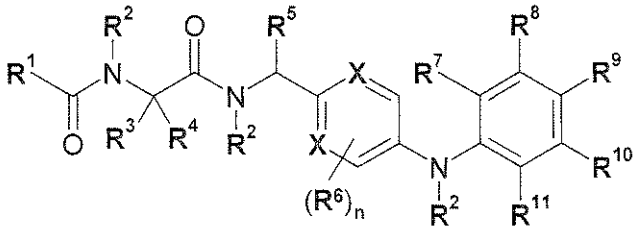
NEW COMPOUNDS

The present invention relates to the compounds of general formula I



, (I)

wherein **n**, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11} and **X** are as defined hereinafter, the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases, which have valuable properties, the preparation thereof, the medicaments containing the pharmacologically effective compounds, the preparation thereof and the use thereof.

DETAILED DESCRIPTION OF THE INVENTION

In the above general formula I in one embodiment 1

n denotes one of the numbers 0, 1 or 2,

R^1 denotes

(a) a C_{1-6}-alkyl group optionally substituted by a group $R^{1.1}$,

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(c) a substituted C_{3-6}-cycloalkyl group optionally substituted by a group $R^{1.2}$ wherein a $-CH_2-$ unit may be replaced by a -C(O)- group,

(d) an aryl-C_{0-2}-alkylene group optionally substituted by 1, 2 or 3 groups $R^{1.3}$,

(e) a five-membered heteroaryl-C_{0-2}-alkylene group optionally substituted by 1, 2 or 3 groups $R^{1.4}$, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms and which may additionally be benzo-condensed,

(f) a six-membered heteroaryl-C_{0-2}-alkylene group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms and which may additionally be benzo-condensed,

(g) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$ substituted, which contains one, two or three N-atoms,

(h) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, in which a $-CH_2-$ unit may be replaced by a -C(O)- group,

(i) $-O-\mathbf{R^{1.1.1}}$,

(j) $-N\mathbf{R^{1.1.3}}\mathbf{R^{1.1.4}}$ or

(k) $-C(=N\mathbf{R^{1.5}})-CN$,

$\mathbf{R^{1.1}}$ denotes halogen, $-NO_2$, -CN, C_{3-6}-cycloalkyl, $-O\mathbf{R^{1.1.1}}$, $-S\mathbf{R^{1.1.1}}$, $-C(O)\mathbf{R^{1.1.1}}$, $-S(O)_2-\mathbf{R^{1.1.2}}$, $-O-S(O)_2-\mathbf{R^{1.1.1}}$, $-CO_2\mathbf{R^{1.1.1}}$, $-O-C(O)-\mathbf{R^{1.1.1}}$, $-N\mathbf{R^{1.1.3}}\mathbf{R^{1.1.4}}$, $-N\mathbf{R^{1.1,3}}-C(O)-\mathbf{R^{1.1.1}}$, $-N\mathbf{R^{1.1,3}}-C(O)-\mathbf{R^{1.1.1}}$, $-N\mathbf{R^{1.1,3}}-CO_2-\mathbf{R^{1.1.1}}$ or $-C(O)-N\mathbf{R^{1.1.3}}\mathbf{R^{1.1.4}}$,

$\mathbf{R^{1.1.1}}$ denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.1.1.1}}$,

(e) C_{3-6}-cycloalkyl or

(f) a pyridyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.1.1.2}}$,

$\mathbf{R^{1.1.1.1}}$ independently of one another denote

(a) halogen, $-NO_2$, -CN, -OH, $-O-C_{1-4}$-alkyl, C_{3-6}-cycloalkyl, C_{1-4}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^{1.1.1.2}}$ independently of one another denote halogen or C_{1-4}-alkyl,

$\mathbf{R^{1.1.2}}$ denotes

(a) C_{1-4}-alkyl,

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(c) -O-C_{1-4}-alkyl or

(d) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.1.1.1}}$ substituted,

$\mathbf{R^{1.1.3}}$,

$\mathbf{R^{1.1.4}}$ independently of one another denote

(a) H,

(b) a C_{1-4}-alkyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.1.4.1}}$,

(c) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.1.1.1}}$,

(d) C_{3-6}-cycloalkyl, or

$\mathbf{R^{1.1.3}}$ and $\mathbf{R^{1.1.4}}$ together with the N atom to which they are attached form a 5- or 6-membered heterocyclic ring, which may additionally contain a further heteroatom selected from N, O and S, or

$\mathbf{R^{1.1.3}}$ and $\mathbf{R^{1.1.4}}$ together with the N atom to which they are attached, form a cyclic imide,

$\mathbf{R^{1.1.4.1}}$ independently of one another halogen denote -NH_2, -NH(C_{1-4}-alkyl), -N(C_{1-4}-alkyl)$_2$ or -SO_2-$\mathbf{R^{1.1.2}}$,

$\mathbf{R^{1.2}}$ denotes halogen, -NO_2, -CN, OH, -O-CH_3 or phenyl,

$\mathbf{R^{1.3}}$ denotes

(a) halogen, -NO_2, -CN, -$\mathbf{OR^{1.1.1}}$, -$\mathbf{SR^{1.1.1}}$, -$CO_2\mathbf{R^{1.1.1}}$, C_{1-6}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^{1.4}}$ independently of one another denote

(a) halogen, -NO_2, -CN, -$\mathbf{OR^{1.1.1}}$, -$\mathbf{SR^{1.1.1}}$, -S(O)-$\mathbf{R^{1.1.2}}$, -$S(O)_2$-$\mathbf{R^{1.1.2}}$, -$\mathbf{NR^{1.1.3}R^{1.1.4}}$, -N($\mathbf{R^{1.4.1}}$)-C(O)-$C_{1-4}$-alkyl, C_{1-6}-alkyl,

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, or

(c) an oxo group,

$R^{1.4.1}$ denotes H or C_{1-4}-alkyl,

$R^{1.5}$ denotes -OH or -O-C_{1-3}-alkyl,

R^2 denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) C_{1-4}-alkyl-C(O)-,

R^3 and R^4 together with the carbon atom to which they are bound denote a C_{3-6}-cycloalkylene group optionally substituted by a group $R^{3.1}$ wherein a -CH_2- unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO_2,

$R^{3.1}$ denotes H, -OH,

R^5 denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^6 independently of one another denote

(a) H, halogen, -CN, -OH, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, -O-C_{1-4}-alkyl, -O-CF_3, -O-C_{3-6}-cycloalkyl, -N(C_{1-3}-alkyl)$_2$, -C(O)-NH_2, -(SO_2)NH_2, -SO_2-C_{1-3}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^7 denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,

(e) -O-C_{1-6}-alkyl,

(f) -O-C_{3-7}-cycloalkyl,

(g) $-NH_2$, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,

(h) -C(O)-$R^{7.1}$,

(i) -S-C_{1-4}-alkyl, -SO_2-$R^{7.2}$,

(j) a five-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl, or

(k) a six-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,

$R^{7.1}$ denotes $-NH_2$, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, -OH, -O-C_{1-6}-alkyl or -O-C_{3-7}-cycloalkyl,

$R^{7.2}$ denotes $-NH_2$, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl or *N*-morpholinyl and

R^8 denotes H, halogen, C_{1-4}-alkyl,

R^9 denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,
(e) C_{2-4}-alkynyl,
(f) -O-C_{1-6}-alkyl,
(g) -O-C_{3-7}-cycloalkyl,
(h) $-NH_2$, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,
(i) -C(O)-$\mathbf{R^{9.1}}$,
(j) -S-C_{1-4}-alkyl, -SO-C_{1-4}-alkyl, $-SO_2$-C_{1-4}-alkyl,

$\mathbf{R^{9.1}}$ denotes $-NH_2$, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, -OH, -O-C_{1-8}-alkyl or -O-C_{3-7}-cycloalkyl,

$\mathbf{R^{10}}$ denotes H, halogen, C_{1-4}-alkyl,

$\mathbf{R^{11}}$ denotes
(a) H, halogen, -CN, -OH,
(b) C_{1-6}-alkyl,
(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(d) C_{3-7}-cycloalkyl,
(e) -O-C_{1-6}-alkyl,
(f) -O-C_{3-7}-cycloalkyl,
(g) $-NH_2$, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,
(h) -C(O)-$\mathbf{R^{11.1}}$,
(i) -S-C_{1-3}-alkyl, $-SO_2$-$\mathbf{R^{11.2}}$,
(j) a five-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl, or
(k) a six-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,

$\mathbf{R^{11.1}}$ denotes $-NH_2$, $-NH(C_{1-6}\text{-alkyl})$,$-N(C_{1-6}\text{-alkyl})_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, -OH, $-O-C_{1-8}$-alkyl or $-O-C_{3-7}$-cycloalkyl,

$\mathbf{R^{11.2}}$ denotes $-NH_2$, $-NH(C_{1-6}\text{-alkyl})$,$-N(C_{1-6}\text{-alkyl})_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl or *N*-morpholinyl and

X independently of one another denote C-$\mathbf{R^6}$ or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

One embodiment **2** of the present invention comprises the compounds of the above general formula **I**, wherein $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, **n** and **X** are defined as mentioned hereinbefore in embodiment **1** and

$\mathbf{R^1}$ denotes

(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(c) a C_{3-6}-cycloalkyl group optionally substituted by a group $\mathbf{R^{1.2}}$ wherein a $-CH_2-$ unit may be replaced by a -C(O)- group,

(d) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.3}}$,

(e) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.4}}$, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,

(f) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms,

(g) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms,

(h) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, in which a $-CH_2-$ unit may be replaced by a -C(O)- group,

(i) $-O-\mathbf{R^{1.1.1}}$ or

(j) $-N\mathbf{R^{1.1.3}}\mathbf{R^{1.1.4}}$,

$R^{1.1}$ denotes -CN, C_{3-6}-cycloalkyl, -$OR^{1.1.1}$, -$NR^{1.1.3}R^{1.1.4}$,

$R^{1.1.1}$ denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$R^{1.1.3}$,

$R^{1.1.4}$ independently of one another denote

(a) H,

(b) C_{1-4}-alkyl,

(c) C_{3-6}-cycloalkyl, or

$R^{1.1.3}$ and $R^{1.1.4}$ together with the N atom to which they are attached form a 5- or 6-membered heterocyclic ring, which may additionally contain a further heteroatom selected from N, O and S, or

$R^{1.2}$ denotes halogen, -NO_2, -CN, -OH, -O-CH_3 or phenyl,

$R^{1.3}$ independently of one another denote

(a) halogen, -NO_2, -CN, -$OR^{1.1.1}$, C_{1-6}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$R^{1.4}$ independently of one another denote

(a) halogen, -NO_2, -CN, -$OR^{1.1.1}$, -$NR^{1.1.3}R^{1.1.4}$, -N($R^{1.4.1}$)-C(O)-C_{1-4}-alkyl, C_{1-6}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$R^{1.4.1}$ denotes H or C_{1-4}-alkyl,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **3** of the present invention comprises the compounds of the above general formula **I**, wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as mentioned hereinbefore in embodiment **1** and

R^1 denotes

(a) a C_{1-6}-alkyl group optionally substituted by a group $R^{1.1}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $R^{1.3}$,

(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $R^{1.4}$, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,

(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $R^{1.4}$, which contains one, two or three N-atoms,

(e) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups $R^{1.4}$, which contains one, two or three N-atoms,

(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $R^{1.4}$, in which a $-CH_2-$ unit may be replaced by a -C(O)- group,

$R^{1.1}$ denotes -CN, C_{3-6}-cycloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$R^{1.3}$ independently of one another denote

(a) F, Cl, Br, -OH, $-OCH_3$, C_{1-6}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$R^{1.4}$ independently of one another denote

(a) F, Cl, Br, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC_{2-3}$-alkyl, $-N(C_{2-3}$-alkyl$)_2$ -NH-C(O)-C_{1-4}-Alkyl, C_{1-6}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

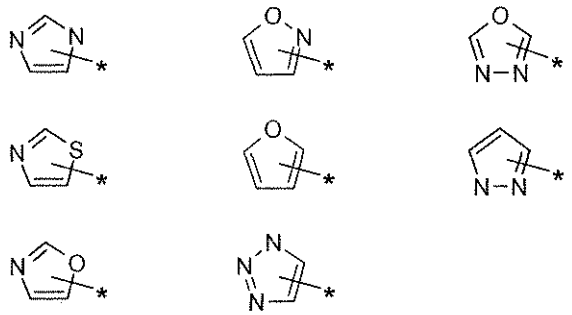
An embodiment **4** of the present invention comprises the compounds of the above general formula **I**, wherein $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, **n** and **X** are defined as mentioned hereinbefore in embodiment **1** and

$\mathbf{R^1}$ denotes

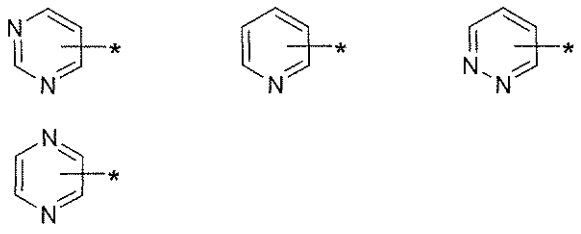
(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.3}}$,

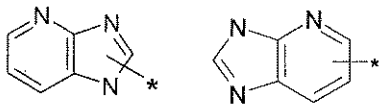
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.4}}$, which is selected from among



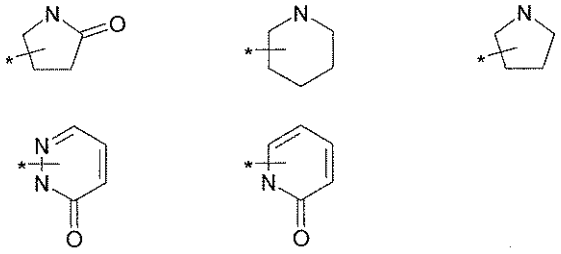
(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$ which is selected from among



(e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $R^{1.4}$, which is selected from among



$R^{1.1}$ denotes -CN, cyclopropyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$R^{1.3}$ independently of one another denotes

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, C_{1-4}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$R^{1.4}$ independently of one another denotes

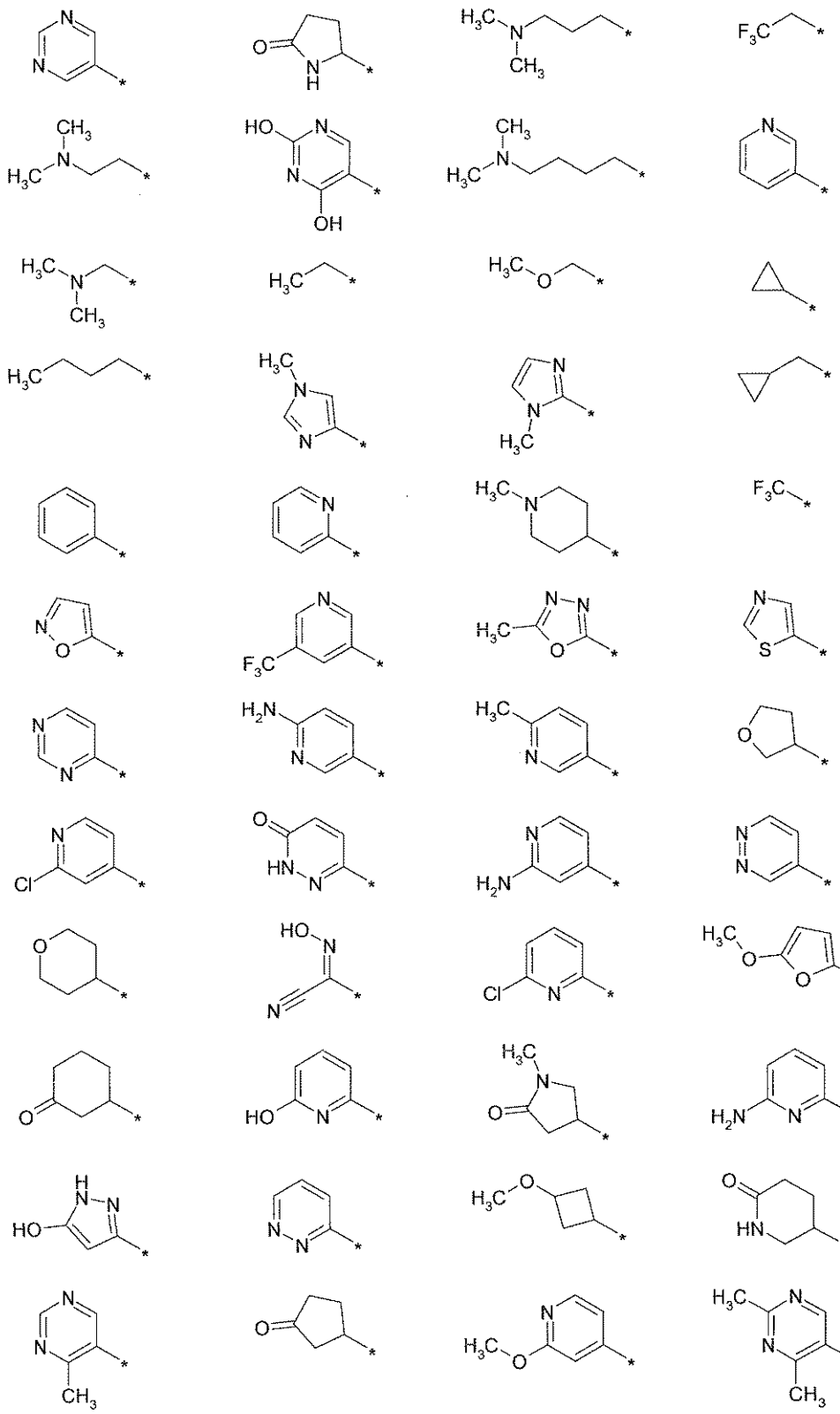
(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, $-NH_2$, $-NH-C_{1-4}$-alkyl, $-N(C_{1-4}$-alkyl$)_2$, $-NH-C(O)-C_{1-4}$-alkyl, C_{1-6}-alkyl, or

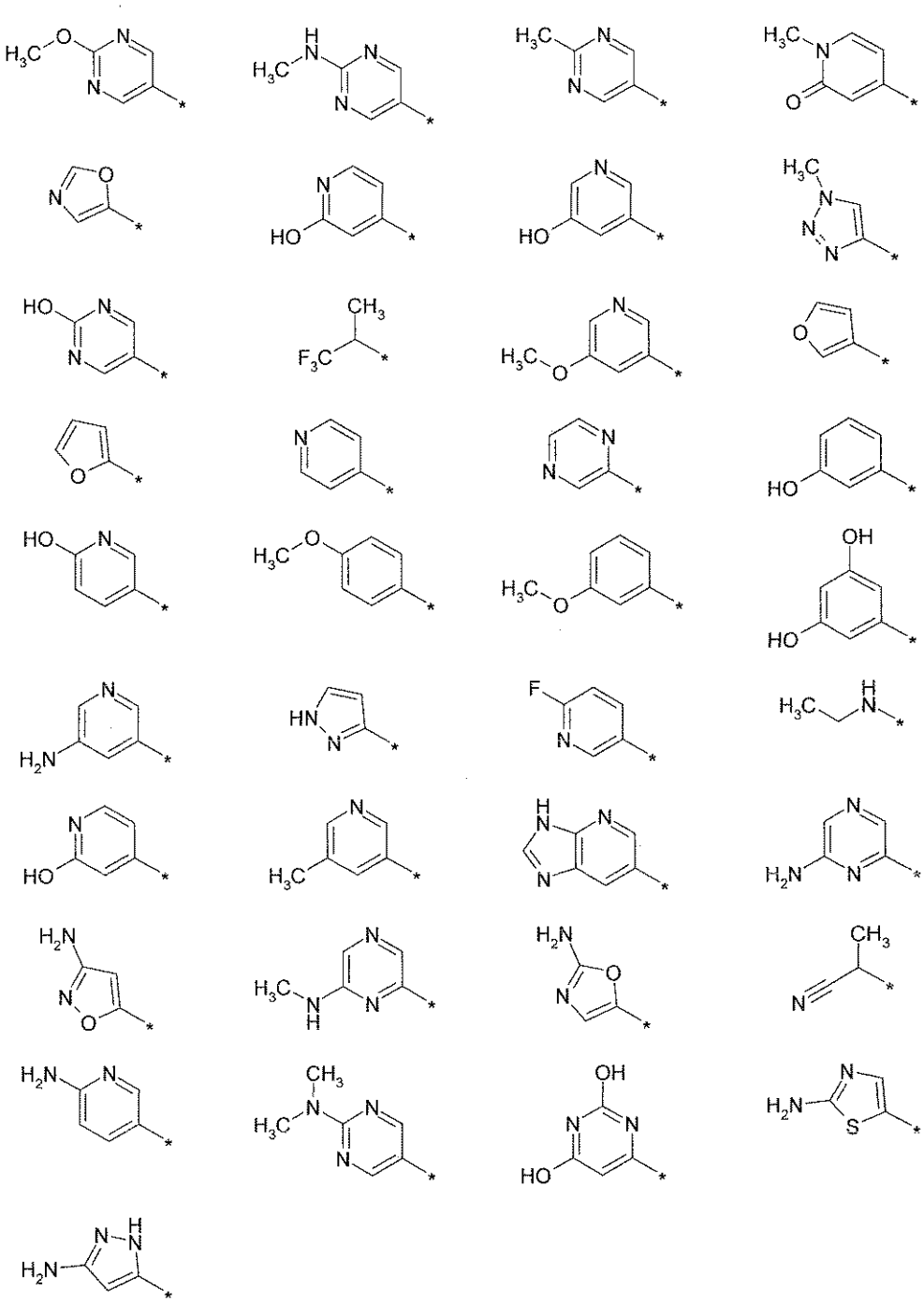
(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **5** of the present invention comprises the compounds of the above general formula **I**, wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as mentioned hereinbefore in embodiment **1** and

R^1 is selected from among

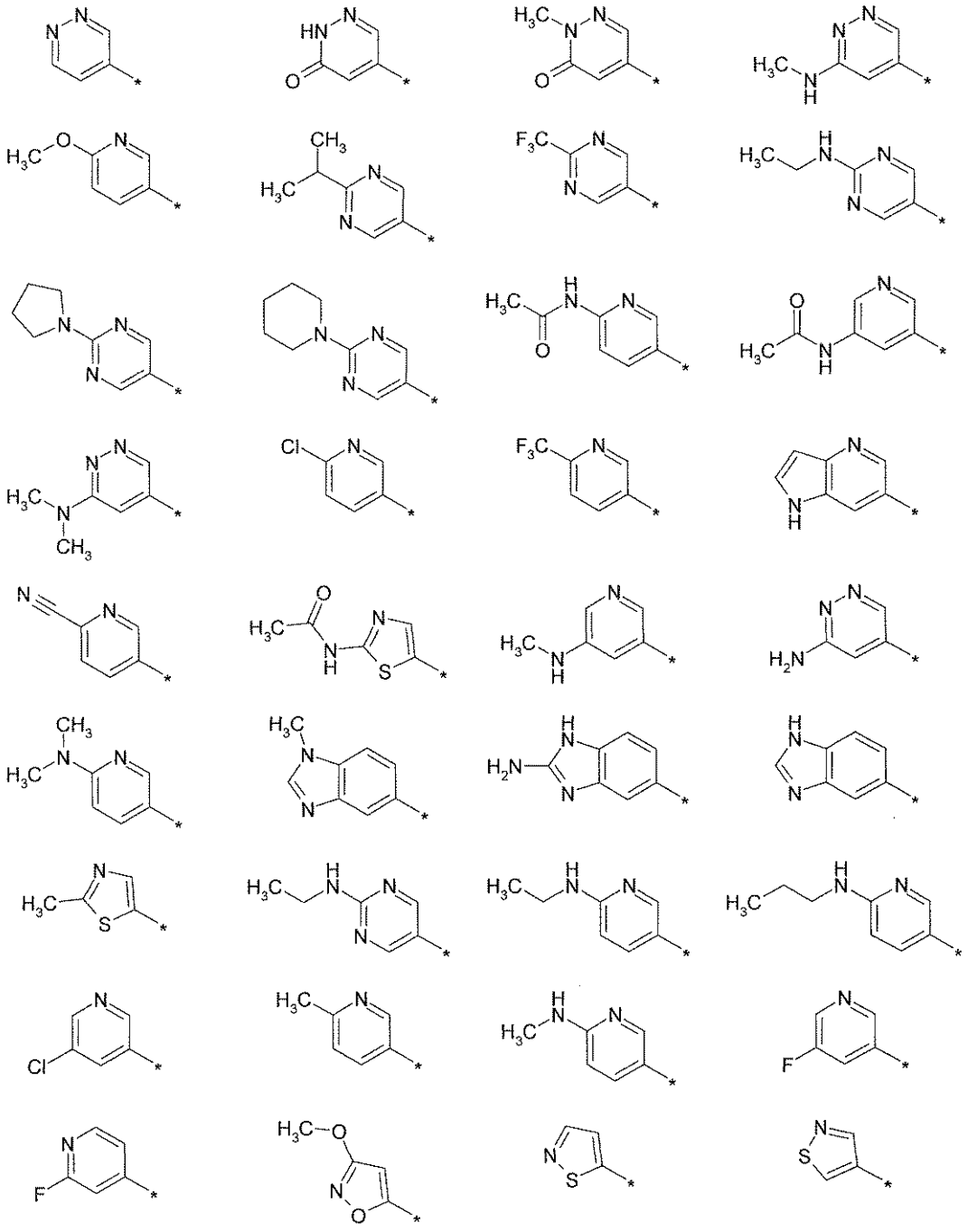


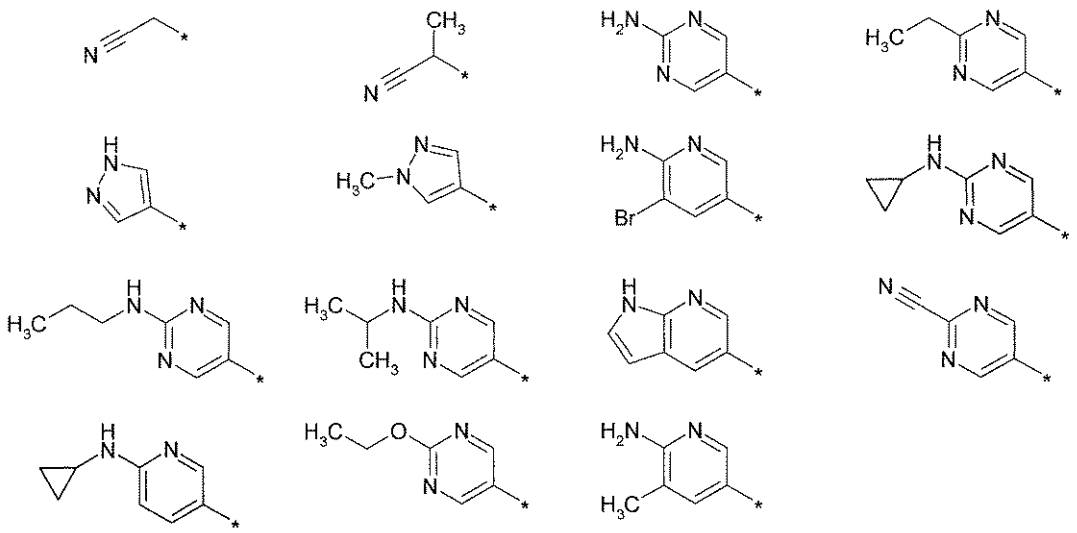


the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **6** of the present invention comprises the compounds of the above general formula **I**, wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as mentioned hereinbefore in embodiment **1** and

R^1 is selected from among





the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **7** of the present invention consists of the compounds of the above general formula **I**, wherein R^1 is defined as mentioned hereinbefore under embodiment **1**, **2**, **3**, **4**, **5** or **6** and

n denotes one of the numbers 0, 1 or 2,

R^2 denotes
(a) H,
(b) C_{1-4}-alkyl,

R^3 and R^4 together with the carbon atom to which they are bound denote a C_{3-6}-cycloalkylene group optionally substituted by a group $R^{3.1}$ wherein a $-CH_2$ unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO_2,

$R^{3.1}$ denotes H, -OH,

R^5 denotes
(a) H,
(b) C_{1-4}-alkyl,

(c) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^6 independently of one another denotes

(a) H, halogen, -CN, -OH, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, -O-C_{1-4}-alkyl, -O-CF_3, -O-C_{3-6}-cycloalkyl, -N(C_{1-3}-alkyl)$_2$, -C(O)-NH_2, -(SO_2)NH_2, -SO_2-C_{1-3}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^7 denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,

(e) -O-C_{1-6}-alkyl,

(f) -O-C_{3-7}-cycloalkyl,

(g) -NH_2, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,

(h) -C(O)-$R^{7.1}$,

(i) -S-C_{1-4}-alkyl,

$R^{7.1}$ denotes -NH_2, , -OH, -O-C_{1-8}-alkyl,

R^8 denotes H, halogen, C_{1-4}-alkyl,

R^9 denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,
(e) C_{2-4}-alkynyl,
(f) -O-C_{1-6}-alkyl,
(g) -O-C_{3-7}-cycloalkyl,
(h) $-NH_2$, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,
(i) -C(O)-$\mathbf{R^{9.1}}$,
(j) -S-C_{1-4}-alkyl, -SO-C_{1-4}-alkyl, $-SO_2$-C_{1-4}-alkyl,

$\mathbf{R^{9.1}}$ denotes $-NH_2$, -OH, -O-C_{1-8}-alkyl,

$\mathbf{R^{10}}$ denotes H, halogen, C_{1-4}-alkyl,

$\mathbf{R^{11}}$ denotes
(a) H, halogen, -CN, -OH,
(b) C_{1-6}-alkyl,
(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(d) C_{3-7}-cycloalkyl,
(e) -O-C_{1-6}-alkyl,
(f) -O-C_{3-7}-cycloalkyl,
(g) $-NH_2$, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,
(h) -C(O)-$\mathbf{R^{11.1}}$,
(i) -S-C_{1-3}-alkyl,

$\mathbf{R^{11.1}}$ denotes $-NH_2$, , -OH, -O-C_{1-8}-alkyl, and

X independently of one another represent C-$\mathbf{R^6}$ or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **8** of the present invention comprises the compounds of the above general formula **I**, wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as mentioned hereinbefore in embodiment **1**, **2**, **3**, **4**, **5** or **6** and

R^2 denotes H or CH_3,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **8** of the present invention comprises the compounds of the above general formula **I**, wherein R^1, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as mentioned hereinbefore in embodiment **1**, **2**, **3**, **4**, **5**, **6** or **7** and

R^2 denotes H or CH_3,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **9** of the present invention comprises the compounds of the above general formula **I**, wherein R^1, R^2, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as mentioned hereinbefore in embodiment **1**, **2**, **3**, **4**, **5**, **6** or **7** and

R^2 denotes H,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

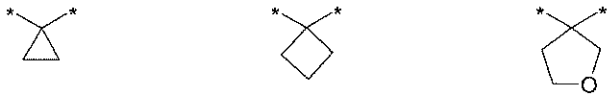
An embodiment **10** of the present invention comprises the compounds of the above general formula **I**, wherein R^1, R^2, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as mentioned hereinbefore in embodiment **1**, **2**, **3**, **4**, **5**, **6**, **7** , **8** or **9** and

R^3 and R^4 together with the carbon atom to which they are bonded denote a C_{3-6}-cycloalkylene group wherein a $-CH_2-$ unit may be replaced by an oxygen atom,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **11** of the present invention comprises the compounds of the above general formula **I**, wherein R^1, R^2, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as mentioned hereinbefore in embodiment **1**, **2**, **3**, **4**, **5**, **6**, **7** , **8** or **9** and

R^3 and R^4 together with the carbon atom to which they are bonded denote a group selected from



the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **12** of the present invention comprises the compounds of the above general formula **I**, wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as mentioned hereinbefore in embodiment **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10** or **11** and

R^5 denotes H or CH_3,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **13** of the present invention comprises the compounds of the above general formula **I**, wherein R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as mentioned hereinbefore in embodiment **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10** , **11** or **12** and

R^6 denotes H, F, Cl or methyl,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **14** of the present invention comprises the compounds of the above general formula **I**, wherein R^1, R^2, R^3, R^4, R^5, R^6, **n** and **X** are defined as mentioned hereinbefore in embodiment **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, **11** ,**12** or **13** and

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^8 denotes H,

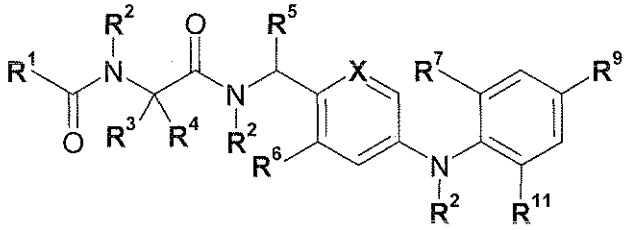
R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

R^{10} denotes H and

R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **15** of the present invention comprises the compounds of general formula **Ia**



, (**Ia**)

wherein

R^1 denotes

(a) a C_{1-6}-alkyl group optionally substituted by a group $R^{1.1}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $R^{1.3}$,

(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $R^{1.4}$, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,

(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms,

(e) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms,

(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, in which a $-CH_2-$ unit may be replaced by a -C(O)- group,

$\mathbf{R^{1.1}}$ denotes -CN, C_{3-6}-cycloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$\mathbf{R^{1.3}}$ independently of one another denotes

(a) F, Cl, Br, -OH, $-OCH_3$, C_{1-6}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$\mathbf{R^{1.4}}$ independently of one another denotes

(a) F, Cl, Br, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -NH-C(O)-C_{1-4}-alkyl, C_{1-6}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^2}$ denotes H or CH_3,

$\mathbf{R^3}$ and $\mathbf{R^4}$ together with the carbon atom to which they are bonded denote a C_{3-6}-cycloalkylene group wherein a $-CH_2$ unit may be replaced by an oxygen atom,

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

$\mathbf{R^6}$ denotes H, F, Cl, Br or C_{1-4}-alkyl,

$\mathbf{R^7}$ denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

$\mathbf{R^9}$ denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

$\mathbf{R^{11}}$ denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

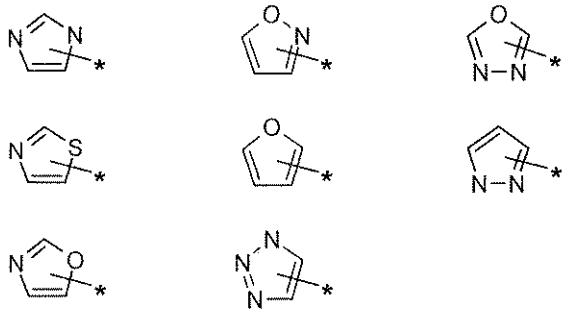
An embodiment **16** of the present invention comprises the compounds of general formula **Ia**, wherein

$\mathbf{R^1}$ denotes

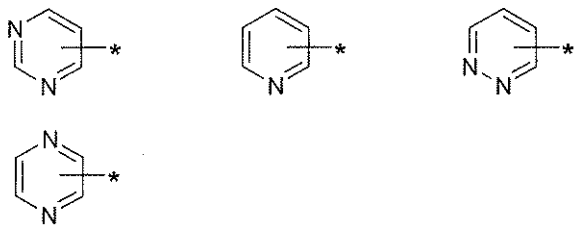
(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.3}}$,

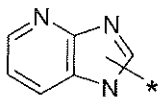
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.4}}$, which is selected from among



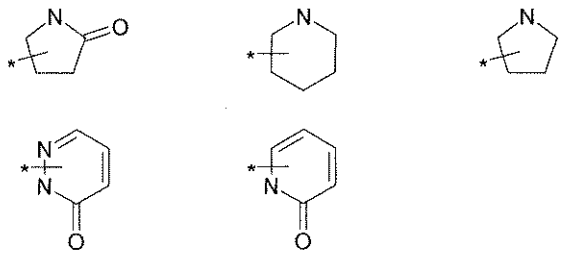
(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



(e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



$\mathbf{R^{1.1}}$ denotes -CN, cyclopropyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$\mathbf{R^{1.3}}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, C_{1-4}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$\mathbf{R^{1.4}}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, $-NH_2$, $-NH-C_{1-4}$-alkyl, $-N(C_{1-4}$-alkyl$)_2$, $-NH-C(O)-C_{1-4}$-alkyl, C_{1-6}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^2}$ denotes H or CH_3,

$\mathbf{R^3}$ and $\mathbf{R^4}$ together with the carbon atom to which they are bonded denote a C_{3-6}-cycloalkylene group wherein a $-CH_2$ unit may be replaced by an oxygen atom,

$\mathbf{R^5}$ denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

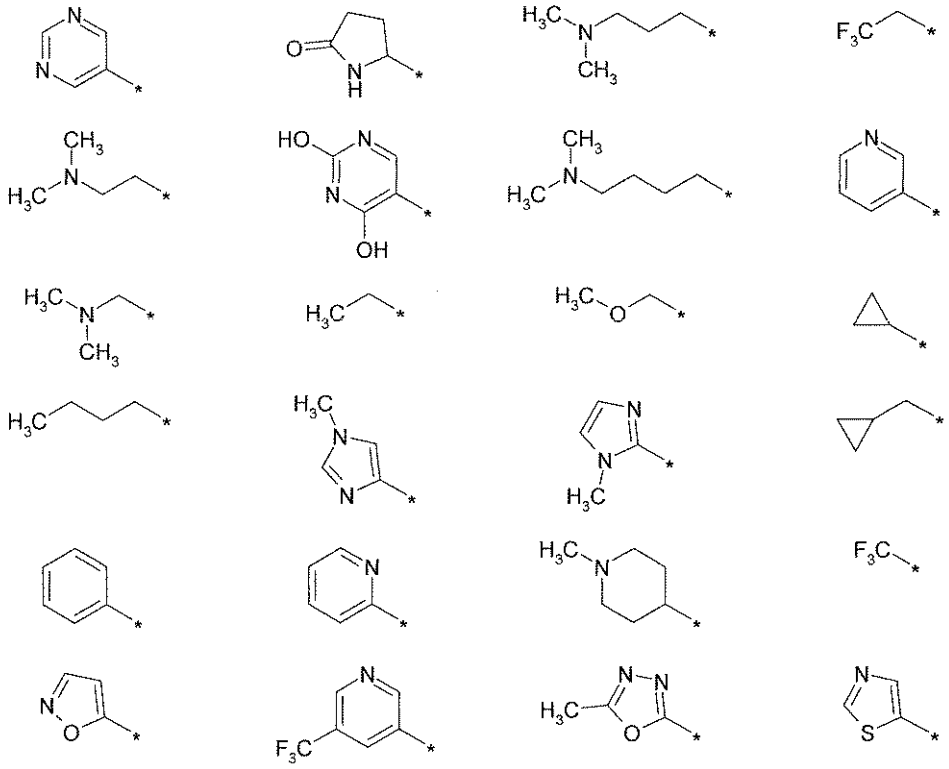
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

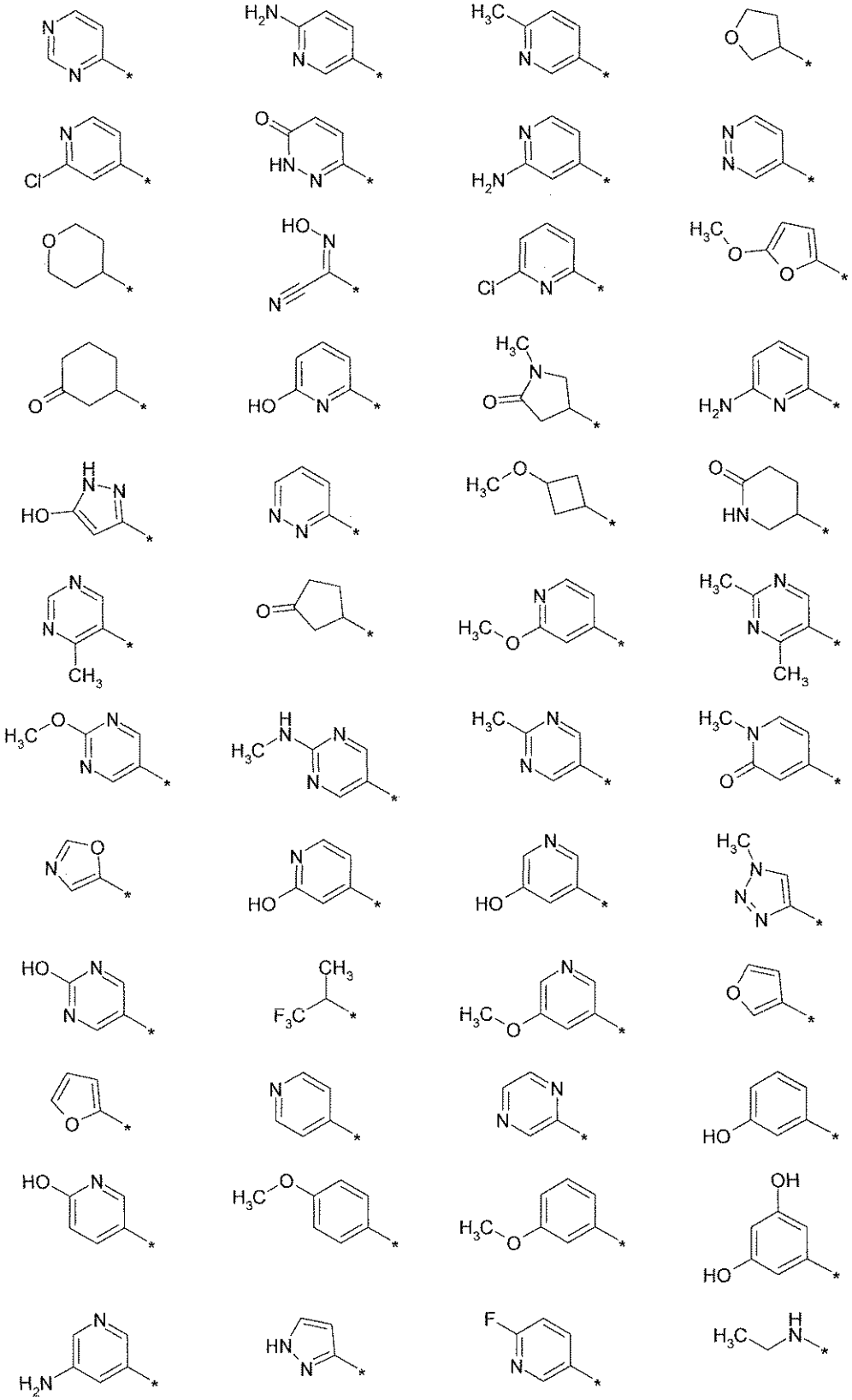
X denotes CH or N,

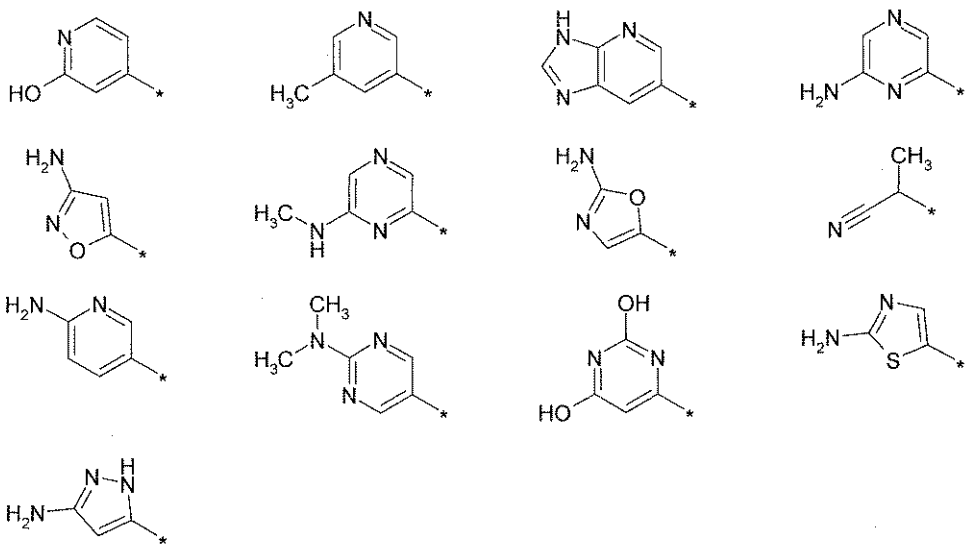
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **17** of the present invention comprises the compounds of general formula **Ia**, wherein

R^1 denotes a group selected from







R^2 denotes H or CH_3,

R^3 and **R^4** together with the carbon atom to which they are bonded denote a C_{3-6}-cycloalkylene group wherein a $-CH_2$ unit may be replaced by an oxygen atom,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

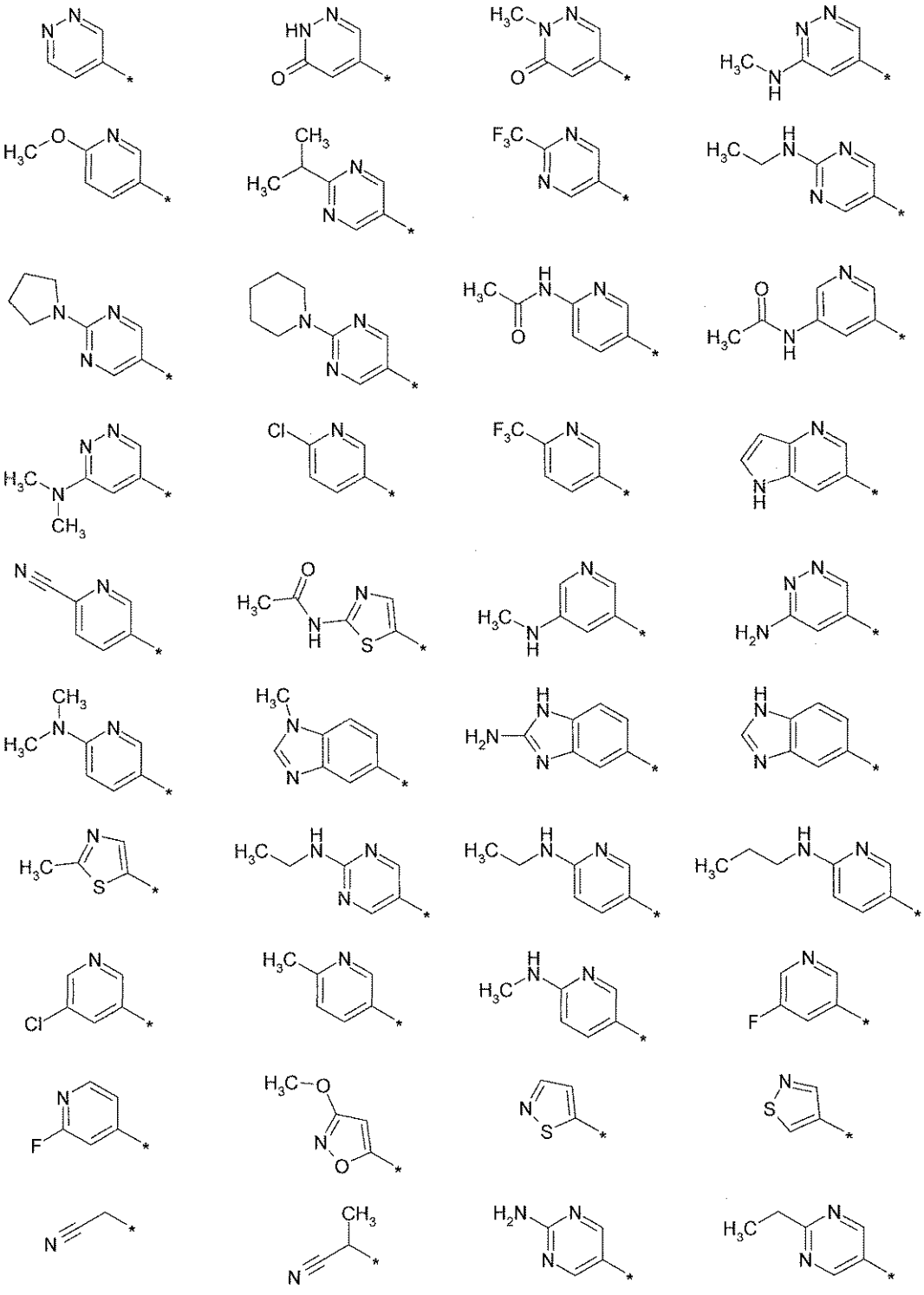
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

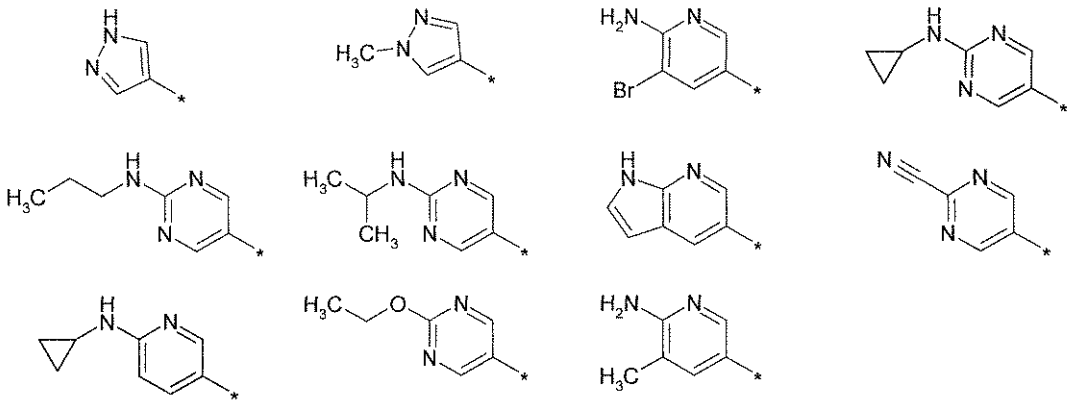
X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **18** of the present invention comprises the compounds of general formula **Ia** wherein

