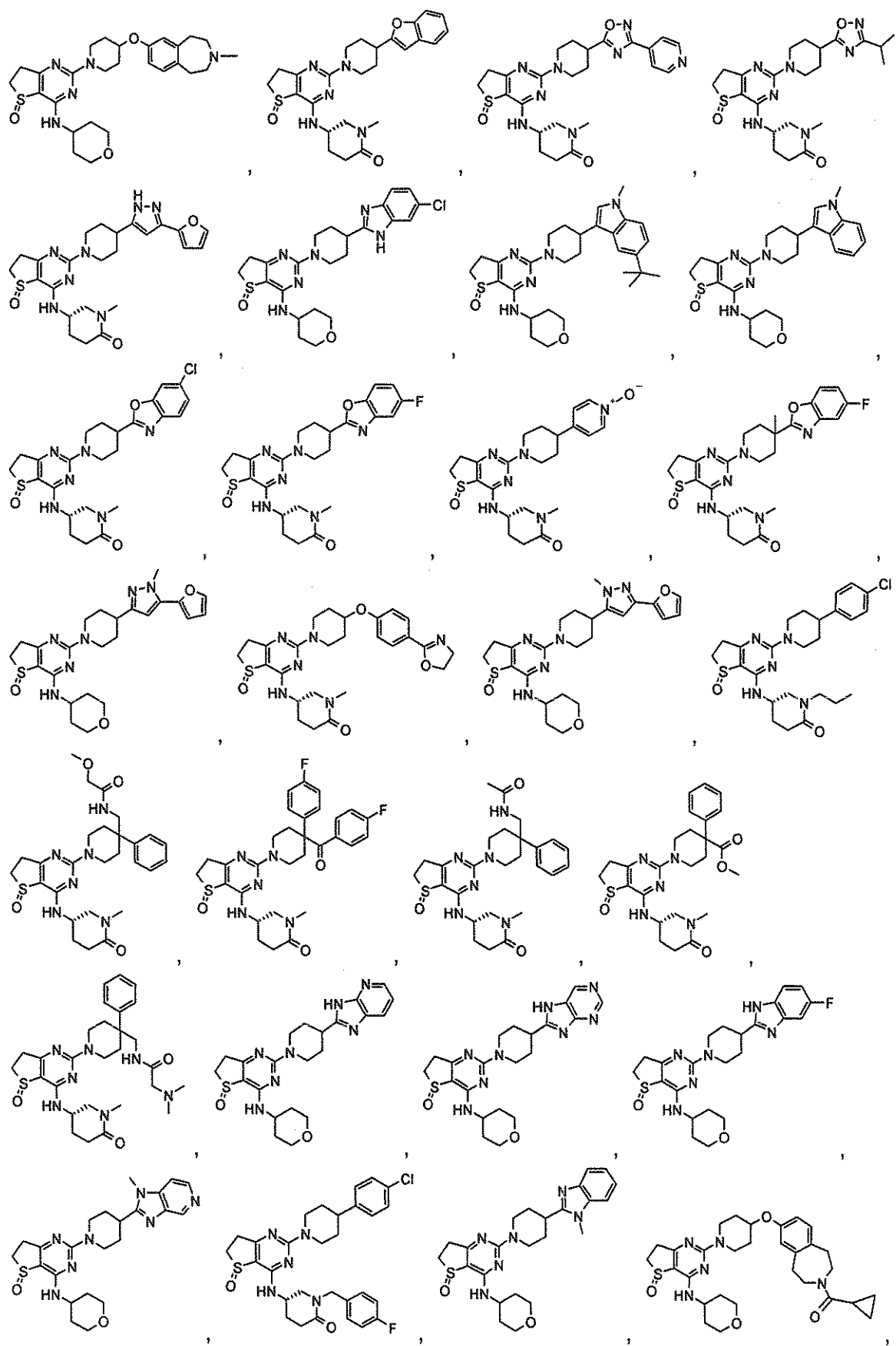


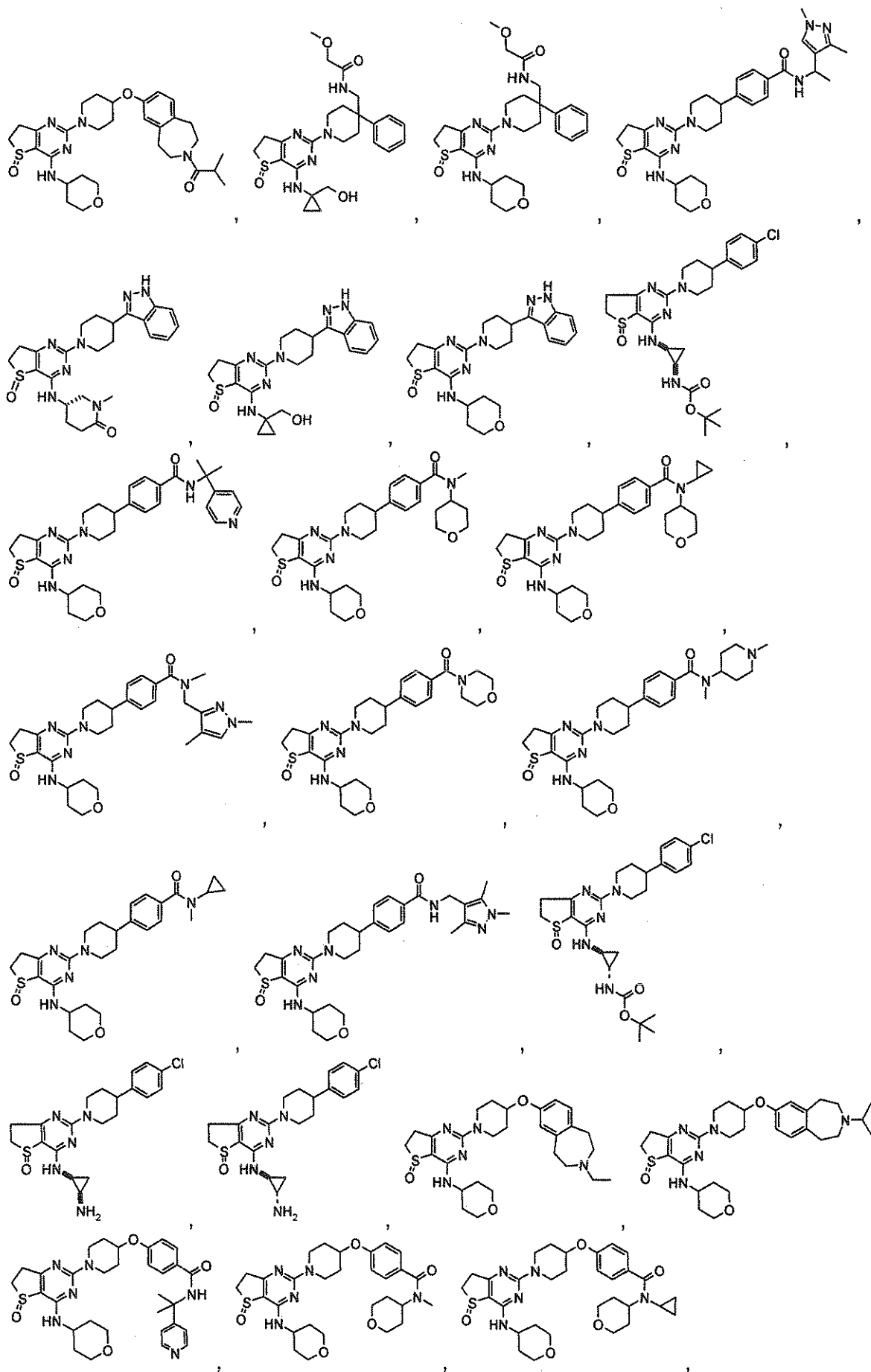


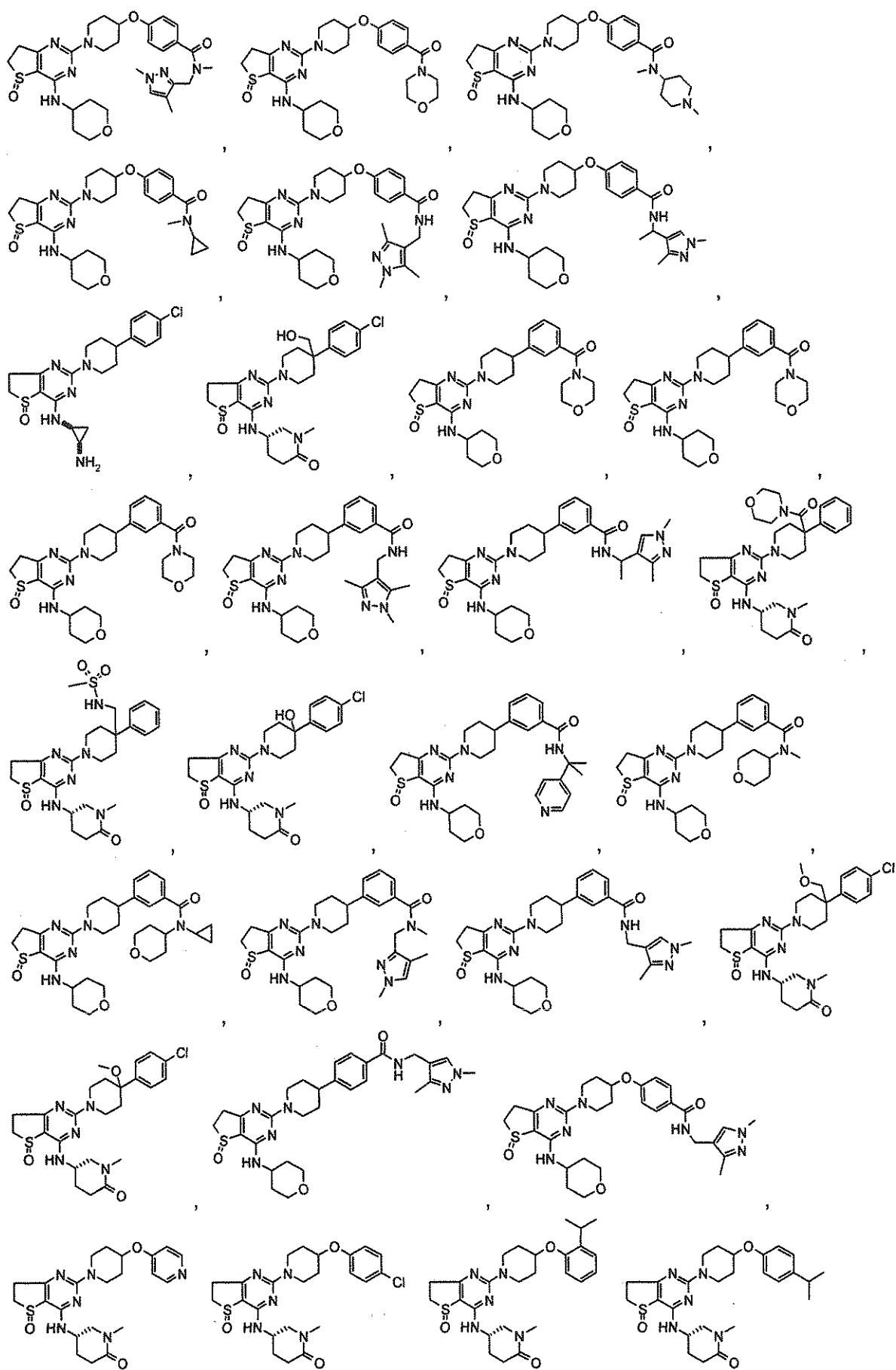


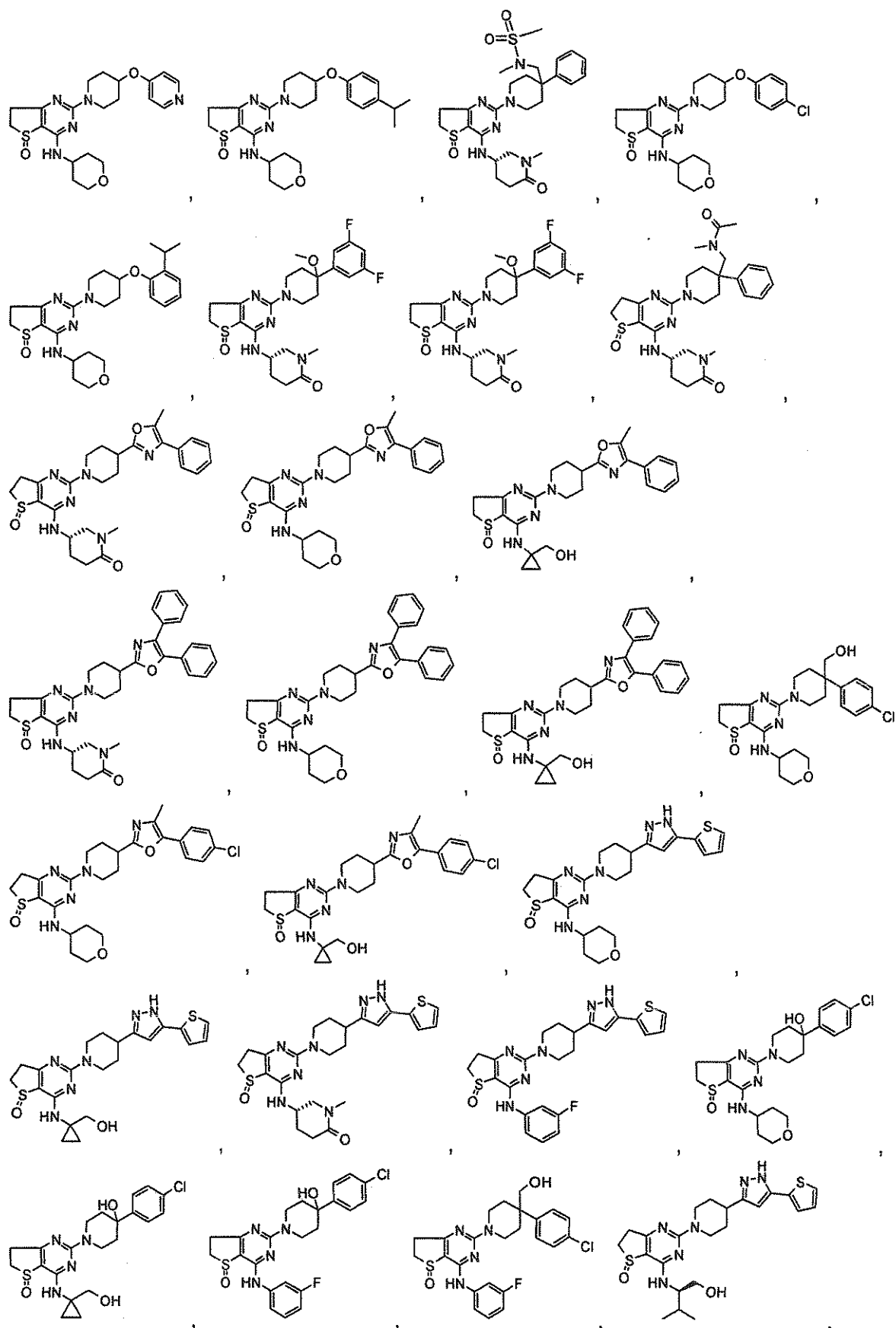


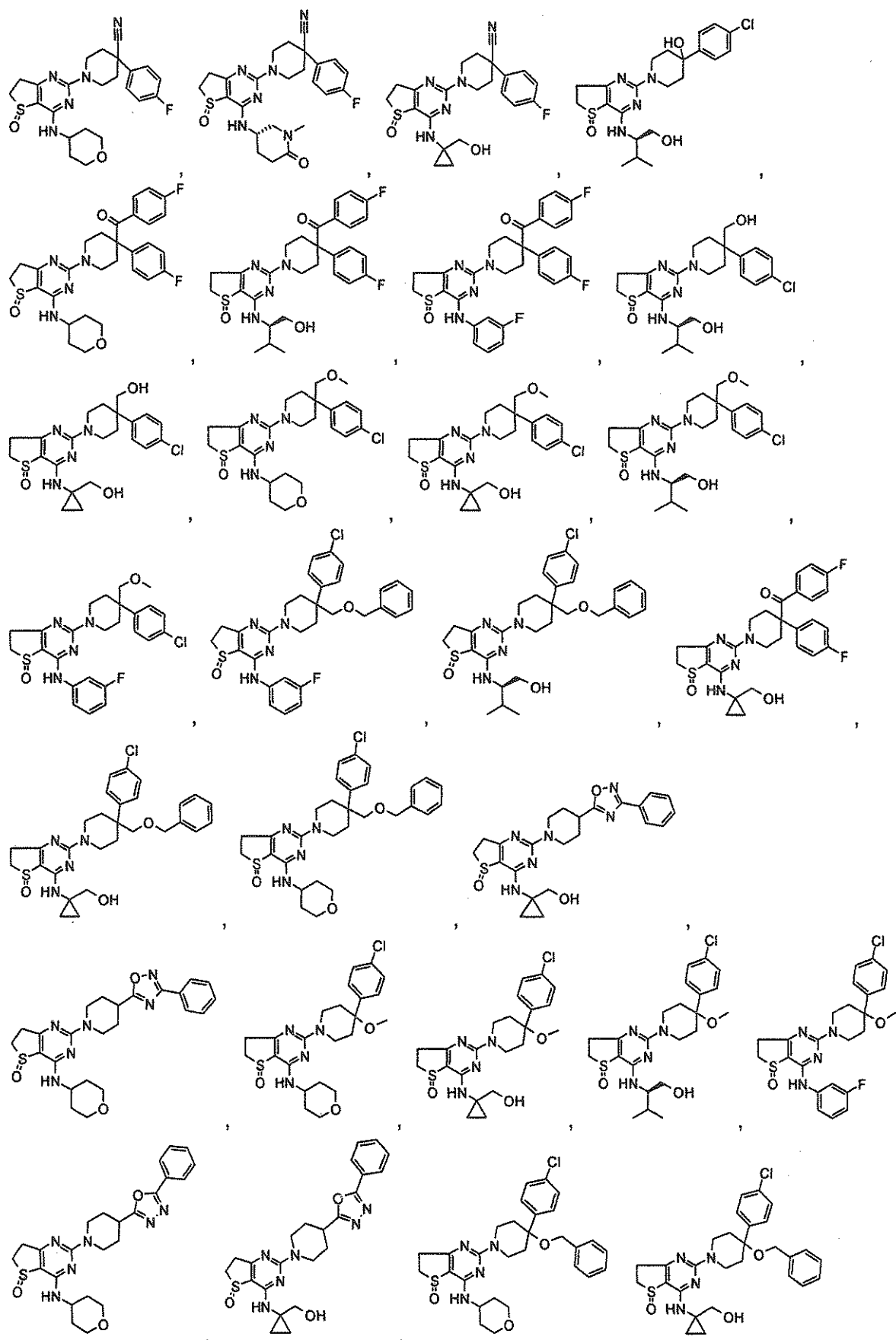


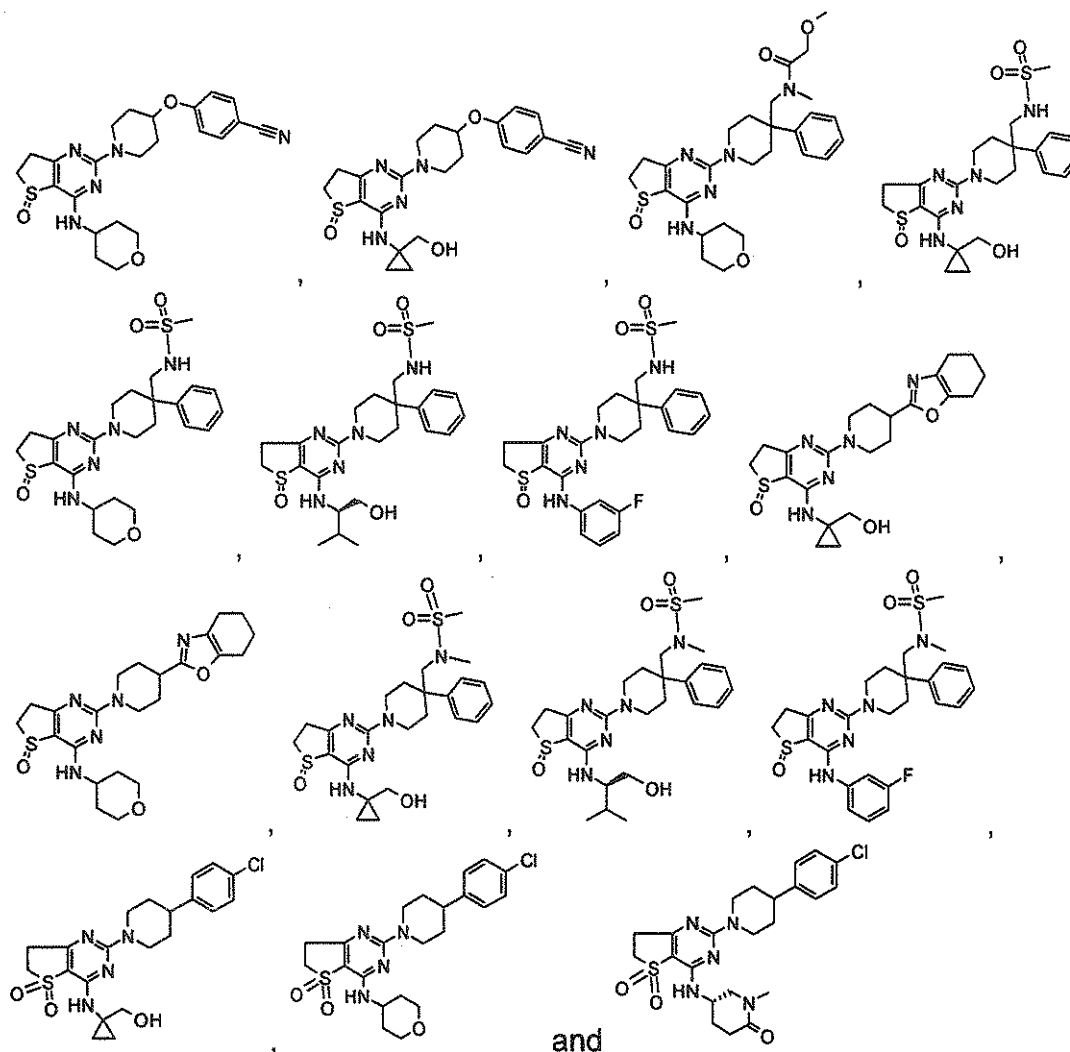












as well as pharmacologically acceptable salts thereof.

23. Compounds according to one of Claims 1 to 22 as medicaments.