R^1 denotes a group selected from





R^2 denotes H or CH_3,

R^3 and **R^4** together with the carbon atom to which they are bound denote a C_{3-6}-cycloalkylene group wherein a $-CH_2$ unit may be replaced by an oxygen atom,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

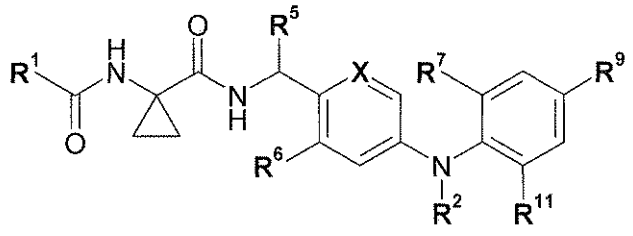
R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **19** of the present invention comprises the compounds of general formula **Ib**



, (**Ib**)

wherein

R^1 denotes

(a) a C_{1-6}-alkyl group optionally substituted by a group **$R^{1.1}$**,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups **$R^{1.3}$**,

(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups **$R^{1.4}$**, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,

(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups **$R^{1.4}$**, which contains one, two or three N-atoms,

(e) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups **$R^{1.4}$**, which contains one, two or three N-atoms,

(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups **$R^{1.4}$**, in which a $-CH_2-$ unit may be replaced by a -C(O)- group,

$R^{1.1}$ denotes -CN, C_{3-6}-cycloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$R^{1.3}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, C_{1-6}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$R^{1.4}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -NH-C(O)-C_{1-4}-alkyl, C_{1-6}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^2}$ denotes H or CH_3,

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

$\mathbf{R^6}$ denotes H, F, Cl, Br or C_{1-4}-alkyl,

$\mathbf{R^7}$ denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

$\mathbf{R^9}$ denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

$\mathbf{R^{11}}$ denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

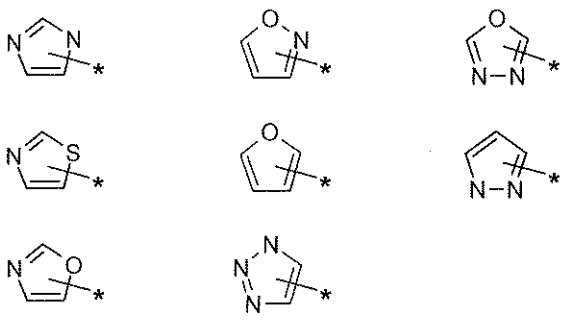
An embodiment **20** of the present invention comprises the compounds of general formula **Ib**, wherein

$\mathbf{R^1}$ denotes

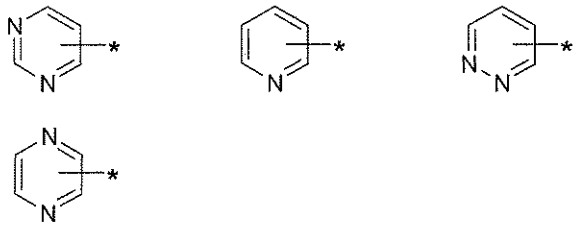
(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.3}}$,

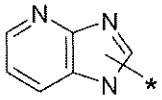
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.4}}$, which is selected from among



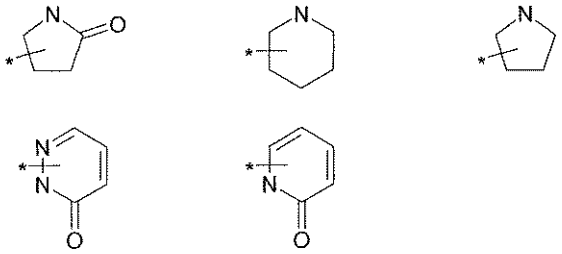
(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



(e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



$\mathbf{R^{1.1}}$ denotes -CN, cyclopropyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$\mathbf{R^{1.3}}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, C_{1-4}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$\mathbf{R^{1.4}}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, $-NH_2$, -NH-C_{1-4}-alkyl, $-N(C_{1-4}\text{-alkyl})_2$, -NH-C(O)-$C_{1-4}$-alkyl, C_{1-6}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^2 denotes H or CH_3,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

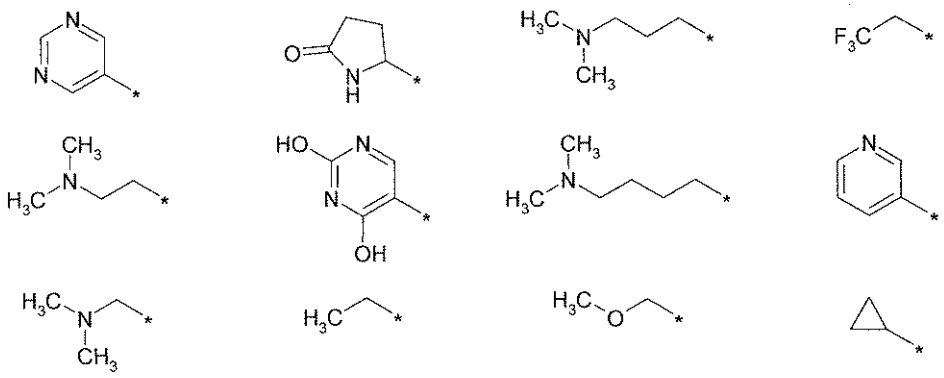
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

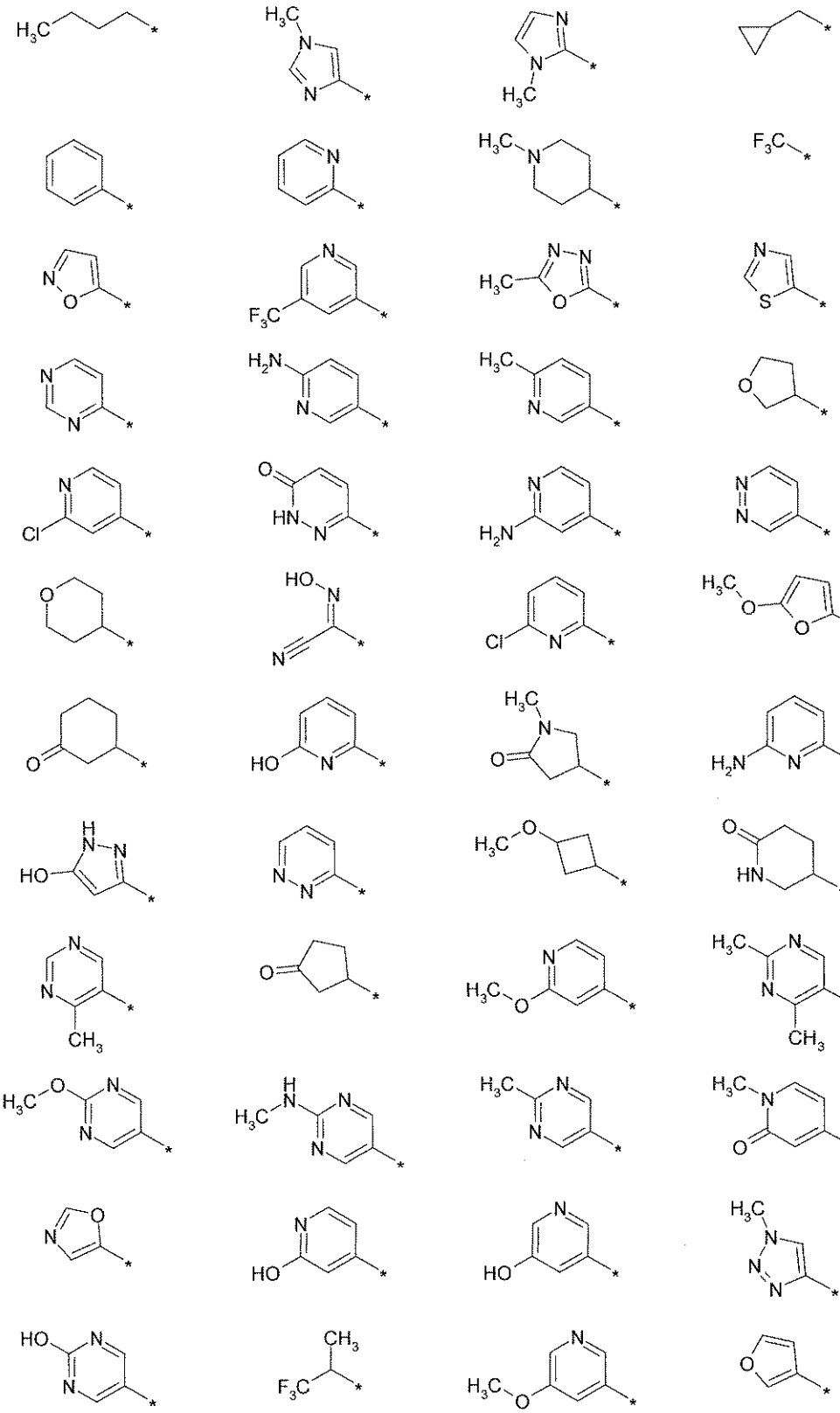
X denotes CH or N,

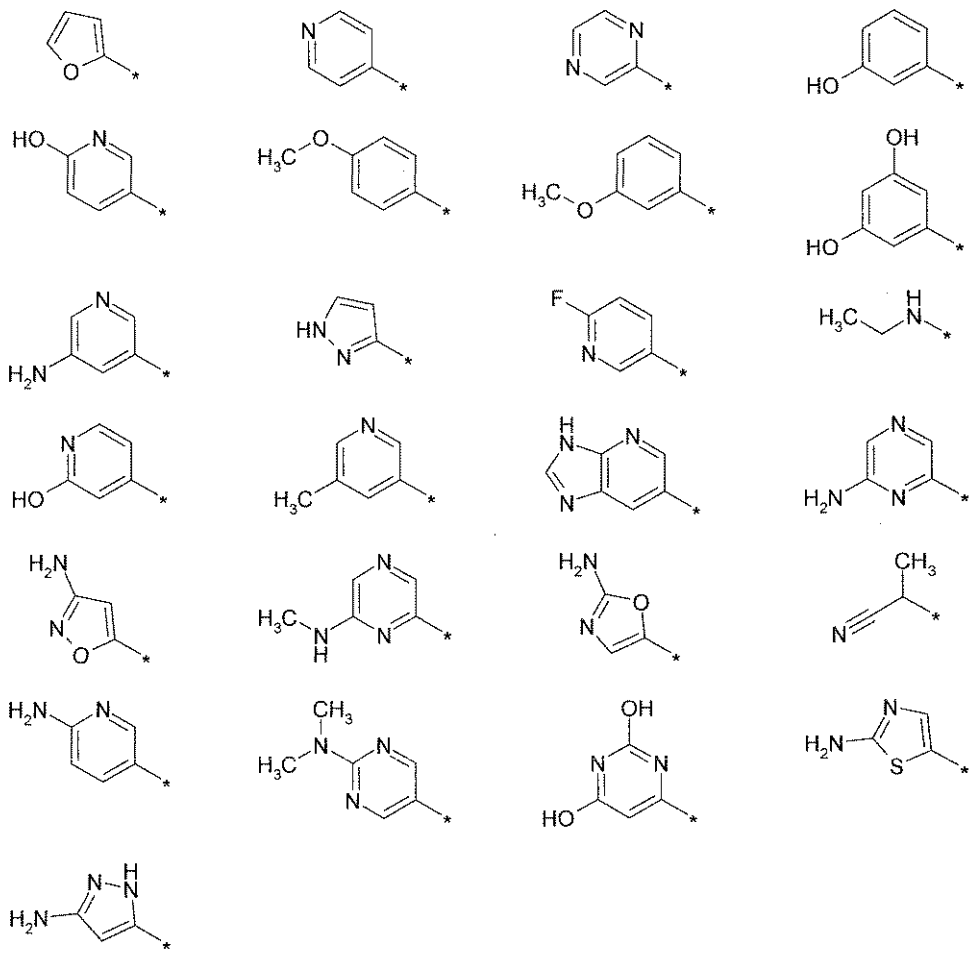
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **21** of the present invention comprises the compounds of general formula **Ib**, wherein

R^1 denotes a group selected from







R^2 denotes H or CH_3,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

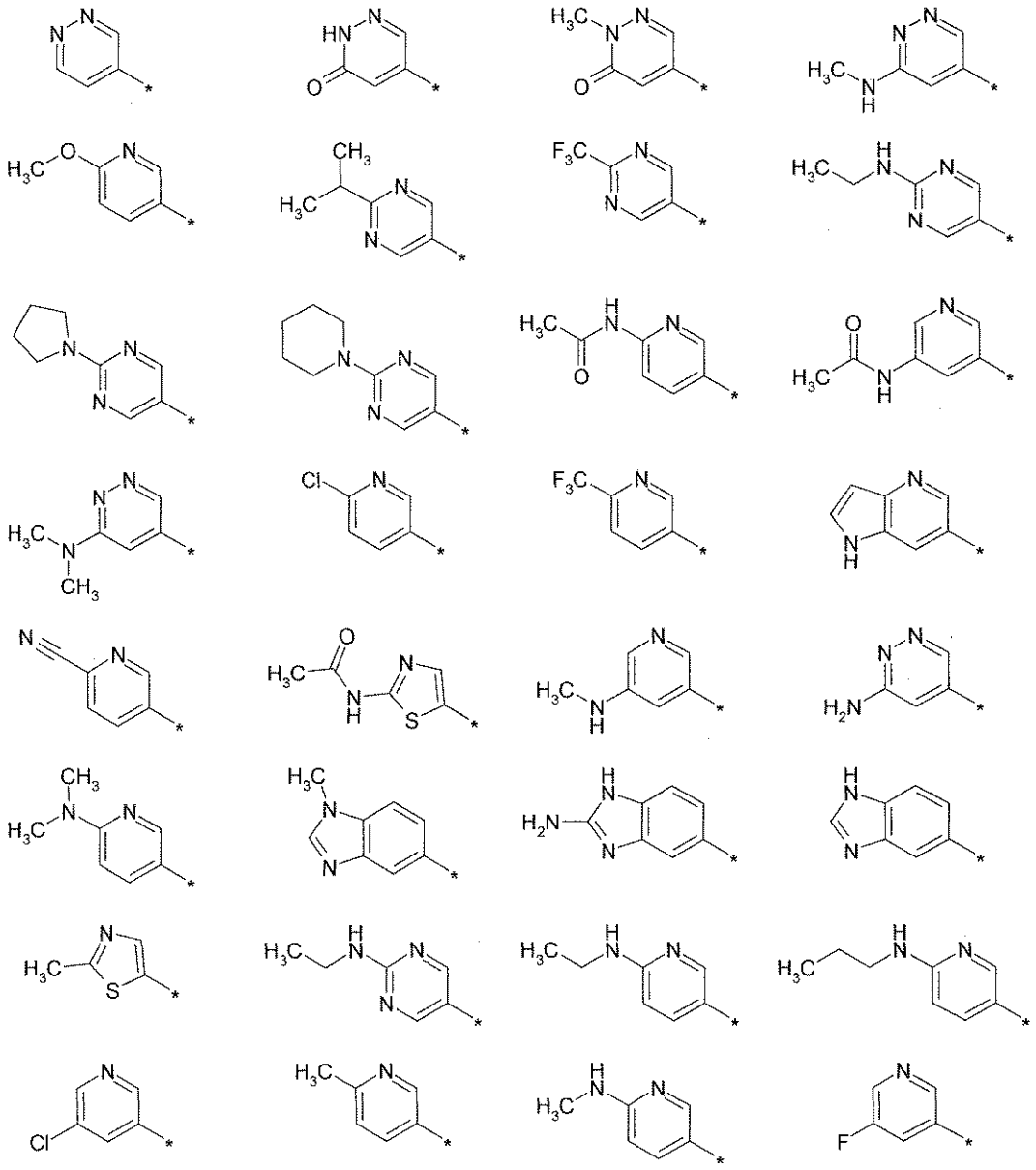
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

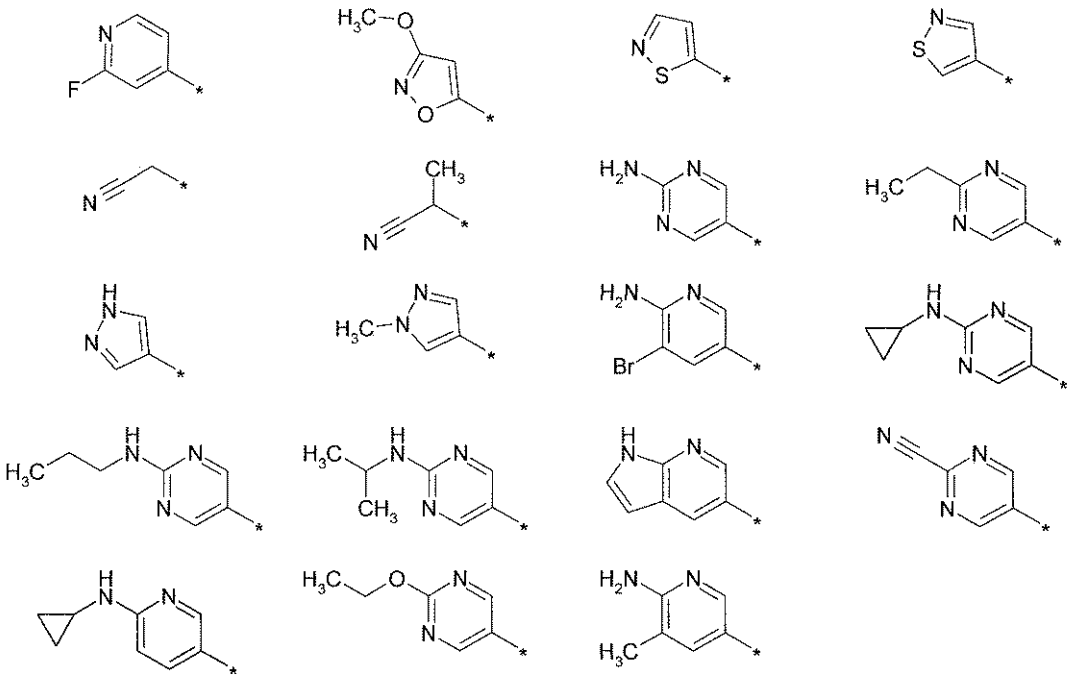
X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **22** of the present invention comprises the compounds of general formula **Ib**, wherein

R^1 denotes a group selected from





R^2 denotes H,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

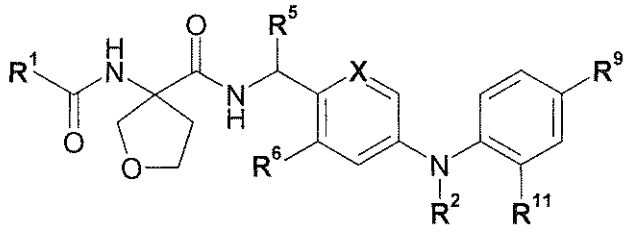
R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **23** of the present invention comprises the compounds of general formula **Ic**



, (Ic)

wherein

$\mathbf{R^1}$ denotes

(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.3}}$,

(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.4}}$, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,

(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms,

(e) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$ which contains one, two or three N-atoms,

(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, wherein a $-CH_2-$ unit may be replaced by a -C(O)- group,

$\mathbf{R^{1.1}}$ denotes -CN, C_{3-6}-cycloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$\mathbf{R^{1.3}}$ independently of one another denote

(a) F, Cl, Br, -OH, $-OCH_3$, C_{1-6}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$\mathbf{R^{1.4}}$ independently of one another denote

(a) F, Cl, Br, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -NH-C(O)-C_{1-4}-alkyl, C_{1-6}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^2}$ denotes H or CH_3,

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

$\mathbf{R^6}$ denotes H, F, Cl, Br or C_{1-4}-alkyl,

$\mathbf{R^7}$ denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

$\mathbf{R^9}$ denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

$\mathbf{R^{11}}$ denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

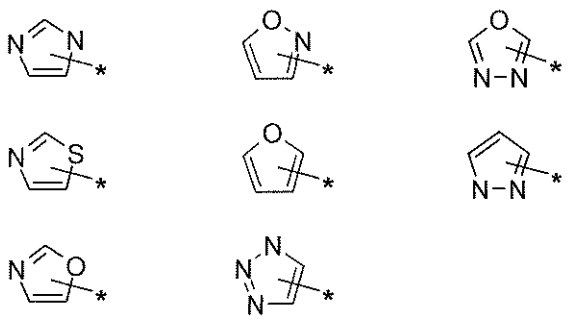
An embodiment **24** of the present invention comprises the compounds of general formula **Ic**, wherein

$\mathbf{R^1}$ denotes

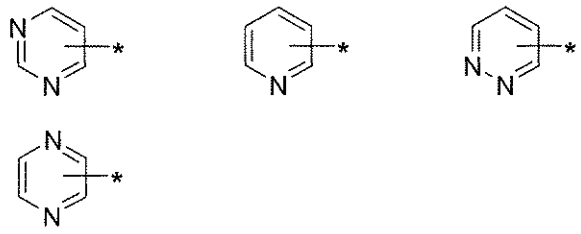
(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.3}}$,

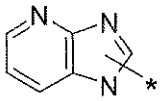
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.4}}$, which is selected from among



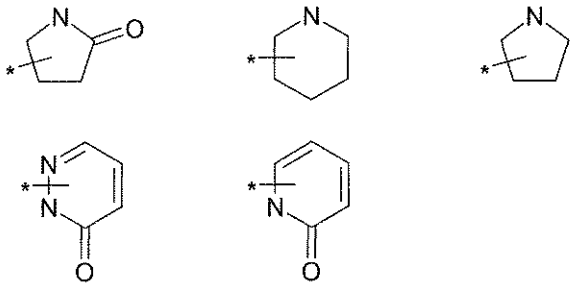
(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



(e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



$\mathbf{R^{1.1}}$ denotes -CN, cyclopropyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$\mathbf{R^{1.3}}$ independently of one another denotes

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, C_{1-4}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$\mathbf{R^{1.4}}$ independently of one another denote

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, $-NH_2$, $-NH-C_{1-4}$-alkyl, $-N(C_{1-4}\text{-alkyl})_2$, $-NH-C(O)-C_{1-4}$-alkyl, C_{1-6}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^2 denotes H or CH_3,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

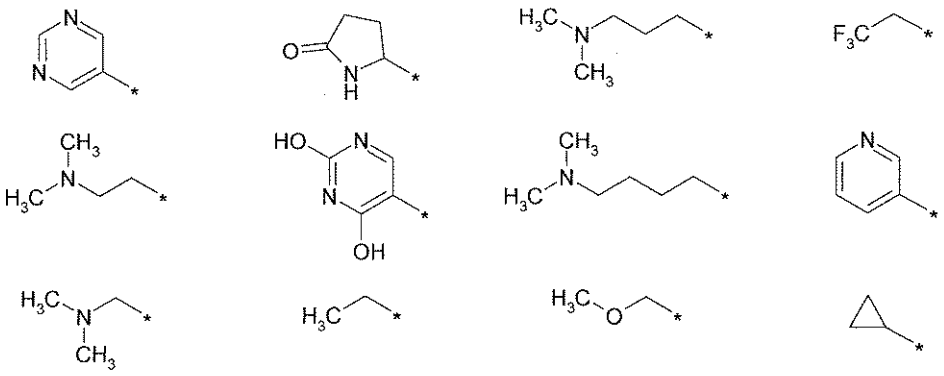
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

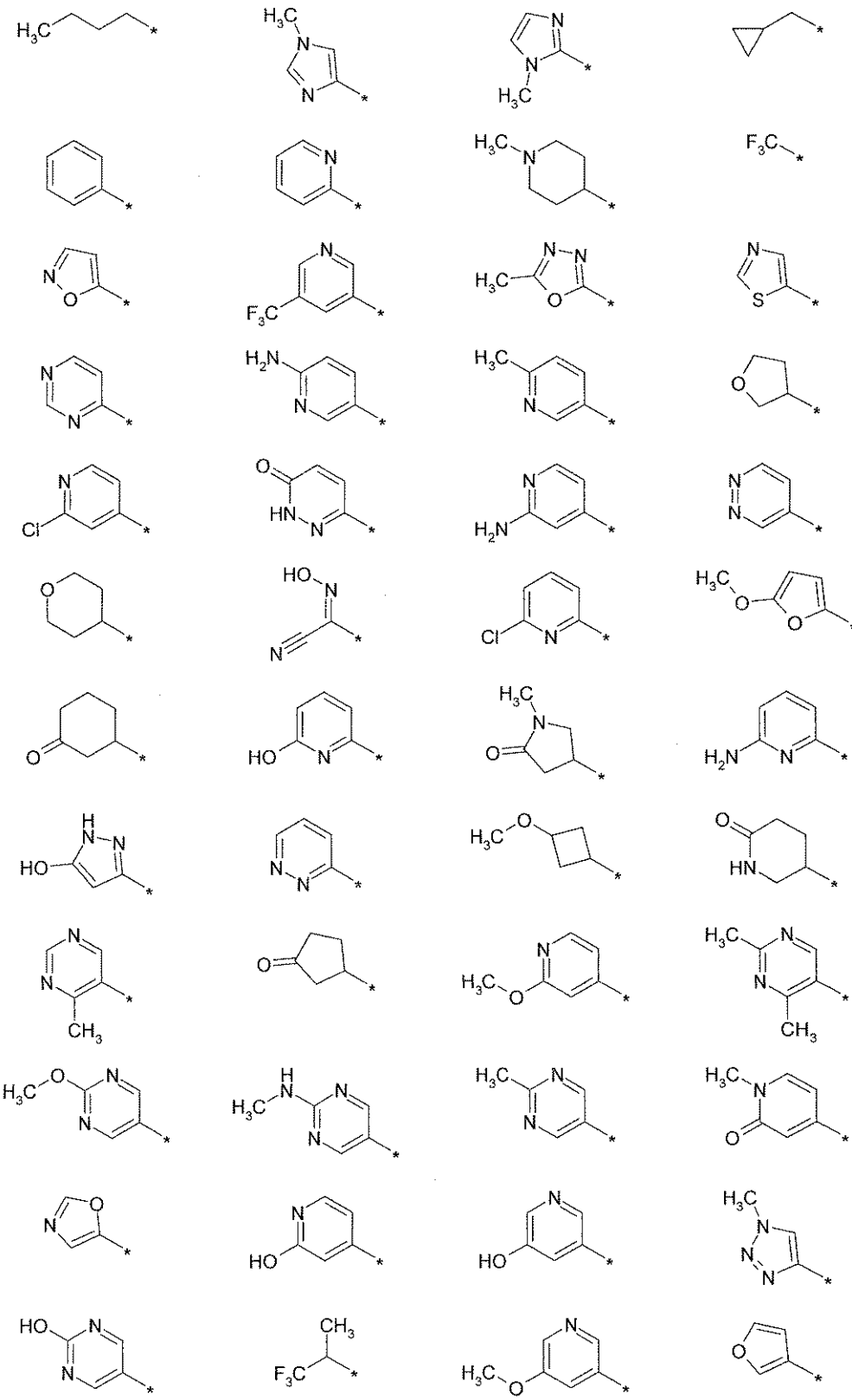
X denotes CH or N,

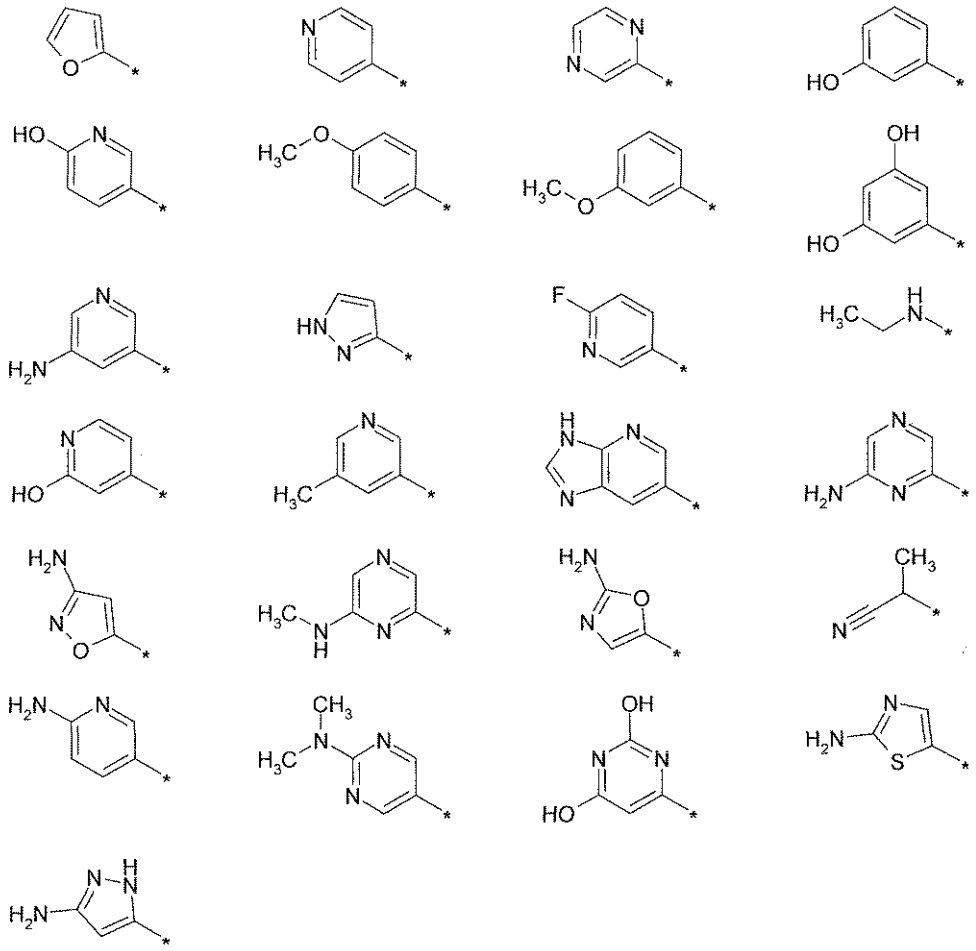
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **25** of the present invention comprises the compounds of general formula **Ic**, *wherein*

R^1 denotes a group selected from







R^2 denotes H or CH_3,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

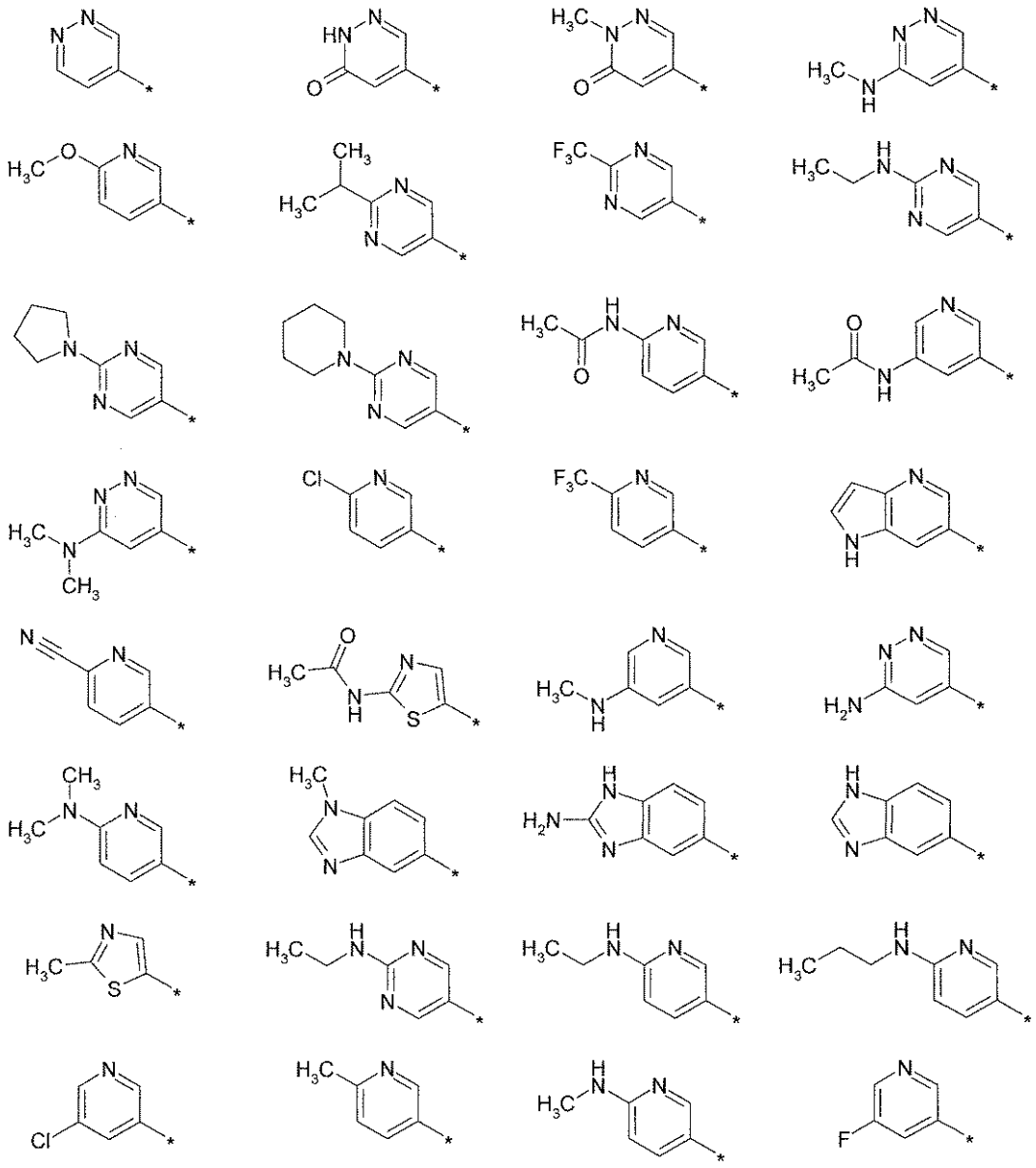
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

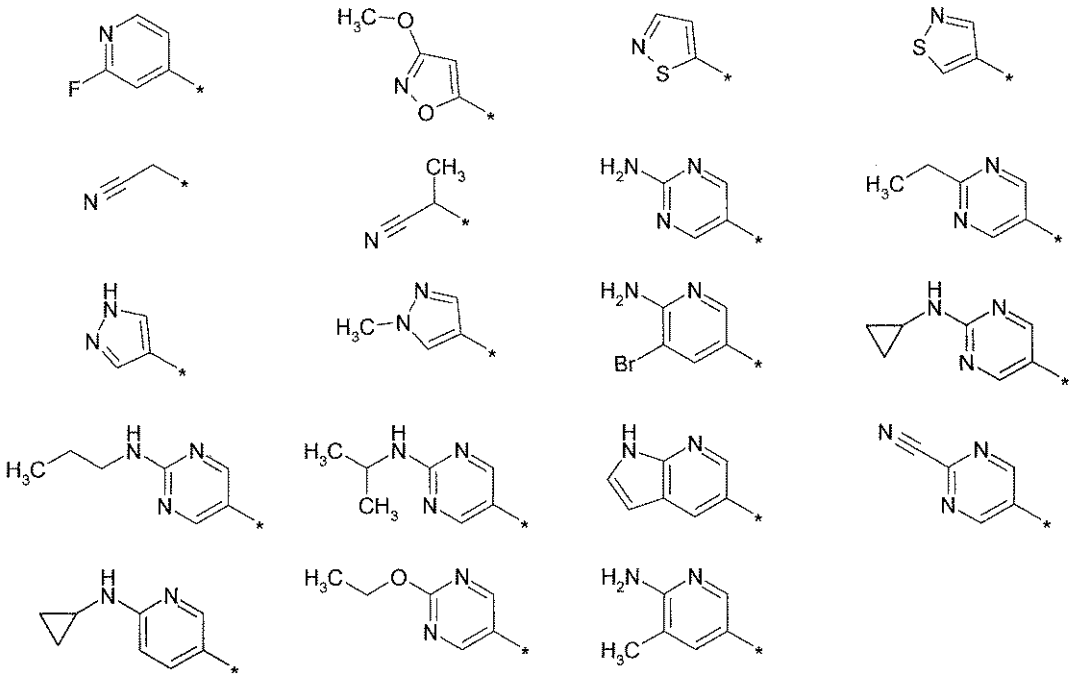
X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **26** of the present invention comprises the compounds of general formula **Ic**, wherein

R^1 denotes a group selected from





R^2 denotes H or CH_3,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

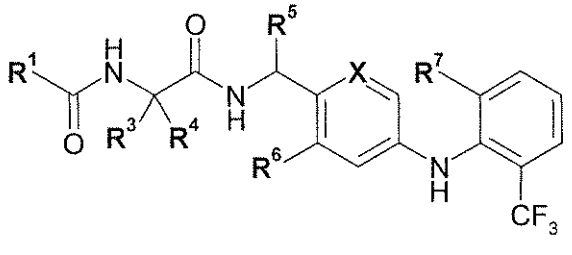
R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

X denotes CH or N,

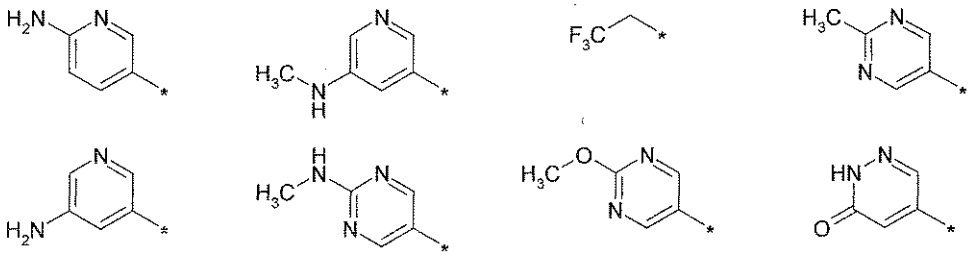
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

An embodiment **27** of the present invention comprises the compounds of general formula **Id**


, (**Id**)

wherein

R^1 denotes a group selected from



R^3 and **R^4** together with the carbon atom to which they are attached denote a C_{3-6}-cycloalkylene group wherein a $-CH_2$ unit may be replaced by an oxygen atom,

R^5 denotes H or CH_3,

R^6 denotes Cl or CH_3,

R^7 denotes H or F,

X denotes CH or N,

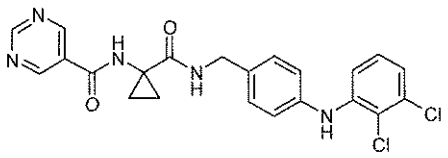
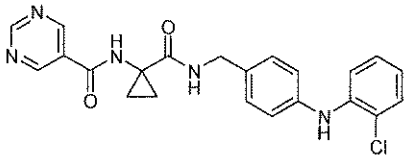
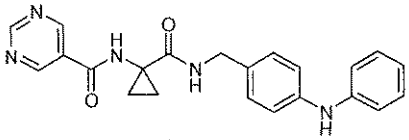
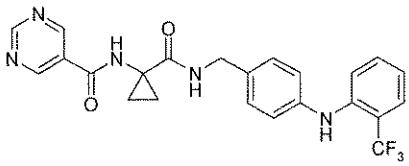
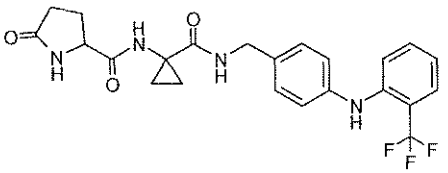
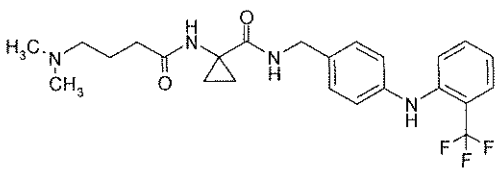
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

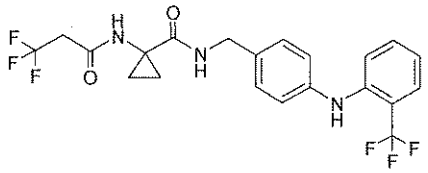
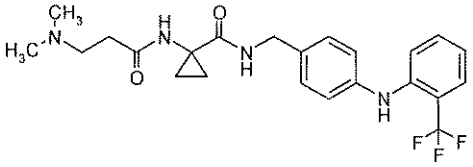
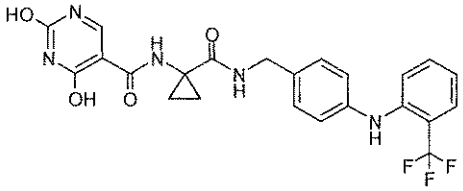
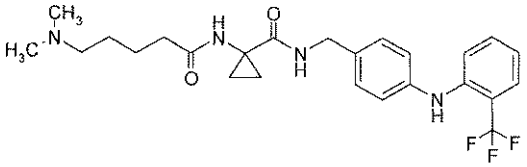
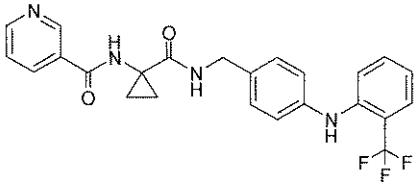
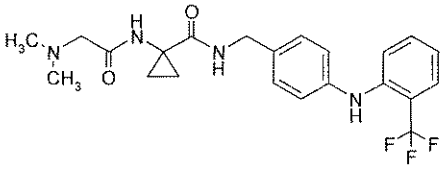
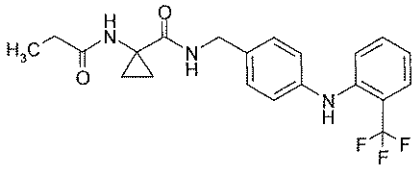
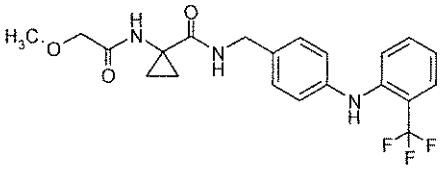
An embodiment **28** of the present invention comprises the compounds of general formula **I**, **Ia**, **Ib**, **Ic** or **Id**, wherein **n**, **R^1**, **R^3**, **R^4**, **R^5**, **R^6**, **R^7**, **R^8**, **R^9**, **R^{10}**, **R^{11}** and **X** are defined as described hereinbefore in embodiment 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26 or 27 and

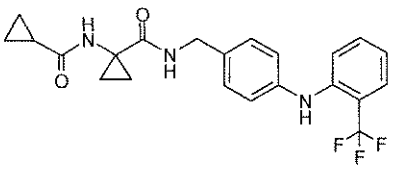
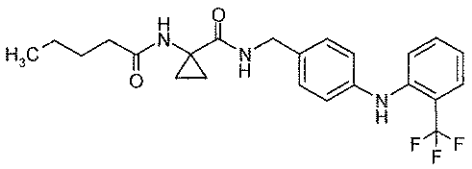
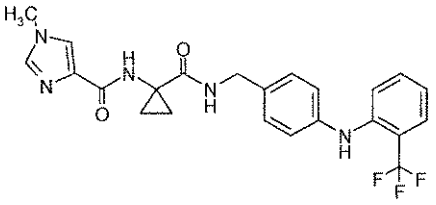
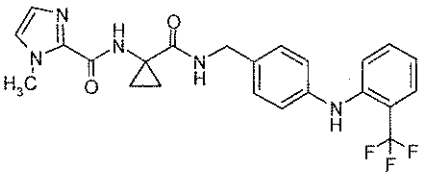
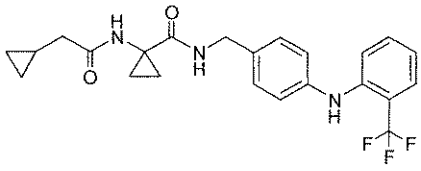
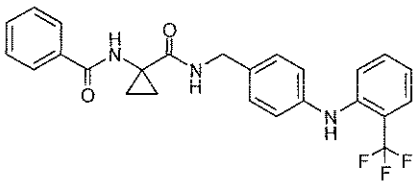
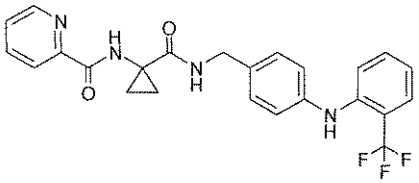
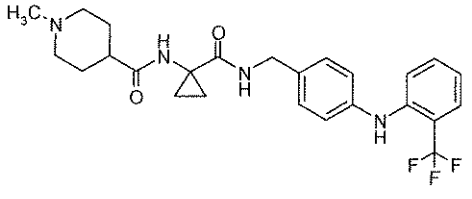
R^2 denotes H,

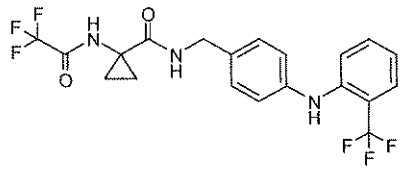
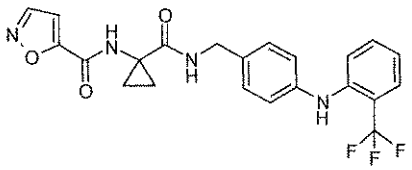
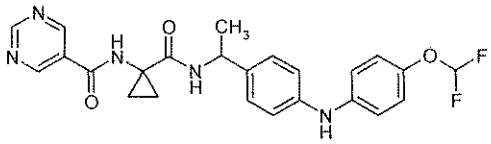
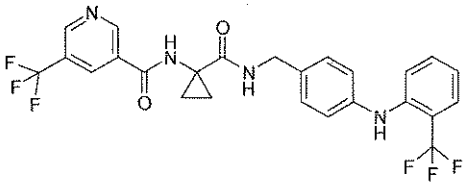
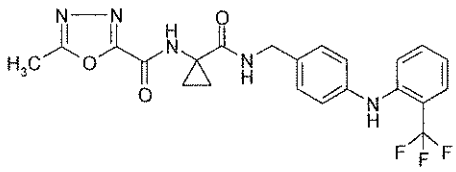
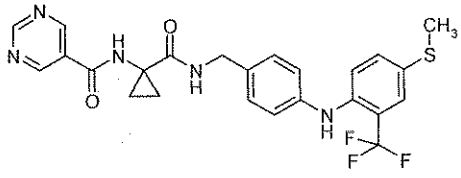
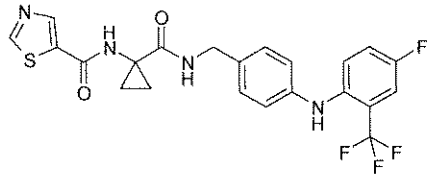
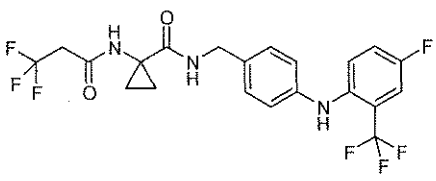
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

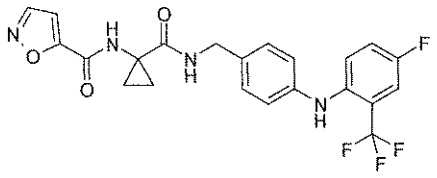
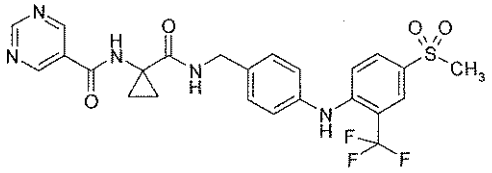
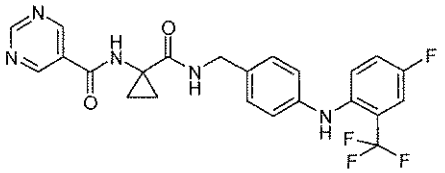
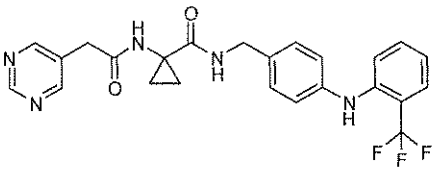
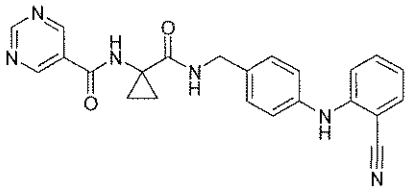
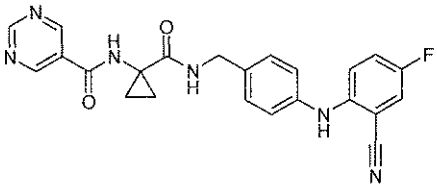
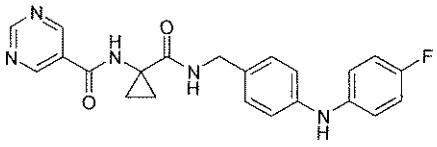
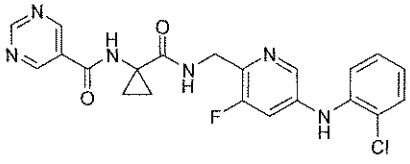
The following are mentioned as examples of most particularly preferred compounds of the above general formula I:

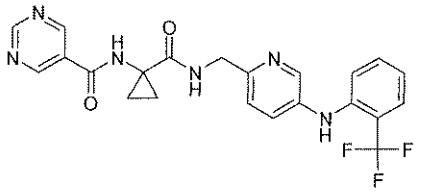
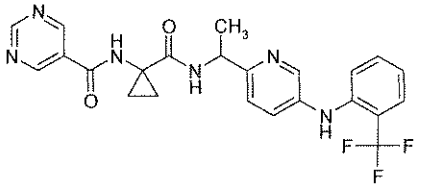
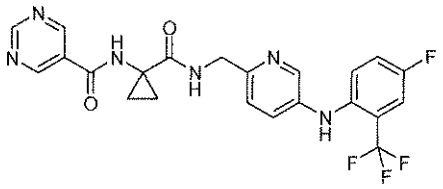
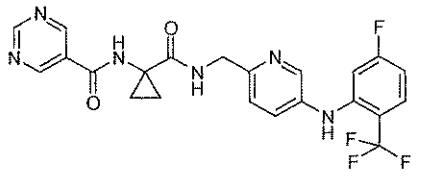
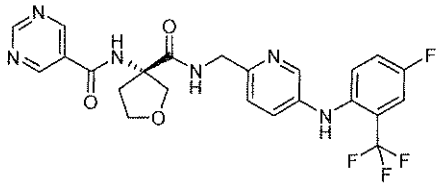
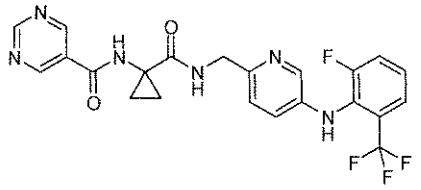
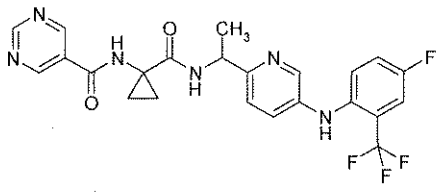
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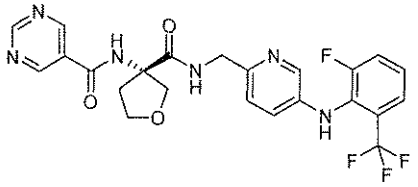
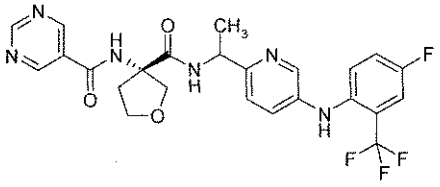
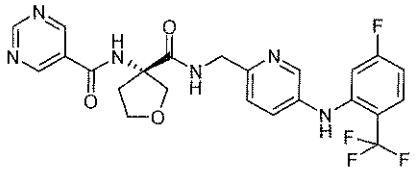
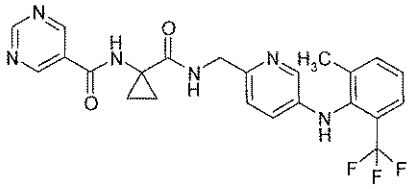
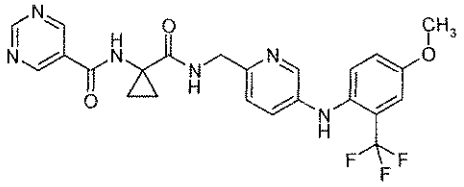
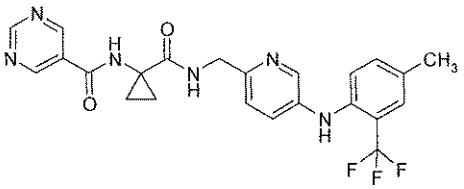
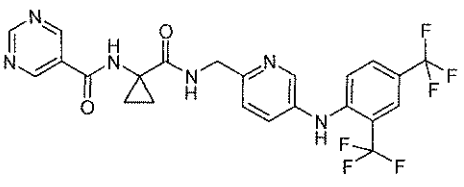
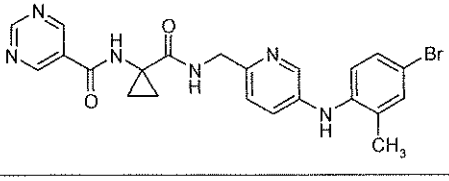
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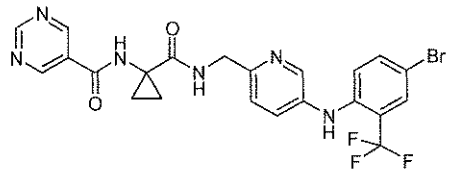
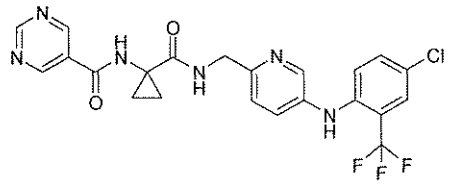
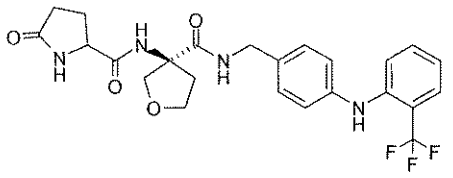
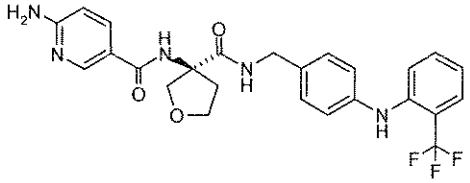
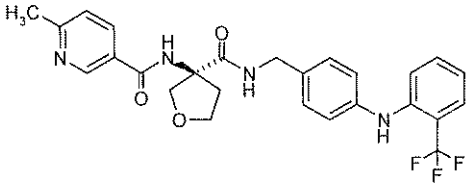
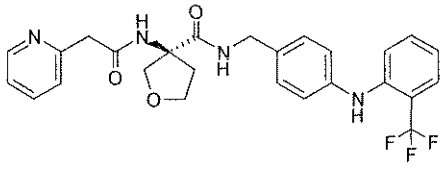
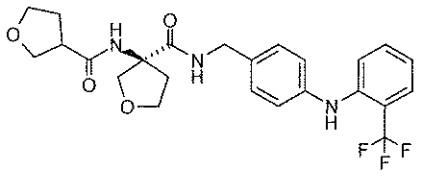
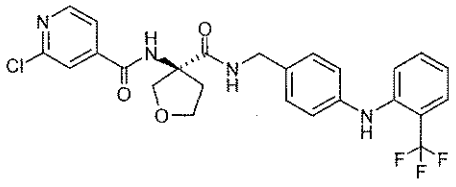
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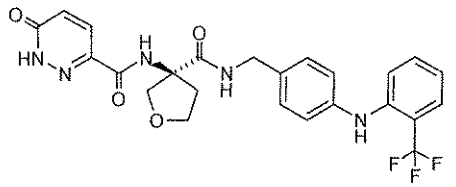
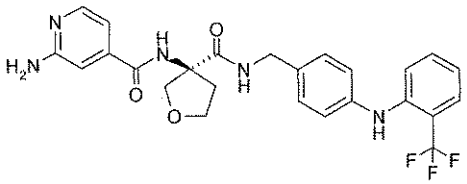
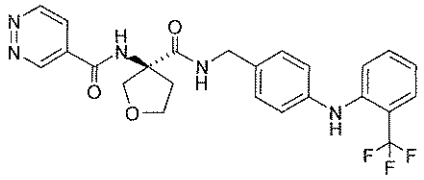
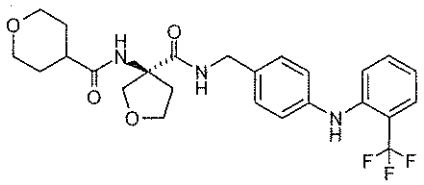
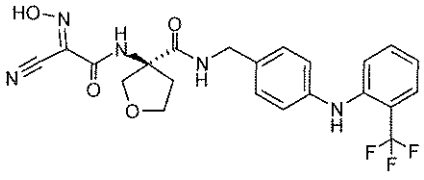
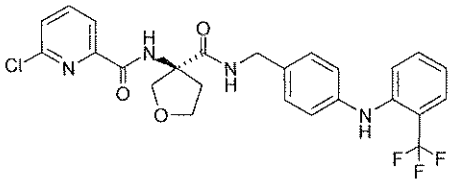
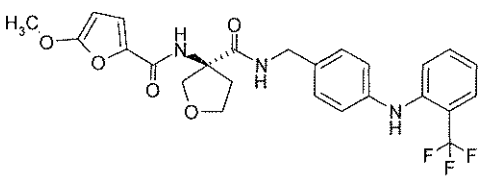
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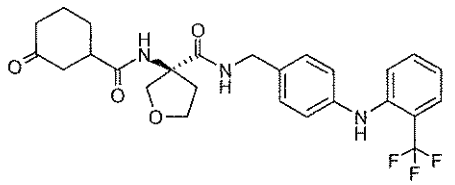
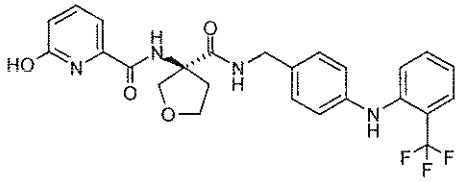
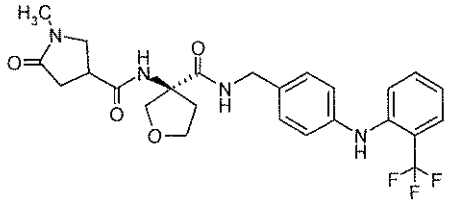
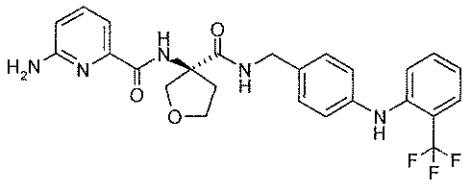
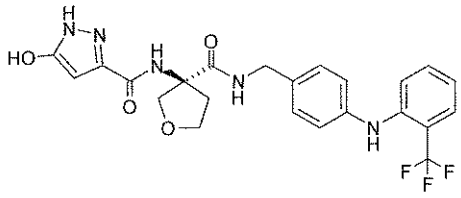
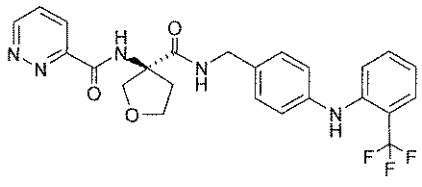
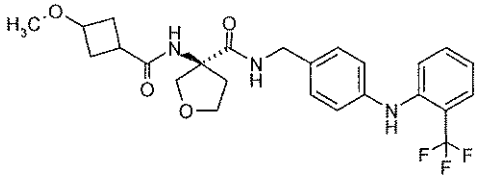
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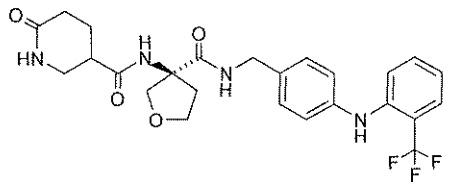
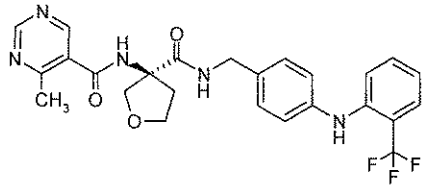
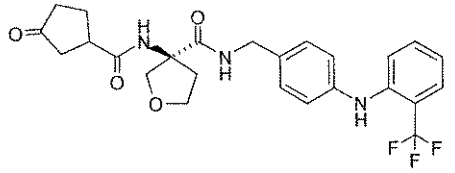
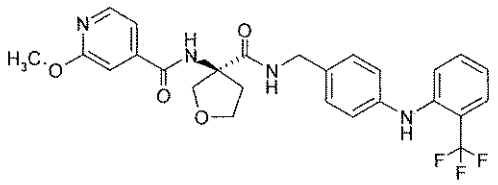
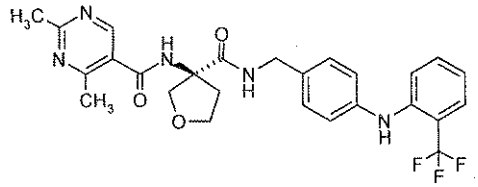
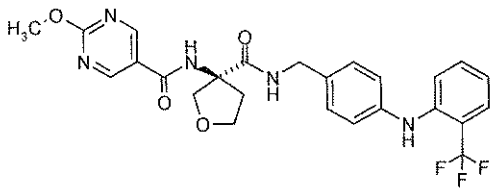
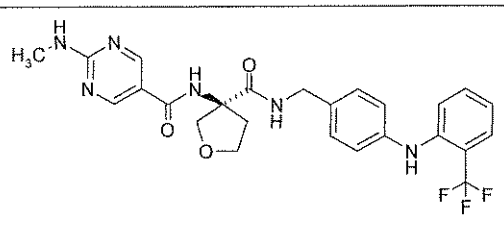
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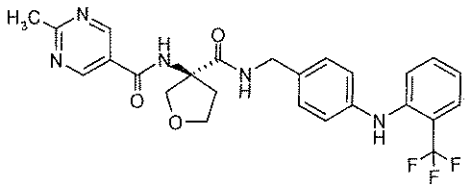
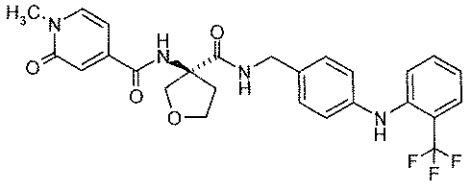
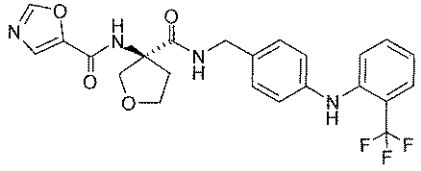
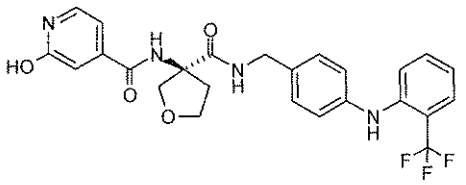
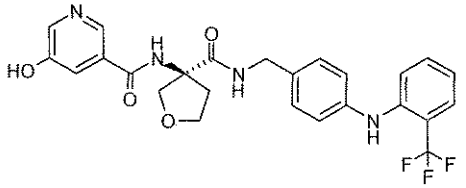
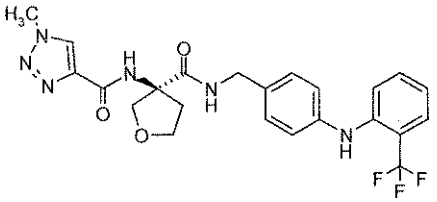
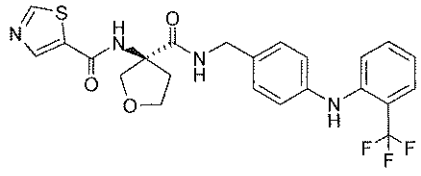
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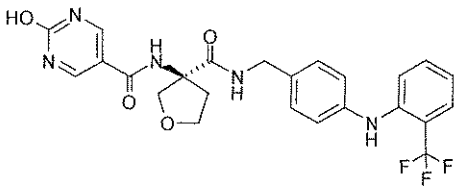
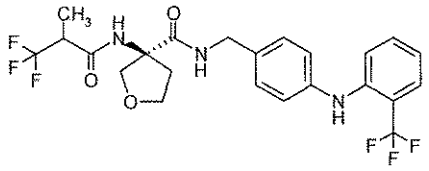
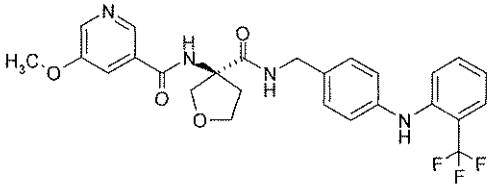
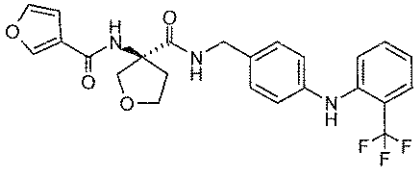
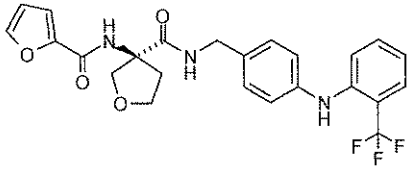
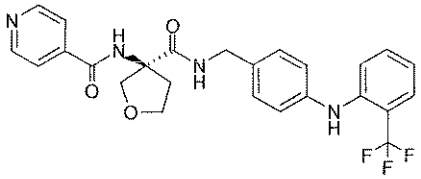
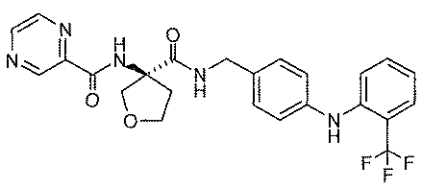
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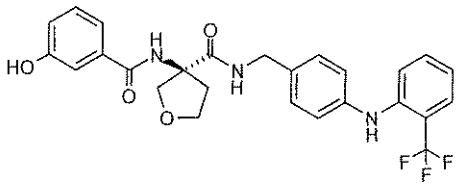
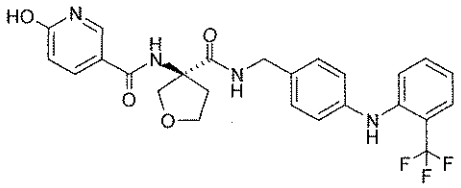
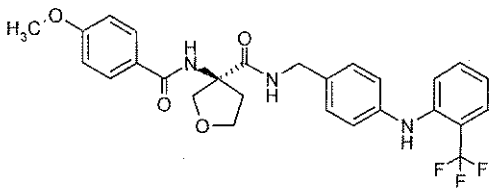
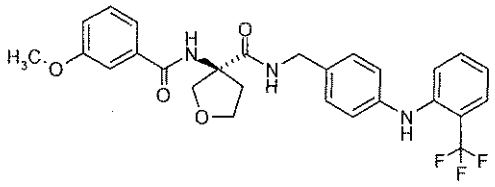
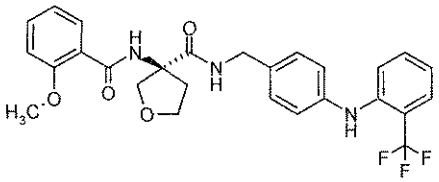
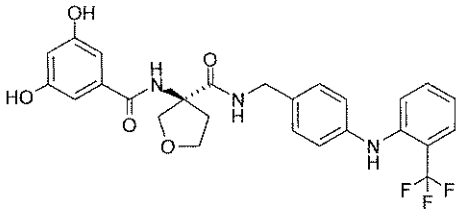
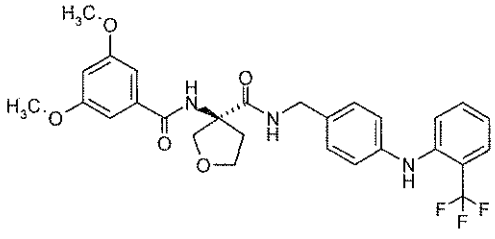
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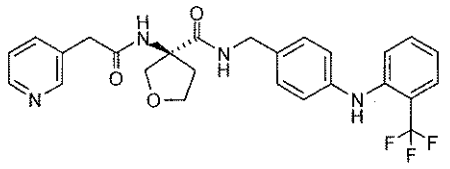
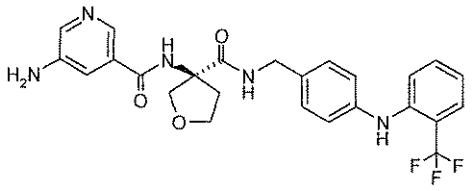
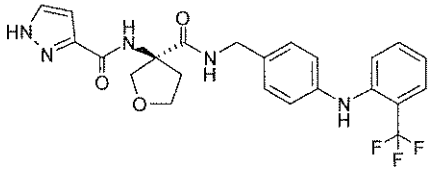
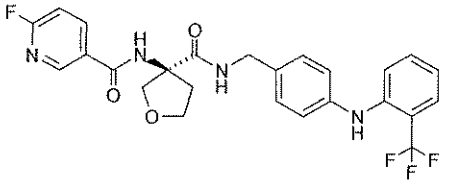
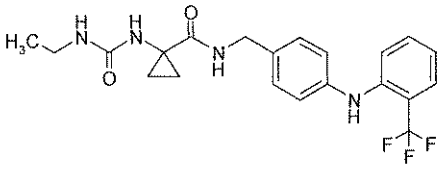
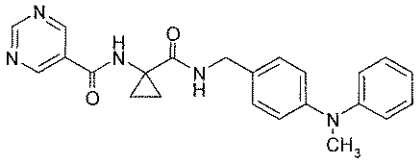
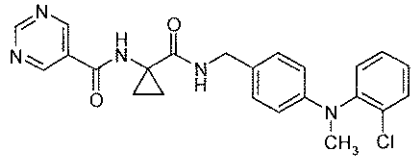
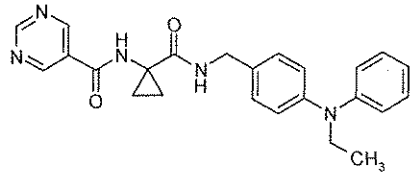
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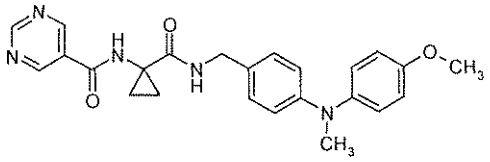
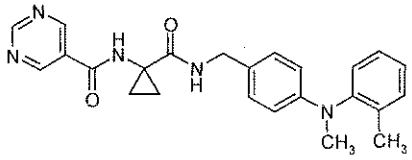
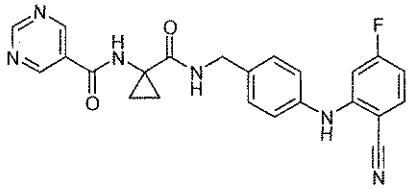
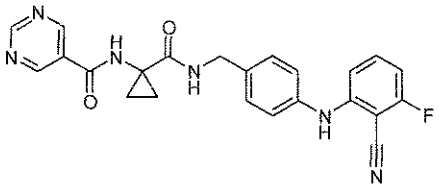
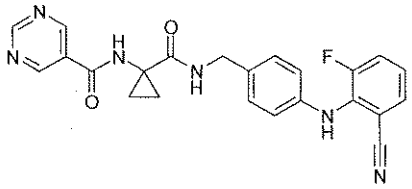
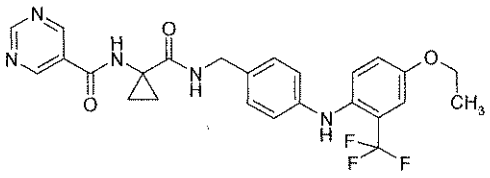
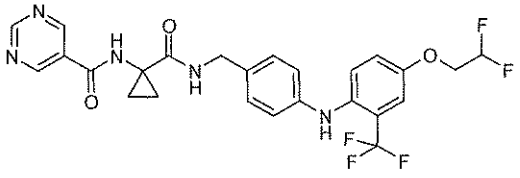
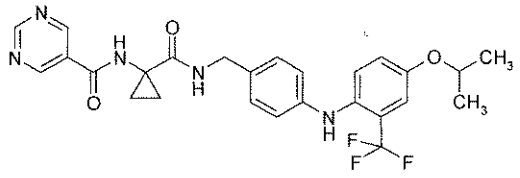
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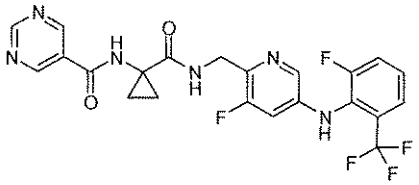
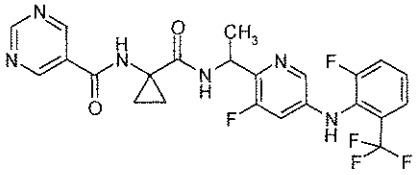
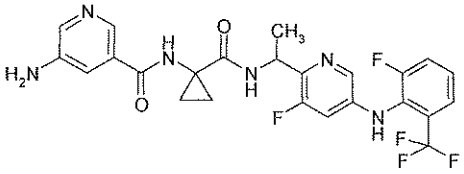
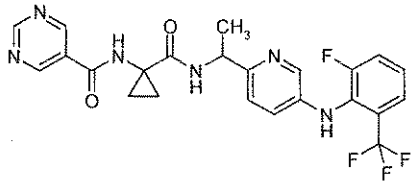
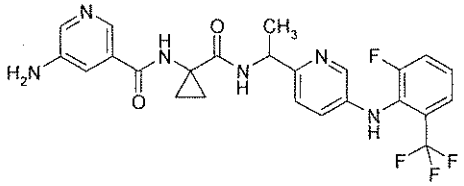
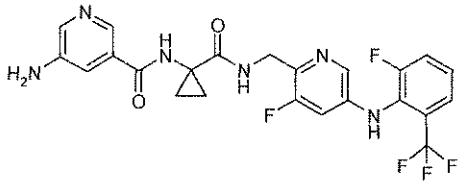
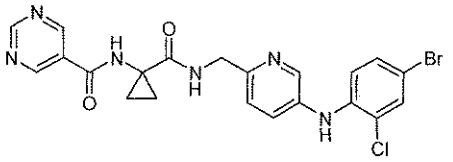
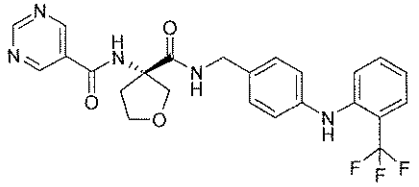
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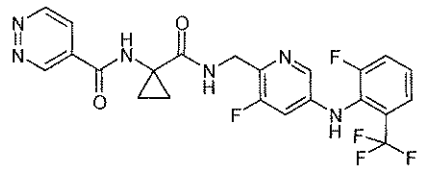
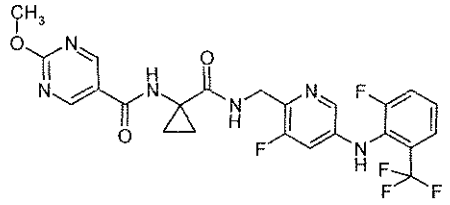
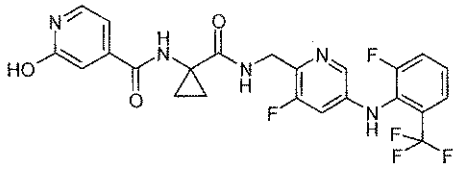
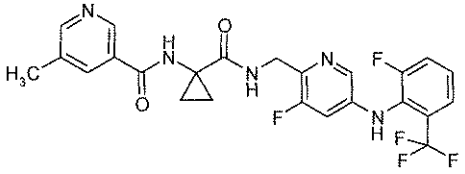
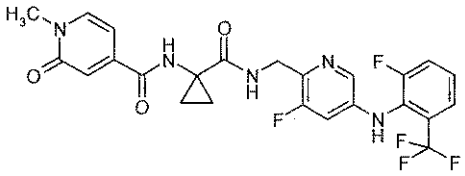
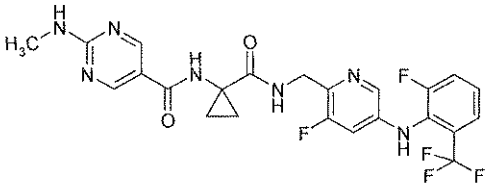
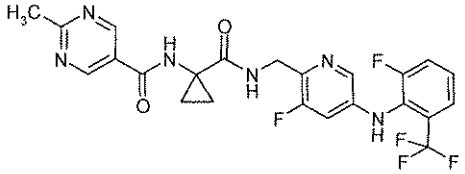
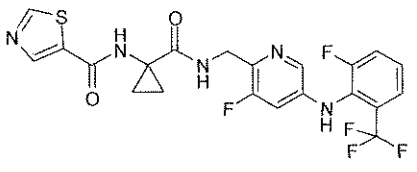
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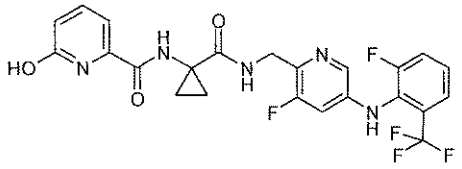
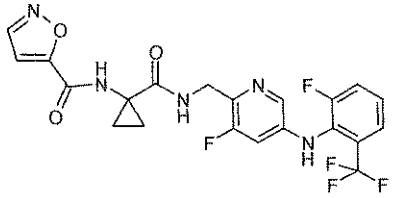
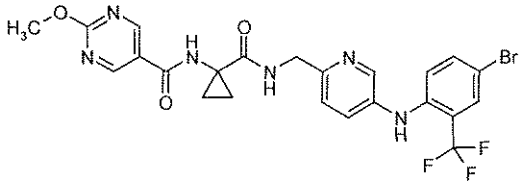
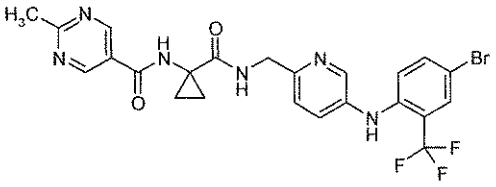
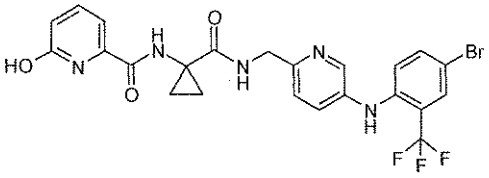
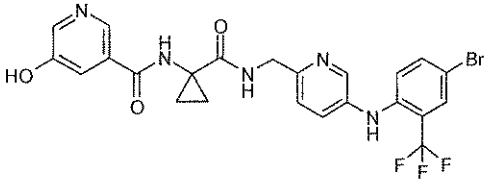
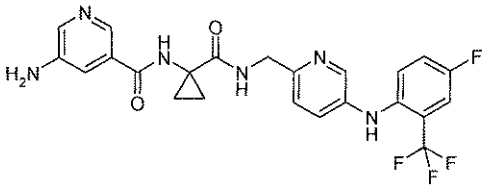
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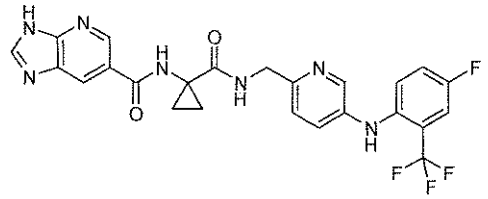
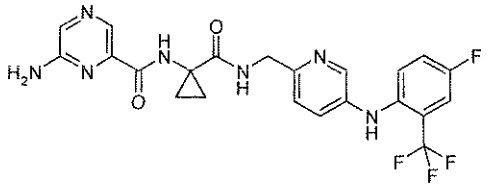
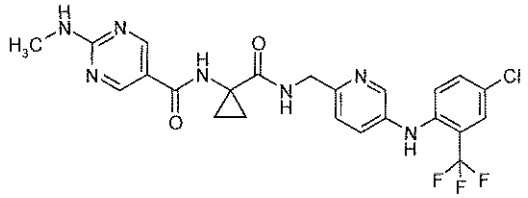
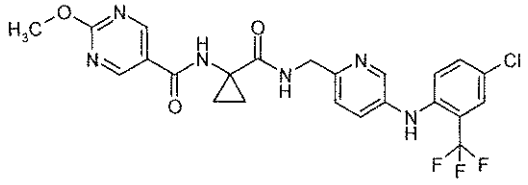
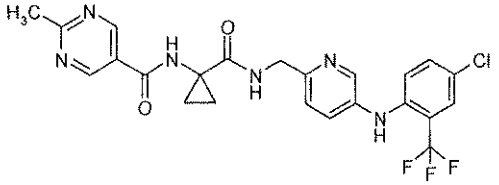
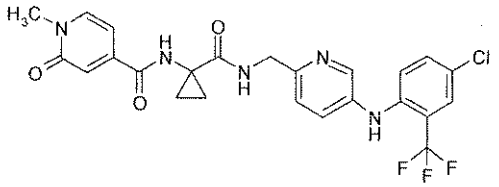
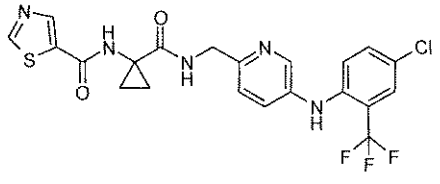
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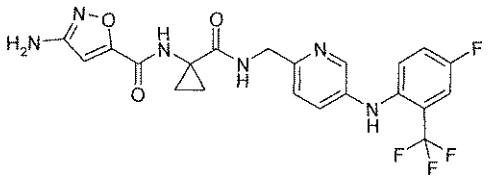
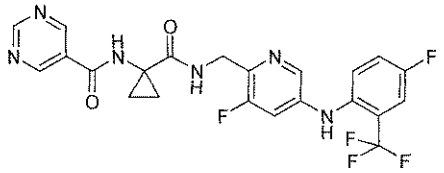
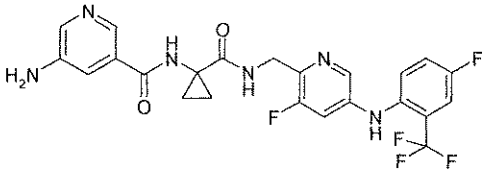
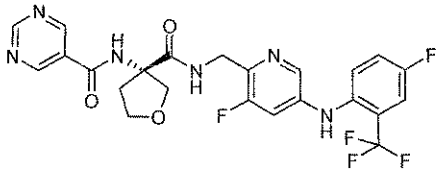
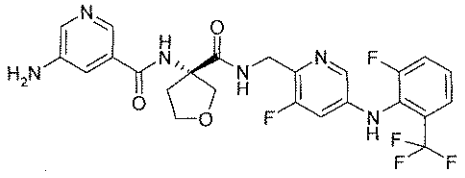
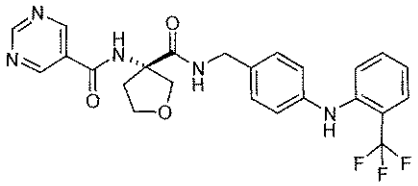
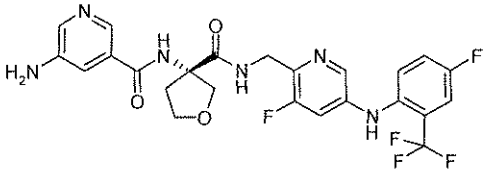
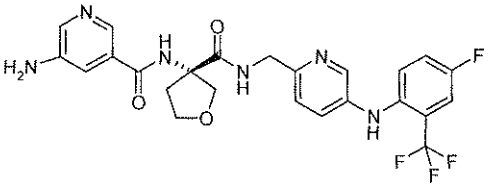
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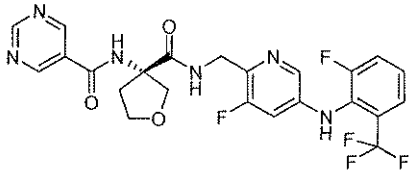
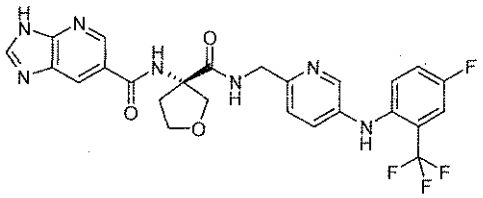
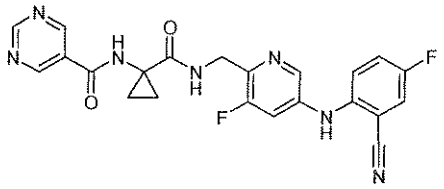
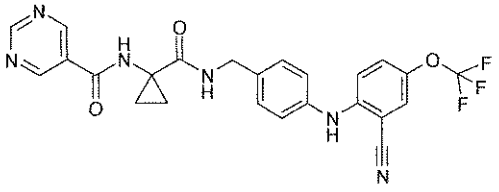
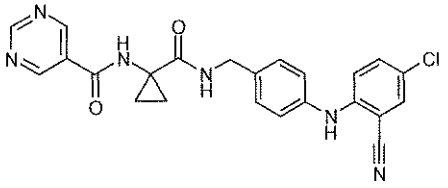
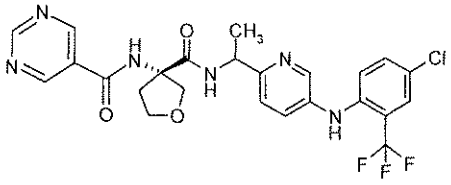
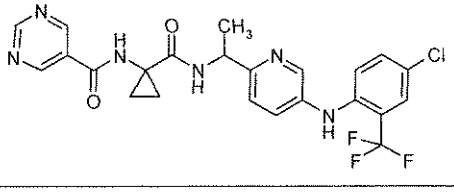
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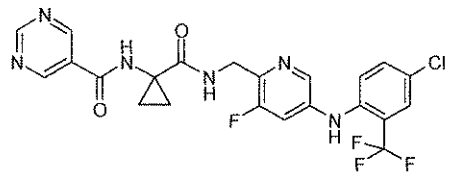
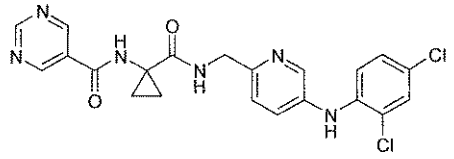
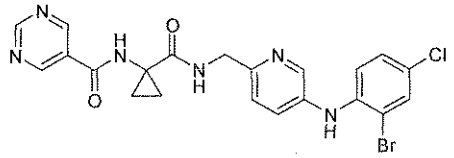
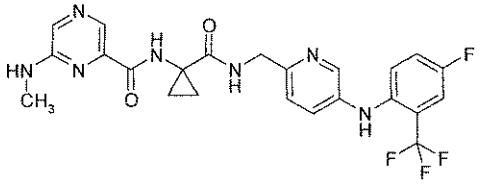
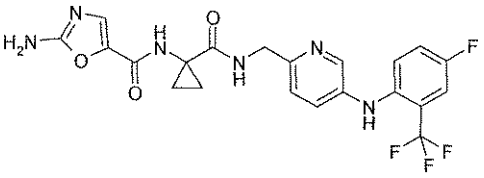
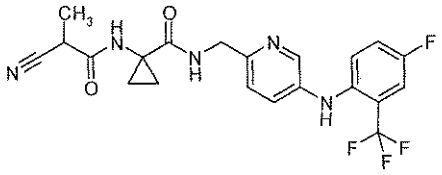
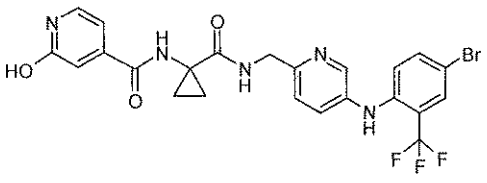
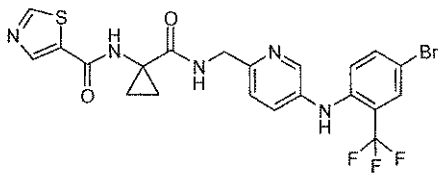
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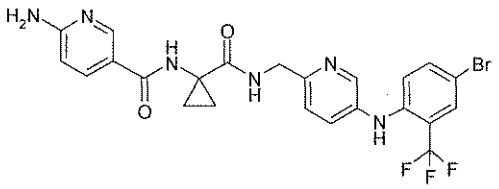
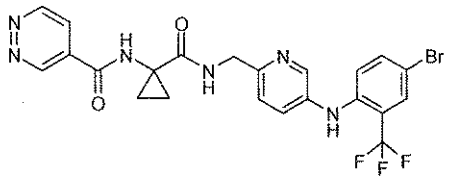
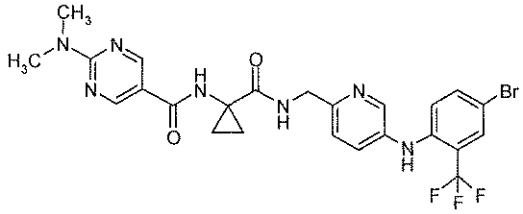
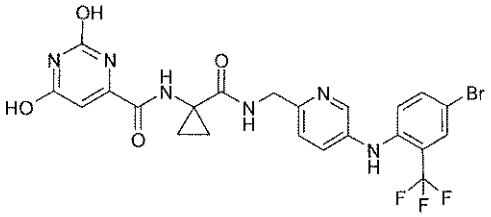
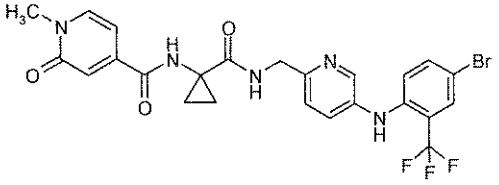
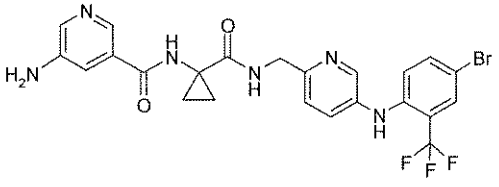
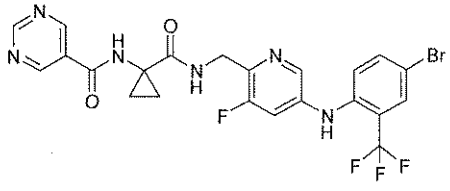
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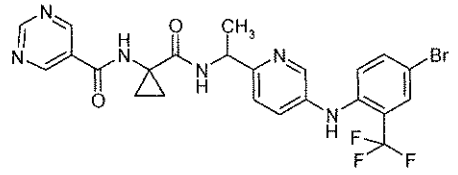
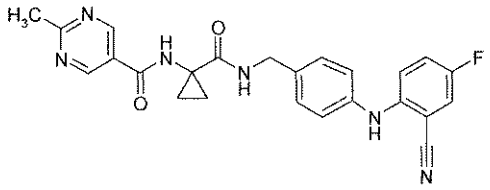
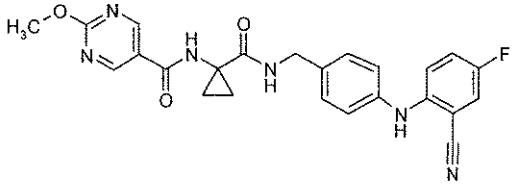
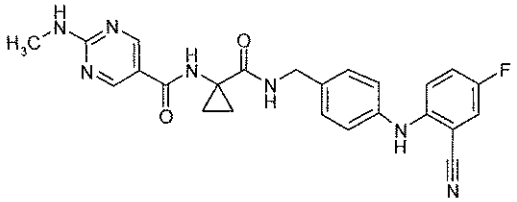
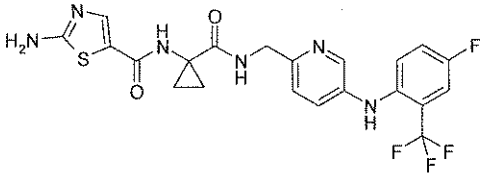
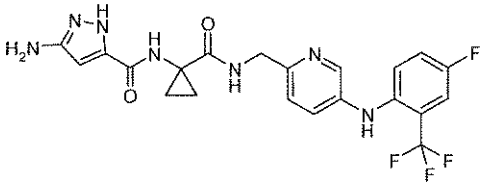
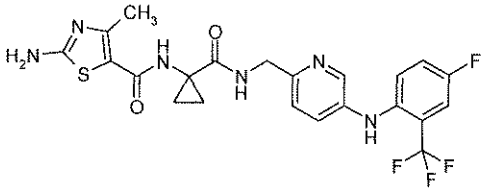
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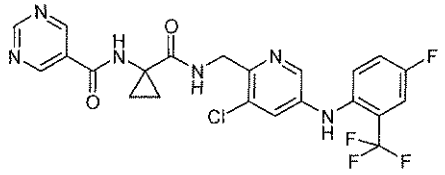
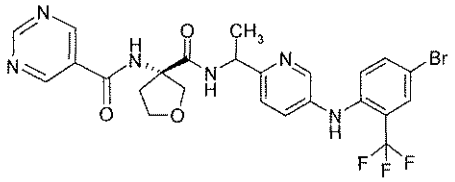
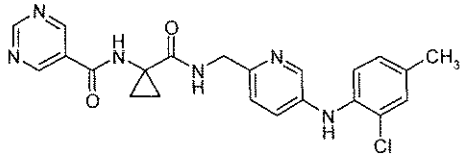
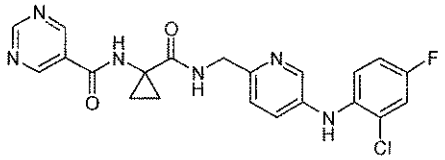
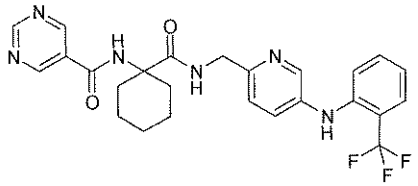
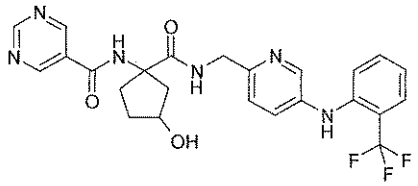
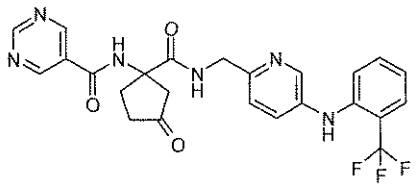
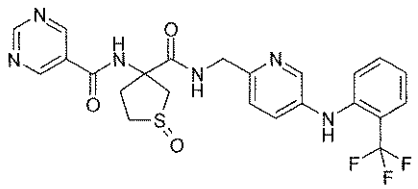
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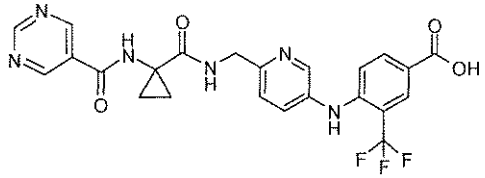
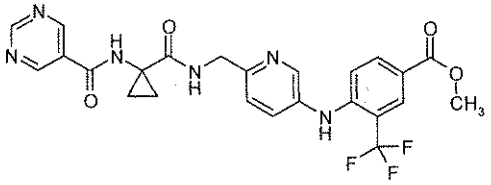
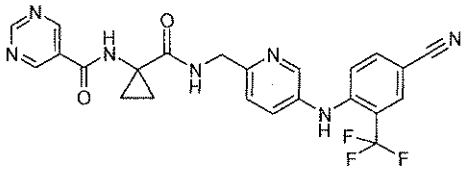
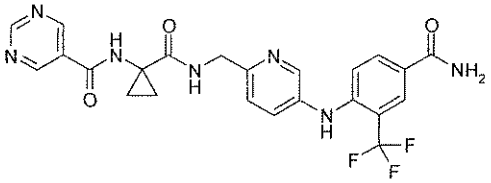
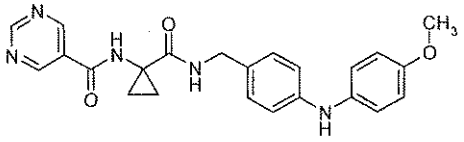
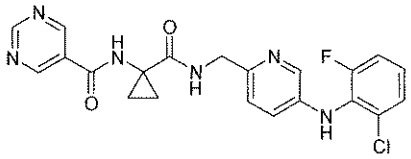
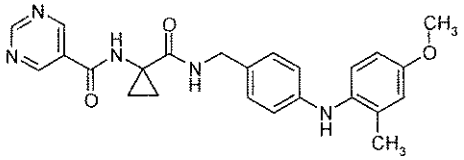
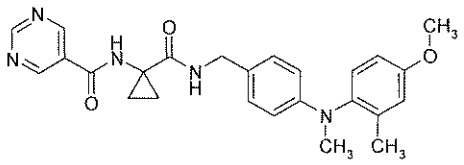
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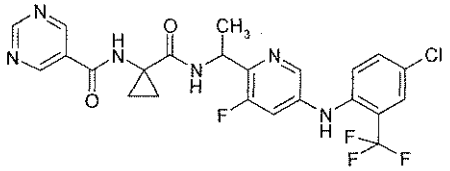
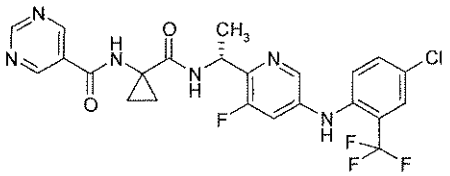
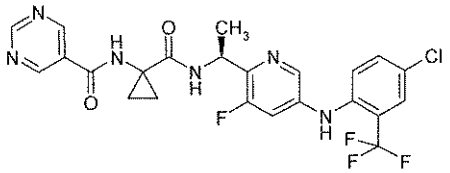
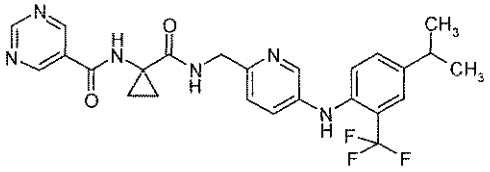
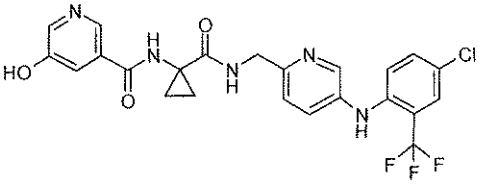
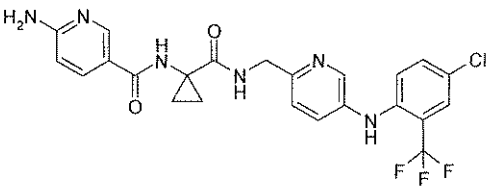
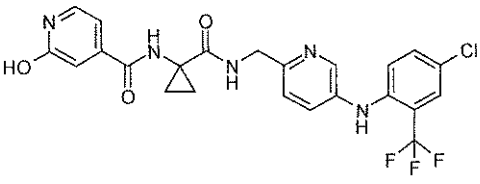
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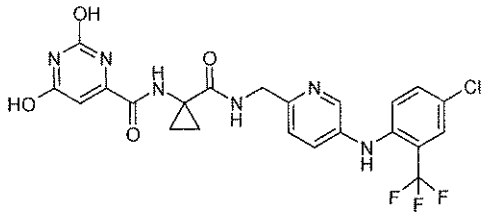
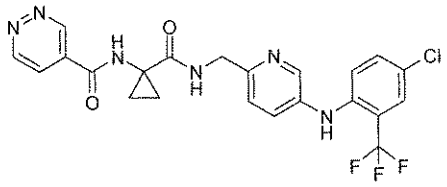
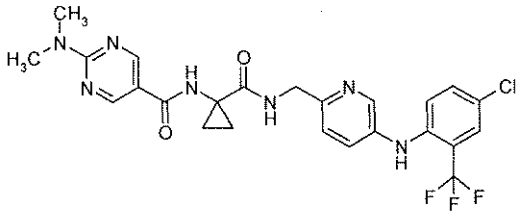
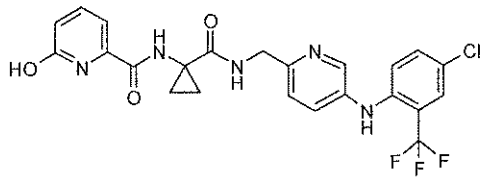
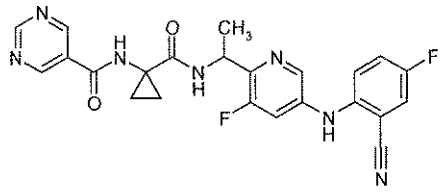
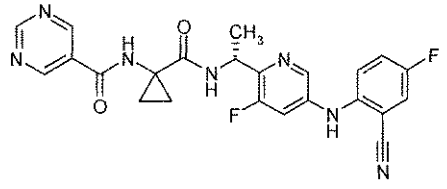
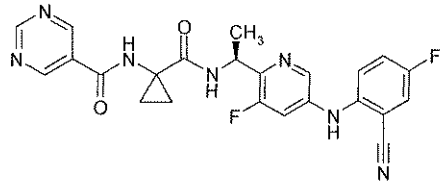
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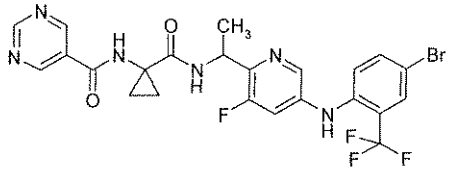
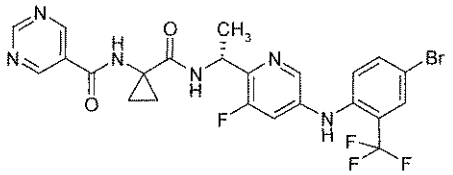
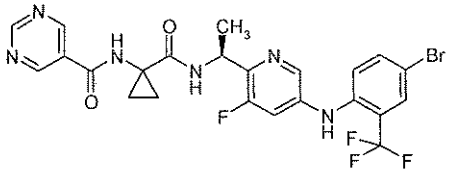
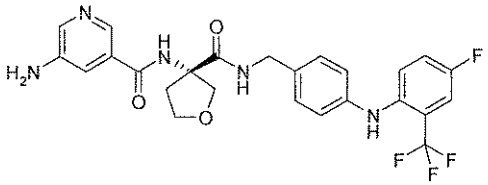
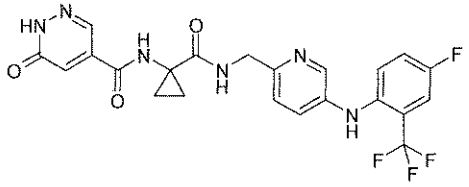
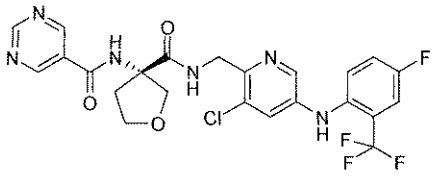
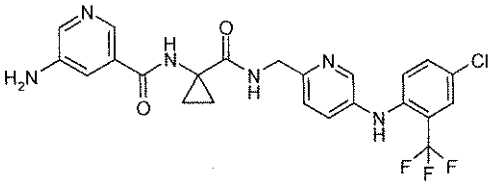