24. Use of compounds according to one of Claims 1 to 22, for preparing a medicament for the treatment of diseases which can be treated by inhibition of the PDE4 enzyme.

25. Use of compounds according to one of Claims 1 to 22 for preparing a medicament for the treatment of respiratory or gastrointestinal diseases or complaints, as well as inflammatory diseases of the joints, skin or eyes, cancers, and diseases of the peripheral or central nervous system.

26. Use of compounds according to one of Claims 1 to 22 for preparing a medicament for the prevention and treatment of respiratory or pulmonary diseases

which are accompanied by increased mucus production, inflammations and/or obstructive diseases of the respiratory tract.

27. Use of compounds according to one of Claims 1 to 22 for preparing a medicament for the treatment of inflammatory and/or obstructive diseases such as COPD, chronic sinusitis, asthma, Crohn's disease and ulcerative colitis.
28. Use of compounds according to one of Claims 1 to 22 for preparing a medicament for the treatment of inflammatory diseases of the gastrointestinal tract.
29. Use of compounds according to one of Claims 1 to 22 for preparing a medicament for 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 and brain damage caused by stroke, hypoxia or cranio-cerebral trauma.
30. Pharmaceutical formulations, characterised in that they contain one or more of the above compounds according to formula 1 according to one of Claims 1 to 22.
31. Pharmaceutical formulations, characterised in that they contain one or more compounds of formula 1 according to one of claims 1 to 22 in combination with one or more active substances selected from among betamimetics, corticosteroids, other PDE4-inhibitors, EGFR-inhibitors and LTD4-antagonists, CCR3-inhibitors, iNOS-inhibitors and SYK-inhibitors.