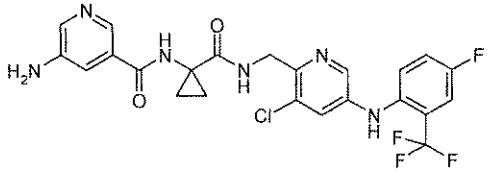
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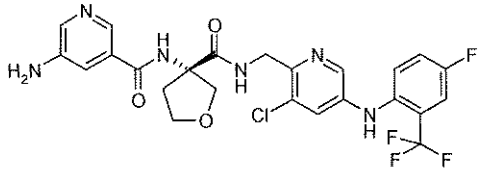
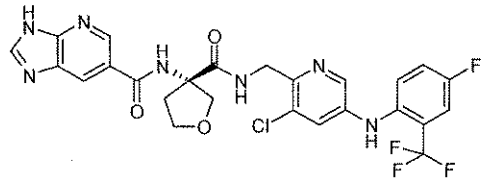
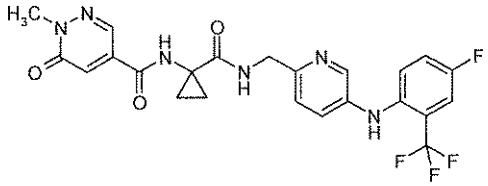
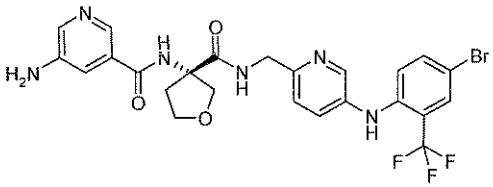
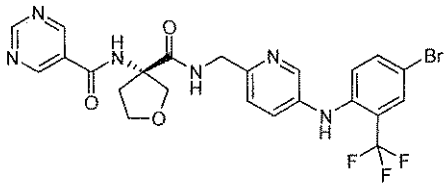
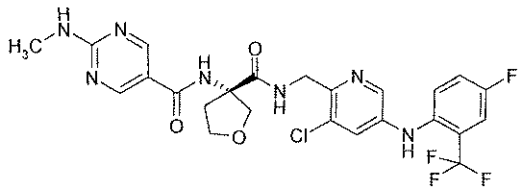
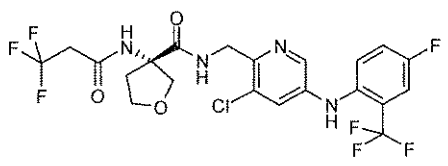
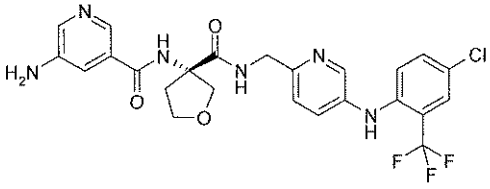
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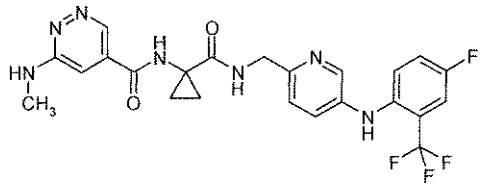
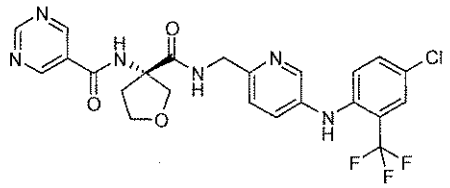
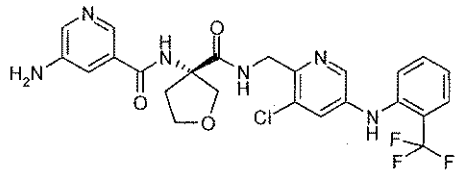
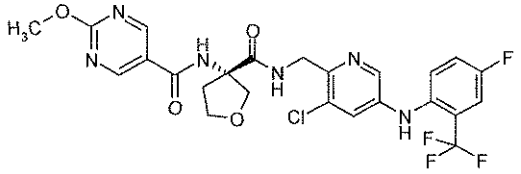
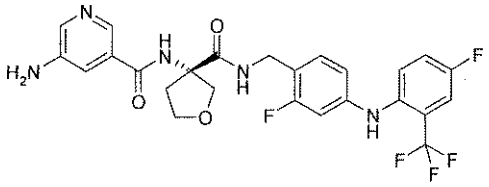
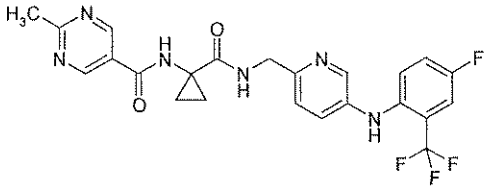
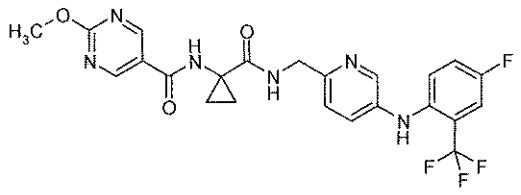
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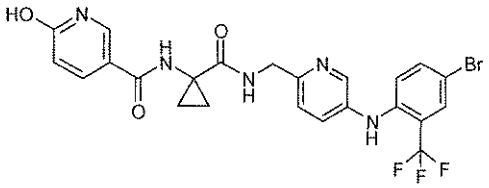
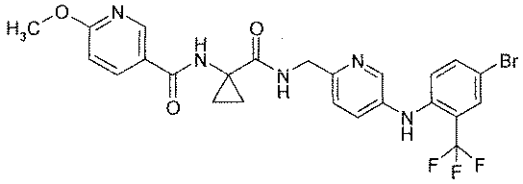
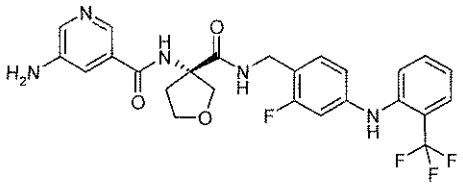
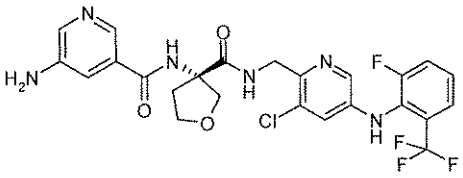
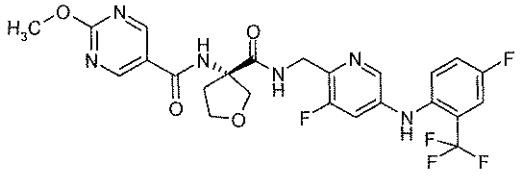
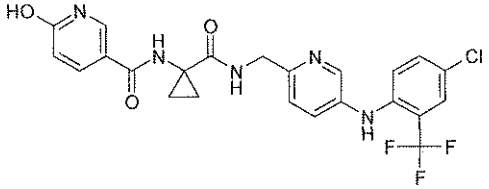
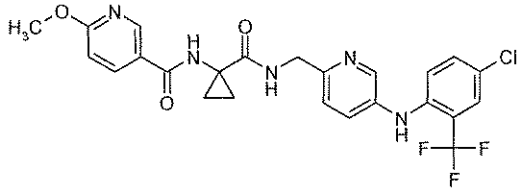
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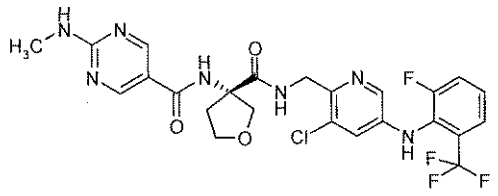
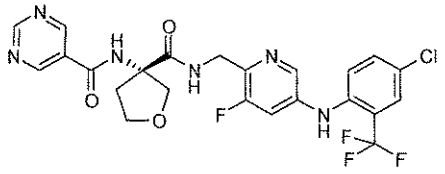
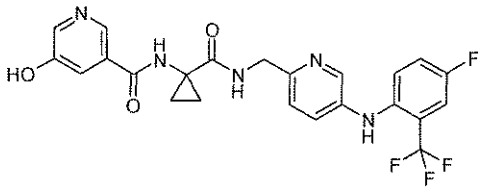
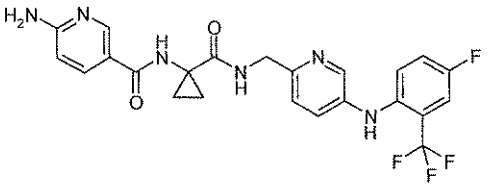
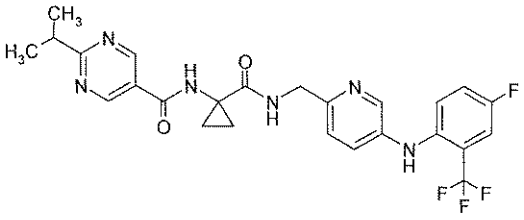
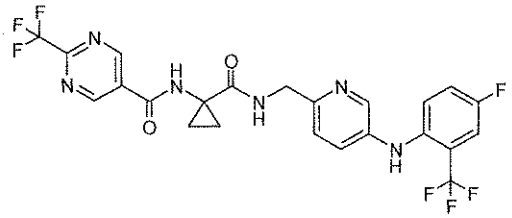
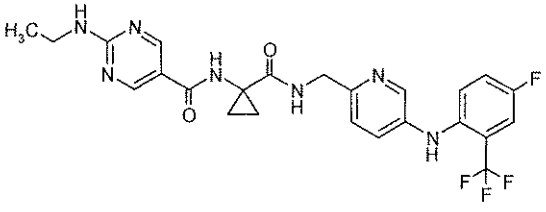
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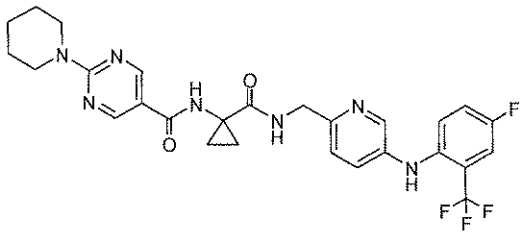
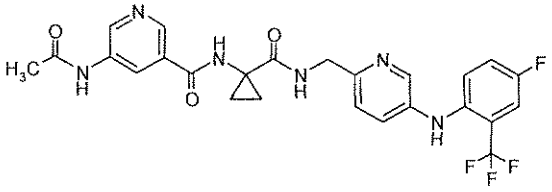
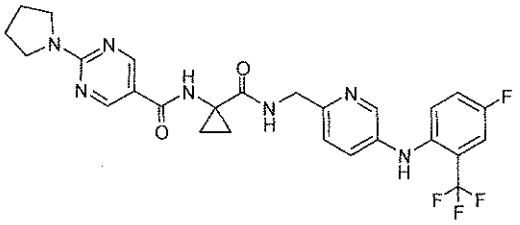
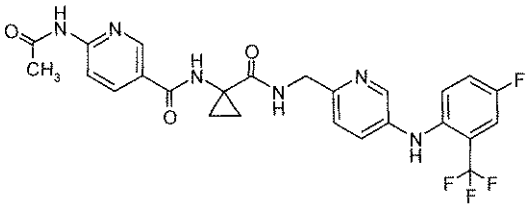
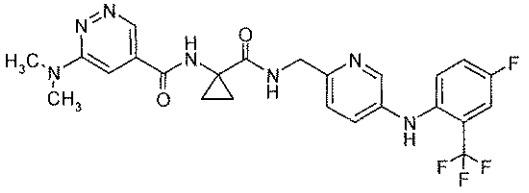
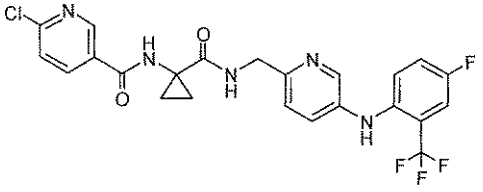
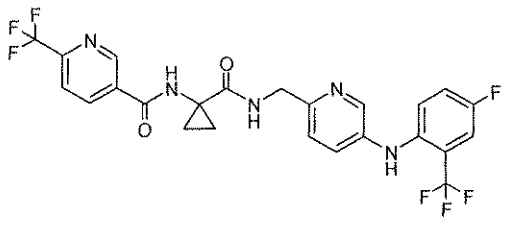
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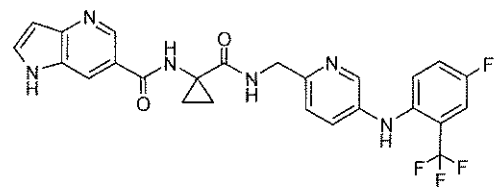
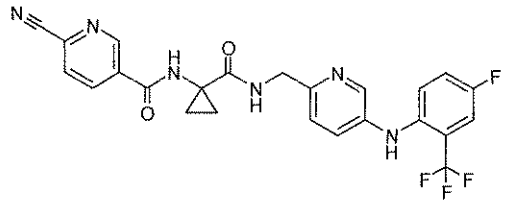
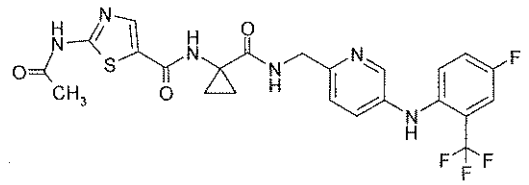
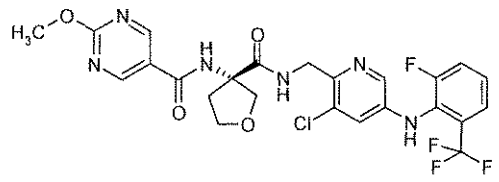
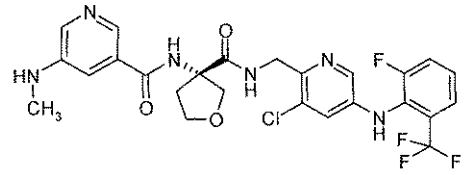
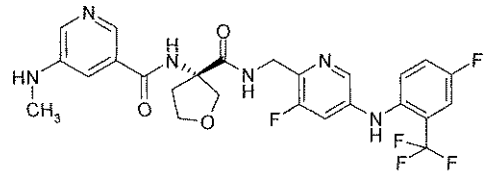
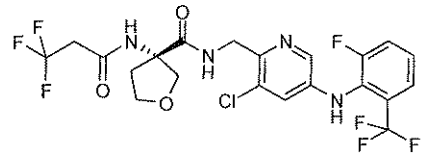
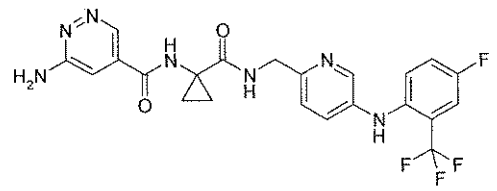
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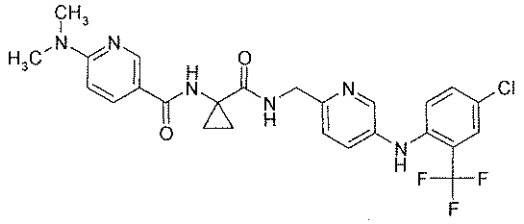
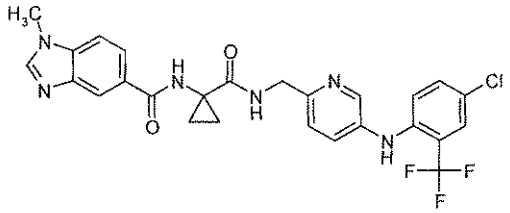
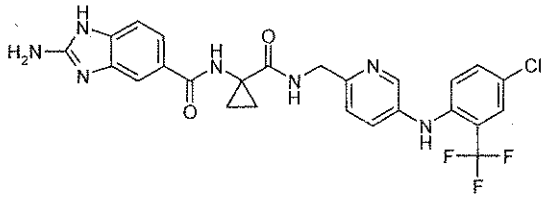
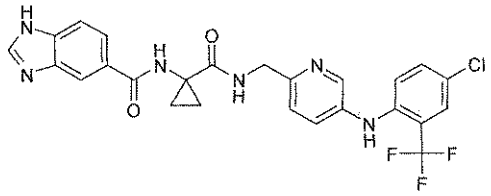
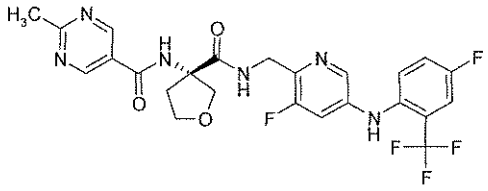
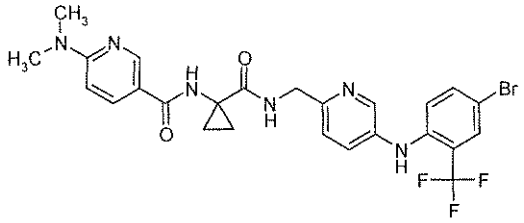
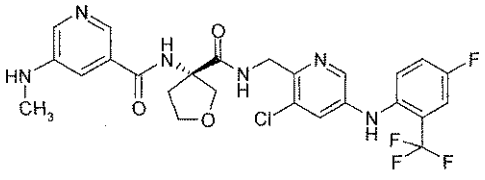
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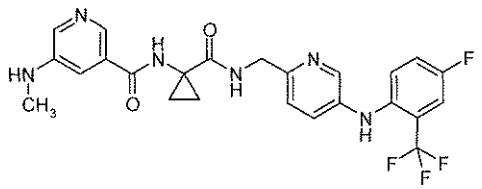
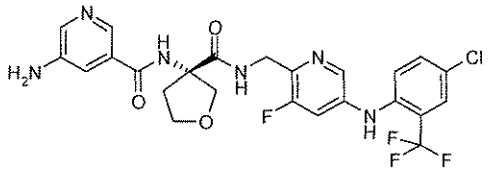
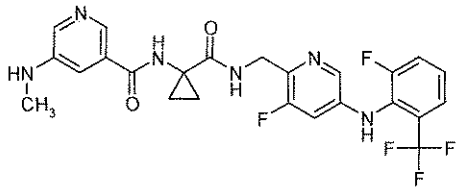
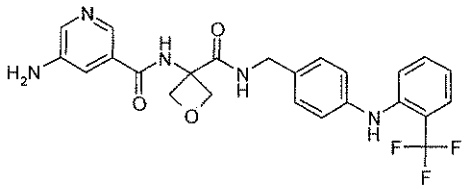
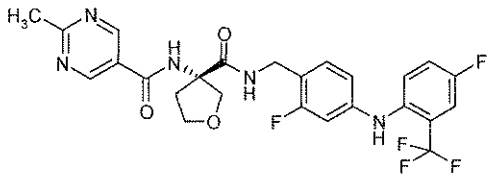
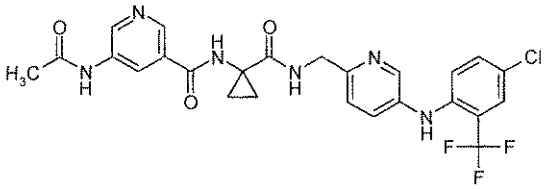
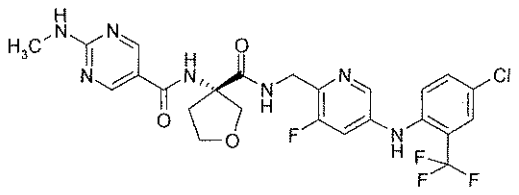
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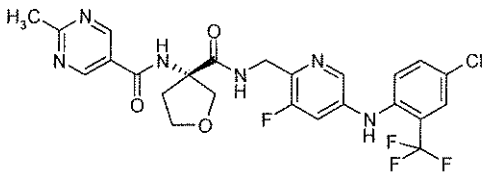
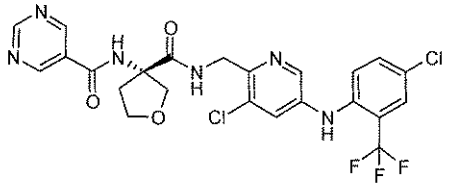
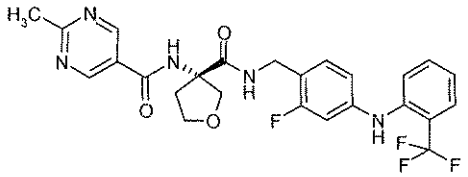
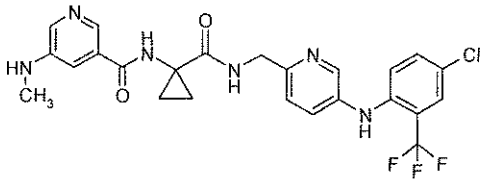
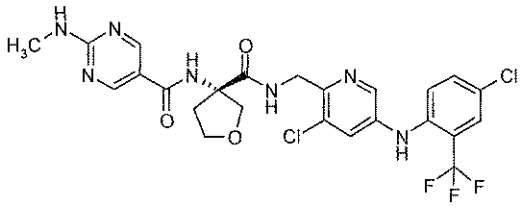
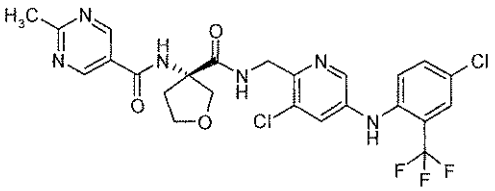
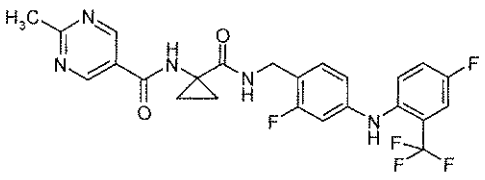
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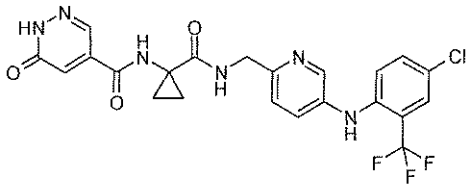
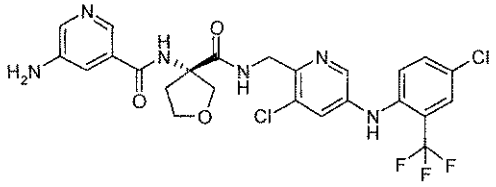
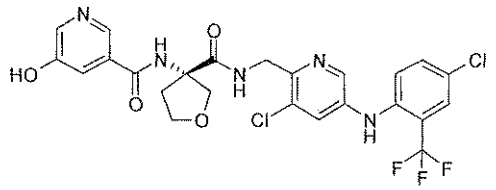
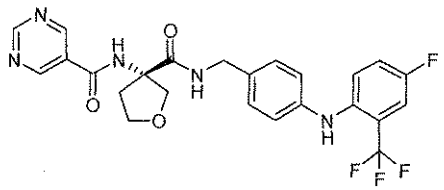
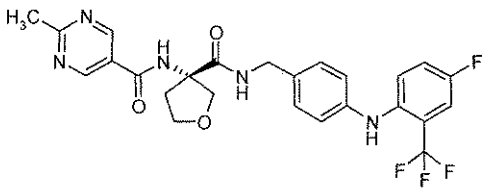
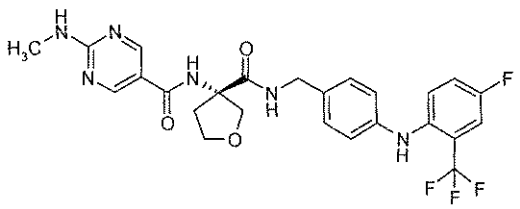
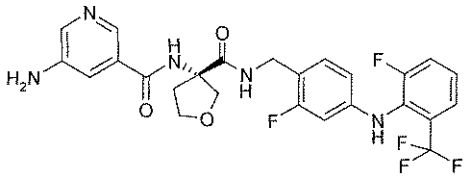
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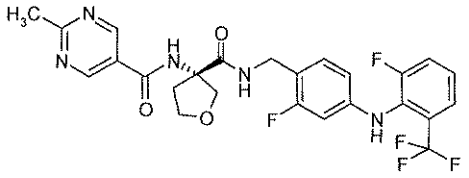
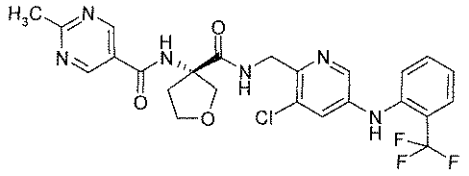
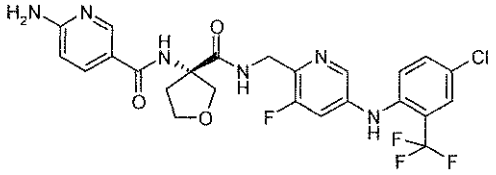
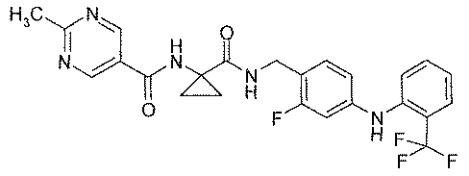
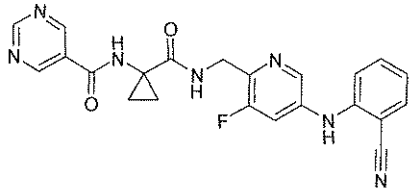
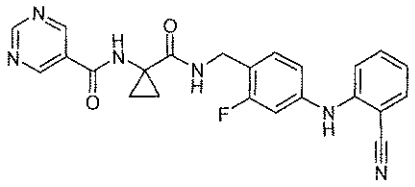
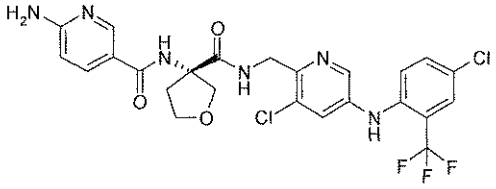
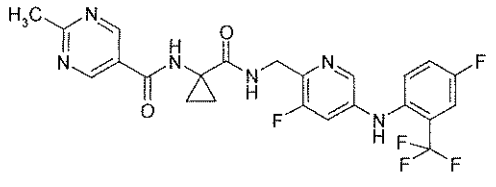
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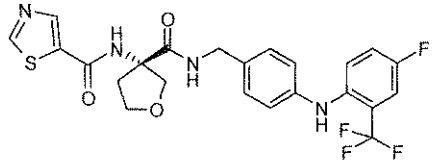
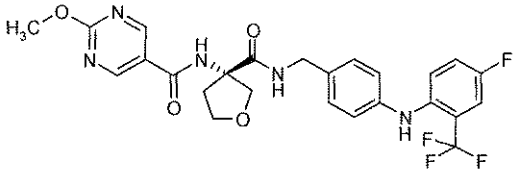
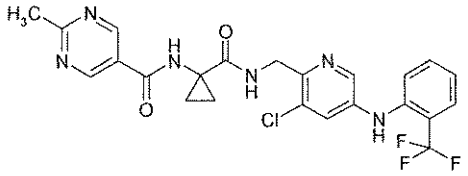
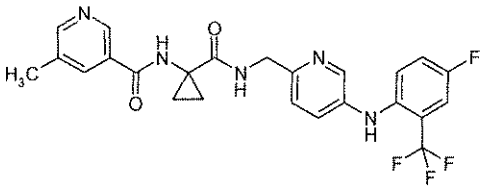
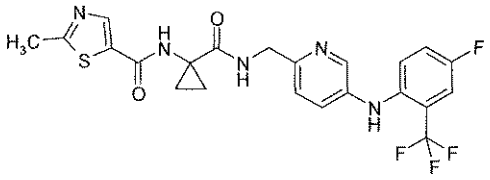
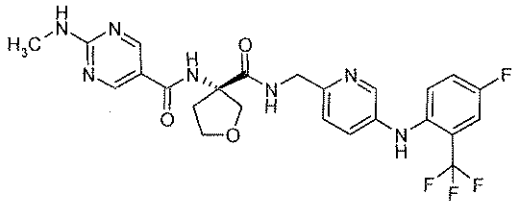
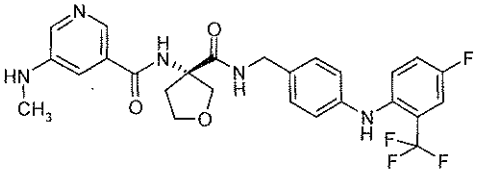
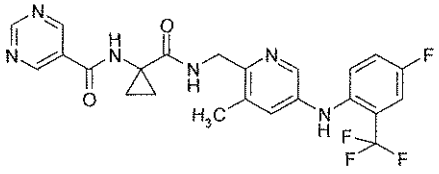
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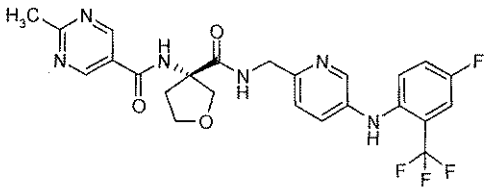
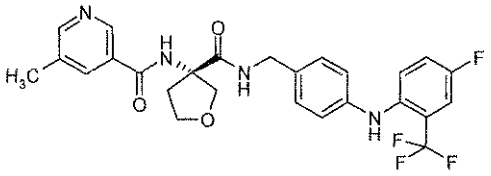
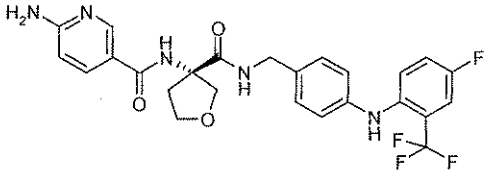
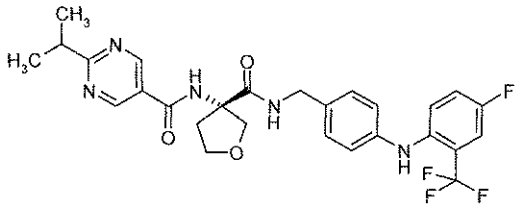
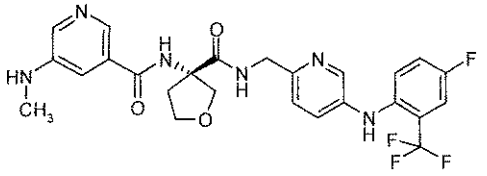
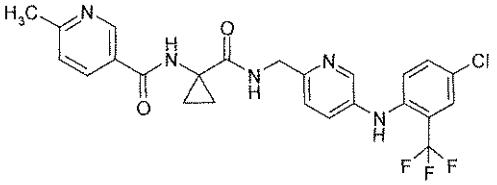
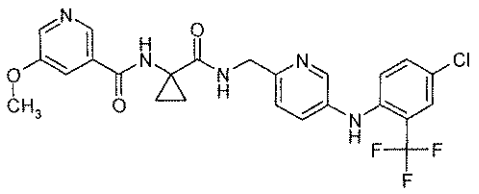
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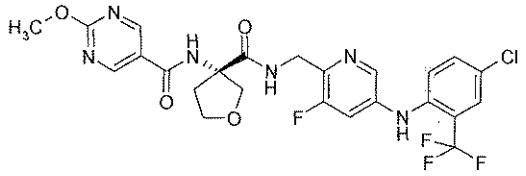
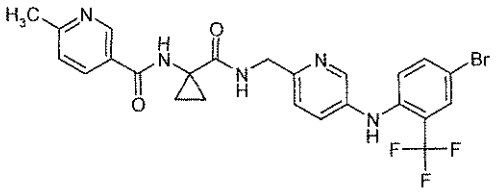
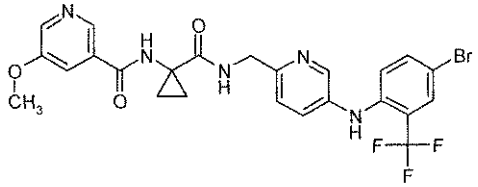
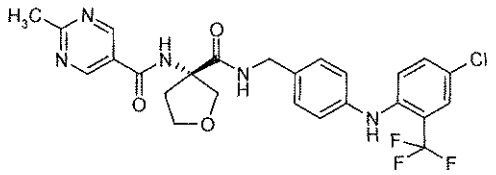
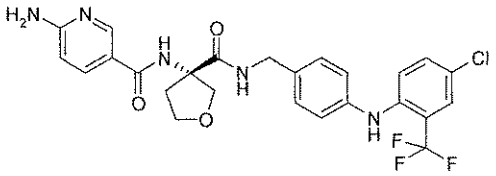
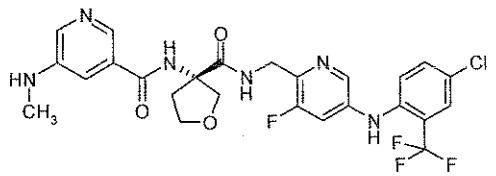
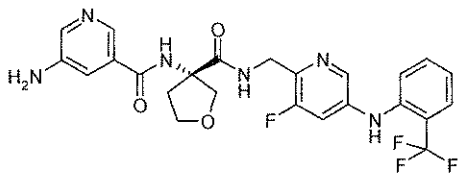
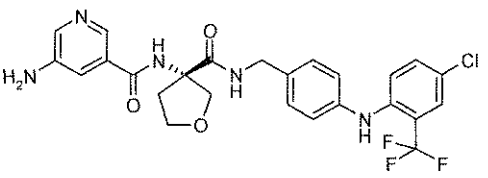
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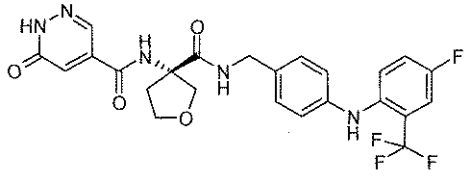
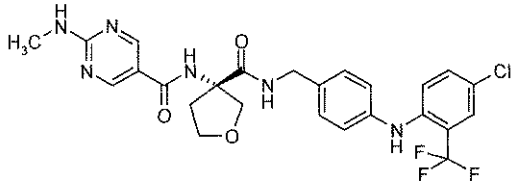
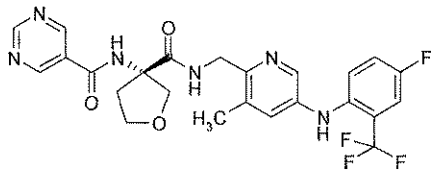
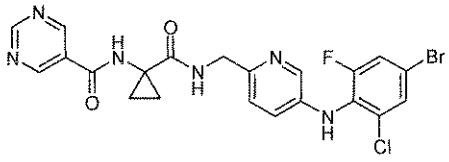
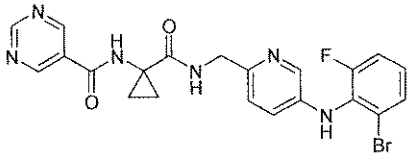
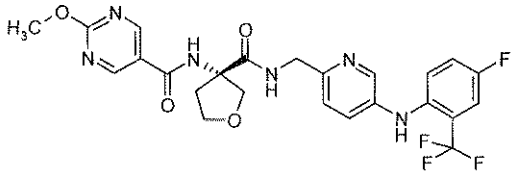
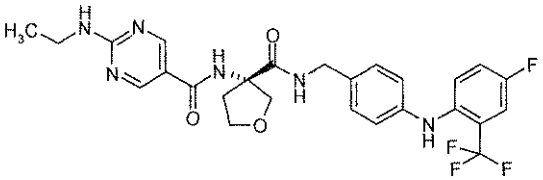
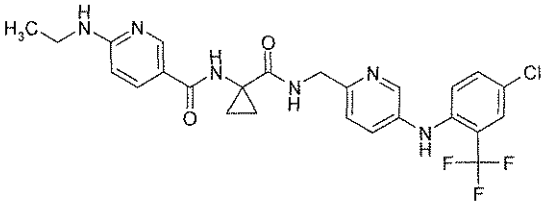
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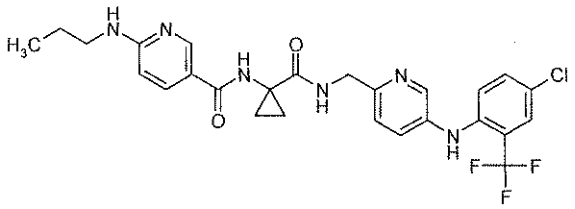
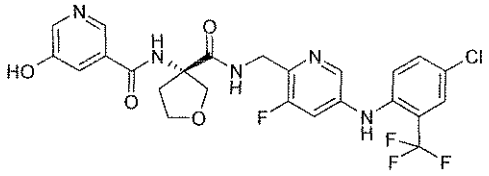
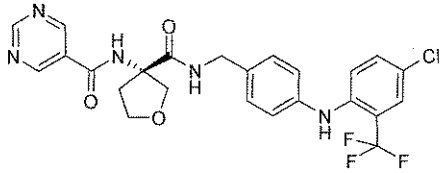
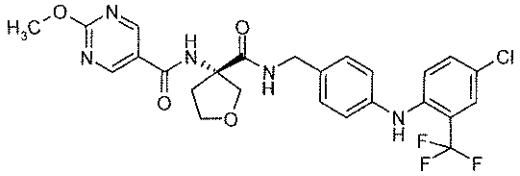
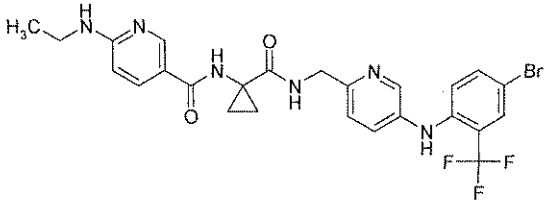
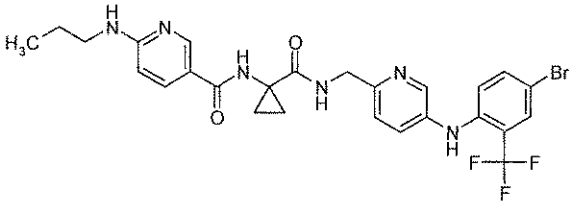
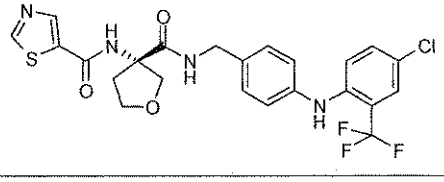
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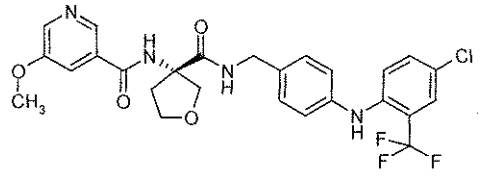
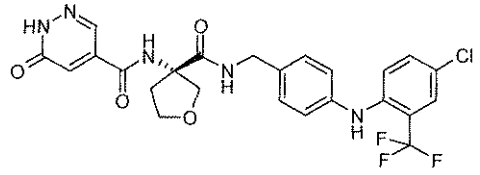
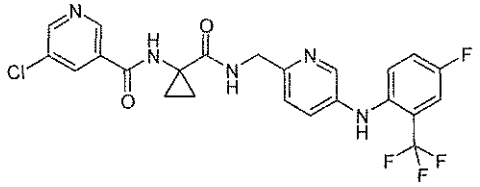
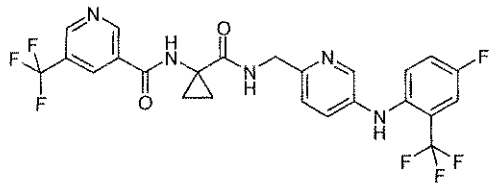
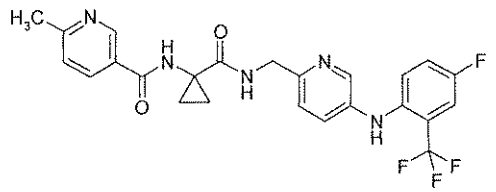
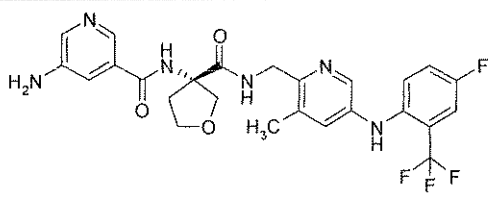
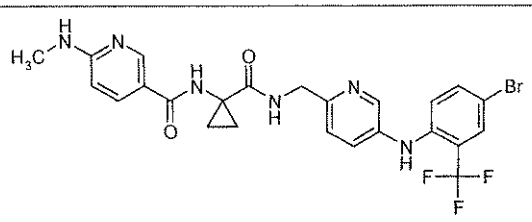
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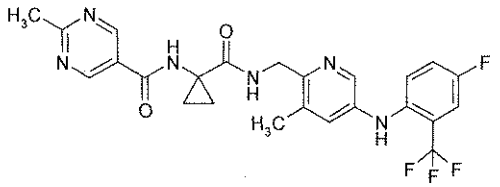
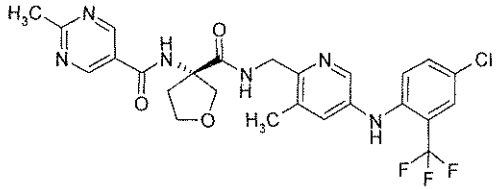
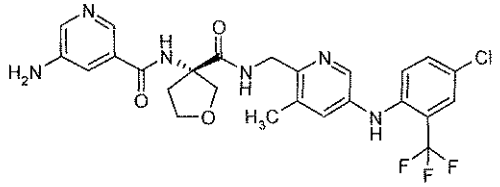
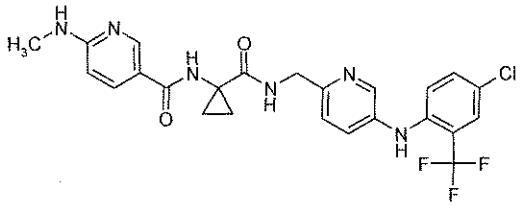
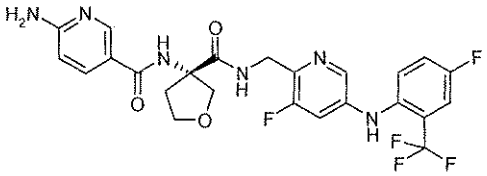
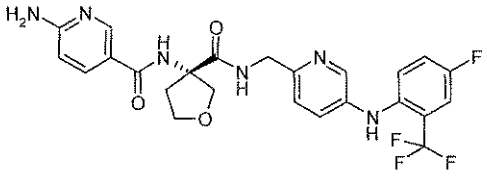
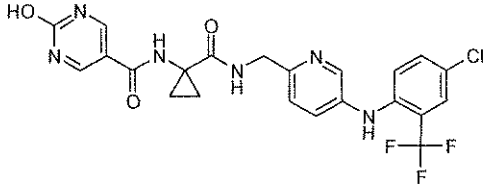
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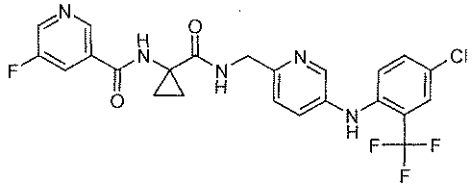
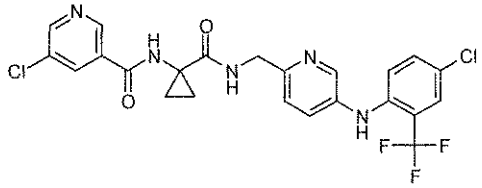
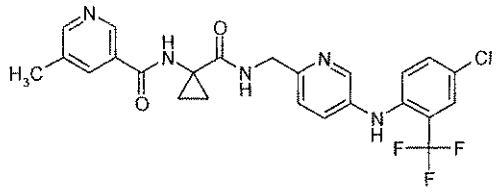
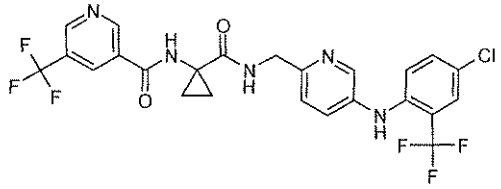
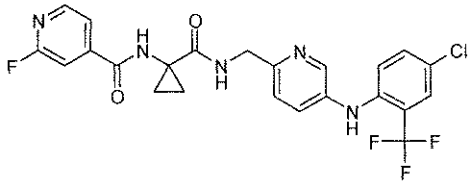
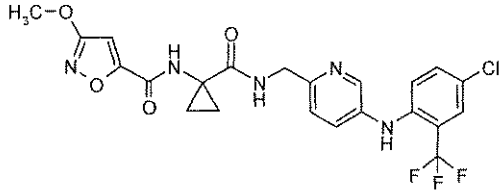
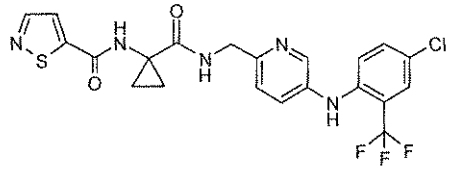
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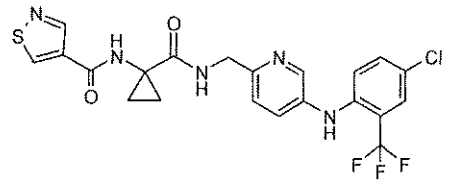
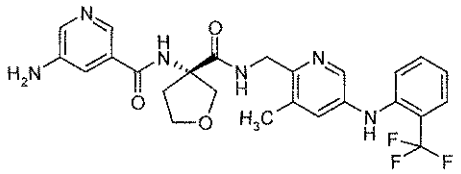
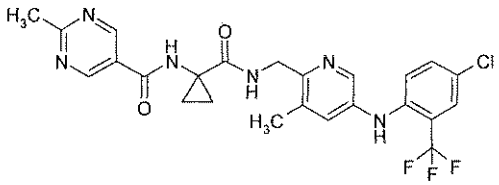
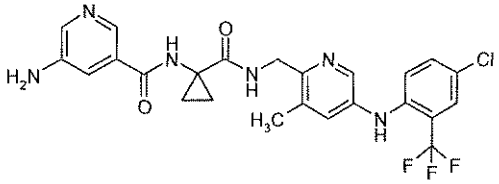
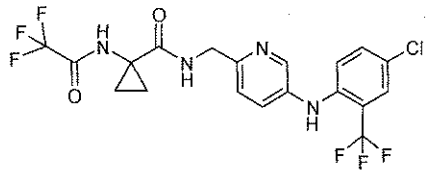
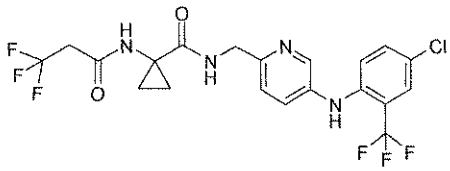
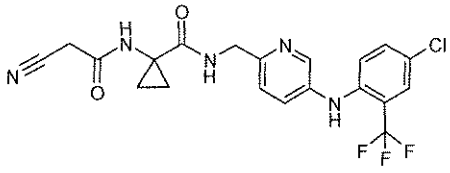
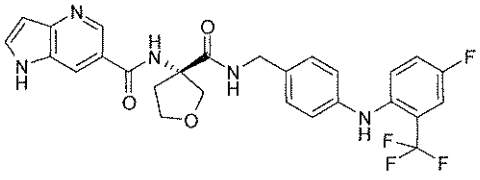
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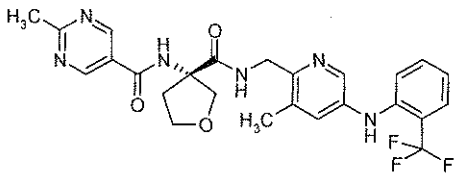
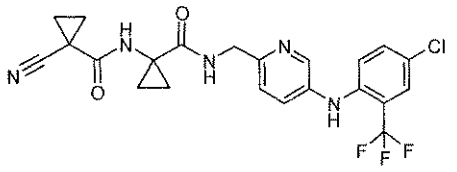
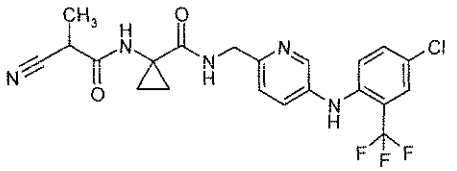
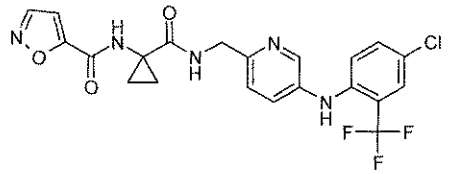
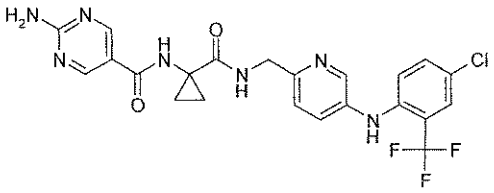
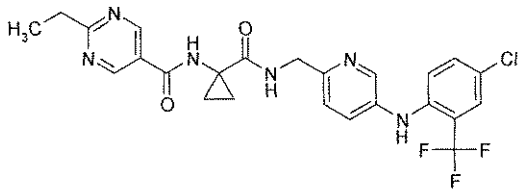
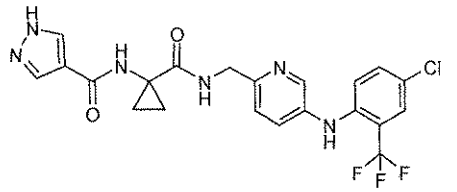
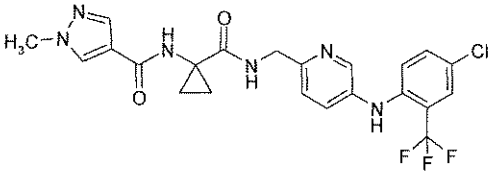
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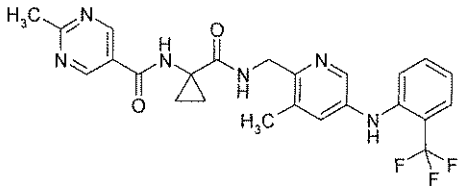
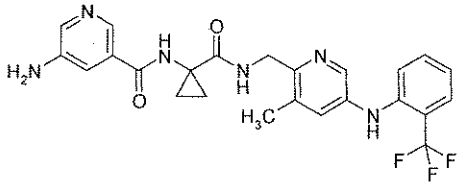
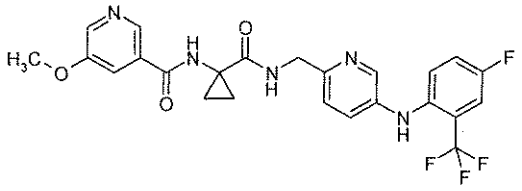
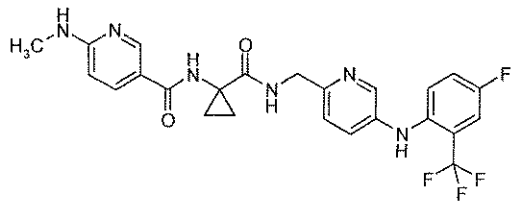
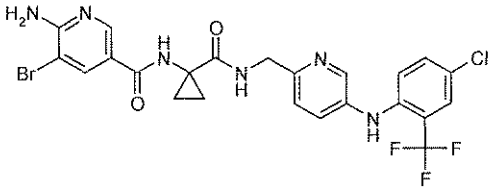
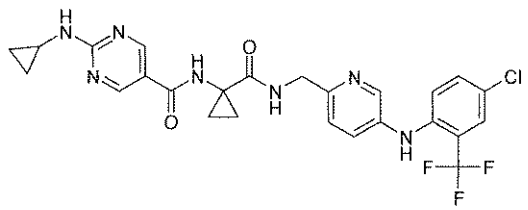
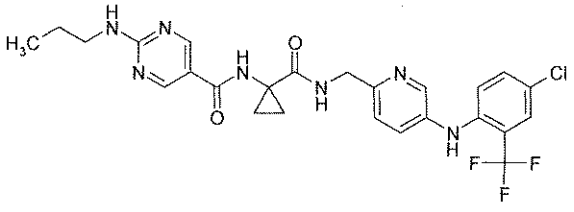
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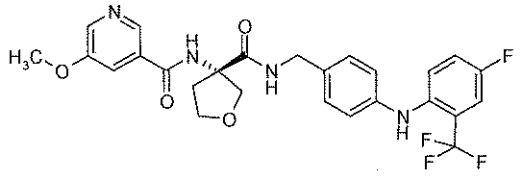
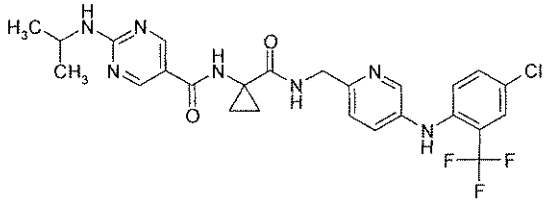
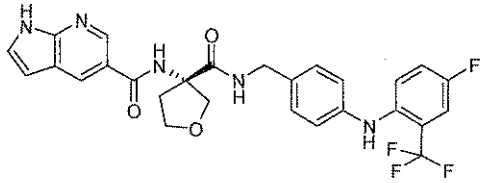
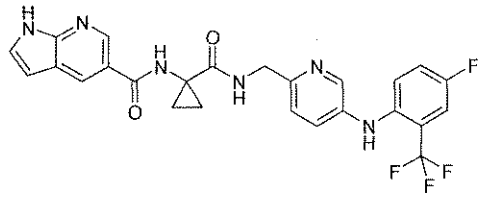
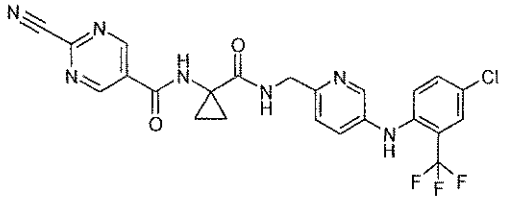
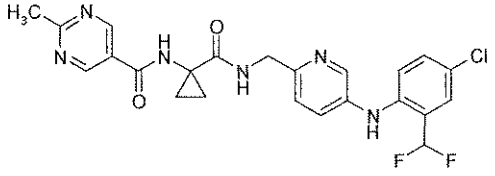
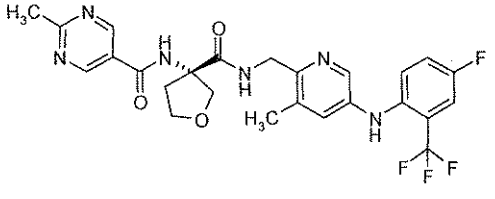
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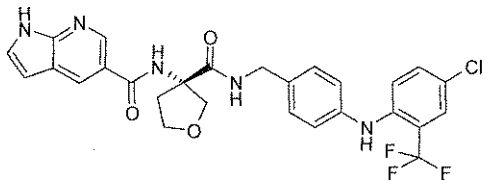
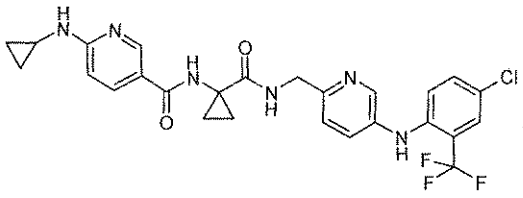
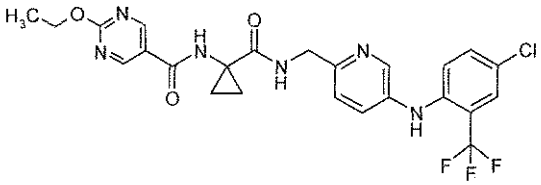
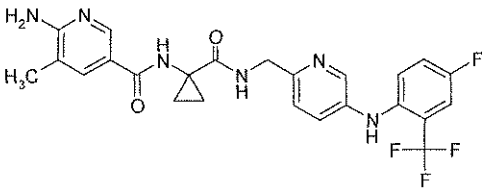
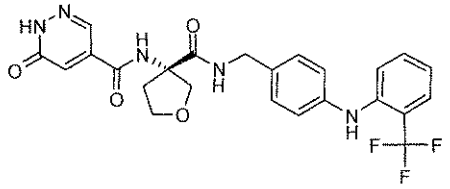
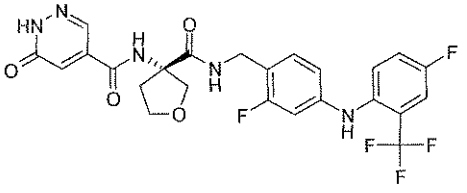
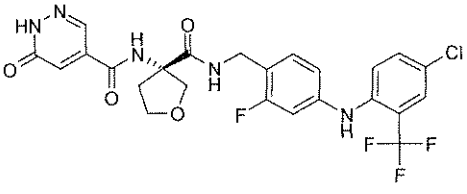
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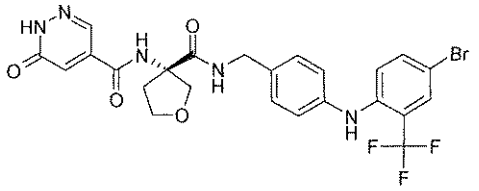
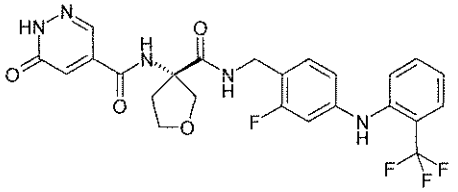
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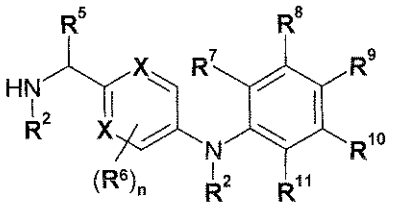
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No.	Structure
(395)	
(396)	

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A further embodiment of the present invention comprises the compounds of general formula **II**



, **(II)**

wherein

n denotes one of the numbers 0, 1 or 2,

R^2 denotes
(a) H,
(b) C_{1-4}-alkyl,
(c) C_{1-4}-alkyl-C(O)-,

R^5 denotes
(a) H,
(b) C_{1-4}-alkyl,

(c) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^6 independently of one another denotes

(a) H, halogen, -CN, -OH, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, -O-C_{1-4}-alkyl, -O-CF_3, -O-C_{3-6}-cycloalkyl, -N(C_{1-3}-alkyl)$_2$, -C(O)-NH_2, -(SO_2)NH_2, -SO_2-C_{1-3}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^7 denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,

(e) -O-C_{1-6}-alkyl,

(f) -O-C_{3-7}-cycloalkyl,

(g) -NH_2, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,

(h) -C(O)-**$R^{7.1}$**,

(i) -S-C_{1-4}-alkyl, -SO_2-**$R^{7.2}$**,

(j) a five-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl, or

(k) a six-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,

$R^{7.1}$ denotes -NH_2, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, -OH, -O-C_{1-8}-alkyl or -O-C_{3-7}-cycloalkyl,

$R^{7.2}$ denotes $-NH_2$, $-NH(C_{1-6}\text{-alkyl})$,$-N(C_{1-6}\text{-alkyl})_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl or *N*-morpholinyl and

R^8 denotes H, halogen, C_{1-4}-alkyl,

R^9 denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or $-O-C_{1-3}$-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,

(e) C_{2-4}-alkynyl,

(f) $-O-C_{1-6}$-alkyl,

(g) $-O-C_{3-7}$-cycloalkyl,

(h) $-NH_2$, $-NH(C_{1-3}\text{-alkyl})$, $-N(C_{1-3}\text{-alkyl})_2$,

(i) $-C(O)-R^{9.1}$,

(j) $-S-C_{1-4}$-alkyl, $-SO-C_{1-4}$-alkyl, $-SO_2-C_{1-4}$-alkyl,

$R^{9.1}$ denotes $-NH_2$, $-NH(C_{1-6}\text{-alkyl})$,$-N(C_{1-6}\text{-alkyl})_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, -OH, $-O-C_{1-8}$-alkyl or $-O-C_{3-7}$-cycloalkyl,

R^{10} denotes H, halogen, C_{1-4}-alkyl,

R^{11} denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or $-O-C_{1-3}$-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,

(e) $-O-C_{1-6}$-alkyl,

(f) $-O-C_{3-7}$-cycloalkyl,

(g) $-NH_2$, $-NH(C_{1-3}\text{-alkyl})$, $-N(C_{1-3}\text{-alkyl})_2$,

(h) -C(O)-$\mathbf{R}^{11.1}$,

(i) -S-C_{1-3}-alkyl, -SO_2-$\mathbf{R}^{11.2}$,

(j) a five-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl, or

(k) a six-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,

$\mathbf{R}^{11.1}$ denotes -NH_2, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, -OH, -O-C_{1-8}-alkyl or -O-C_{3-7}-cycloalkyl,

$\mathbf{R}^{11.2}$ denotes -NH_2, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl or *N*-morpholinyl and

X independently of one another denotes C-$\mathbf{R}^6$ or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A further embodiment of the present invention comprises the compounds of the above general formula **II**, wherein

n denotes one of the numbers 0, 1 or 2,

$\mathbf{R}^2$ denotes H or CH_3,

$\mathbf{R}^5$ denotes H or CH_3,

$\mathbf{R}^6$ denotes H, F, Cl or methyl,

$\mathbf{R}^7$ denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

$\mathbf{R^8}$ denotes H,

$\mathbf{R^9}$ denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

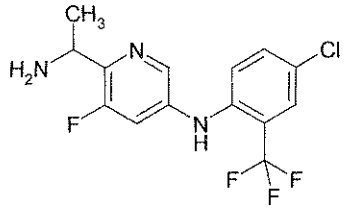
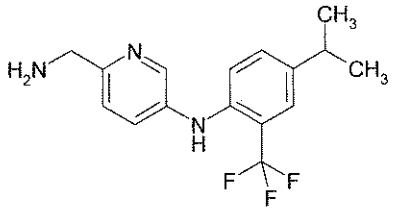
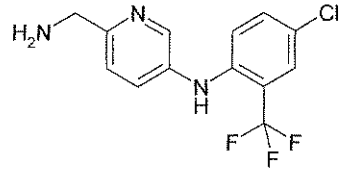
$\mathbf{R^{10}}$ denotes H,

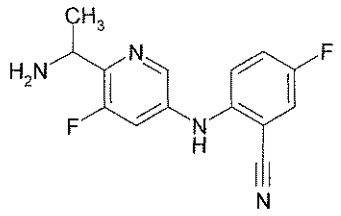
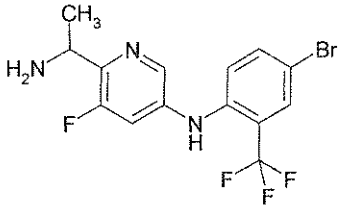
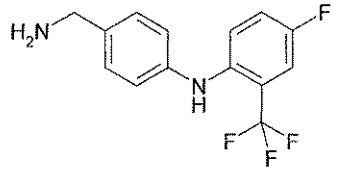
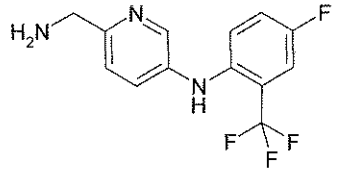
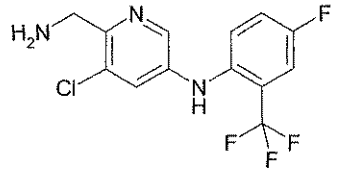
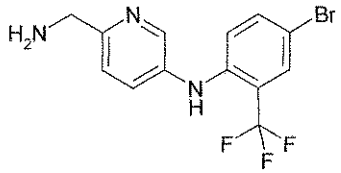
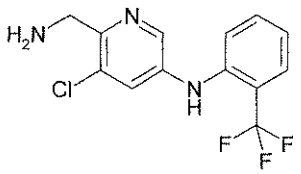
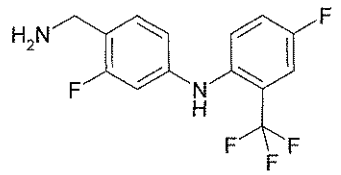
$\mathbf{R^{11}}$ denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

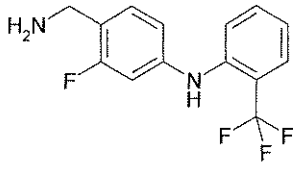
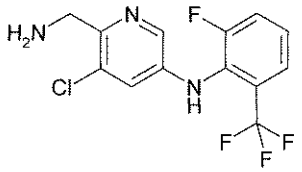
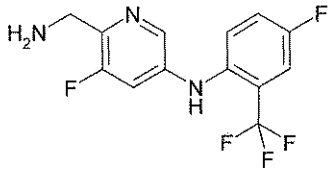
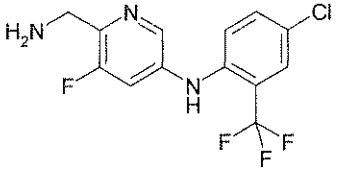
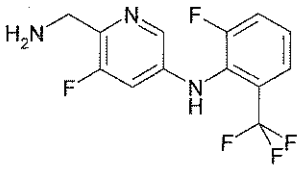
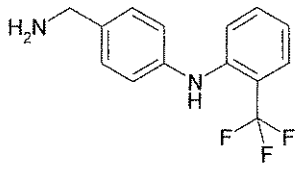
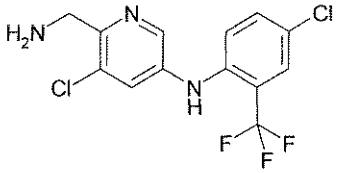
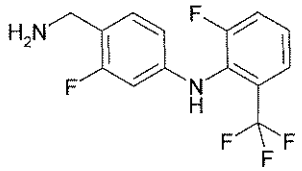
X independently of one another represent C-$\mathbf{R^6}$ or N,

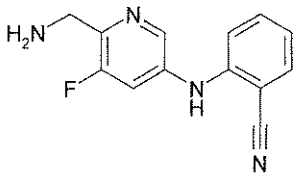
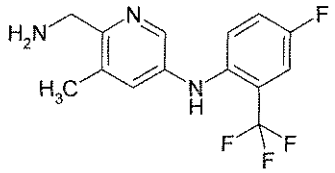
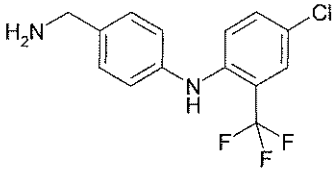
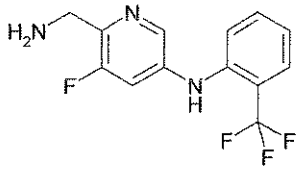
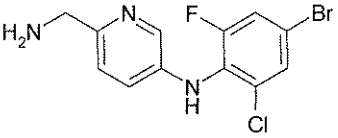
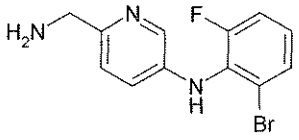
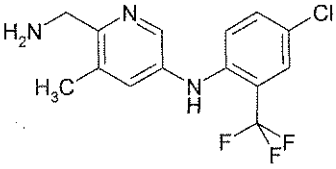
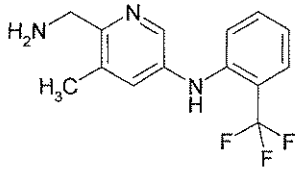
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

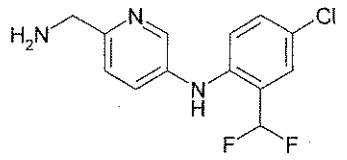
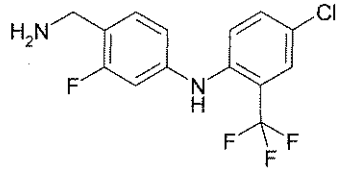
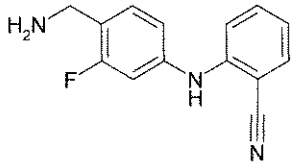
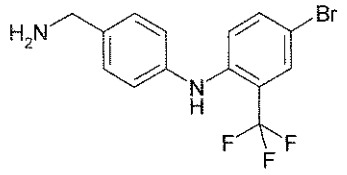
The following compounds are mentioned as examples of particularly preferred compounds of the above general formula **II**:

No.	Structure
(1.1)	
(1.2)	
(1.3)	

No.	Structure
(1.4)	
(1.5)	
(1.6)	
(1.7)	
(1.8)	
(1.9)	
(1.10)	
(1.11)	

No.	Structure
(1.12)	
(1.13)	
(1.14)	
(1.15)	
(1.16)	
(1.17)	
(1.18)	
(1.19)	

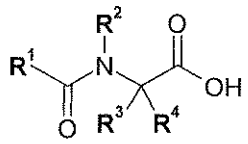
No.	Structure
(1.20)	
(1.21	
(1.22)	
(1.23)	
(1.24)	
(1.25)	
(1.26)	
(1.27)	

No.	Structure
(1.28)	
(1.29)	
(1.30)	
(1.31)	

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A further embodiment of the present application relates to the use of the compounds of general formula **II**, wherein R^2, R^5, R^6, R^7, R^8, R^9, R^{10} and R^{11} are as hereinbefore defined, the diastereomers, the enantiomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases for preparing compounds of general formula **I**, which have B1-antagonistic properties.

A further embodiment of the present invention comprises the compounds of general formula **III**



wherein

$\mathbf{R^1}$ denotes

(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(c) a C_{3-6}-cycloalkyl group optionally substituted by a group $\mathbf{R^{1.2}}$ wherein a $-CH_2-$ unit may be replaced by a -C(O)- group,

(d) an aryl-C_{0-2}-alkylene group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.3}}$,

(e) a five-membered heteroaryl-C_{0-2}-alkylene group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.4}}$, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms and which may additionally be benzo-condensed,

(f) a six-membered heteroaryl-C_{0-2}-alkylene group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms and which may additionally be benzo-condensed,

(g) a nine or ten-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms,

(h) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, wherein a $-CH_2-$ unit may be replaced by a -C(O)- group,

(i) $-O-\mathbf{R^{1.1.1}}$,

(j) $-N\mathbf{R^{1.1.3}}\mathbf{R^{1.1.4}}$ or

(k) $-C(=N\mathbf{R^{1.5}})-CN$,

$\mathbf{R^{1.1}}$ denotes halogen, $-NO_2$, -CN, C_{3-6}-cycloalkyl, $-O\mathbf{R^{1.1.1}}$, $-S\mathbf{R^{1.1.1}}$, $-C(O)\mathbf{R^{1.1.1}}$, $-S(O)_2-\mathbf{R^{1.1.2}}$, $-O-S(O)_2-\mathbf{R^{1.1.1}}$, $-CO_2\mathbf{R^{1.1.1}}$, $-O-C(O)-\mathbf{R^{1.1.1}}$, $-N\mathbf{R^{1.1.3}}\mathbf{R^{1.1.4}}$, $-N\mathbf{R^{1.1.3}}-C(O)-\mathbf{R^{1.1.1}}$, $-N\mathbf{R^{1.1.3}}-C(O)-\mathbf{R^{1.1.1}}$, $-N\mathbf{R^{1.1.3}}-CO_2-\mathbf{R^{1.1.1}}$ or $-C(O)-N\mathbf{R^{1.1.3}}\mathbf{R^{1.1.4}}$,

$\mathbf{R^{1.1.1}}$ denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.1.1.1}}$,

(e) C_{3-6}-cycloalkyl or

(f) a pyridyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R}^{1.1.1.2}$,

$\mathbf{R}^{1.1.1.1}$ independently of one another denotes

(a) halogen, $-NO_2$, -CN, -OH, $-O-C_{1-4}$-alkyl, C_{3-6}-cycloalkyl, C_{1-4}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R}^{1.1.1.2}$ independently of one another denotes halogen or C_{1-4}-alkyl,

$\mathbf{R}^{1.1.2}$ denotes

(a) C_{1-4}-alkyl,

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(c) $-O-C_{1-4}$-alkyl or

(d) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R}^{1.1.1.1}$,

$\mathbf{R}^{1.1.3}$,

$\mathbf{R}^{1.1.4}$ independently of one another denote

(a) H,

(b) a C_{1-4}-alkyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R}^{1.1.4.1}$,

(c) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R}^{1.1.1.1}$,

(d) C_{3-6}-cycloalkyl, or

$\mathbf{R}^{1.1.3}$ and $\mathbf{R}^{1.1.4}$ together with the N atom to which they are attached form a 5- or 6-membered heterocyclic ring, which may additionally contain a further heteroatom selected from N, O and S, or

$\mathbf{R}^{1.1.3}$ and $\mathbf{R}^{1.1.4}$ together with the N atom to which they are attached, form a cyclic imide,

$\mathbf{R}^{1.1.4.1}$ independently of one another denote halogen, $-NH_2$, $-NH(C_{1-4}\text{-alkyl})$, $-N(C_{1-4}\text{-alkyl})_2$ or $-SO_2-\mathbf{R}^{1.1.2}$,

$R^{1.2}$ denotes halogen, $-NO_2$, -CN, OH, $-O-CH_3$ or phenyl,

$R^{1.3}$ denotes

(a) halogen, $-NO_2$, -CN, $-OR^{1.1.1}$, $-SR^{1.1.1}$, $-CO_2R^{1.1.1}$, C_{1-6}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$R^{1.4}$ independently of one another denotes

(a) halogen, $-NO_2$, -CN, $-OR^{1.1.1}$, $-SR^{1.1.1}$, $-S(O)-R^{1.1.2}$, $-S(O)_2-R^{1.1.2}$, $-NR^{1.1.3}R^{1.1.4}$, $-N(R^{1.4.1})-C(O)-C_{1-4}$-alkyl, C_{1-6}-alkyl,

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, or

(c) a oxo group,

$R^{1.4.1}$ denotes H or C_{1-4}-alkyl,

$R^{1.5}$ denotes -OH or $-O-C_{1-3}$-alkyl,

R^2 denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) C_{1-4}-alkyl-C(O)-,

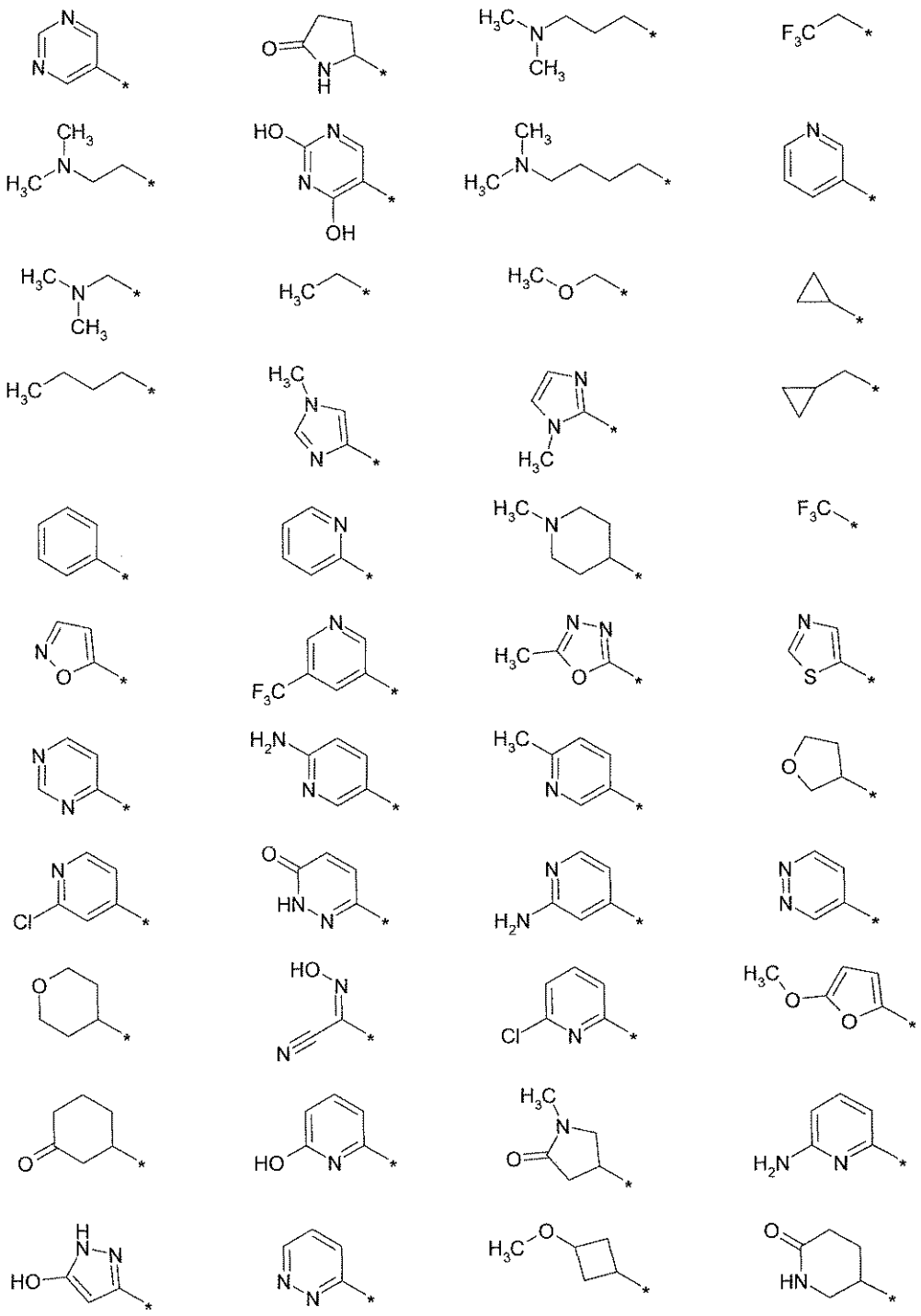
R^3 and R^4 together with the carbon atom to which they are attached denote a C_{3-6}-cycloalkylene group optionally substituted by a group $R^{3.1}$ wherein a $-CH_2-$ unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO_2, and

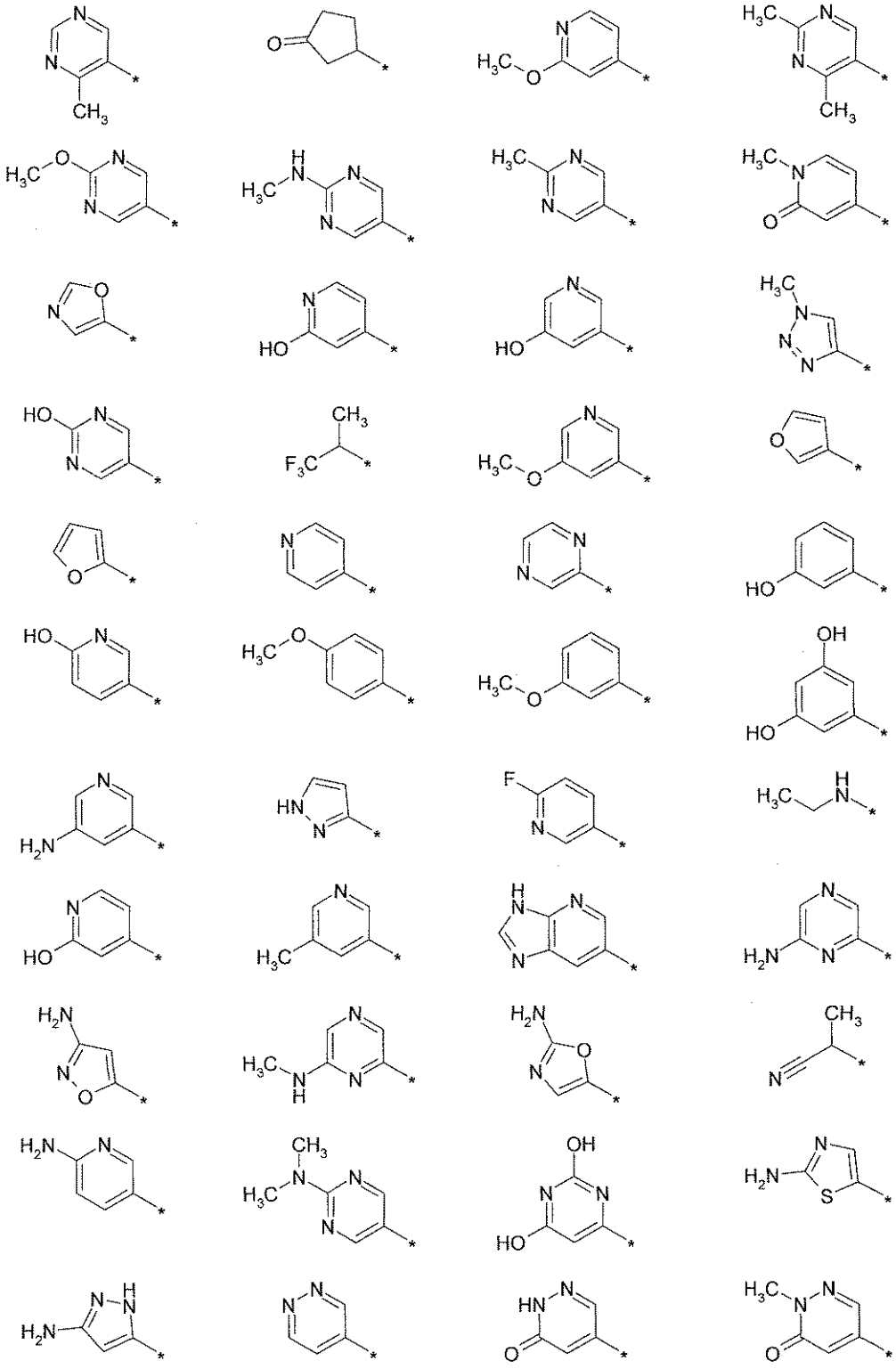
$R^{3.1}$ denotes H, -OH,

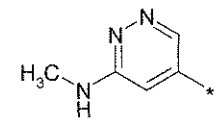
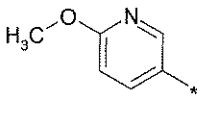
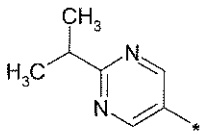
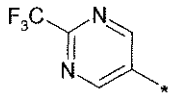
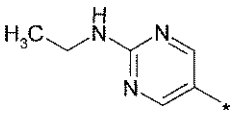
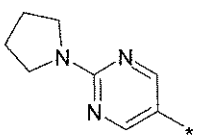
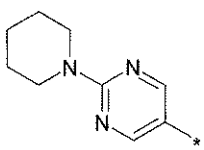
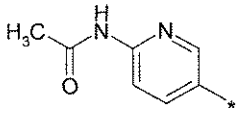
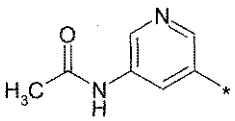
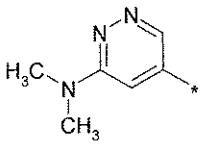
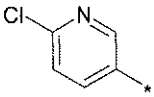
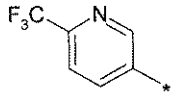
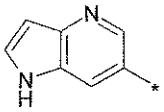
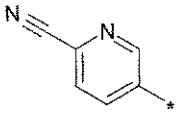
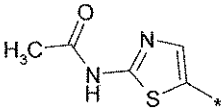
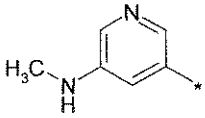
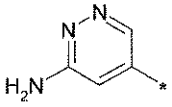
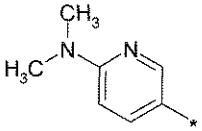
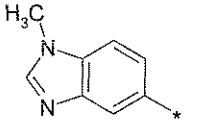
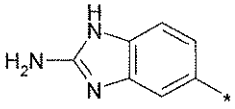
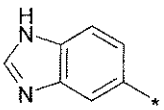
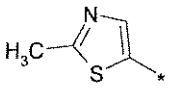
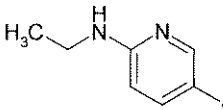
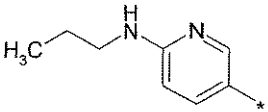
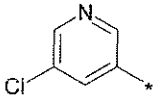
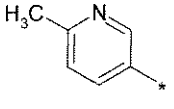
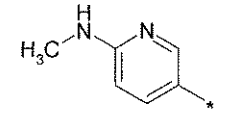
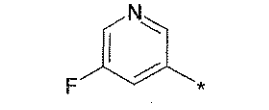
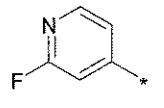
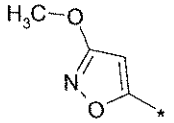
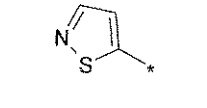
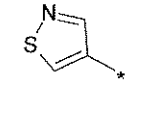
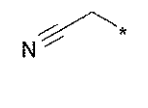
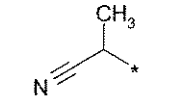
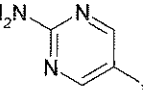
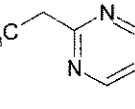
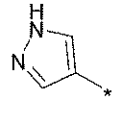
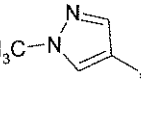
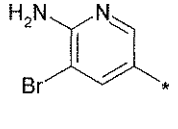
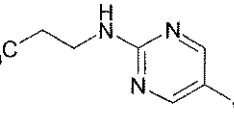
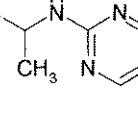
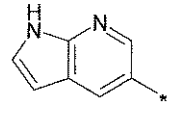
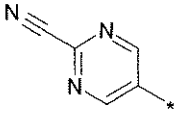
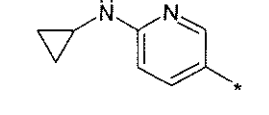
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

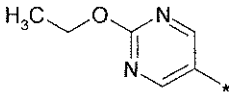
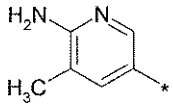
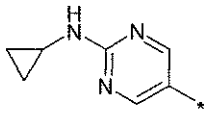
A further embodiment of the present invention comprises the compounds of the above general formula **III**, wherein

R^1 is selected from among





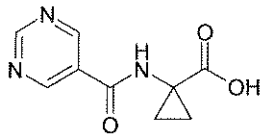
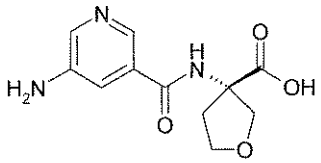
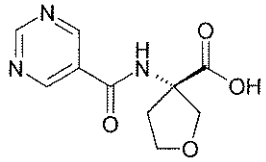
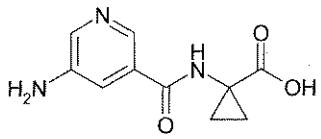
$\mathbf{R^2}$ denotes H or CH_3,

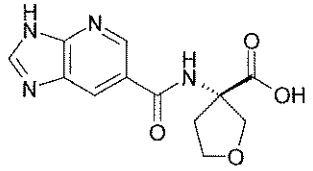
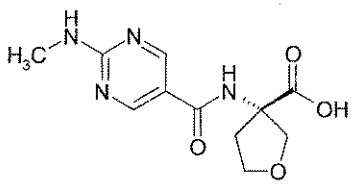
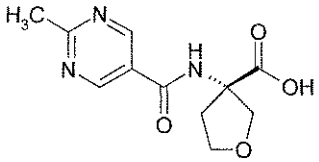
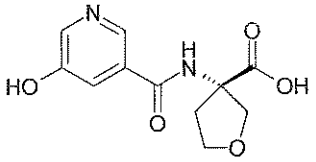
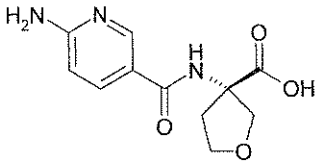
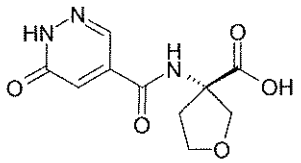
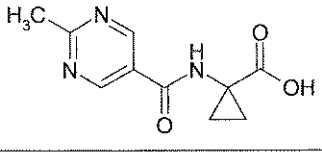
$\mathbf{R^3}$ and $\mathbf{R^4}$ together with the carbon atom to which they are attached denote a C_{3-6}-cycloalkylene group optionally substituted by a group $\mathbf{R^{3.1}}$ wherein a $-CH_2-$ unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO_2, and

$\mathbf{R^{3.1}}$ denotes H, -OH,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

The following compounds are mentioned as examples of most particularly preferred compounds of the above general formula **III**:

No.	Structure
(2.1)	
(2.2)	
(2.3)	
(2.4)	

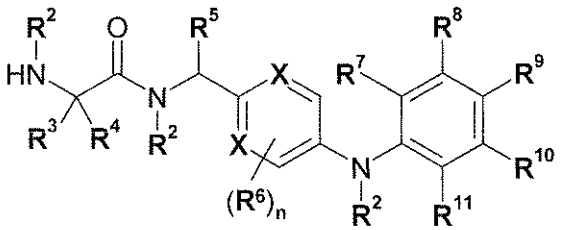
No.	Structure
(2.5)	
(2.6)	
(2.7)	
(2.8)	
(2.9)	
(2.10)	
(2.11)	

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A further embodiment of the present application relates to the use of the compounds of general formula **III**, wherein $\mathbf{R^2}$, $\mathbf{R^3}$, and $\mathbf{R^4}$ are as hereinbefore defined, the diastereomers, the enantiomers and the salts thereof, particularly the physiologically

acceptable salts thereof with inorganic or organic acids or bases for preparing compounds of general formula **I** which have B1-antagonistic properties.

A further embodiment of the present invention comprises the compounds of general formula **IV**



, (**IV**)

wherein

n denotes one of the numbers 0, 1 or 2,

R^2 denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) C_{1-4}-alkyl-C(O)-,

R^3 and R^4 together with the carbon atom to which they are attached denote a C_{3-6}-cycloalkylene group optionally substituted by a group $R^{3.1}$ wherein a $-CH_2-$ unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO_2,

$R^{3.1}$ denotes H, -OH,

R^5 denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^6 independently of one another denote

(a) H, halogen, -CN, -OH, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, -O-C_{1-4}-alkyl, -O-CF_3, -O-C_{3-6}-cycloalkyl, -N(C_{1-3}-alkyl)$_2$, -C(O)-NH_2, -(SO_2)NH_2, -SO_2-C_{1-3}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^7}$ denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,

(e) -O-C_{1-6}-alkyl,

(f) -O-C_{3-7}-cycloalkyl,

(g) -NH_2, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,

(h) -C(O)-$\mathbf{R^{7.1}}$,

(i) -S-C_{1-4}-alkyl, -SO_2-$\mathbf{R^{7.2}}$,

(j) a five-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl, or

(k) a six-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,

$\mathbf{R^{7.1}}$ denotes -NH_2, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, -OH, -O-C_{1-8}-alkyl or -O-C_{3-7}-cycloalkyl,

$\mathbf{R^{7.2}}$ denotes -NH_2, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl or *N*-morpholinyl and

$\mathbf{R^8}$ denotes H, halogen, C_{1-4}-alkyl,

R^9 denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,

(e) C_{2-4}-alkynyl,

(f) -O-C_{1-6}-alkyl,

(g) -O-C_{3-7}-cycloalkyl,

(h) $-NH_2$, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,

(i) -C(O)-$R^{9.1}$,

(j) -S-C_{1-4}-alkyl, -SO-C_{1-4}-alkyl, $-SO_2$-C_{1-4}-alkyl,

$R^{9.1}$ denotes $-NH_2$, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, -OH, -O-C_{1-6}-alkyl or -O-C_{3-7}-cycloalkyl,

R^{10} denotes H, halogen, C_{1-4}-alkyl,

R^{11} denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,

(e) -O-C_{1-6}-alkyl,

(f) -O-C_{3-7}-cycloalkyl,

(g) $-NH_2$, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,

(h) -C(O)-$R^{11.1}$,

(i) -S-C_{1-3}-alkyl, $-SO_2$-$R^{11.2}$,

(j) a five-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyrrolyl, oxazolyl, isoxazolyl,

oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl, or

(k) a six-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,

$R^{11.1}$ denotes $-NH_2$, $-NH(C_{1-6}\text{-alkyl})$,$-N(C_{1-6}\text{-alkyl})_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, -OH, $-O-C_{1-8}$-alkyl or $-O-C_{3-7}$-cycloalkyl,

$R^{11.2}$ $-NH_2$, $-NH(C_{1-6}\text{-alkyl})$,$-N(C_{1-6}\text{-alkyl})_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl or *N*-morpholinyl and

X independently of one another denotes C-R^6 or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A further embodiment of the present invention comprises the compounds of the above general formula **IV**, wherein

n denotes one of the numbers 0, 1 or 2,

R^2 denotes H or CH_3,

R^3 and R^4 together with the carbon atom to which they are attached denote a C_{3-6}-cycloalkylene group optionally substituted by a group $R^{3.1}$ wherein a $-CH_2$ unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO_2,

$R^{3.1}$ denotes H, -OH,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^8 denotes H,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

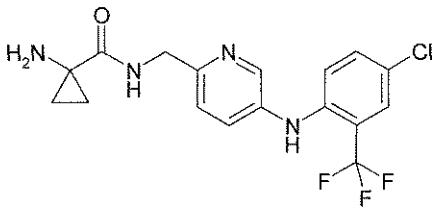
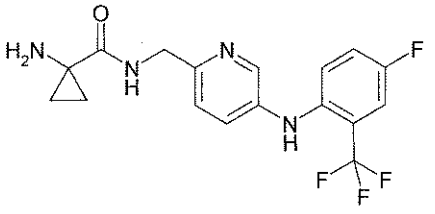
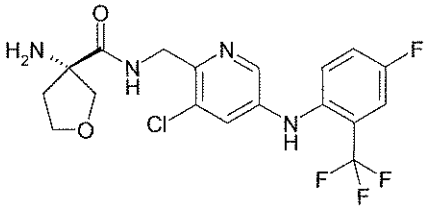
R^{10} denotes H,

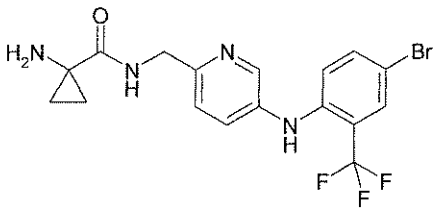
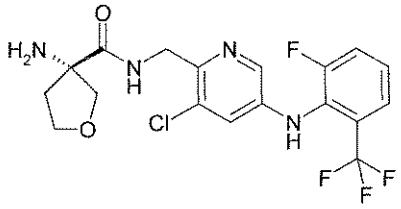
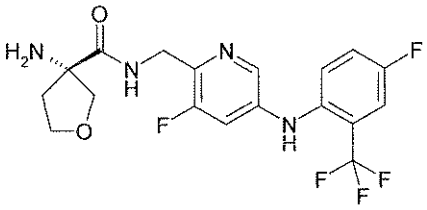
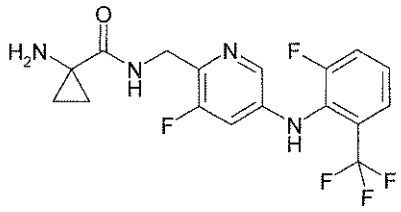
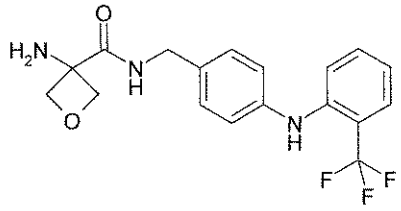
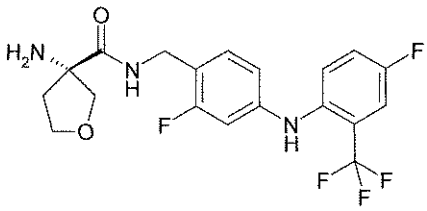
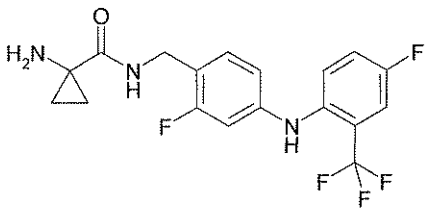
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

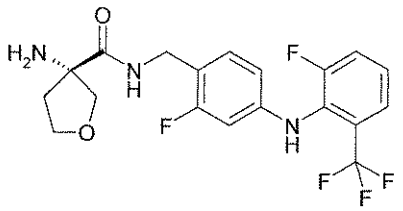
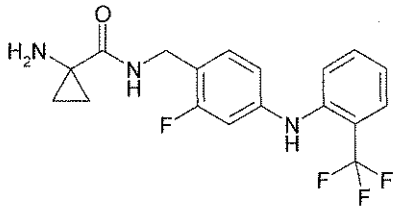
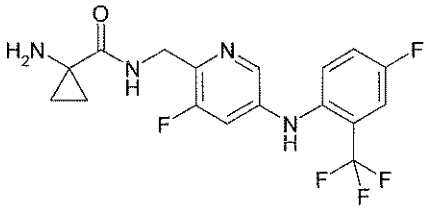
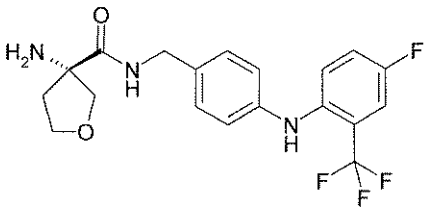
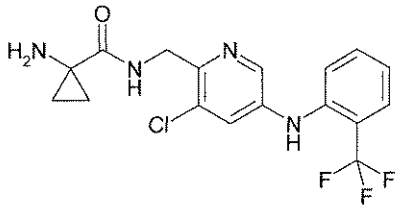
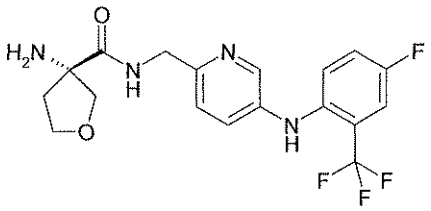
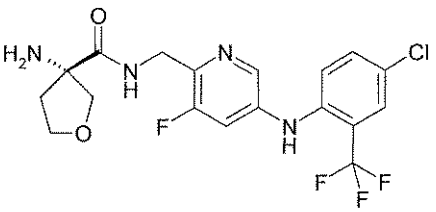
X independently of one another denotes C-**R^6** or N,

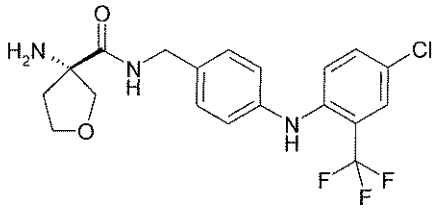
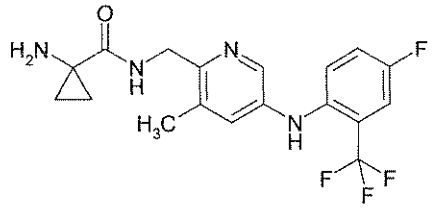
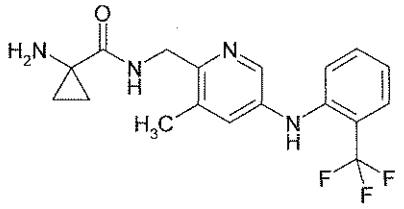
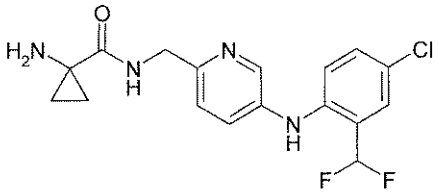
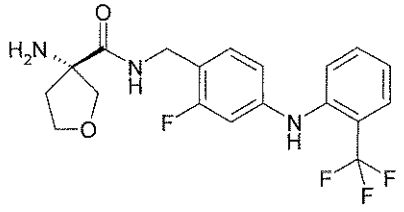
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

The following compounds are mentioned as examples of most particularly preferred compounds of the above general formula **IV**:

No.	Structure
(3.1)	
(3.2)	
(3.3)	

No.	Structure
(3.4)	
(3.5)	
(3.6)	
(3.7)	
(3.8)	
(3.9)	
(3.10)	

No.	Structure
(3.11)	
(3.12)	
(3.13)	
(3.14)	
(3.15)	
(3.16)	
(3.17)	

No.	Structure
(3.18)	
(3.19)	
(3.20)	
(3.21	
(3.22)	

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

A further embodiment of the present application relates to the use of the compounds of general formula **IV**, wherein $\mathbf{R^2}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$ and $\mathbf{R^{11}}$ are as hereinbefore defined, the diastereomers, the enantiomers and the salts thereof, particularly the physiologically acceptable salts thereof with inorganic or organic acids or bases for preparing compounds of general formula **I** which have B1-antagonistic properties.

TERMS AND DEFINITIONS USED

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

Within the scope of this application, in the definition of possible substituents, these may also be represented in the form of a structural formula. If present, an asterisk (*) in the structural formula of the substituent is to be understood as being the linking point to the rest of the molecule.

Also included in the subject matter of this invention are the compounds according to the invention, including the salts thereof, in which one or more hydrogen atoms, for example one, two, three, four or five hydrogen atoms, are replaced by deuterium.

By the term "C_{1-3}-alkyl" (including those that are part of other groups) are meant alkyl groups with 1 to 3 carbon atoms, by the term "C_{1-4}-alkyl" are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms, by the term "C_{1-6}-alkyl" are meant branched and unbranched alkyl groups with 1 to 6 carbon atoms, and by the term "C_{1-8}-alkyl" are meant branched and unbranched alkyl groups with 1 to 8 carbon atoms. Examples include: methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, neopentyl, *n*-hexyl, *n*-heptyl and *n*-octyl. The abbreviations Me, Et, n-Pr, i-Pr, n-Bu, i-Bu, t-Bu, etc. May optionally also be used for the above-mentioned groups. Unless stated otherwise, the definitions propyl and butyl 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.

Moreover the definitions mentioned previously also include those groups wherein each methylene group may be substituted by up to two and each methyl group may be substituted by up to three fluorine atoms.

By the term "C_{0-2}-alkylene" are meant branched and unbranched alkylene groups with 0 to 2 carbon atoms, while a C_0-alkylene group denotes a bond. Examples include: methylene, ethylene and ethane-1,1-diyl. Moreover the definitions mentioned previously

also include those groups wherein each methylene group may be substituted by up to two fluorine atoms.

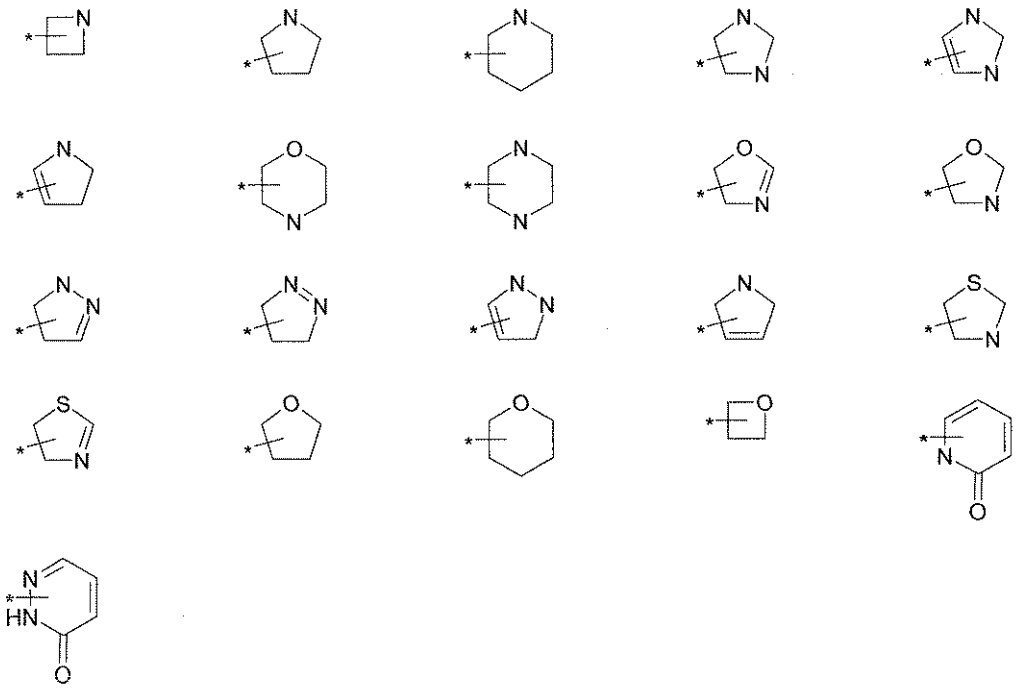
By the term "C_{3-7}-cycloalkyl" (including those that are part of other groups) are meant cyclic alkyl groups with 3 to 7 carbon atoms and by the term "C_{3-6}-cycloalkyl" are meant cyclic alkyl groups with 3 to 6 carbon atoms. Examples include: cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. 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 "C_{3-6}-cycloalkylene" (including those that are part of other groups) are meant cyclic alkylene groups with 3 to 6 carbon atoms. Examples include: cyclopropylene, cyclobutylene, cyclopentylene or cyclohexylene. Unless otherwise stated, the cyclic alkylene 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 "C_{2-4}-alkynyl" (including those that are part of other groups) are meant branched and unbranched alkynyl groups with 2 to 4 carbon atoms, provided that they have at least one triple bond. Examples include: ethynyl, propynyl or butynyl. Unless stated otherwise, the definitions propynyl and butynyl include all the possible isomeric forms of the groups in question. Thus for example propynyl includes 1-propynyl and 2-propynyl, butynyl includes 1-butynyl, 2-butynyl and 3-butynyl etc.

"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.

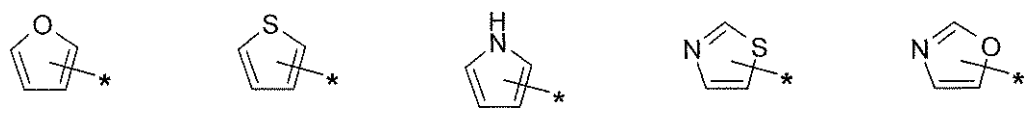
By the term "heterocyclic rings" or "heterocyclic group" are meant stable 5- or 6-membered monocyclic ring systems, which may be both saturated and mono- or di-unsaturated and besides carbon atoms may carry one or two heteroatoms, which are selected from among nitrogen, oxygen and sulphur. Both nitrogen and sulphur heteroatoms may optionally be oxidised. The previously mentioned heterocycles may be attached to the rest of the molecule via a carbon atom or a nitrogen atom. The following compounds are mentioned as examples:

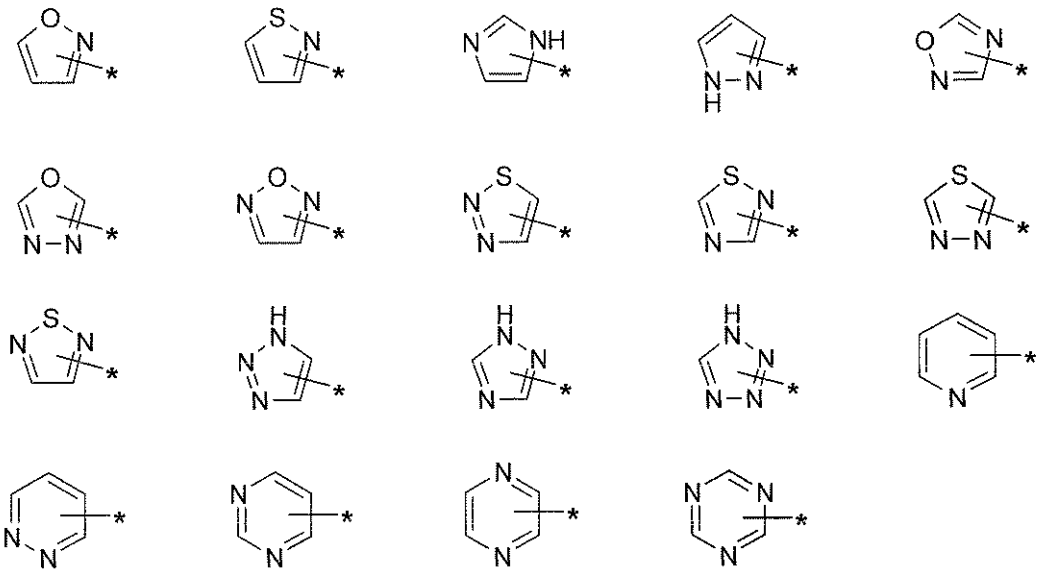


"Cyclic imides" includes for example succinimides, maleimide and phthalimide.

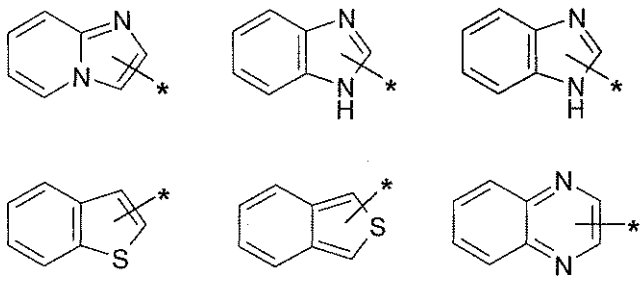
By the term "aryl" (including those that are part of other groups) are meant aromatic ring systems with 6 or 10 carbon atoms. Examples of these are phenyl, 1-naphthyl or 2-naphthyl; the preferred aryl group is phenyl. Unless otherwise stated, the aromatic groups may be substituted by one or more groups selected from among methyl, ethyl, *n*-propyl, *iso*-propyl, *tert*-butyl, hydroxy, methoxy, trifluoromethoxy, fluorine, chlorine, bromine and iodine, while the groups may be identical or different.

By the term "heteroaryl" are meant five- or six-membered heterocyclic aromatic groups, which may contain one, two, three or four heteroatoms, selected from among oxygen, sulphur and nitrogen, and additionally contain so many conjugated double bonds that an aromatic system is formed. These heteroaryls may additionally be benzo-condensed with a phenyl ring, so as to form nine- or ten-membered bicyclic heteroaryls.
The following are examples of five- or six-membered heteroaromatic groups:





The following are examples of nine- or ten-membered heteroaromatic groups:



Unless otherwise stated, the heteroaryls mentioned previously may be substituted by one or more groups selected from among methyl, ethyl, *n*-propyl, *iso*-propyl, *tert*-butyl, hydroxy, methoxy, trifluoromethoxy, fluorine, chlorine, bromine and iodine, while the groups may be identical or different.
In addition, any nitrogen atom present in the heteroaryl group may be oxidised, thereby forming an N-oxide.

By the term "oxo group" is meant an oxygen substituent at a carbon atom, which leads to the formation of a carbonyl group -C(O)-. The introduction of an oxo group as substituent at a non-aromatic carbon atom leads to a conversion of a $-CH_2$ group into a -C(O)- group. The introduction of an oxo group at an aromatic carbon atom leads to the conversion of a -CH- group into a -C(O)- group and may result in the loss of aromaticity.

If they contain suitable basic functions, for example amino groups, compounds of general formula **I** may be converted, particularly for pharmaceutical use, into the physiologically acceptable salts thereof with inorganic or organic acids. Examples of inorganic acids for this purpose include hydrobromic acid, phosphoric acid, nitric acid, hydrochloric acid, sulphuric acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid or *p*-toluenesulphonic acid, while organic acids that may be used include malic acid, succinic acid, acetic acid, fumaric acid, maleic acid, mandelic acid, lactic acid, tartaric acid or citric acid.

In addition, the compounds of general formula **I**, if they contain suitable carboxylic acid functions, may be converted into the physiologically acceptable salts thereof with inorganic or organic bases, particularly for pharmaceutical applications. Examples of inorganic bases include alkali or alkaline earth metal hydroxides, e.g. sodium hydroxide or potassium hydroxide, or carbonates, ammonia, zinc or ammonium hydroxides; examples of organic amines include diethylamine, triethylamine, ethanolamine, diethanolamine, triethanolamine, cyclohexylamine or dicyclohexylamine.

The compounds according to the invention may be present as racemates, provided that they have only one chiral element, but may also be obtained as pure enantiomers, i.e. In the (*R*) or (*S*) form.

However, the application also includes the individual diastereomeric pairs of antipodes or mixtures thereof, which are obtained if there is more than one chiral element in the compounds of general formula **I**, as well as the individual optically active enantiomers of which the above-mentioned racemates are made up.

Compounds with a carbon double bond may be present in both the E and Z form.

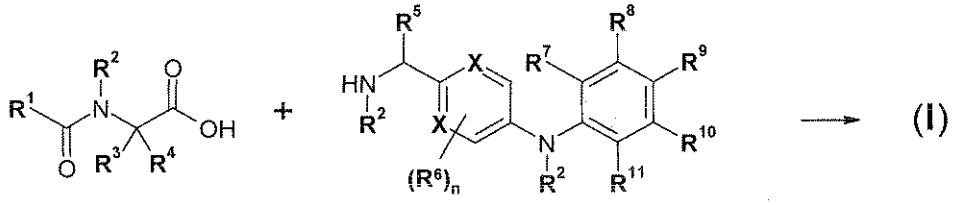
If a compound is present in different tautomeric forms, the compound prepared is not limited to one tautomeric form but includes all the tautomeric forms. This also applies particularly to nitrogen-containing heteroaryls:



PREPARATION METHODS

According to the invention the compounds of general formula I are obtained by methods known per se, for example by the following methods:

(A) amide coupling:



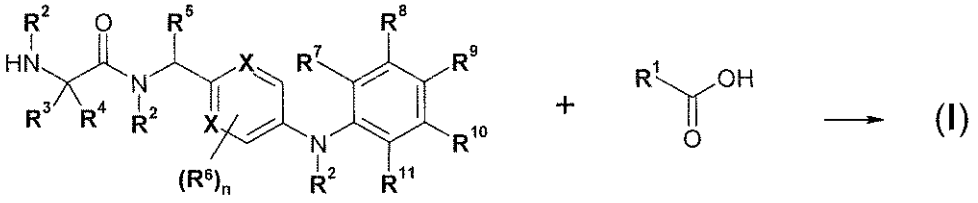
(II) (III)

The linking of carboxylic acids of general formula **II** as shown, wherein all the groups are as hereinbefore defined, with amines of general formula **III**, wherein all the groups are as hereinbefore defined, to form carboxylic acid amides of general formula I wherein all the groups are as hereinbefore defined, may be carried out by conventional methods of amide formation.

The coupling is preferably carried out using methods known from peptide chemistry (cf. e.g. Houben-Weyl, Methoden der Organischen Chemie, Vol. 15/2), for example using carbodiimides such as e.g. dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC) or ethyl-(3-dimethylaminopropyl)-carbodiimide, O-(1H-benzotriazol-1-yl)- N,N-N',N'-tetramethyluronium hexafluorophosphate (HBTU) or tetrafluoroborate (TBTU) or 1H-benzotriazol-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP). By adding 1-hydroxybenzotriazole (HOBt) or 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine (HOObt) the reaction speed can be increased. The couplings are normally carried out with equimolar amounts of the coupling components as well as the coupling reagent in solvents such as dichloromethane, tetrahydrofuran (THF),

acetonitrile, dimethyl formamide (DMF), dimethyl acetamide (DMA), N-methylpyrrolidone (NMP) or mixtures. If necessary, an auxiliary base such as diisopropylethylamine (DIPEA, Hünig base) is additionally used.

B) Amide coupling:



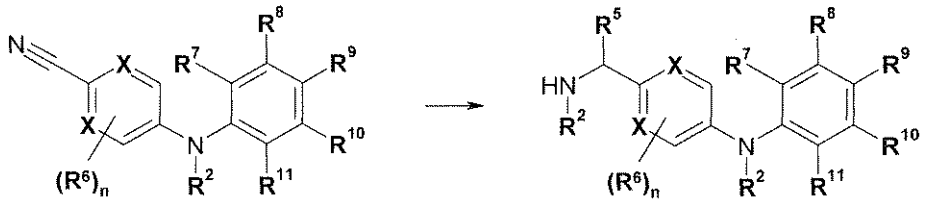
(IV) (V) (I)

An alternative method of preparing compounds of general formula **I** consists in linking carboxylic acids of general formula **V**, wherein all the groups are as hereinbefore defined, with amines of general formula **IV**, wherein all the groups are as hereinbefore defined.

The compounds of general formula **V** are either commercially obtainable or may be prepared by methods known from the literature

It is also possible to convert the carboxylic acids of general formula **V** into carboxylic acid chlorides and then react these with amines of general formula **IV**. Carboxylic acid chlorides are synthesised by methods known from the literature (cf. e.g. Houben-Weyl, Methoden der Organischen Chemie, vol. E5/1).

(C) Reduction of the nitrile group:



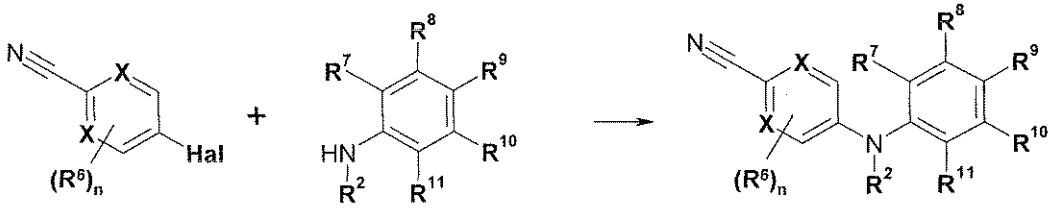
(VI) (III)

The reduction of a nitrile of general formula **VI** to an amine of general formula **III**, wherein the group R^2 at the amine nitrogen denotes hydrogen and all the other groups are as hereinbefore defined, may be carried out under standard conditions of catalytic hydrogenolysis with a catalyst such as Raney nickel, for example, in a solvent such as ammoniacal methanol or ethanol or with a reducing agent such as lithium aluminium hydride or sodium borohydride in a solvent such as tetrahydrofuran, optionally in the presence of a Lewis acid such as aluminium chloride.

Compounds of general formula **III**, wherein the group R^2 at the amine nitrogen denotes not hydrogen but an alkyl group, for example, may also be prepared from compounds of general formula **VI**. Thus, for example, the reaction of a nitrile of general formula **VI** with an alkyl Grignard reagent produces ketones which can be converted by reductive amination into the compounds of general formula **III**. The reductive amination is carried out using known methods, for example with a reducing agent such as sodium triacetoxyborohydride, sodium borohydride or sodium cyanoborohydride, conveniently in a solvent such as tetrahydrofuran or dichloromethane optionally substituted by the addition of acetic acid.

Alternatively the ketones obtained may also be converted into oximes. The subsequent reduction of the oximes then yields compounds of general formula **III**.

(D) nucleophilic aromatic substitution or transition-metal-catalysed coupling:



(VII) (VIII) (VI)

The reaction of an aniline of general formula **VIII**, wherein all the groups are as hereinbefore defined, with a nitrile of general formula **VII**, wherein **X**, R_6 and **n** are as hereinbefore defined, and **Hal** denotes a fluorine, chlorine or bromine atom, is carried out using known methods, for example in a solvent such as tetrahydrofuran, dimethylformamide or dimethylsulphoxide and conveniently in the presence of a base such as triethylamine, sodium hydroxide solution or potassium carbonate at a temperature

of 20°C to 160°C. If the aniline of general formula **VIII** is liquid, the reaction may also be carried out without a solvent and additional base.

An alternative method of preparing compounds of general formula **VI** is the palladium-catalysed reaction of a nitrile of general formula **VII**, wherein **Hal** denotes bromine or chlorine, with an aniline of general formula **VIII**. Reaction conditions for this reaction, which is also known as a Buchwald-Hartwig reaction, are known from the literature.

Description of the method of binding the cynoBK1-receptor

CHO cells that express the cynomolgus BK1-receptor are cultivated in "HAM´S F-12 Medium". The medium is removed from confluent cultures, the cells are washed with PBS buffer, scraped off or detached using Versene and isolated by centrifuging. Then the cells are homogenised in suspension, the homogenate is centrifuged and resuspended. After the protein content has been determined 200 µl of the homogenate (50 to 250 µg protein/assay) are incubated for 60-180 minutes at ambient temperature with 0.5 to 5.0 nM kallidine (DesArg10,Leu9), [3,4-Prolyl-3,43H(N)] and increasing concentrations of the test substance in a total volume of 250 µl. The incubation is stopped by rapid filtration through GF/B glass fibre filters that have been pre-treated with polyethyleneimine (0.3%). The radioactivity bound to the protein is measured with a TopCount NXT. The radioactivity bound in the presence of 1.0 µM kallidine (DesArg10) is defined as non-specific binding. The concentration binding curve may be analysed using computer-aided non-linear curve fitting to determine the corresponding K_i value for the test substance.

Test results of the cynoBK1-receptor binding assay:

Example No.	**% inhibition at 10 µmol/L**	**K_i [nM]**
(1)	54	
(2)	100	25
(3)	65	
(4)	109	
(5)	88	
(6)	59	
(7)	100	

Example No.	% inhibition at 10 μmol/L	K_i [nM]
(8)	75	
(9)	78	
(10)	58	
(11)	99	
(12)	78	
(13)	101	
(14)	84	
(15)	99	
(16)	91	
(17)	75	
(18)	67	
(19)	96	
(20)	81	
(21)	68	
(22)	60	
(23)	110	
(24)	107	
(25)	86	
(26)	109	
(27)	104	
(28)	101	0.6
(29)	113	6.2
(30)	111	13
(31)	112	13
(32)	93	200
(33)	110	1.9
(34)	94	>500
(35)	111	70
(36)	113	21
(37)	77	>500
(38)		

Example No.	% inhibition at 10 μmol/L	K_i [nM]
(39)	110	5.5
(40)	110	2.9
(41)	108	2.6
(42)	89	
(43)	94	36
(44)	109	7.0
(45)	104	2
(46)	88	290
(47)	94	39
(48)	71	
(49)	103	365
(50)	115	0.7
(51)	112	38
(52)	63	312
(53)	101	197
(54)	112	3.8
(55)	108	3.3
(56)	99	
(57)	111	77
(58)	109	
(59)	22	
(60)	84	
(61)	97	>500
(62)	60	
(63)	108	118
(64)	109	98
(65)	76	
(66)	81	
(67)	63	
(68)	78	
(69)	42	

Example No.	% inhibition at 10 µmol/L	K_i [nM]
(70)	107	
(71)	80	
(72)	89	416
(74)	56	
(75)	71	
(76)	80	
(77)	96	
(78)	73	
(79)	104	292
(80)	88	
(81)	113	
(82)	107	
(83)	113	9
(84)	104	90
(85)	93	
(86)	108	100
(87)	112	
(88)	80	
(89)	96	
(90)	109	135
(91)	100	
(92)	110	62
(93)	84	
(94)	57	
(95)	86	
(96)	78	
(97)		132
(98)	103	417
(99)	96	
(100)	103	
(102)	105	87

Example No.	% inhibition at 10 μmol/L	K_i [nM]
(103)	87	
(104)	54	
(105)	113	20
(106)	69	
(107)	95	
(108)	101	135
(109)	27	
(110)	33	
(111)	20	
(112)	45	
(113)	7	
(114)	77	>500
(115)	99	>500
(116)	83	>500
(117)	111	2.8
(118)	109	64
(119)	82	375
(120)	113	2.4
(121)	113	2
(122)	113	6.3
(123)	110	8.3
(124)	112	33
(125)	108	12
(126)	103	46
(127)	108	17
(128)	103	84
(129)	107	11
(130)	101	101
(131)	105	33
(132)	98	180
(133)	101	

Example No.	% inhibition at 10 µmol/L	K_i [nM]
(134)	101	4.7
(135)	106	15
(136)	104	42
(138)	107	6.7
(139)	107	2.8
(140)	106	14
(141)	100	7.6
(142)	106	12
(143)	106	12
(144)	97	126
(145)	99	2.8
(146)	107	7.6
(147)	107	4.4
(148)	96	
(149)	100	
(150)	105	37
(151)	107	1.8
(152)	105	3.2
(153)	106	9.7
(154)	101	89
(155)	101	143
(156)	107	8.5
(157)	96	56
(158)	101	115
(159)	91	97
(160)	106	17
(161)	69	>500
(162)	104	17
(163)	87	288
(164)	106	3.4
(165)	101	

Example No.	% inhibition at 10 μmol/L	K_i [nM]
(166)	104	45
(167)	104	19
(168)	90	235
(169)	90	292
(170)	104	35
(171)	97	
(172)	100	9.8
(173)	105	2.7
(174)	99	
(175)	96	63
(176)	100	
(177)	99	
(178)	107	11
(179)	101	
(180)	106	1.6
(181)	99	19
(182)	99	20
(183)	100	21
(184)	99	
(185)	87	
(186)	82	
(187)	100	
(188)	92	43
(189)	96	>500
(190)	91	
(191)	56	
(192)	95	
(193)	101	
(194)	95	
(195)	42	>500
(196)	82	>500

Example No.	% inhibition at 10 µmol/L	K_i [nM]
(197)	81	>500
(198)	64	>500
(200)	92	
(201)		
(202)		
(203)		1.9
(204)		402
(205)		17
(206)		5.1
(207)		84
(208)		6.8
(209)		73
(210)		187
(211)		25
(212)		8
(213)		1.9
(214)		13
(215)		3.5
(216)		7.8
(217)		12
(218)		3.7
(219)		8.9
(220)		15
(221)		13
(222)		68
(223)		75
(224)		6.3
(225)		68
(226)		157
(227)		97
(228)		78

Example No.	% inhibition at 10 µmol/L	K_i [nM]
(229)		27
(230)		6.1
(231)		4.2
(232)		5.6
(233)		10
(234)		105
(235)		489
(236)		8.2
(237)		151
(238)		6.6
(239)		182
(240)		506
(241)		68
(242)		15
(243)		28
(244)		8.4
(245)		18
(246)		21
(247)		3.9
(248)		276
(249)		518
(250)		175
(251)		14
(252)		120
(253)		49
(254)		257
(255)		15
(256)		72
(257)		17
(258)		37
(259)		394

Example No.	% inhibition at 10 μmol/L	K_i [nM]
(260)		43
(261)		456
(262)		37
(263)		485
(264)		60
(265)		75
(266)		78
(267)		5.5
(268)		281
(269)		47
(270)		51
(271)		17
(272)		35
(273)		141
(274)		4.0
(275)		405
(276)		17
(277)		10
(278)		16
(279)		5.5
(280)		25
(281)		21
(282)		7.9
(283)		1.3
(284)		5.1
(285)		27
(286)		36
(287)		11
(288)		9.1
(289)		21
(290)		46

Example No.	% inhibition at 10 μmol/L	K_i [nM]
(291)		40
(292)		7.2
(293)		65
(294)		1.2
(295)		31
(296)		28
(297)		59
(298)		0.7
(299)		222
(300)		45
(301)		1.1
(302)		42
(303)		82
(304)		135
(305)		76
(306)		2.0
(307)		54
(308)		427
(309)		184
(310)		39
(311)		349
(312)		57
(313)		95
(314)		15
(315)		40
(316)		57
(317)		30
(318)		316
(319)		58
(320)		19
(321)		57

Example No.	% inhibition at 10 µmol/L	K_i [nM]
(322)		12
(323)		69
(324)		22
(325)		374
(326)		504
(327)		89
(328)		33
(329)		24
(330)		35
(331)		66
(332)		41
(333)		89
(334)		20
(335)		28
(336)		567
(337)		312
(338)		27
(339)		49
(340)		28
(341)		69
(342)		50
(343)		7.2
(344)		1.9
(345)		17
(346)		48
(347)		12
(348)		31
(349)		648
(350)		43
(351)		24
(352)		59

Example No.	% inhibition at 10 µmol/L	K_i [nM]
(353)		52
(354)		27
(355)		433
(356)		22
(357)		44
(358)		37
(359)		125
(360)		2.5
(361)		10
(362)		101
(363)		45
(364)		77
(365)		376
(366)		33
(367)		508
(368)		42
(369)		37
(370)		1.4
(371)		6.1
(372)		24
(373)		95
(374)		5.5
(375)		48
(376)		61
(377)		45
(378)		4.6
(379)		5.5
(380)		6.5
(381)		93
(382)		6.8
(383)		225

Example No.	% inhibition at 10 µmol/L	K_i [nM]
(384)		21
(385)		9.4
(386)		15
(387)		10
(388)		386
(389)		15
(390)		7.3
(391)		9.3
(392)		11
(393)		
(394)		
(395)		37
(396)		6.6

INDICATIONS

In view of their pharmacological properties, the novel compounds and their physiologically acceptable salts are suitable for treating diseases and symptoms of diseases caused at least to some extent by stimulation of bradykinin-B1 receptors, or in which antagonisation of the of bradykinin-B1 receptor can bring about an improvement in symptoms.

In a further aspect the present invention encompasses the compounds of the above-mentioned general formula **I** according to the invention for use as medicaments.

In view of their pharmacological effect the substances are suitable for the treatment of (a) **acute pain** such as for example toothache, peri- and postoperative pain, traumatic pain, muscle pain, the pain caused by burns, sunburn, trigeminal neuralgia, pain caused by colic, as well as spasms of the gastro-intestinal tract or uterus;

(b) **visceral pain** such as for example chronic pelvic pain, gynaecological pain, pain before and during menstruation, pain caused by pancreatitis, peptic ulcers, interstitial cystitis, renal colic, cholecystitis, prostatitis, angina pectoris, pain caused by irritable

bowel, non-ulcerative dyspepsia and gastritis, prostatitis, non-cardiac thoracic pain and pain caused by myocardial ischaemia and cardiac infarct;

(c) **neuropathic pain** such as for example painful neuropathies, pain of diabetic neuropathy, AIDS-associated neuropathic pain non-herpes-associated neuralgia, post-zoster neuralgia, nerve damage, cerebro-cranial trauma, pain of nerve damage caused by toxins or chemotherapy, phantom pain, pain of multiple sclerosis, nerve root tears and painful traumatically-caused damage to individual nerves, and central pain such as for example pain after stroke, spinal injuries or tumours;

d) **inflammatory / pain receptor-mediated pain** in connection with diseases such as for example osteoarthritis, rheumatoid arthritis, rheumatic fever, tendo-synovitis, bursitis, tendonitis, gout and gout-arthritis, traumatic arthritis, vulvodynia, damage to and diseases of the muscles and fascia, juvenile arthritis, spondylitis, psoriasis-arthritis, myositides, dental disease, influenza and other viral infections such as colds, systemic lupus erythematodes or pain caused by burns,

(e) **tumour pain** associated with cancers such asfe lymphatic or myeloid leukaemia, Hodgkin's disease, non-Hodgkin's lymphomas, lymphogranulomatosis, lymphosarcomas, solid malignant tumours and extensive metastases;

(f) **headache diseases** of various origins, such as for example cluster headaches, migraine (with or without aura) and tension headaches.

(g) painful conditions of mixed origin, such as for example chronic back pain including lumbago, or fibromyalgia.

The compounds are also suitable for treating

(h) inflammatory complaints or phenomena caused by sunburn and burns, inflammation of the gums, oedema after burns trauma, cerebral oedema and angiooedema, intestinal complaints including Crohn's disease and ulcerative colitis, irritable bowel syndrome, pancreatitis, nephritis, cystitis (interstitial cystitis), uveitis; inflammatory skin diseases (such as psoriasis and eczema), vascular diseases of the connective tissue, sprains and fracture, and musculoskeletal diseases with inflammatory symptoms such as acute

rheumatic fever, polymyalgia rheumatica, reactive arthritis, rheumatoid arthritis, spondylarthritis, and also osteoarthritis, and inflammation of the connective tissue of other origins, and collagenoses of all origins such as systemic lupus erythematodes, scleroderma, polymyositis, dermatomyositis, Sjögren syndrome, Still's disease or Felty syndrome;

(i) inflammatory changes connected with diseases of the airways such as bronchial asthma, including allergic asthma (atopic and non-atopic) as well as bronchospasm on exertion, occupationally induced asthma, viral or bacterial exacerbation of an existing asthma and other non-allergically induced asthmatic diseases;

(j) chronic bronchitis and chronic obstructive pulmonary disease (COPD) including pulmonary emphysema, viral or bacterial exacerbation of chronic bronchitis or chronic obstructive bronchitis, acute adult respiratory distress syndrome (ARDS), bronchitis, lung inflammation, allergic rhinitis (seasonal and all year round) vasomotor rhinitis and diseases caused by dust in the lungs such as aluminosis, anthracosis, asbestosis, chalicosis, siderosis, silicosis, tabacosis and byssinosis, exogenous allergic alveolitis, cystic fibrosis, bronchiectasis, pulmonary diseases in alpha1-antitrypsin deficiency and cough;

(k) diabetes mellitus and its effects (such as e.g. diabetic vasculopathy, diabetic neuropathy, diabetic retinopathy) and diabetic symptoms in insulitis (for example hyperglycaemia, diuresis, proteinuria and increased renal excretion of nitrite and kallikrein);

(l) sepsis and septic shock after bacterial infections or after trauma;

(m) syndromes that cause itching and allergic skin reactions;

(n) damage to the central nervous system;

(o) wounds and tissue damage;

(p) benign prostatic hyperplasia and hyperactive bladder;

(q) neurodegenerative diseases such as Parkinson´s disease and Alzheimer's disease;

(m) osteoporosis;

epilepsy;

(q) vascular diseases such as panarteriitis nodosa, polyarthritis nodosa, periarteriitis nodosa, arteriitis temporalis, Wegner's granulomatosis, giant cell arteriitis, arteriosclerosis and erythema nodosum;

inflammation of the gums;

(r) disorders of the motility or spasms of respiratory, genito-urinary, gastro-intestinal including biliary or vascular structures and organs;

(s) post-operative fever;

(t) for the treatment and prevention of cardiovascular diseases such as high blood pressure and related complaints;

(u) for the treatment and prevention of cancer and related complaints;

(v) for the treatment and prevention of psychiatric diseases such as depression;

(w) for the treatment and prevention of urinary incontinence and related complaints;

(x) for the treatment and prevention of morbid obesity and related complaints;

(y) for the treatment and prevention of atherosclerosis and related complaints.

(z) for the treatment and prevention of epilepsy.

The substances are suitable for causal treatment in the sense of slowing down or stopping the progress of chronically progressive diseases, particularly osteoarthritis, rheumatoid arthritis and spondylarthritis.

In another aspect the present invention encompasses the use of the compounds of the above-mentioned general formula **I** according to the invention for preparing a medicament for therapeutic use in the above-mentioned indications.

Preferably, the compounds of general formula I according to the invention are used for the treatment of osteoarthritis, rheumatoid arthritis or COPD.

The term "treatment" or "therapy" refers to a therapeutic treatment of patients with a manifest, acute or chronic indication, including on the one hand symptomatic (palliative) treatment to relieve the symptoms of the disease and on the other hand causal or curative treatment of the indication with the aim of ending the pathological condition, reducing the severity of the pathological condition or delaying the progression of the pathological condition, depending on the nature or gravity of the indication.

The present invention further relates to the use of a compound of general formula **I** for preparing a medicament for the acute and prophylactic treatment of acute pain, visceral pain, neuropathic pain, inflammatory / pain receptor-mediated pain, tumour pain, headache pain and pain of mixed causes and other diseases as mentioned above. This

use is characterised in that it comprises administering an effective amount of a compound of general formula I or a physiologically acceptable salt thereof to a patient requiring such treatment.

The term "patient" preferably refers to a human being.

In addition to their suitability as therapeutic drugs for humans, these substances are also useful in the veterinary medical treatment of domestic pets, exotic animals and farmed animals.

COMBINATIONS

For treating pain, it may be advantageous to combine the compounds according to the invention with stimulating substances such as caffeine or other pain-alleviating active compounds. If active compounds suitable for treating the cause of the pain are available, these can be combined with the compounds according to the invention.

The following compounds may be used for combination therapy, for example:

Non-steroidal antirheumatics (NSAR) such as for example propionic acid derivatives which may be selected from among alminoprofen bucloxic acid, carprofen, fenoprofen, ibuprofen, ketoprofen, naproxen, oxaprozin, pirprofen, pranoprofen and tiaprofenic acid; acetic acid derivatives which may be selected from among indomethacin, acemetacin, alclofenac, isoxepac, sulindac and tolmetin; fenamic derivatives which may be selected from among meclofenamic acid, mefenamic acid and tolfenamic acid; biphenyl-carboxylic acid derivatives; oxicams which may be selected from among meloxicam, piroxicam and tenoxicam; salicylic acid derivatives which may be selected from among acetylsalicylic and sulphasalazine; pyrazolones which may be selected from among apazone and feprazone; and coxibs which may be selected from among celecoxib and etoricoxib).

Opiate receptor agonists which may for example be selected from among morphine, Darvon, tramadol and buprenorphine;

Cannabinoid agonists such as for example GW-1000;

Sodium channel blockers which may for example be selected from among carbamazepine, mexiletin, pregabalin, tectin and ralfinamide.

N-type calcium channel blockers such as for example ziconotide.

Serotonergic and noradrenergic modulators which may be selected from among for example duloxetine and amitriptyline.

Corticosteroids which may be selected from among for example betamethasone, budesonide, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone and triamcinolone.

Histamine H1-receptor antagonists which may for example be selected from among bromopheniramine, chloropheniramine, dexchloropheniramine, triprolidine, clemastine, diphenhydramine, diphenylpyraline, tripelennamine, hydroxyzine, methdilazine, promethazine, trimeprazine azatadine, cyproheptadine, antazoline, pheniramine, pyrilamine, loratadine, cetirizine, desloratadine, fexofenadine and levocetirizine.

Leukotriene antagonists and 5-lipoxygenase inhibitors which may for example be selected from among zafirlukast, montelukast, pranlukast and zileuton.

Local anaesthetics which may for example be selected from among ambroxol and lidocaine.

TRVP1 antagonists which may for example be selected from among AZD-1386, JTS-653 and PHE-377.

Nicotine receptor agonists such as for example A-366833.

P2X3-receptor antagonists such as e.g. A-317491.

anti-NGF antibodies and NGF antagonists which may for example be selected from among JNJ-42160443 and PPH 207.

NK1 and NK2 antagonists such as e.g. CP-728663.

NMDA antagonists which may for example be selected from among CNS-5161, AZ-756 and V-3381.

Potassium channel modulators such as e.g. CL-888.

GABA modulators such as e.g. baclofen.

Anti-migraine drugs such as e.g. sumatriptan, zolmitriptan, naratriptan and eletriptan.

For treating one or more of the above-mentioned respiratory complaints it may be advantageous to combine the compounds of general formula I according to the invention with other active substances for treating respiratory complaints. If suitable active substances for treating the cause of the respiratory complaints are available, these may be combined with the compounds according to the invention.

The compounds of general formula I may optionally also be used in conjunction with other pharmacologically active substances. It is preferable to use active substances of the type selected from among the betamimetics, anticholinergics, corticosteroids, other PDE4-inhibitors, LTD4-receptor (CysLT1, CysLT2, CysLT3) antagonists, inhibitors of MAP kinases such as for example p38, ERK1, ERK2, JNK1, JNK2, JNK3 or SAP, LTB4-receptor (BLT1, BLT2) antagonists, EGFR-inhibitors, H1-receptor antagonists, antihistamines, H4-receptor antagonists, PAF-antagonists and PI3-kinase inhibitors CXCR1 and/or CXCR2 receptor antagonists and anti-tussives.

The compounds of general formula I may also be used in the form of double or triple combinations thereof, such as for example combinations of compounds of formula I 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 which are mentioned in WO 2006/120176, and SYK-inhibitors (spleen tyrosine kinase inhibitors),
- anticholinergics, betamimetics, corticosteroids, PDE4-inhibitors and MRP4-inhibitors.

Combinations of three active substances of one of the above mentioned categories of compounds are also covered by the invention.

Betamimetics used according to the invention are preferably compounds selected from among arformoterol, carmoterol, formoterol, indacaterol, salmeterol, albuterole, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, fenoterol, hexoprenalin, ibuterol, isoetharin, isoprenalin, levosalbutamol, mabuterol, meluadrin, metaproterenol, milveterol, orciprenalin, pirbuterol, procaterol, reproterol, rimiterol, ritodrin, salmefamol, soterenol, sulphonterol, terbutalin, tiaramid, tolubuterol and zinterol or

- 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one,
- 8-{2-[2-(2,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one,
- 8-{2-[2-(3,5-difluoro-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,
- 8-{2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one,
- N-(5-{2-[3-(4.4-diethyl-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulphonamide,
- N-(5-{2-[3-(4,4-diethyl-6-fluoro-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulphonamide,

- N-(5-{2-[3-(4,4-diethyl-6-methoxy-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulphonamide,
- N-(5-{2-[1,1-dimethyl-3-(2-oxo-4,4-dipropyl-4H-benzo[d][1,3]oxazin-1-yl)-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulphonamide,
- 8-{2-[1,1-dimethyl-3-(2-oxo-2,3-dihydro-benzimidazol-1-yl)-propylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one,
- 8-{2-[1,1-dimethyl-3-(6-methyl-2-oxo-2,3-dihydro-benzimidazol-1-yl)-propylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one,
- 8-{2-[1,1-dimethyl-3-(2-oxo-5-trifluoromethyl-2,3-dihydro-benzimidazol-1-yl)-propylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one,
- 8-{2-[1,1-dimethyl-3-(3-methyl-2-oxo-2,3-dihydro-benzimidazol-1-yl)-propylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one,
- N-[2-hydroxy-5-((1R)-1-hydroxy-2-{2-[4-(2-hydroxy-2-phenyl-ethylamino)-phenyl]-ethylamino}-ethyl)-phenyl]-formamide,
- 8-hydroxy-5-((1R)-1-hydroxy-2-{2-[4-(6-methoxy-biphenyl-3-ylamino)-phenyl]-ethylamino}-ethyl)-1H-quinolin-2-one,
- 8-hydroxy-5-[(1R)-1-hydroxy-2-(6-phenethylamino-hexylamino)-ethyl]-1H-quinolin-2-one,
- 5-[(1R)-2-(2-{4-[4-(2-amino-2-methyl-propoxy)-phenylamino]-phenyl}-ethylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one,
- [3-(4-{6-[(2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-5-methyl-phenyl]-urea,
- 4-((1R)-2-{6-[2-(2,6-dichloro-benzyloxy)-ethoxy]-hexylamino}-1-hydroxy-ethyl)-2-hydroxymethyl-phenol,
- 3-(4-{6-[(2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-hexyloxy}-butyl)-benzenesulphonamide,
- 3-(3-{7-[(2R)-2-hydroxy-2-(4-hydroxy-3-hydroxymethyl-phenyl)-ethylamino]-heptyloxy}-propyl)-benzenesulphonamide,
- 4-((1R)-2-{6-[4-(3-cyclopentanesulphonyl-phenyl)-butoxy]-hexylamino}-1-hydroxy-ethyl)-2-hydroxymethyl-phenol,
- *N*-1-Adamantanyl-2-{3-[(2R)-2-({(2R)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)-phenyl]ethyl}amino)propyl]phenyl}acetamide,

- (1R)-5-{2-[6-(2.2-difluoro-2-phenyl-ethoxy)-hexylamino]-1-hydroxy-ethyl}-8-hydroxy-1H-quinolin-2-one
- (R,S)-4-(2-{[6-(2.2-difluoro-4-phenylbutoxy)hexyl]amino}-1-hydroxy-ethyl)-2-(hydroxyl-methyl)phenol,
- (R,S)-4-(2-{[6-(2.2-difluoro-2-phenylethoxy)hexyl]amino}-1-hydroxy-ethyl)-2-(hydroxyl-methyl)phenol,
- (R,S)-4-(2-{[4,4-difluoro-6-(4-phenylbutoxy)hexyl]amino}-1-hydroxy-ethyl)-2-(hydroxyl-methyl)phenol,
- (R,S)-4-(2-{[6-(4,4-difluoro-4-phenylbutoxy)hexyl]amino}-1-hydroxy-ethyl)-2-(hydroxyl-methyl)phenol,
- (R,S)-5-(2-{[6-(2.2-difluoro-2-phenylethoxy)hexyl]amino}-1-hydroxy-ethyl)-8-hydroxyquinolin-2(1H)-one,
- (R,S)-[2-({6-[2.2-difluoro-2-(3-methylphenyl)ethoxy]hexyl}amino)-1- hydroxyethyl]-2-(hydroxymethyl)phenol,
- 4-(1R)-2-{[6-(2.2-difluoro-2-phenylethoxy)hexyl]amino}-1-hydroxyethyl)-2-(hydroxyl-methyl)phenol,
- (R,S)-2-(hydroxymethyl)-4-(1-hydroxy-2-{[4.4.5I5-tetrafluoro-6-(3-phenylpropoxy)-hexyl]amino}ethyl)phenol,
- (R,S)-[5-(2-{[6-(2.2-difluoro-2-phenylethoxy)hexyl]amino}-1-hydroxy-ethyl)-2-hydroxy-phenyl]formamide,
- (R,S)-4-[2-({6-[2-(3-bromophenyl)-2.2-difluoroethoxy]hexyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol,
- (R, S)-N-[3-(1.1 -difluoro-2-{[6-({2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]-ethyl}amino)hexyl]oxy}ethyl)phenyl]-urea,
- 3-[3-(1,1-difluoro-2-{[6-({2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl) phenyl]ethyl}-amino)hexyl]oxy}ethyl)phenyl]imidazolidin-2,4-dione,
- (R,S)-4-[2-({6-[2.2-difluoro-2-(3-methoxyphenyl)ethoxy]hexyl}amino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol,
- 5-((1R)-2-{[6-(2.2-difluoro-2-phenylethoxy)hexyl]amino}-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one,
- 4-((1R)-2-{[4,4-difluoro-6-(4-phenylbutoxy)hexyl]amino}-1-hydroxy-ethyl)-2-(hydroxyl-methyl)phenol,

- (R,S)-4-(2-{[6-(3.3-difluoro-3-phenylpropoxy)hexyl]amino}-1-hydroxy-ethyl)-2-(hydroxylmethyl)phenol,
- (R,S)-(2-{[6-(2.2-difluoro-2-phenylethoxy)-4,4-difluorohexyl]amino}-1-hydroxyethyl)-2-(hydroxymethyl)phenol,
- (R,S)-4-(2-{[6-(2.2-difluoro-3-phenylpropoxy)hexyl]amino}-1-hydroxyethyl)-2-(hydroxyl-methyl)phenol,
- 3-[2-(3-chloro-phenyl)-ethoxy]-N-(2-diethylamino-ethyl)-N-{2-[2-(4-hydroxy-2-oxo-2,3-dihydro-benzothiazole-7-yl)-ethylamino]-ethyl}-propionamide,
- N-(2-diethylamino-ethyl)-N-{2-[2-(4-hydroxy-2-oxo-2,3-dihydro-benzothiazole-7-yl)-ethylamino]-ethyl}-3-(2-naphthalen-1-yl-ethoxy)-propionamide,
- 7-[2-(2-{3-[2-(2-chloro-phenyl)-ethylamino]-propylsulphanyl}-ethylamino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one,

optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. Preferably, according to the invention, the acid addition salts of the betamimetics are selected from among hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

Anticholinergics used according to the invention are preferably compounds selected from among the tiotropium salts, preferably the bromide salt, oxitropium salts, preferably the bromide salt, flutropium salts, preferably the bromide salt, Ipratropiumsalzen, preferably the bromide salt, aclidinium salts, preferably the bromide salt, glycopyrronium salts, preferably the bromide salt, trospium salts, preferably the chloride salt, tolterodine, (3R)-1-phenethyl-3-(9H-xanthene-9-carbonyloxy)-1-azoniabicyclo[2,2,2]octane salts. In the above-mentioned salts the cations are the pharmacologically active constituents. As anions X^- 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 the chloride, bromide, iodide, sulphate, methanesulphonate or p-toluenesulphonate are preferred as counter-ions. Of all the salts the chlorides, bromides, iodides and methanesulphonates are particularly preferred.

Other anticholinergics may be selected from among

- 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,
- cyclopropyltropin 9-methyl-xanthene-9- carboxylate methobromide,
- cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide,
- cyclopropyltropine methyl 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, and
- scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide.

The above-mentioned compounds may also be used as salts within the scope of the present invention, wherein the metho-X salts are used instead of the methobromide, where X may have the meanings given for X^- hereinbefore.

Corticosteroids used according to the invention are preferably compounds selected from among beclomethasone betamethasone, budesonide, butixocort, ciclesonide, deflazacort, dexamethasone, etiprednol, flunisolide, fluticasone, loteprednol, mometasone, prednisolone, prednisone, rofleponide, triamcinolone and tipredane orpregna-1,4-dien-3,20-dione, 6-fluoro-11-hydroxy-16.17-[(1-methylethyliden)-bis(oxy)]-21-[[4-[(nitroxy)methyl]benzoyl]oxy], (6-alpha,11-beta,16-alpha)-(9Cl) (NCX-1024)

- 16,17-butylidenedioxy-6,9-difluoro-11-hydroxy-17-(methylthio)androst-4-en-3-one (RPR-106541),
- (S)-fluoromethyl 6,9-difluoro-17-[(2-furanylcarbonyl)oxy]-11-hydroxy-16-methyl-3-oxo-androsta-1,4-diene-17-carbothionate,
- (S)-(2-oxo-tetrahydrofuran-3S-yl) 6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-propionyloxy-androsta-1,4-diene-17-carbothionate, and
- cyanomethyl 6-alpha,9-alpha-difluoro-11-beta-hydroxy-16alpha-methyl-3-oxo-17alpha-(2,2,3,3-tetramethylcyclopropylcarbonyl)oxy-androsta-1,4-diene-17beta-carboxylate,

optionally in the form of their racemates, enantiomers or diastereomers and optionally in the form of the salts and derivatives thereof, the solvates and/or hydrates thereof. Every 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, sulphobenzoates, phosphates, isonicotinates, acetates, dichloroacetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.

PDE4-inhibitors used according to the invention are preferably compounds selected from among enprofyllin, theophyllin, roflumilast, ariflo (cilomilast), tofimilast, pumafentrin, lirimilast, apremilast, arofyllin, atizoram, oglemilast and tetomilast or

- 5-[(N-(2,5-dichloro-3-pyridinyl)-carboxamid]-8-methoxy-quinoline (D-4418),
- N-(3,5-dichloro-1-oxido-4-pyridinyl)-carboxamid]-8-methoxy-2-(trifluoromethyl)-quinoline (D-4396 (Sch-351591)),N-(3,5-dichloropyrid-4-yl)-[1-(4-fluorobenzyl)-5-

hydroxy-indol-3-yl]glyoxylamide (AWD-12-281 (GW-842470)), 9-[(2-fluorophenyl)methyl]-N-methyl-2-(trifluoromethyl)-9H-purin-6-amine (NCS-613),

- 4-[(2R)-2-[3-(cyclopentyloxy)-4-methoxyphenyl]-2-phenylethyl]-pyridine (CDP-840),
- N-[(3R)-3,4,6,7-tetrahydro-9-methyl-4-oxo-1-phenylpyrrolo[3,2,1-jk][1,4]benzodiazepin-3-yl]-4-pyridinecarboxamide (PD-168787),
- 4-[6,7-diethoxy-2,3-bis(hydroxymethyl)-1-naphthalenyl]-1-(2-methoxyethyl)-2(1H)-pyridinone (T-440),
- 2-[4-[6,7-diethoxy-2,3-bis(hydroxymethyl)-1-naphthalenyl]-2-pyridinyl]-4-(3-pyridinyl)-1(2H)-phthalazinone (T-2585),
- (3-(3-cyclopenyloxy-4-methoxybenzyl)-6-ethylamino-8-isopropyl-3H-purine (V-11294A),
- beta-[3-(cyclopentyloxy)-4-methoxyphenyl]-1,3-dihydro-1,3-dioxo-2H-isoindole-2-propanamide (CDC-801),
- imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one, 9-ethyl-2-methoxy-7-methyl-5-propyl- (D-22888)
- 5-[3-(cyclopentyloxy)-4-methoxyphenyl]-3-[(3-methylphenyl)methyl], (3S,5S)-2-piperidinone (HT-0712),
- 4-[1-[3,4-bis(difluoromethoxy)phenyl]-2-(3-methyl-1-oxido-4-pyridinyl)ethyl]-alpha,alpha-bis(trifluoromethyl)-benzenemethanol (L-826141),
- N-(3,5-dichloro-1-oxo-pyridin-4-yl)-4-difluoromethoxy-3-cyclopropylmethoxybenzamide,
- (-)p-[(4*a*R*,10*b*S*)-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)-cyclohexan-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)-9*H*-pyrazolo[3,4-c]-1,2,4-triazolo-[4.3-a]pyridine and
- 9-cyclopentyl-5,6-dihydro-7-ethyl-3-(*tert*-butyl)-9*H*-pyrazolo[3,4-c]-1,2,4-triazolo-[4.3-a]pyridine,

optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. Preferably, according to the invention, acid addition salts are selected from among hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

EGFR-inhibitors used according to the invention are preferably compounds selected from among cetuximab, trastuzumab, panitumumab (= ABX-EGF), Mab ICR-62, gefitinib, canertinib and erlotinib or

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

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

- 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,
- 4-[(3-chloro-4-fluorophenyl)amino]-6-({4-[N,N-bis-(2-methoxy-ethyl)-amino]-1-oxo-2-buten-1-yl}amino)-7-[(tetrahydrofuran-2-yl)methoxy]-quinazoline,
- 4-[(3-ethynyl-phenyl)amino]-6-{[4-(5,5-dimethyl-2-oxo-morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-7-[(R)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-(2,2-dimethyl-6-oxo-morpholin-4-yl)-ethoxy]-6-[(S)-(tetrahydrofuran-2-yl)methoxy]-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{2-[4-(2-oxo-morpholin-4-yl)-piperidin-1-yl]-ethoxy}-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[1-(*tert*-butyloxycarbonyl)-piperidin-4-yloxy]-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-amino-cyclohexane-1-yloxy)-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methanesulphonylamino-cyclohexane-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]-cyclohexane-1-yloxy}-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)carbonylamino]-cyclohexane-1-yloxy}-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{trans-4-[(morpholin-4-yl)sulphonylamino]-cyclohexane-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}-cyclohexane-1-yloxy)-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexane-1-yloxy)-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-{N-[(morpholin-4-yl)sulphonyl]-N-methyl-amino}-cyclohexane-1-yloxy)-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-ethansulphonylamino-cyclohexane-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-cyclohexane-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}-cyclohexane-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}-cyclohexane-1-yloxy)-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[(morpholin-4-yl)carbonylamino]-cyclohexane-1-yloxy}-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[2-(2-oxopyrrolidin-1-yl)ethyl]-piperidin-4-yloxy}-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{1-[(morpholin-4-yl)carbonyl]-piperidin-4-yloxy}-7-(2-methoxy-ethoxy)-quinazoline,
- 4-[(3-ethynyl-phenyl)amino]-6-(1-acetyl-piperidin-4-yloxy)-7-methoxy-quinazoline,
- 4-[(3-ethynyl-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7-methoxy-quinazoline,
- 4-[(3-ethynyl-phenyl)amino]-6-(1-methanesulphonyl-piperidin-4-yloxy)-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-methyl-piperidin-4-yloxy)-7(2-methoxy-ethoxy)-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(1-isopropyloxycarbonyl-piperidin-4-yloxy)-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(cis-4-methylamino-cyclohexane-1-yloxy)-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-{cis-4-[N-(2-methoxy-acetyl)-N-methyl-amino]-cyclohexane-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)-cyclohexane-1-yloxy]-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[cis-4-(N-acetyl-N-methyl-amino)-cyclohexane-1-yloxy]-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-methylamino-cyclohexane-1-yloxy)-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-[trans-4-(N-methanesulphonyl-N-methyl-amino)-cyclohexane-1-yloxy]-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-dimethylamino-cyclohexane-1-yloxy)-7-methoxy-quinazoline,
- 4-[(3-chloro-4-fluoro-phenyl)amino]-6-(trans-4-{N-[(morpholin-4-yl)carbonyl]-N-methyl-amino}-cyclohexane-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,

- 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-fluorophenyl)amino]-6-{[4-(homomorpholin-4-yl)-1-oxo-2-buten-1-yl]-amino}-7-[(S)-(tetrahydrofuran-3-yl)oxy]-quinazoline,
- 4-[(3-chloro-4-fluorophenyl)amino]-7-(2-{4-[(S)-(2-oxo-tetrahydrofuran-5-yl)carbonyl]-piperazin-1-yl}-ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline,
- 4-[(3-chloro-4-fluorophenyl)amino]-7-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- 4-[(3-chloro-4-fluorophenyl)amino]-7-[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline,
- 4-[(3-chloro-4-fluorophenyl)amino]-7-[4-((S)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, and
- 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[2-(ethoxycarbonyl)-ethyl]-N-[(ethoxy-carbonyl)methyl]amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline,

optionally in the form of their racemates, enantiomers or diastereomers, optionally in the form of the pharmacologically acceptable acid addition salts, solvates and/or hydrates thereof. Preferably, according to the invention, acid addition salts are selected from among hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

LTD4-receptor antagonists used according to the invention are preferably compounds selected from among montelukast, pranlukast and zafirlukast, or(E)-8-[2-[4-[4-(4-fluorophenyl)butoxy]phenyl]ethenyl]-2-(1H-tetrazol-5-yl)-4H-1-benzopyran-4-one (MEN-91507),

- 4-[6-acetyl-3-[3-(4-acetyl-3-hydroxy-2-propylphenylthio)propoxy]-2-propylphenoxy]-butyric acid (MN-001),
- 1-(((R)-(3-(2-(6,7-difluoro-2-quinolinyl)ethenyl)phenyl)-3-(2-(2-hydroxy-2-propyl)phenyl)thio)methylcyclopropane-acetic acid,
- 1-(((1(R)-3(3-(2-(2,3-dichlorothieno[3,2-b]pyridin-5-yl)-(E)-ethenyl)phenyl)-3-(2-(1-hydroxy-1-methylethyl)phenyl)propyl)thio)methyl)cyclopropaneacetic acid and

- [2-[[2-(4-*tert*-butyl-2-thiazolyl)-5-benzofuranyl]oxymethyl]phenyl]acetic acid,

optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. Preferably, according to the invention, acid addition salts are selected from among hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate. By salts or derivatives which the LTD4-receptor antagonists may optionally be capable of forming are meant, for example: alkali metal salts, such as for example sodium or potassium salts, alkaline earth salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates.

Histamine H1 receptor antagonists used according to the invention are preferably compounds selected from among epinastin, cetirizin, azelastin, fexofenadin, levocabastin, loratadin, mizolastin, ketotifen, emedastin, dimetinden, clemastin, bamipin, cexchlorpheniramin, pheniramin, doxylamine, chlorophenoxamin, dimenhydrinat, diphenhydramin, promethazin, ebastin, olopatadine, desloratidin and meclozin, optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. Preferably, according to the invention, the acid addition salts are selected from among hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate.

Histamine H4 receptor antagonists used according to the invention are preferably compounds such as for example (5-chloro-1H-indol-2-yl)-(4-methyl-1-piperazinyl)-methanone (JNJ-7777120), optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, solvates or hydrates thereof. Preferably, according to the invention, acid addition salts selected from among hydrochloride, hydrobromide, hydriodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate,

hydrocitrate, hydrofumarate, hydrotartrate, hydroxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate are used.

MAP Kinase inhibitors used according to the invention are preferably compounds selected from among:

- Bentamapimod (AS-602801)
- Doramapimod,
- 5-carbamoylindole (SD-169),
- 6-[(aminocarbonyl)(2,6-difluorophenyl)amino]-2-(2,4-difluorophenyl)-3-pyridinecarboxamide (VX-702),
- alpha-[2-[[2-(3-pyridinyl)ethyl]amino]-4-pyrimidinyl]-2-benzothiazoleacetonitrile (AS-601245),
- 9,12-epoxy-1H-diindolo[1,2,3-fg:3'.2'.1'-kl]pyrrolo[3,4-i][1.6]benzodiazocine-10-carboxylic acid (CEP-1347), and
- 4-[3-(4-chlorophenyl)-5-(1-methyl-4-piperidinyl)-1H-pyrazol-4-yl]-pyrimidine (SC-409),

optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, prodrugs, solvates or hydrates thereof.

Neurokinin (NK1 or NK2) antagonists used according to the invention are preferably compounds selected from among: Saredutant, Nepadutant and Figopitant, optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, prodrugs, solvates or hydrates thereof.

Antitussive substances used according to the invention are preferably compounds selected from among hydrocodone, caramiphen, carbetapentane and dextramethorphane, optionally in the form of their racemates, enantiomers, diastereomers and optionally in the form of the pharmacologically acceptable acid addition salts, prodrugs, solvates or hydrates thereof.

Substances of preferred **CXCR1 or CXCR2 antagonists** used according to the invention are preferably compounds such as e.g. 3-[[3-[(dimethylamino)carbonyl]-2-

hydroxyphenyl]amino]-4-[[(R)-1-(5-methylfuran-2-yl)propyl]amino]cyclobut-3-ene-1,2-dione (SCH-527123),
optionally in the form of its racemates, enantiomers, diastereomers and optionally in the form of its pharmacologically acceptable acid addition salts, prodrugs, solvates or hydrates.

The dosage necessary for obtaining a pain-alleviating effect is, in the case of intravenous administration, expediently from 0.01 to 3 mg/kg of body weight, preferably from 0.1 to 1 mg/kg, and, in the case of oral administration, from 0.1 to 8 mg/kg of body weight, preferably from 0.5 to 3 mg/kg, in each case 1 to 3 times per day. The compounds prepared according to the invention can be administered intravenously, subcutaneously, intramuscularly, intrarectally, intranasally, by inhalation, transdermally or orally, aerosol formulations being particularly suitable for inhalation. They can be incorporated into customary pharmaceutical preparations, such as tablets, coated tablets, capsules, powders, suspensions, solutions, metered-dose aerosols or suppositories, if appropriate together with one or more customary inert carriers and/or diluents, for example with maize starch, lactose, cane sugar, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethylene glycol, propylene glycol, cetylstearyl alcohol, carboxymethylcellulose or fatty substances, such as hardened fat, or suitable mixtures thereof.

EXPERIMENTAL SECTION

Generally, there are mass spectra and ^{1}H NMR spectra for the compounds that have been prepared. The ratios given for the eluants are in volume units of the solvents in question. For ammonia, the given volume units are based on a concentrated solution of ammonia in water.

Unless indicated otherwise, the acid, base and salt solutions used for working up the reaction solutions are aqueous systems having the stated concentrations.

For chromatographic purification, silica gel from Millipore (MATREX^{TM}, 35 to 70 µm) or Alox (E. Merck, Darmstadt, Alumina 90 standardized, 63 to 200 µm, article No.

1.01097.9050) is used.

In the descriptions of the experiments, the following abbreviations are used:

TLC	thin layer chromatograph
DIPEA	diisopropylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulphoxide
HATU	*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate
RP	reverse phase
R_t	retention time
tert	tertiary
TBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate
TEA	triethylamine
THF	tetrahydrofuran

The following analytical HPLC methods were used:

Method 1: Column: Interchim Strategy C18, 5 µM, 4.6 x 50 mm
Detection: 220 – 320 nm
Eluant A: water / 0.1% acetic acid
Eluant B: acetonitrile
Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	3.0
0.3	95.0	5.0	3.0
2.0	2.0	98.0	3.0
2.4	2.0	98.0	3.0
2.45	95.0	5.0	3.0
2.8	95.0	5.0	3.0

Method 2: Column: Merck Cromolith Flash RP18e, 4.6 x 25 mm
Eluant A: water / 0.1% formic acid
Eluant B: acetonitrile / 0.1% formic acid
Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	90.0	10.0	1.6
2.7	10.0	90.0	1.6
3.0	10.0	90.0	1.6
3.3	90.0	10.0	1.6

Method 3: Column: YMC-Pack ODS-AQ, 3 µM, 4.6 x 75 mm
Eluant A: water / 0.15% formic acid
Eluant B: acetonitrile
Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
2.0	10.0	90.0	1.6
5.0	10.0	90.0	1.6
5.5	90.0	10.0	1.6

Method 4: Column: Zorbax Stable Bond C18, 1.8 µM, 3 x 30 mm
Eluant A: water / 0.15% formic acid
Eluant B: acetonitrile
Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
1.0	10.0	90.0	1.6
2.5	10.0	90.0	1.6
2.75	95.0	5.0	1.6

Method 5: Column: Sunfire C18, 3.5 µM, 4.6 x 50 mm
Detection: 180 – 820 nm
Eluant A: water / 0.1% trifluoroacetic acid

Eluant B: acetonitrile / 0.1% trifluoroacetic acid

Temperature: 40°C

Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.5
2.0	0.0	100.0	1.5
2.5	0.0	100.0	1.5
2.6	95.0	5.0	1.5

Method 6: Column: Sunfire C18, 3.5 µM, 4.6 x 50 mm

Detection: 180 – 820 nm

Eluant A: water / 0.1% trifluoroacetic acid

Eluant B: acetonitrile / 0.1% trifluoroacetic acid

Temperature: 40°C

Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.5
2.0	0.0	100.0	1.5
3.0	0.0	100.0	1.5
3.4	95.0	5.0	1.5

Method 7: Column: YMC-Pack ODS-AQ, 3 µM, 4.6 x 75 mm

Eluant A: water / 0.15% formic acid

Eluant B: acetonitrile

Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
4.5	10.0	90.0	1.6
5.0	10.0	90.0	1.6
5.50	90.0	10.0	1.6

Method 8: Column: Zorbax Stable Bond C18, 1.8 µM, 3 x 30 mm

Eluant A: water / 0.15% formic acid

Eluant B: acetonitrile

Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
2.00	50.0	50.0	1.6
2.25	10.0	90.0	1.6
2.50	10.0	90.0	1.6
2.75	95.0	5.0	1.6

Method 9: Column: Zorbax Stable Bond C18, 1.8 µM, 3 x 30 mm

Eluant A: water / 0.15% formic acid

Eluant B: acetonitrile

Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
2.25	10.0	90.0	1.6
2.50	10.0	90.0	1.6
2.75	95.0	5.0	1.6

Method 10: Column: Zorbax Stable Bond C18, 3.5 µM, 4.6 x 75 mm

Eluant A: water / 0.15% formic acid

Eluant B: acetonitrile

Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
4.5	10.0	90.0	1.6
5.0	10.0	90.0	1.6
5.50	90.0	10.0	1.6

Method 11: Column: X Terra C18, 3.5 µM, 4.6 x 50 mm

Detection: 180 – 820 nm

Eluant A: water / 0.1% trifluoroacetic acid

Eluant B: acetonitrile / 0.1% trifluoroacetic acid

Temperature: 40°C

Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.5
2.0	0.0	100.0	1.5
3.0	0.0	100.0	1.5
3.4	95.0	5.0	1.5

Method 12: Column: Merck Cromolith Flash RP18e, 4.6 x 25 mm

Eluant A: water / 0.1% formic acid

Eluant B: acetonitrile / 0.1% formic acid

Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	90.0	10.0	1.6
2.7	10.0	90.0	1.6
3.0	10.0	90.0	1.6
3.3	95.0	5.0	1.6

Method 13: Column: Merck Cromolith SpeedROD RP-18e, 4.6 x 50 mm

Eluant A: water / 0.1% formic acid

Eluant B: acetonitrile / 0.1% formic acid

Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	90.0	10.0	1.5
4.5	10.0	90.0	1.5
5.0	10.0	90.0	1.5
5.5	95.0	5.0	1.5

Method 14: Column: Zorbax Stable Bond C18, 3.5 µM, 4.6 x 75 mm

Eluant A: water / 0.15% formic acid

Eluant B: acetonitrile

Gradient:

time in min	%A	%B	flow rate in mL/min

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	1.6
2.0	10.0	90.0	1.6
5.0	10.0	90.0	1.6
5.5	90.0	10.0	1.6

The following preparative methods were used for the reversed-phase chromatography:

Method 1: Column: Atlantis C18, 5 µM, 100 x 30 mm
Detection: 210 – 500 nm
Eluant A: water / 0.1% trifluoroacetic acid
Eluant B: acetonitrile
Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	5
0.5	95.0	5.0	50
8.0	5.0	95.0	50
9.0	5.0	95.0	50
9.5	95.0	5.0	50
10.0	95.0	5.0	50
10.1	95.0	5.0	5

Method 2: Column: Varian Pursuit 5 µM, 50 x 200 mm
Eluant A: water / 0.1% trifluoroacetic acid
Eluant B: acetonitrile / 0.1% trifluoroacetic acid
Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	180
1.15	95.0	5.0	180
12.4	2.0	98.0	180
14.0	2.0	98.0	180
15.3	95.0	5.0	180

time in min	%A	%B	flow rate in mL/min
15.3	95.0	5.5	180

Method 3: Column: YMC-Pack ODS-AQ 5 µM, 30 x 100 mm

Eluant A: water / 0.15% formic acid

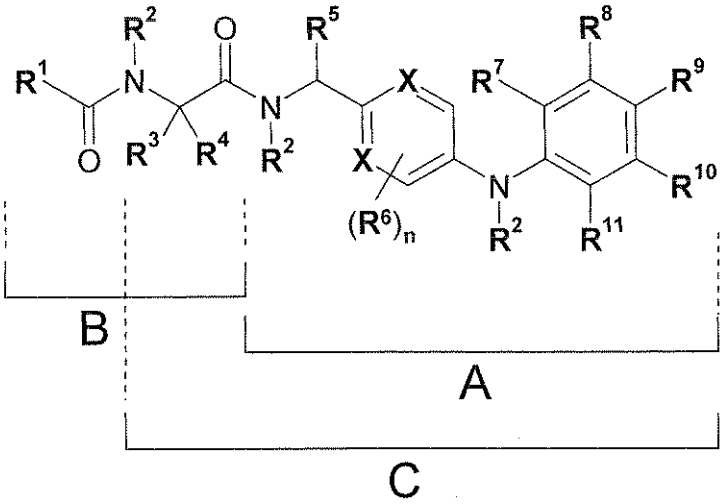
Eluant B: acetonitrile

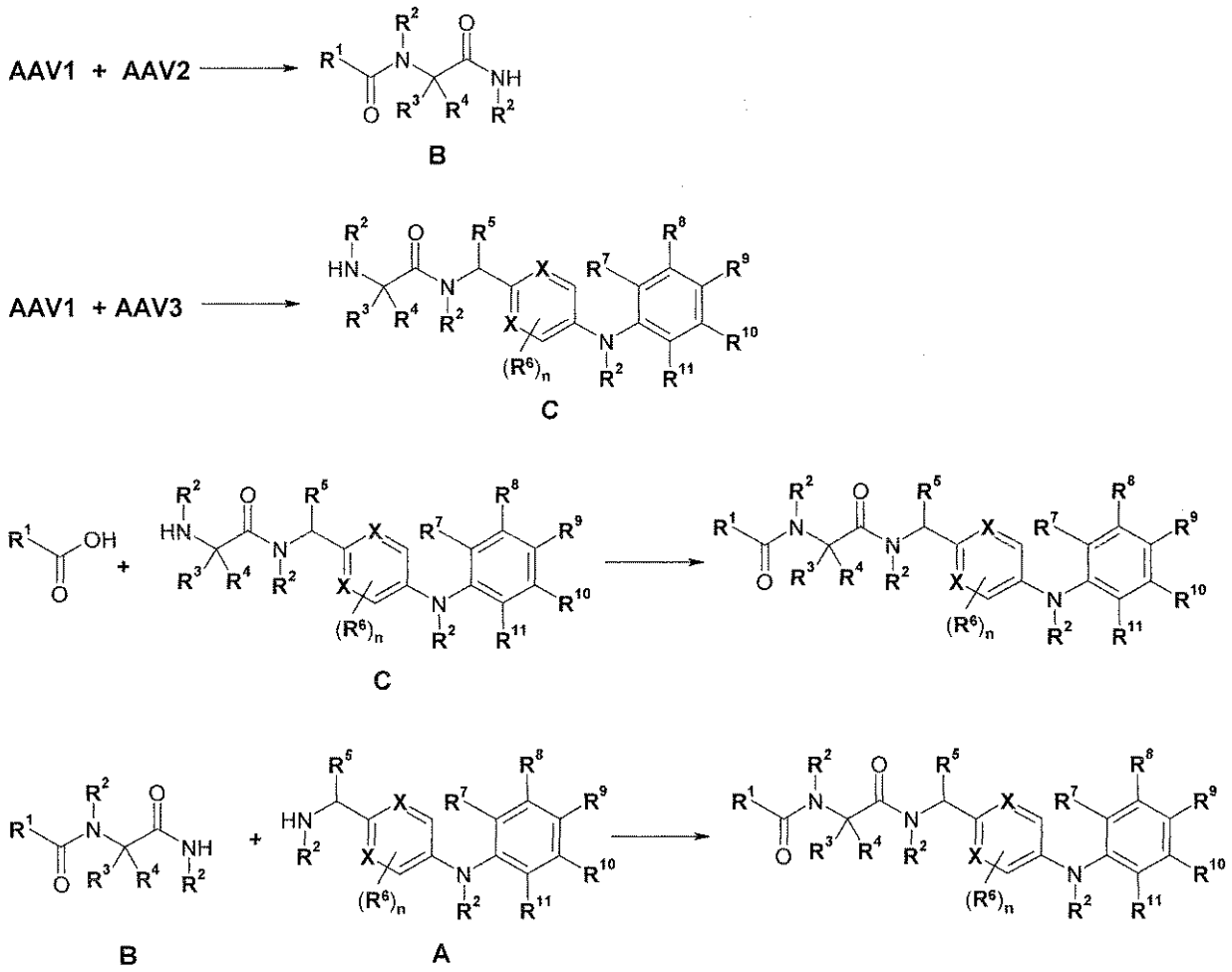
Gradient:

time in min	%A	%B	flow rate in mL/min
0.0	95.0	5.0	50
2.0	95.0	5.0	50
6.0	10.0	90.0	50
12.0	10.0	90.0	50
13	90.0	10.0	50

Preparation of the starting compounds:

The compounds of general formula **I** may be prepared from the following intermediates **A**, **B** and **C**:





AAV 1: amide coupling

A solution of the carboxylic acid component (1 mol-equivalent), triethylamine (2.5 mol-equivalents) and TBTU (1.1 mol-equivalents) in THF was stirred for 30 minutes at ambient temperature. Then the amine component (1.1 mol-equivalent as hydrochloride) was added and stirring was continued overnight. Then the mixture was evaporated down, mixed with water, made alkaline with dilute potassium carbonate solution and extracted with ethyl acetate. The product was isolated and purified by column chromatography (either silica gel or reversed phase chromatography).

AAV 2: Ester hydrolysis

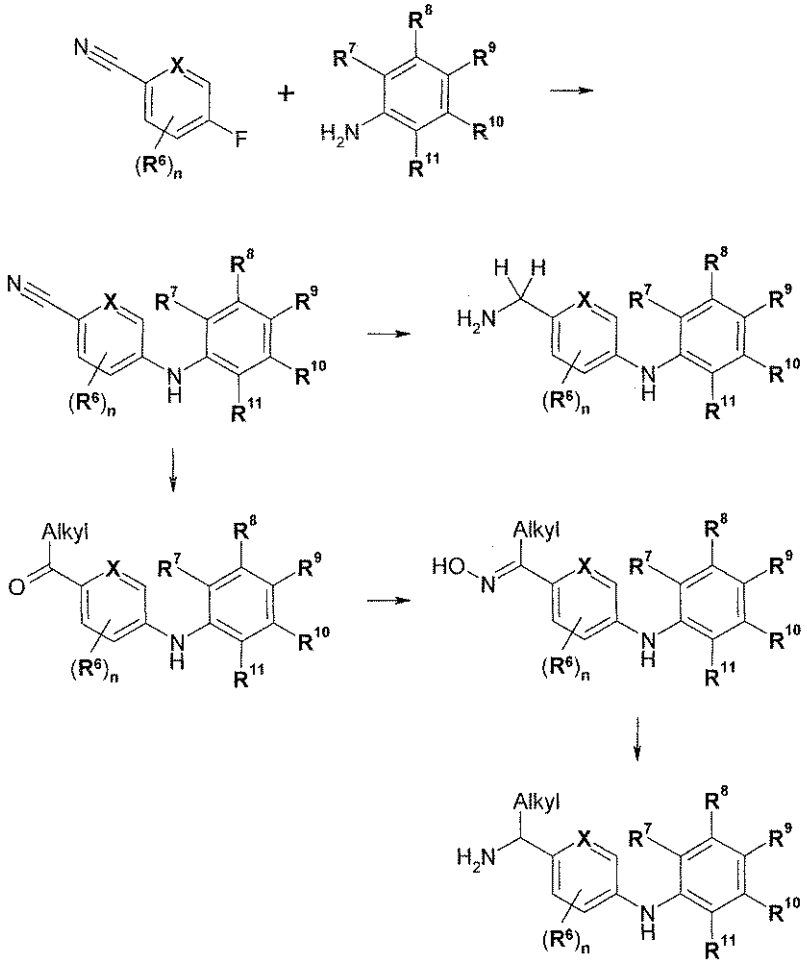
2N sodium hydroxide solution (2 mol-equivalents) was added to a solution of the ester (1 mol-equivalent) in methanol and the mixture was stirred for 1 to 5 hours at ambient temperature. Then it was acidified with acetic acid and the mixture was evaporated to

dryness in vacuo. The crude product thus obtained was purified in the normal way by column chromatography on silica gel.

AAV 3: Cleaving the *tert*-butyloxycarbonyl protective group

A solution of the *tert*-butoxycarbonyl-amino compound (1 mol-equivalent) in dichloromethane was combined with trifluoroacetic acid (3 to 10 mol-equivalents) and stirred at ambient temperature until the protective group had been cleaved completely. The reaction mixture was then evaporated to dryness and the crude product thus obtained was purified by chromatography.

AAV 4: Preparation of the intermediate A



A solution of the aniline component (1 mol-equivalent) and a strong base such as e.g. potassium-*tert*-butoxide (1 mol-equivalent) in DMSO was stirred for one hour at ambient

temperature, then combined with the 4-fluoro-benzonitrile component (1 mol-equivalent) and stirred overnight at approx. 80°C. For working up the mixture was filtered through Alox and evaporated to dryness in vacuo.

The nitrile group of the diphenylamine intermediate product thus obtained was then reduced to the aminomethyl group with the addition of Raney nickel at 55°C and 3 bar excess hydrogen pressure and the product obtained was purified by chromatography.

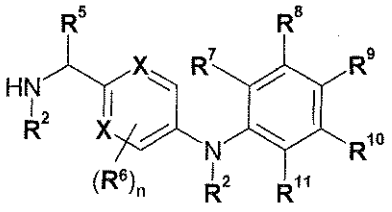
In order to prepare the intermediate **A** with an alpha-alkylbenzyl group (e.g. A1, A4, A5) the nitrile derivative (1 mol-equivalent) was dissolved in diethyl ether and at 0 to 5°C it was added with stirring to a solution of alkylmagnesium bromide (4 mol-equivalents) in diethyl ether and then stirred for another 30 minutes approx. The reaction mixture was then stirred into 1M hydrochloric acid at -5°C and the alkylketone thus obtained was isolated and purified by chromatography in the usual way.

A solution of the ketone thus obtained (1 mol-equivalent) in acetonitrile was combined with triethylamine (2 mol-equivalents) and hydroxylamine-hydrochloride (1.3 mol-equivalents) and refluxed for 4 hours. Then water was added and the mixture was extracted with dichloromethane. The resulting oxime was isolated from the organic phase and purified by conventional methods.

A solution of the oxime (1 mol-equivalent) in methanol was combined with methanolic hydrochloric acid (6.6 mol-equivalents). After the addition of zinc powder (1.4 mol-equivalents) the mixture was refluxed for 3 hours with stirring. After cooling the mixture was combined with water and extracted with dichloromethane. If necessary, the amine thus obtained was purified by chromatography.

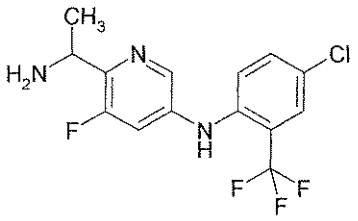
Another possible way of reducing the oxime to the corresponding amine is by catalytic hydrogenation. For this, the oxime was hydrogenated in methanolic ammonia solution after the addition of Raney nickel at 50°C and at an excess hydrogen pressure of 50 psi until the uptake of hydrogen had ended. If necessary, the amine thus obtained was purified by chromatography.

Preparation of the Intermediates A



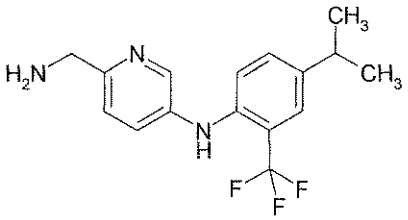
The following intermediates A1 to A31 were prepared according to general working method AAV4:

intermediate A1: [6-(1-amino-ethyl)-5-fluoro-pyridin-3-yl]-(4-chloro-2-trifluoromethyl-phenyl)-amine



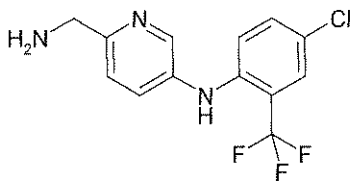
HPLC: R_t = 1.98 minutes (method 2)
Mass spectrum (ESI): [M+H]+ = 334

intermediate A2: (6-aminomethyl-pyridin-3-yl)-(4-isopropyl-2-trifluoromethyl-phenyl)-amine



HPLC: R_t = 1.95 minutes (method 2)
Mass spectrum (ESI): [M+H]+ = 310

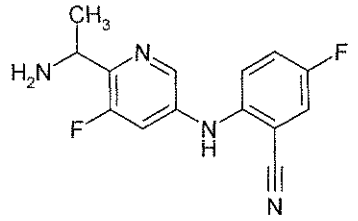
intermediate A3: (6-aminomethyl-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine



HPLC: R_t = 1.74 minutes (method 13)

Mass spectrum (ESI): [M+H]+ = 302

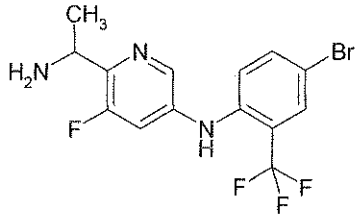
intermediate A4: 2-[6-(1-amino-ethyl)-5-fluoro-pyridin-3-ylamino]-5-fluoro-benzonitrile



HPLC: R_t = 1.39 minutes (method 2)

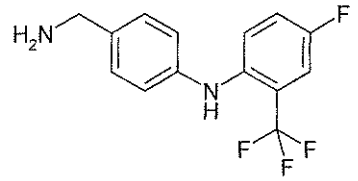
Mass spectrum (ESI): [M+H]+ = 275; [M-H]- = 273

intermediate A5: [6-(1-amino-ethyl)-5-fluoro-pyridin-3-yl]-(4-bromo-2-trifluoromethyl-phenyl)-amine



HPLC: R_t = 1.92 minutes (method 2)

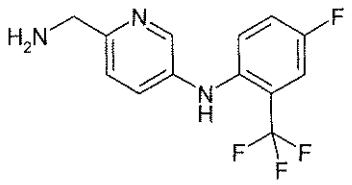
intermediate A6: (4-aminomethyl-phenyl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine



Mass spectrum (ESI): [M+H]+ = 285

thin layer chromatogram (silica gel, CH_2Cl_2/ethanol 19:1): R_f = 0.16

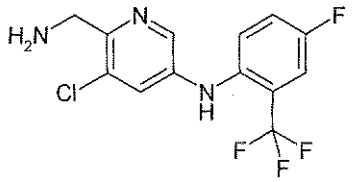
intermediate A7: (6-aminomethyl-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine



HPLC: R_t = 2.06 minutes (method 3)

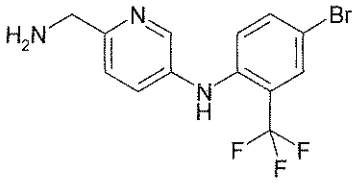
Mass spectrum (ESI): [M+H]+ = 286; [M-H]- = 284

intermediate A8: (6-aminomethyl-5-chloro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine



Mass spectrum (ESI): [M+H]+ = 320; [M-H]- = 320

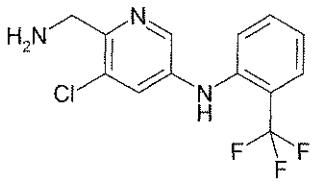
intermediate A9: (6-aminomethyl-pyridin-3-yl)-(4-bromo-2-trifluoromethyl-phenyl)-amine



HPLC: R_t = 1.97 minutes (method 2)

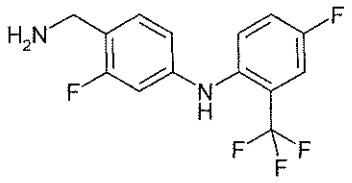
Mass spectrum (ESI): [M+H]+ = 346

intermediate A10: (6-aminomethyl-5-chloro-pyridin-3-yl)-(2-trifluoromethyl-phenyl)-amine



thin layer chromatogram (silica gel, CH_2Cl_2/ethanol/NH_4OH 9:1:0.1): R_f = 0.52

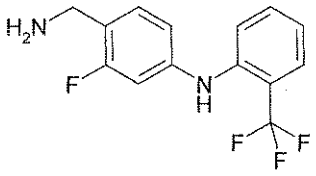
intermediate A11: (4-aminomethyl-3-fluoro-phenyl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine



Mass spectrum (ESI): [M+H]+ = 303

thin layer chromatogram (silica gel, CH_2Cl_2/ethanol 19:1): R_f = 0.08

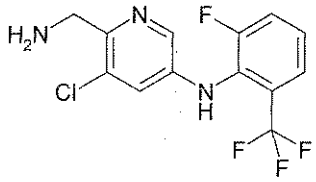
intermediate A12: (4-aminomethyl-3-fluoro-phenyl)-(2-trifluoromethyl-phenyl)-amine



Mass spectrum (ESI): [M-H]- = 283

thin layer chromatogram (silica gel, CH_2Cl_2/ethanol 19:1): R_f = 0.09

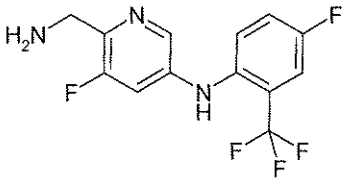
intermediate A13: (6-aminomethyl-5-chloro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine



Mass spectrum (ESI): [M+H]+ = 320

thin layer chromatogram (silica gel, CH_2Cl_2/ethanol/NH_4OH 9:1:0.1): R_f = 0.58

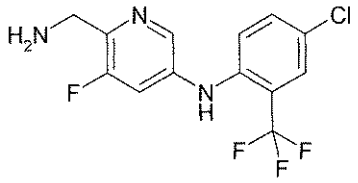
intermediate A14: (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine



Mass spectrum (ESI): [M+H]+ = 304

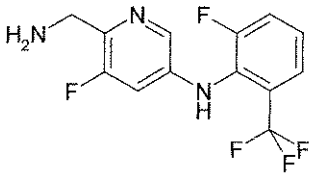
thin layer chromatogram (silica gel, CH_2Cl_2/ethanol/NH_4OH 9:1:0.1): R_f = 0.56

intermediate A15: (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine



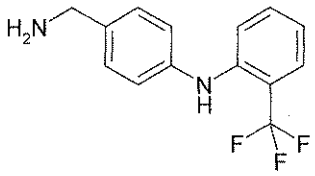
Mass spectrum (ESI): [M+H]+ = 320; [M-H]- = 318

intermediate A16: (6-aminomethyl-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine



HPLC: R_t = 1.44 minutes (method 2)

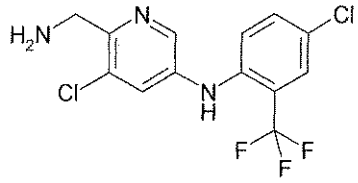
intermediate A17: (4-aminomethyl-phenyl)-(2-trifluoromethyl-phenyl)-amine



HPLC: R_t = 1.36 minutes (method 1)

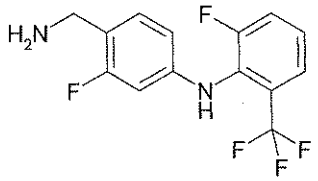
Mass spectrum (ESI): [M+H-NH_3]+ = 250

intermediate A18: (6-aminomethyl-5-chloro-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine



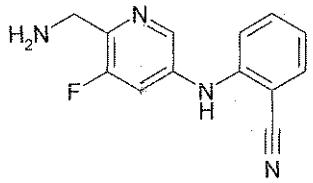
HPLC: R_t = 2.05 minutes (method 2)

intermediate A19: (4-aminomethyl-3-fluoro-phenyl)-(6-fluoro-2-trifluoromethyl-phenyl)-amine



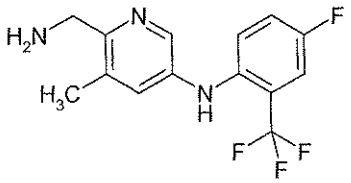
thin layer chromatogram (silica gel, CH_2Cl_2/ethanol 9:1): R_f = 0.18

intermediate A20: 2-(6-aminomethyl-5-fluoro-pyridin-3-ylamino)-benzonitrile



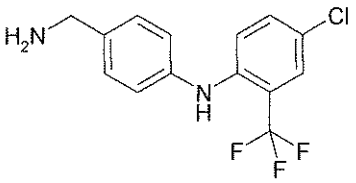
HPLC: R_t = 1.14 minutes (method 2)
Mass spectrum (ESI): [M+H]+ = 243

intermediate A21: (6-aminomethyl-5-methyl-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine



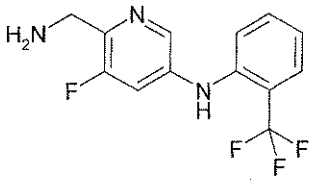
HPLC: R_t = 1.79 minutes (method 2)
Mass spectrum (ESI): [M+H]+ = 300

intermediate A22: (4-aminomethyl-phenyl)-(4-chloro-2-trifluoromethyl-phenyl)-amine



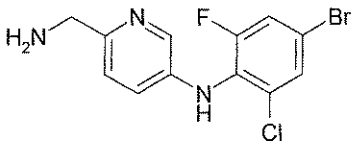
Mass spectrum (ESI): [M+H-NH_3]+ = 284/286

intermediate A23: (6-aminomethyl-5-fluoro-pyridin-3-yl)-(2-trifluoromethyl-phenyl)-amine



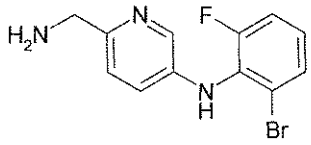
Mass spectrum (ESI): [M+H]+ = 286

intermediate A24: (6-aminomethyl-pyridin-3-yl)-(4-bromo-2-chloro-6-fluorophenyl)-amine



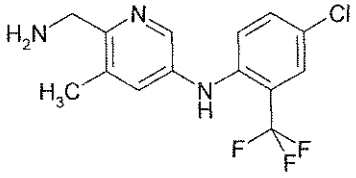
HPLC: R_t = 1.87 minutes (method 2)
Mass spectrum (ESI): [M+H]+ = 330

intermediate A25: (6-aminomethyl-pyridin-3-yl)-(2-bromo-6-fluoro-phenyl)-amine



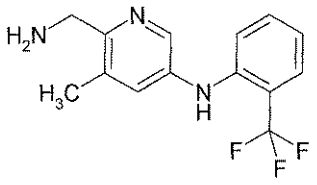
HPLC: R_t = 2.18 minutes (method 2)
Mass spectrum (ESI): [M+H]+ = 296

intermediate A26: (6-aminomethyl-5-methyl-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine



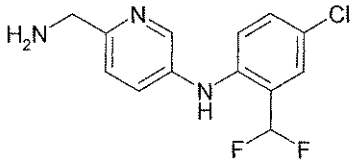
HPLC: R_t = 2.33 minutes (method 2)

intermediate A27: (6-aminomethyl-5-methyl-pyridin-3-yl)-(2-trifluoromethyl-phenyl)-amine



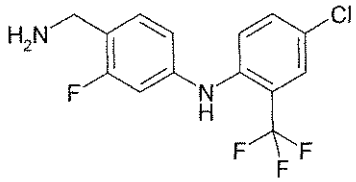
Mass spectrum (ESI): [M+H]+ = 282

intermediate A28: (6-aminomethyl-pyridin-3-yl)-(4-chloro-2-difluoromethyl-phenyl)-amine



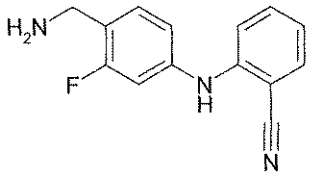
HPLC: R_t = 1.66 minutes (method 2)
Mass spectrum (ESI): [M+H]+ = 284

intermediate A29: (4-aminomethyl-3-fluoro-phenyl)-(4-chloro-2-trifluoromethyl-phenyl)-amine



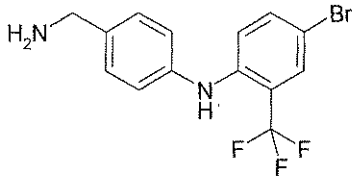
HPLC: R_t = 1.83 minutes (method 2)

intermediate A30: 2-(4-aminomethyl-3-fluoro-phenylamino)-benzonitrile



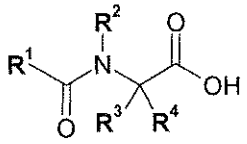
HPLC: R_t = 1.38 minutes (method 2)

intermediate A31: (4-aminomethyl-phenyl)-(4-bromo-2-trifluoromethyl-phenyl)-amine



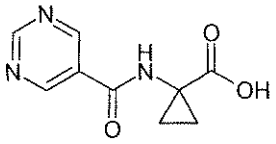
HPLC: R_t = 1.81 minutes (method 2)

Preparation of the Intermediates B



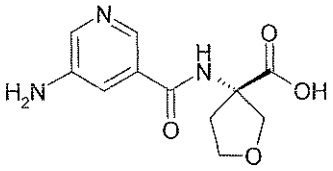
The following Intermediates B1 to B11 were prepared by amide coupling according to general working method AAV1 and subsequent ester saponification according to general working method AAV2:

intermediate B1: 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid



Mass spectrum (ESI): [M+H]+ = 208; [M-H]- = 206

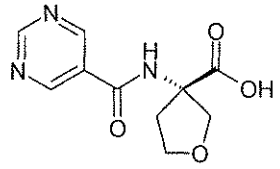
intermediate B2: (*S*)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid



HPLC: R_t = 0.85 minutes (method 7)

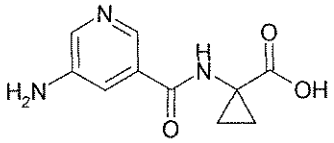
Mass spectrum (ESI): [M+H]+ = 252

intermediate B3: (*S*)-3-[(pyrimidine-5-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid



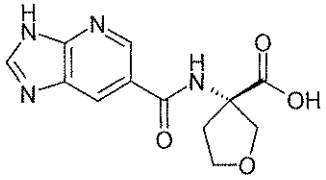
Mass spectrum (ESI): [M+H]+ = 238; [M-H]- = 236

intermediate B4: 1-[(5-amino-pyridine-3-carbonyl)-amino]-cyclopropanecarboxylic acid



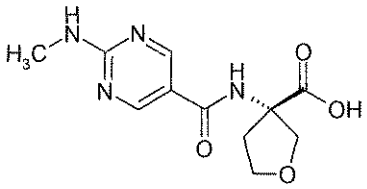
Mass spectrum (ESI): [M+H]+ = 222

intermediate B5: (*S*)-3-[(3H-imidazo[4,5-b]pyridin-6-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid



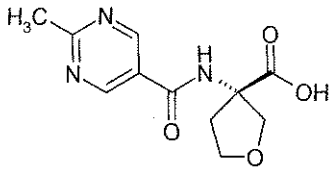
HPLC: R_t = 1.49 minutes (method 3)
Mass spectrum (ESI): [M-H]- = 275

intermediate B6: (*S*)-3-[(2-methylamino-pyrimidine-5-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid



HPLC: R_t = 0.47 minutes (method 2)
Mass spectrum (ESI): [M+H]+ = 267

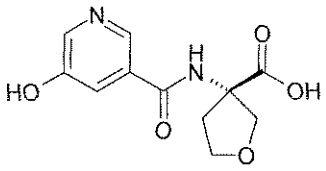
intermediate B7: (*S*)-3-[(2-methyl-pyrimidine-5-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid



HPLC: R_t = 0.43 minutes (method 2)

Mass spectrum (ESI): [M+H]+ = 252; [M-H]- = 250

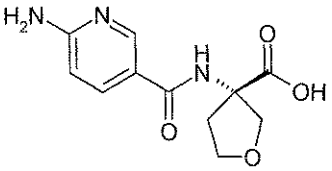
intermediate B8: (*S*)-3-[(5-hydroxy-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid



HPLC: R_t = 0.48 minutes (method 2)

Mass spectrum (ESI): [M+H]+ = 253

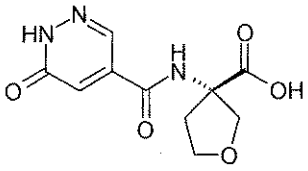
intermediate B9: (*S*)-3-[(6-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid



HPLC: R_t = 0.33 minutes (method 2)

Mass spectrum (ESI): [M+H]+ = 252; [M-H]- = 250

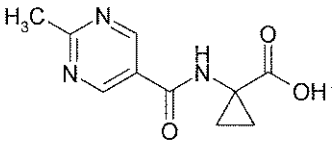
intermediate B10: (*S*)-3-[(6-oxo-1,6-dihydro-pyridazine-4-carbonyl)-amino]-tetrahydro-furan-3-carboxylic acid



HPLC: R_t = 0.33 minutes (method 2)

Mass spectrum (ESI): [M+H]+ = 254

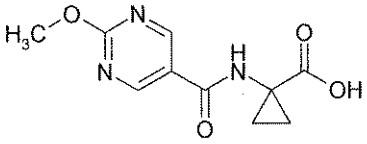
intermediate B11: 1-[(2-methyl-pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid



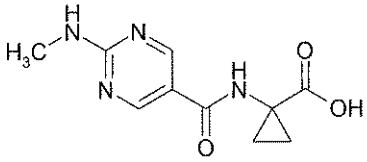
Mass spectrum (ESI): [M+H]+ = 222; [M-H]- = 220

The following Intermediates B12 to B15 may be prepared analogously :

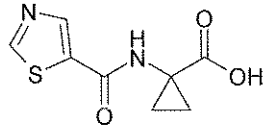
Intermediate B12:



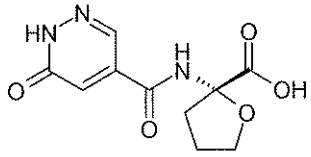
intermediate B13:



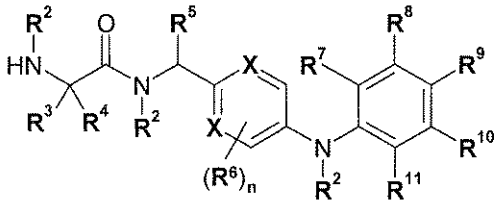
intermediate B14:



intermediate B15:

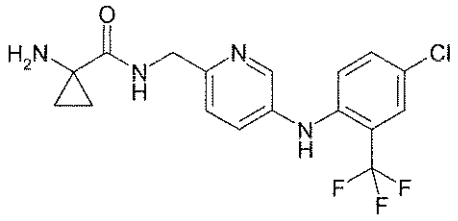


Preparation of the intermediates C



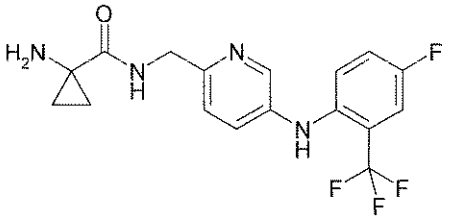
The following Intermediates C1 to C22 were prepared by amide coupling according to general working method AAV1 and subsequent cleaving of the *tert*-butyloxycarbonyl-protective group according to general working method AAV3:

intermediate C1: 1-amino-cyclopropanecarboxylic acid-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



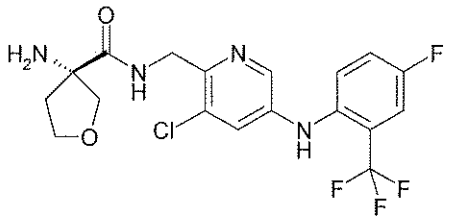
HPLC: R_t = 1.55 minutes (method 13)
Mass spectrum (ESI): [M-H]- = 383

intermediate C2: 1-amino-cyclopropanecarboxylic acid-[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



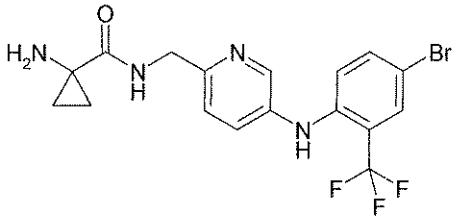
HPLC: R_t = 2.33 minutes (method 7)
Mass spectrum (ESI): [M+H]+ = 369; [M-H]- = 367

intermediate C3: (*S*)-3-amino-tetrahydrofuran-3-carboxylic acid-[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



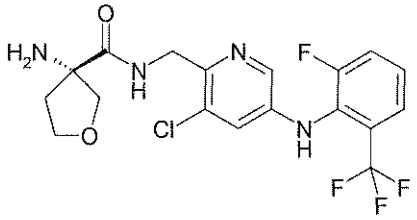
Mass spectrum (ESI): [M+H]+ = 433

intermediate C4: 1-amino-cyclopropanecarboxylic acid-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



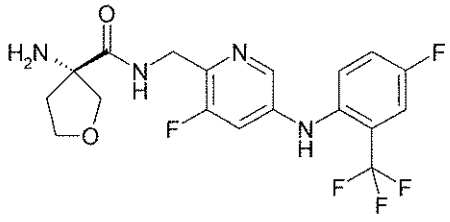
HPLC: R_t = 1.65 minutes (method 2)
Mass spectrum (ESI): [M+H]+ = 429

intermediate C5: (*S*)-3-amino-tetrahydrofuran-3-carboxylic acid-[3-chloro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



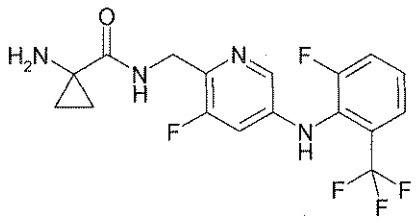
Mass spectrum (ESI): [M+H]+ = 433

intermediate C6: (*S*)-3-amino-tetrahydrofuran-3-carboxylic acid-[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



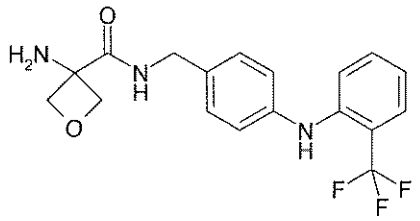
Mass spectrum (ESI): [M+H]+ = 417

intermediate C7: 1-amino-cyclopropanecarboxylic acid-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



HPLC: R_t = 1.50 minutes (method 2)

intermediate C8: 3-amino-oxetan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



(a) 3-dibenzylamino-oxetan-3-carbonitrile

A solution of 3-oxetanone (908 mg, 12.6 mmol), dibenzylamine (6.08 mL, 31.6 mmol) and trimethylsilylcyanide (2.00 mL, 15.8 mmol) in 20 mL concentrated acetic acid was stirred overnight at 60°C. After cooling it was adjusted to pH 10 with concentrated ammonia and the solution was extracted with chloroform. After evaporation, the crude product was obtained, which was purified by chromatography through silica gel.

$C_{18}H_{18}N_2O$ (278.35)

Mass spectrum (ESI): [M+H]+ = 279

(b) 3-dibenzylamino-oxetan-3-carboxylic acid

A solution of 3-dibenzylamino-oxetan-3-carbonitrile (370 mg, 1.33 mmol) and 5 mL 4M sodium hydroxide solution in 20 mL ethanol was refluxed overnight, then neutralised with 1M hydrochloric acid neutralisiert and evaporated to dryness. The crude product thus obtained was purified by chromatography.

$C_{18}H_{19}NO_3$ (297.35)

Mass spectrum (ESI): [M+H]+ = 298

(c) 3-dibenzylamino-oxetan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

Prepared from 3-dibenzylamino-oxetan-3-carboxylic acid and 4-(2-trifluoromethyl-phenylamino)-benzylamine by amide coupling according to general working method AAV1.

$C_{32}H_{30}F_3N_3O_2$ (545.59)

Mass spectrum (ESI): [M+H]+ = 546

(d) 3-amino-oxetan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide

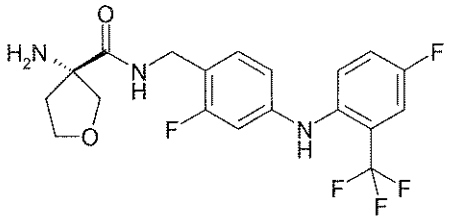
3-dibenzylamino-oxetan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide (32.0 mg, 0.059 mmol) was dissolved in 10 mL methanol, combined with 20 mg Pd/charcoal (10%) and debenzylated at ambient temperature under 3 bar hydrogen pressure.

$C_{18}H_{18}F_3N_3O_2$ (365.35)

HPLC: R_t = 1.93 minutes (method 5)

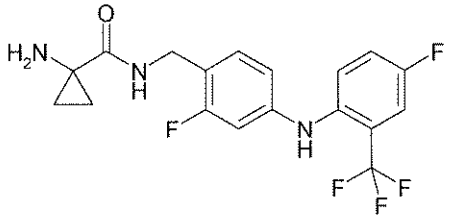
Mass spectrum (ESI): [M+H]+ = 366

intermediate C9: (*S*)-3-amino-tetrahydrofuran-3-carboxlic acid-2-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylamide



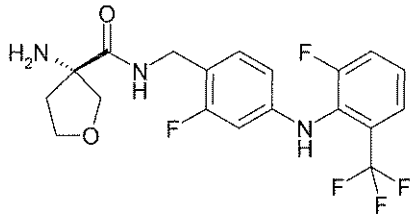
Mass spectrum (ESI): [M+H]+ = 416

intermediate C10: 1-amino-cyclopropanecarboxylic acid-2-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylamide



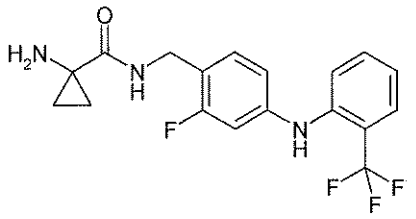
Mass spectrum (ESI): [M+H]+ = 386

intermediate C11: (*S*)-3-amino-tetrahydrofuran-3-carboxylic acid-2-fluoro-4-(2-fluoro-6-trifluoromethyl-phenylamino)-benzylamide



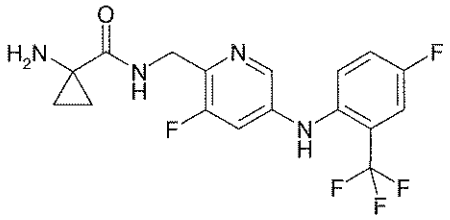
Mass spectrum (ESI): [M+H]+ = 416

intermediate C12: 1-amino-cyclopropanecarboxylic acid-2-fluoro-4-(2-trifluoromethyl-phenylamino)-benzylamide



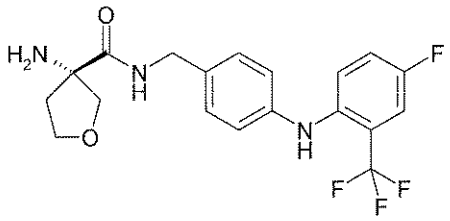
Mass spectrum (ESI): [M+H]+ = 368

intermediate C13: 1-amino-cyclopropanecarboxylic acid-[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



Mass spectrum (ESI): [M+H]+ = 387

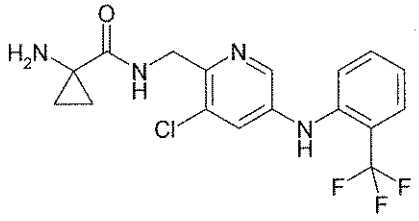
intermediate C14: (*S*)-3-amino-tetrahydrofuran-3-carboxylic acid-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylamide



HPLC: R_t = 1.99 minutes (method 2)

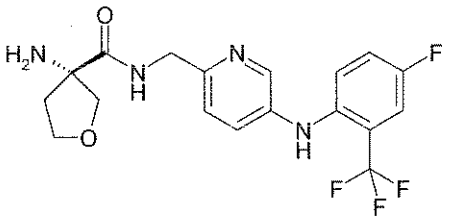
Mass spectrum (ESI): [M+H]+ = 398

intermediate C15: 1-amino-cyclopropanecarboxylic acid-[3-chloro-5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



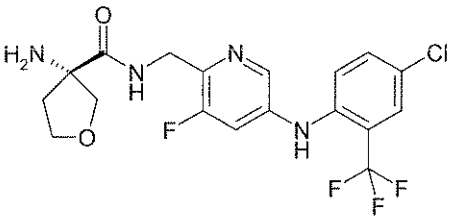
Mass spectrum (ESI): [M+H]+ = 385

intermediate C16: (*S*)-3-amino-tetrahydrofuran-3-carboxylic acid-[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



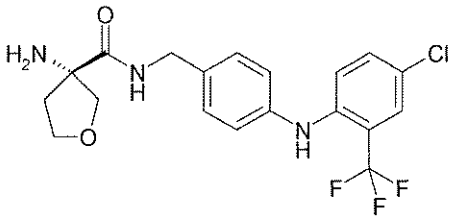
HPLC: R_t = 1.34 minutes (method 2)
Mass spectrum (ESI): [M+H]+ = 399

intermediate C17: (*S*)-3-amino-tetrahydrofuran-3-carboxylic acid-[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-amide



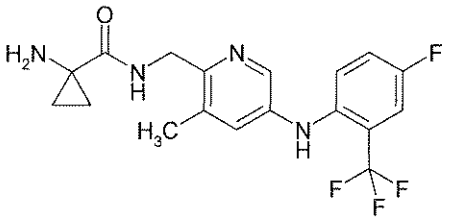
HPLC: R_t = 2.35 minutes (method 2)

intermediate C18: (*S*)-3-amino-tetrahydrofuran-3-carboxylic acid-4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylamide



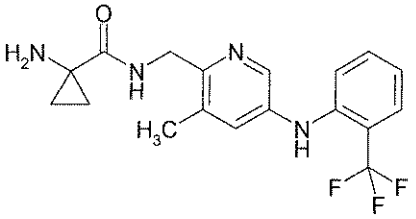
HPLC: R_t = 2.41 minutes (method 2)

intermediate C19: 1-amino-cyclopropanecarboxylic acid-[5-(4-fluoro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-amide



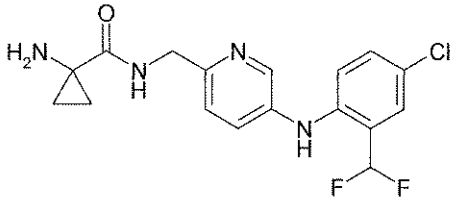
HPLC: R_t = 1.24 minutes (method 2)
Mass spectrum (ESI): [M+H]+ = 383

intermediate C20: 1-amino-cyclopropanecarboxylic acid-[3-methyl-5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



HPLC: R_t = 1.30 minutes (method 2)
Mass spectrum (ESI): [M+H]+ = 365

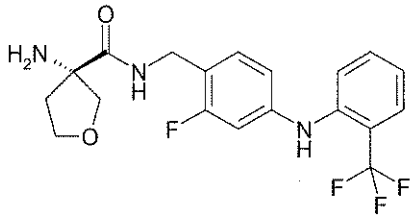
intermediate C21: 1-amino-cyclopropanecarboxylic acid-[5-(4-chloro-2-difluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



HPLC: R_t = 1.48 minutes (method 2)

Mass spectrum (ESI): [M+H]+ = 367

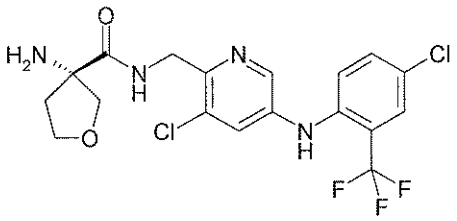
intermediate C22: (*S*)-3-amino-tetrahydrofuran-3-carboxylic acid 2-fluoro-4-(2-trifluoromethyl-phenylamino)-benzylamide



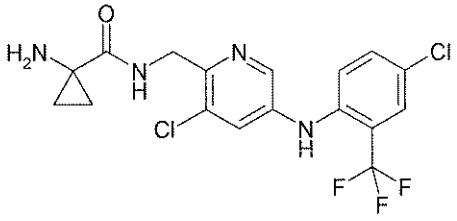
Mass spectrum (ESI): [M+H]+ = 398

The following intermediates C23 to C25 may be prepared analogously:

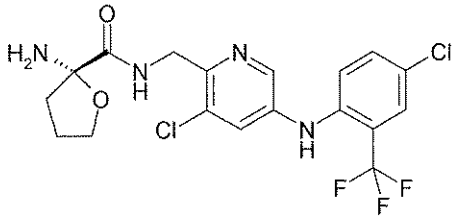
intermediate C23:



intermediate C24:

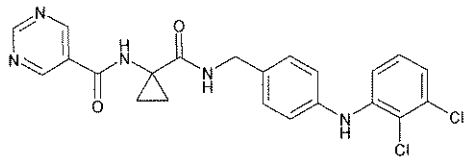


intermediate C25:



Preparation of the End Compounds:

Example 1: Pyrimidine-5-carboxylic acid N-(1-(4-(2,3-dichlorophenylamino)benzyl-carbamoyl)cyclopropyl)amide



1a) ethyl 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylate

A solution of 15.74 g (126.9 mmol) pyrimidine-5-carboxylic acid, 43.57 mL (312.6 mmol) triethylamine and 44.61 g (138.9 mmol) TBTU in 460 mL THF was stirred for 30 minutes at ambient temperature. Then 9.11 g (127.3 mmol) ethyl 1-amino-cyclopropane-carboxylate hydrochloride were added and the mixture was stirred further overnight. Then the mixture was evaporated down and the residue was combined with 200 mL water, made alkaline with dilute potassium carbonate solution and extracted with ethyl acetate. The intermediate product was purified by column chromatography (silica gel, dichloromethane + 0-4% methanol).

Yield:	95% of theory
$C_{11}H_{13}N_3O_3$	(235.24)
R_t= 1.23 min.	method 1

1b) 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid

28.39 mL of a 2N sodium hydroxide solution were added to a solution of 13.36 g (56.79 mmol) ethyl 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylate in 240 mL methanol and the mixture was stirred for one hour at ambient temperature. Then it was acidified with concentrated acetic acid and evaporated to dryness in vacuo. The crude product thus obtained was purified by column chromatography (silica gel, dichloromethane + 5-30% 10% acetic acid in methanol).

Yield:	100% of theory
$C_9H_9N_3O_3$	(207.19)
R_t= 1.23 min.	method 1

1c) N-(4-aminomethyl)phenyl)-2,3-dichloraniline-trifluoroacetate

A solution of 32 mg (0.2 mmol) 2,3-dichloroaniline and 22 mg (0.2 mmol) potassium-tert-butoxide in 9 mL DMSO was stirred for one hour at ambient temperature, then combined with 24 mg (0.2 mmol) 4-fluorobenzonitrile and stirred further overnight at 80°C. For working up the reaction mixture was filtered through Alox B, washed with DMF and evaporated to dryness in vacuo. The residue was hydrogenated in 100 µL methanolic ammonia solution with 20 mg Raney nickel as catalyst at 55°C under a hydrogen pressure of 3 bar for 5 hours. Then the catalyst was filtered off, the filtrate was freed from the solvent and the crude product was purified by HPLC (method 1).

Yield: 47% of theory

$C_{13}H_{12}Cl_2N_2$ (267.15)

1d) pyrimidine-5-carboxylic acid N-(1-(4-(2,3-dichlorophenylamino)benzylcarbamoyl)-cyclopropyl)amide

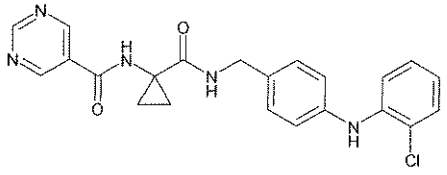
0.5 mL (3.6 mmol) triethylamine, 433 mg (1.35 mmol) TBTU and 326 mg (1.2 mmol) N-(4-aminomethyl)phenyl)-2,3-dichloroaniline-trifluoroacetate (from 1c) were added to a solution of 250 mg (1.2 mmol) 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b) in 15 mL tetrahydrofuran. The mixture was stirred overnight at ambient temperature, then evaporated to dryness and purified by HPLC (method 1).

Yield: 16% of theory

$C_{22}H_{19}Cl_2N_5O_3$ (456.32)

R_t= 2.1 min. method 5

Example 2: pyrimidine-5-carboxylic acid-N-(1-(4-(2-chlorophenylamino)benzylcarbamoyl)cyclopropyl)amide



2a) N-(4-(aminomethyl)phenyl)-2-chloroaniline

Analogously to method (1c) the title compound was prepared starting from 2-chloroaniline, 4-fluorobenzonitrile and Raney nickel.

$C_{13}H_9ClN_2$ (228.68)

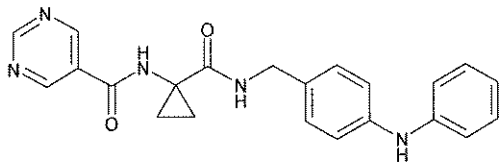
2b) pyrimidine-5-carboxylic acid-N-(1-(4-(2-chlorophenylamino)benzylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared starting from N-(4-(aminomethyl)phenyl)-2-chloroaniline (from 2a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{22}H_{20}ClN_5O_2$ (421.88)

R_t= 2.13 min. method 6

Example 3: pyrimidine-5-carboxylic acid- N-(1-(4-(phenylamino)benzylcarbamoyl)cyclopropyl)amide



3a) 4-(aminomethyl)-N-phenylaniline

Analogously to method (1c) the title compound was prepared starting from aniline, 4-fluorobenzonitrile and Raney nickel.

$C_{13}H_{14}N_2$ (199.26)

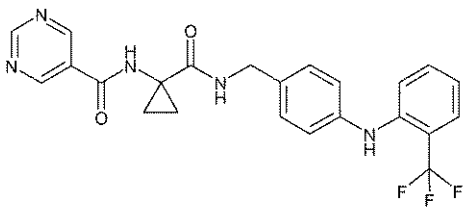
3b) pyrimidine-5-carboxylic acid- N-(1-(4-(phenylamino)benzylcarbamoyl)cyclopropyl)-amide

Analogously to method (1d) the title compound was prepared starting from 4-(aminomethyl)-N-phenylaniline (from 3a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{22}H_{20}ClN_5O_2$ (421.88)

R_t= 1.82 min. method 5

Example 4: pyrimidine-5-carboxylic acid- N-(1-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)cyclopropyl)amide



4a) N-(4-(aminomethyl)phenyl)-2-(trifluoromethyl)aniline

Analogously to method (1c) the title compound was prepared starting from 2-(trifluoromethyl)aniline, 4-fluorobenzonitrile and Raney nickel.

$C_{14}H_{13}F_3N_2$ (266.26)

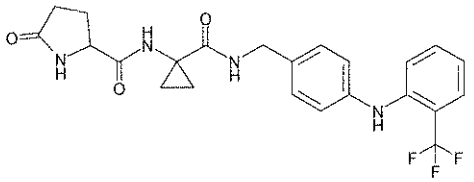
4b) pyrimidine-5-carboxylic acid- N-(1-(4-(2-(trifluoromethyl)phenylamino)benzyl-carbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared starting from N-(4-(aminomethyl)phenyl)-2-(trifluoromethyl)aniline (from 4a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{23}H_{20}F_3N_5O_2$ (455.43)

R_t= 2.27 min. method 6

Example 5: 5-oxo-pyrrolidine-2-carboxylic acid -{1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



5a) 1-amine-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide

A solution of 376 mg (1.87 mmol) 1-(tert-butoxycarbonylamino)cyclopropanecarboxylic acid in 20 mL DMF was combined with 0.4 mL (2.85 mmol) triethylamine and 600 mg (1.87 mmol) TBTU and stirred for 5 minutes at ambient temperature. Then 500 mg N-(4-(aminomethyl)phenyl)-2-(trifluoromethyl)aniline (from 4a) were added and the mixture was stirred at ambient temperature over the weekend. The mixture was then filtered through Alox B, washed with DMF:methanol = 9:1 and evaporated to dryness in vacuo. The residue was combined with a 1:1 mixture of dichloromethane and trifluoroacetic acid and stirred for one hour at ambient temperature. The reaction mixture was evaporated to dryness in vacuo and the crude product was purified by column chromatography (silica gel, dichloromethane + 2-8% methanol:ammonia = 9:1).

Yield: 16% of theory

$C_{22}H_{19}Cl_2N_5O_3$ (456.32)

5b) 5-oxo-pyrrolidine-2-carboxylic acid-{1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide

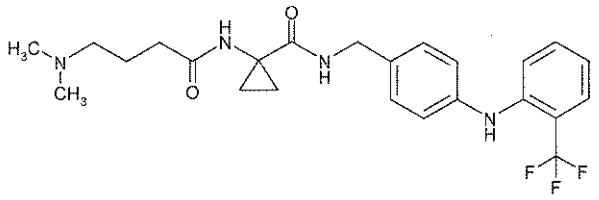
Analogously to method (1d) the title compound was prepared starting from 1-amino-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide (from 5a) and 5-oxopyrrolidine-2-carboxylic acid.

$C_{23}H_{23}F_3N_4O_3$ (460.46)

R_t = 1.89 min. method 5

Examples 6 to 22 that follow were prepared analogously to method (1d) from 1-amino-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide and the corresponding acids:

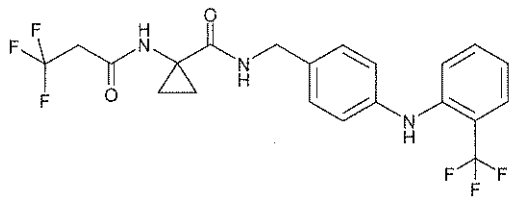
Example 6: 1-(4-dimethylamino-butyrylamino)-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{24}H_{29}F_3N_4O_2$ (462.5)

R_t = 1.67 min. method 5

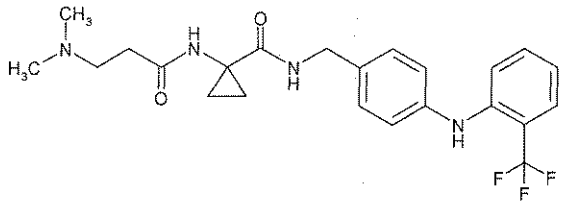
Example 7: 1-(3,3,3-trifluoro-propionylamino)-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{21}H_{19}F_6N_3O_2$ (459.4)

R_t = 2.21 min. method 5

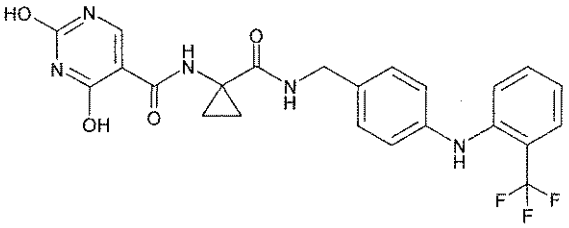
Example 8: 1-(3-dimethylamino-propionylamino)-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{23}H_{27}F_3N_4O_2$ (448.5)

R_t = 1.67 min. method 5

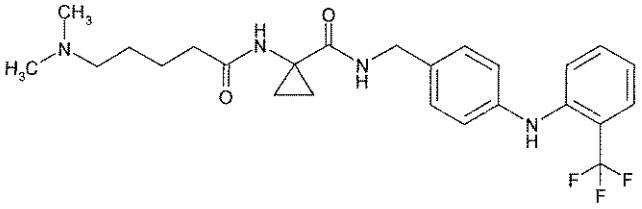
Example 9: 2,4-dihydroxy-pyrimidine-5-carboxylic acid-{1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



$C_{23}H_{20}F_3N_5O_4$ (487.4)

R_t = 1.93 min. method 5

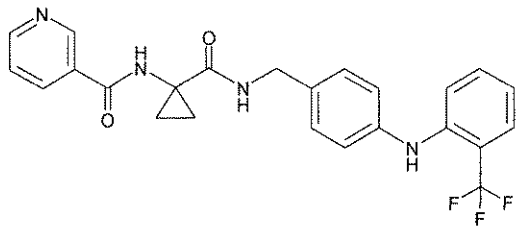
Example 10: 1-(5-dimethylamino-pentanoylamino)-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{25}H_{31}F_3N_4O_2$ (476.5)

R_t = 1.69 min. method 5

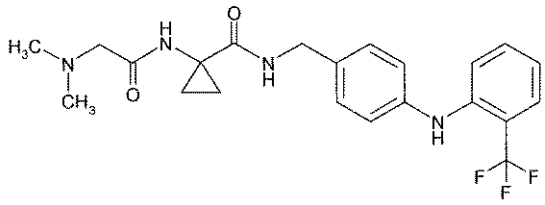
Example 11: N-{1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-nicotinamide



$C_{24}H_{21}F_3N_4O_2$ (454.4)

R_t = 1.79 min. method 5

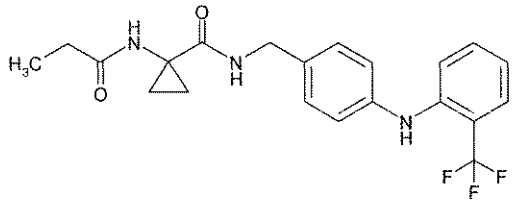
Example 12: 1-(2-dimethylamino-acetylamino)-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{22}H_{25}F_3N_4O_2$ (434.5)

R_t = 1.68 min. method 5

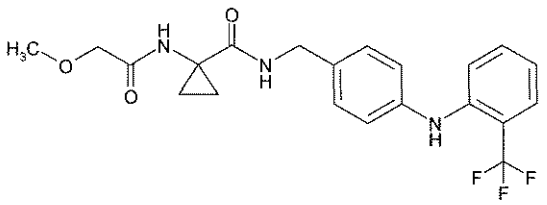
Example 13: 1-propionylamino-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenyl-amino)-benzylamide



$C_{21}H_{22}F_3N_3O_2$ (405.4)

R_t = 2.09 min. method 5

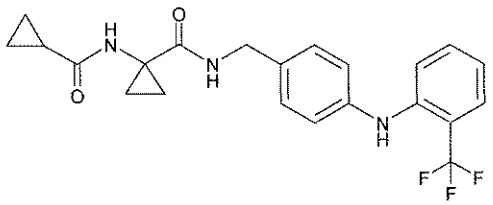
Example 14: 1-(2-methoxy-acetylamino)-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{21}H_{22}F_3N_3O_3$ (421.4)

R_t = 2.07 min. method 5

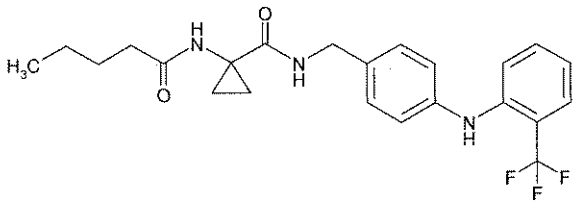
Example 15: 1-(cyclopropanecarbonyl-amino)-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{22}H_{22}F_3N_3O_2$ (417.4)

R_t = 2.13 min. method 5

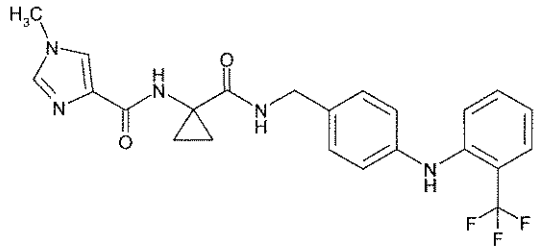
Example 16: 1-pentanoylamino-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenyl-amino)-benzylamide



$C_{23}H_{26}F_3N_3O_2$ (433.5)

R_t = 2.24 min. method 5

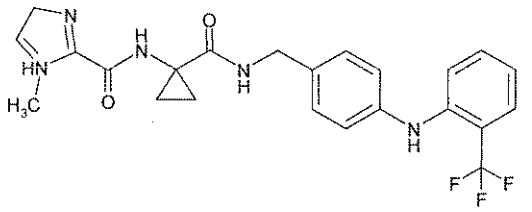
Example 17: 1-methyl-1H-imidazol-4-carboxylic acid-{1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



$C_{23}H_{22}F_3N_5O_2$ (457.5)

R_t = 1.73 min. method 5

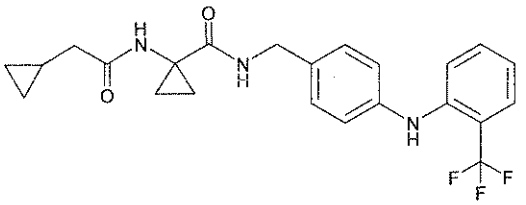
Example 18: 1-methyl-4H-imidazole-2-carboxylic acid-{1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



$C_{23}H_{22}F_3N_5O_2$ (457.5)

R_t = 1.88 min. method 5

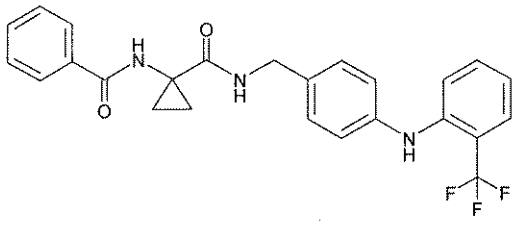
Example 19: 1-(2-cyclopropyl-acetylamino)-cyclopropanecarboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{23}H_{24}F_3N_3O_2$ (431.5)

R_t = 2.18 min. method 5

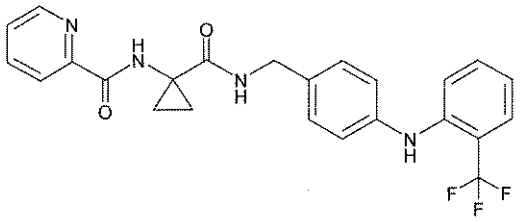
Example 20: N-{1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-benzamide



$C_{25}H_{22}F_3N_3O_2$ (453.5)

R_t = 2.26 min. method 5

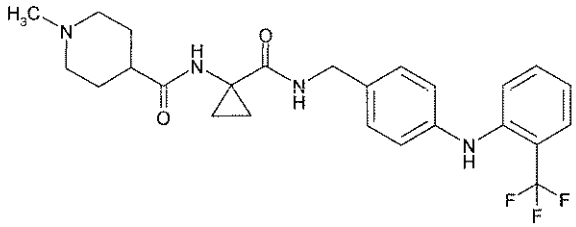
Example 21: pyridine-2-carboxylic acid {1-[4-(2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-cyclopropyl}-amide



$C_{24}H_{21}F_3N_4O_2$ (454.4)

R_t = 2.20 min. method 5

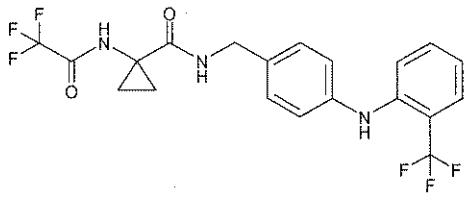
Example 22: 1-methyl-piperidine-4-carboxylic acid {1-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



$C_{25}H_{29}F_3N_4O_2$ (474.5)

R_t = 1.68 min. method 5

Example 23: 1-(2,2,2-trifluoracetamido)-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)-cyclopropanecarboxamide

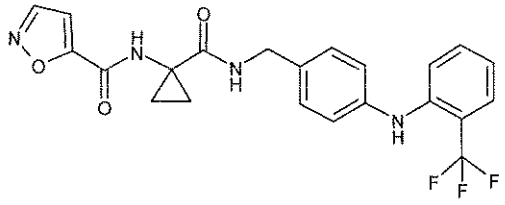


Analogously to method (1d) the title compound was prepared starting from 1-amino-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide (from 5a) and trifluoroacetic acid.

$C_{20}H_{17}F_6N_3O_2$ (445.37)

R_t= 2.27 min. method 5

Example 24: N-(1-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)cyclopropyl)-isoxazole-5-carboxamide



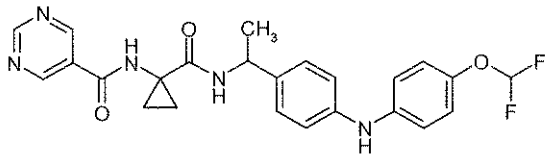
20 mg (0.15 mmol) isoxazole-5-carbonyl chloride were added to a solution of 35 mg (0.1 mmol) 1-amino-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide (from 5a) and 70 µL (0.50 mmol) triethylamine in 1 mL DMF and the mixture was stirred overnight at ambient temperature. The reaction mixture was purified by preparative RP-HPLC-MS with an eluant gradient (water:acetonitrile+0.1%trifluoroacetic acid = 95:5 to 5:95).

Yield: 29% of theory

$C_{22}H_{19}F_3N_4O_3$ (444.41)

R_t= 2.42 min. method 6

Example 25: pyrimidine-5-carboxylic acid N-(1-(1-(4-(4-(difluoromethoxy)phenylamino)-phenyl)ethylcarbamoyl)cyclopropyl)amide



25a) 1-(4-(4-(difluoromethoxy)phenylamino)phenyl)ethanone

The reaction is carried out under protective gas (argon). A mixture of 2.39 g (12 mmol) 1-(4-bromophenyl)ethanone, 0.99 mL (8 mmol) 4-(difluoromethoxy)aniline, 2.21 g (16 mmol) potassium carbonate, 150 mg (0.8 mmol) copper iodide and 180 mg (1.6 mmol) L-proline in 12 mL DMSO was stirred for 72 hours at 95°C. The reaction mixture was added to water, mixed with a little ammonia extracted twice with tert-butyl-methylether. The combined organic phases were dried on sodium sulphate and evaporated to dryness in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether + 30% ethyl acetate). The product was further reacted directly.

Yield: 33% of theory

$C_{15}H_{13}F_2NO_2$ (277.27)

R_t= 1.98 min. method 1

25b) (Z)-1-(4-(4-(difluoromethoxy)phenylamino)phenyl)ethanone-oxime

A mixture of 1.08 g (3.9 mmol) 1-(4-(4-(difluoromethoxy)phenylamino)phenyl)ethanone and 0.92 mL (15.58 mmol) aqueous 50% hydroxylamine solution in 10 mL ethanol was stirred for 3 hours at 100°C. The reaction mixture was evaporated to dryness in vacuo and the residue was purified by preparative HPLC (method 2).

Yield: 19% of theory

$C_{15}H_{14}F_2N_2O_2$ (292.28)

R_t= 1.96 min. method 1

25c) 4-(1-aminoethyl)-N-(4-(difluoromethoxy)phenyl)aniline

0.22 g (0.75 mmol) (Z)-1-(4-(4-(difluoromethoxy)phenylamino)phenyl)ethanone-oxime in 20 mL methanolic ammonia solution were hydrogenated with the addition of 50 mg Raney nickel at 50°C at a hydrogen pressure of 50 psi for 5 hours. Then the catalyst was filtered off and the filtrate was evaporated to dryness. The crude product thus obtained was further reacted directly.

$C_{15}H_{16}F_2N_2O$ (278.3)

R_t= 1.37 min. method 1

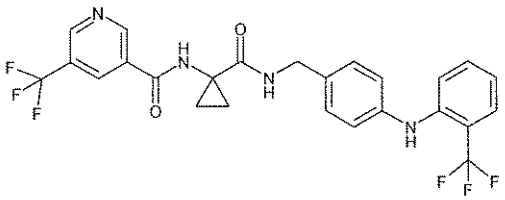
25d) pyrimidine-5-carboxylic acid N-(1-(1-(4-(4-(difluoromethoxy)phenylamino)phenyl)-ethylcarbamoyl)cyclopropyl) amide

Analogously to method (1d) the title compound was prepared starting from 4-(1-aminoethyl)-N-(4-(difluoromethoxy)phenyl)aniline (from 25c) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{24}H_{23}F_2N_5O_3$ (467.47)

R_t= 1.78 min. method 1

Example 26: 5-(trifluoromethyl)-N-(1-(4-(2-(trifluoromethyl)phenylamino)-benzylcarbamoyl)cyclopropyl)nicotinamide



26a) 5-(trifluoromethyl)nicotinic acid

A solution of 1.5 g 3-bromo-5-(trifluoromethyl)pyridine in 50 ml of toluene was added dropwise at -75°C to a mixture of 9.96 mL (15.9 mmol) 1.6 molar butyllithium solution in hexane and 3.98 mL (8 mmol) 2 molar butylmagnesium chloride solution in diethyl ether and 10 mL THF. After 20 minutes 20 g (454 mmol) dry ice were added and the mixture was again stirred for 20 minutes at -75°C and for 3 hours at RT. The reaction mixture was combined with 50 mL 1 molar sodium hydroxide solution and extracted twice with diethyl ether. The aqueous phase was acidified with 4 molar hydrochloric acid and extracted three times with diethyl ether. The combined organic phases were dried on sodium sulphate and evaporated to dryness in vacuo. The residue was mixed with dichloromethane and the precipitate formed was suction filtered and dried in the circulating air dryer at 55°C.

Yield: 9% of theory

$C_7H_4F_3NO_2$ (191.11)

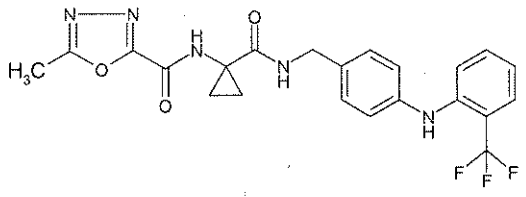
26b) 5-(trifluoromethyl)-N-(1-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)-cyclopropyl)nicotinamide

Analogously to method (1d) the title compound was prepared starting from 1-amine-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide (from 5a) and 5-(trifluoromethyl)nicotinic acid (from 26a).

$C_{22}H_{20}F_3N_5O_3$ (459.42)

R_t= 2.41 min. method 6

Example 27: 5-methyl-N-(1-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)-cyclopropyl)-1,3,4-oxadiazole-2-carboxamide



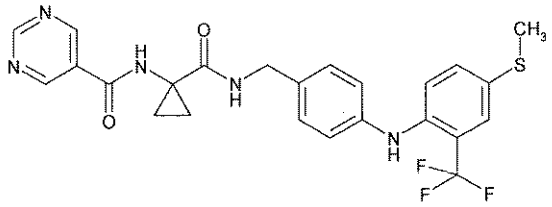
27a) 5-methyl-N-(1-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)cyclopropyl)-1,3,4-oxadiazole-2-carboxamide

Analogously to method (1d) the title compound was prepared starting from 1-amine-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide (from 5a) and 5-methyl-1,3,4-oxadiazole-2-carboxylic acid.

$C_{22}H_{20}F_3N_5O_3$ (459.42)

R_t= 1.66 min. method 6

Example 28: pyrimidine-5-carboxylic acid-N-(1-(4-(4-(methylthio)-2-(trifluoromethyl)phenylamino)benzylcarbamoyl)cyclopropyl)amide



28a) N-(4-(aminomethyl)phenyl)-4-(methylthio)-2-(trifluoromethyl)aniline

Analogously to method (1c) the title compound was prepared starting from 4-(methylthio)-2-(trifluoromethyl)aniline and 4-fluorobenzonitrile.

$C_{15}H_{15}F_3N_2S$ (312.35)

R_t= 1.88 min. method 2

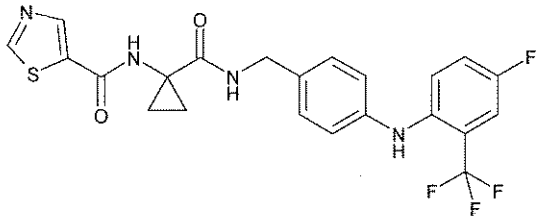
28b) pyrimidine-5-carboxylic acid-N-(1-(4-(4-(methylthio)-2-(trifluoromethyl)phenylamino)benzylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared starting from N-(4-(aminomethyl)phenyl)-4-(methylthio)-2-(trifluoromethyl)aniline (from 28a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{24}H_{22}F_3N_5O_2S$ (501.53)

R_t= 2.33 min. method 2

Example 29: N-(1-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzylcarbamoyl)-cyclopropyl)thiazole-5-carboxamide



29a) N-(4-(aminomethyl)phenyl)-2-(trifluoromethyl)aniline

Analogously to method (1c) the title compound was prepared starting from 2-trifluoromethyl-4-fluoraniline and 4-fluorobenzonitrile.

$C_{14}H_8F_4N_2$ (280.22)

R_t= 0.38 min. method 4

29b) tert-butyl 1-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzylcarbamoyl)-cyclopropylcarbamate

0.98 mL (7.04 mmol) triethylamine and 1.24 g (3.87 mmol) TBTU were added to a solution of 710 mg (3.52 mmol) 1-(tert-butoxycarbonylamino)cyclopropanecarboxylic acid in 60 mL DMF and the mixture was stirred for 30 minutes at ambient temperature. Then 1 g N-(4-(aminomethyl)phenyl)-2-(trifluoromethyl)aniline was added and the mixture was stirred for 1 hour at ambient temperature. The reaction mixture was evaporated to dryness in vacuo. The residue was taken up in ethyl acetate and washed twice with 5% sodium hydrogen carbonate solution. The organic phase was dried on sodium sulphate and evaporated to dryness in vacuo.

Yield: 96% of theory

$C_{23}H_{25}F_4N_3O_3$ (467.46)

R_t= 1.50 min. method 4

29c) 1-amino-N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)-cyclopropanecarboxamide

1.57 g (3.36 mmol) tert-butyl 1-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl-carbamoyl)cyclopropylcarbamate in 10 mL diethyl ether were combined with 20 mL 4 molar hydrogen chloride in dioxane and stirred for 10 minutes at ambient temperature. The reaction mixture was combined with ethyl acetate and made alkaline with saturated potassium carbonate solution. The organic phase was dried on sodium sulphate and evaporated to dryness in vacuo.

Yield: 101% of theory

$C_{18}H_{17}F_4N_3O$ (367.34)

R_t= 1.33 min. method 4

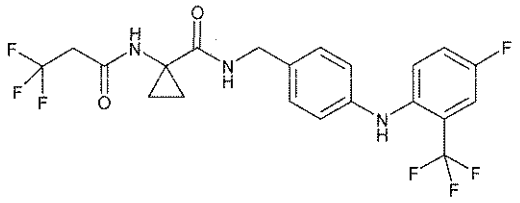
29d) N-(1-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzylcarbamoyl)cyclopropyl)-thiazole-5-carboxamide

Analogously to method (1d) the title compound was prepared starting from 1-amino-N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide (from 29c) and thiazole-5-carboxylic acid.

$C_{22}H_{18}F_4N_4O_3S$ (478.46)

R_t= 2.76 min. method 3

Example 30: N-(4-(4-fluoro-2-(trifluoromethyl)phenylamine)benzyl)-1-(3,3,3-trifluoro-propanamido)cyclopropanecarboxamide



30a) N-(4-(4-fluoro-2-(trifluoromethyl)phenylamine)benzyl)-1-(3,3,3-trifluoropropanamido)cyclopropanecarboxamide

44.0 mg (0.15 mmol) 3,3,3-trifluoropropionyl chloride, dissolved in 5 mL dichloromethane, were added dropwise to a solution of 110.2 mg (0.3 mmol) 1-amino-N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide (from 29c) and 80 µL (0.6 mmol) triethylamine in 10 mL dichloromethane. Then the reaction mixture was left at ambient temperature for the weekend with stirring and it was then purified by preparative

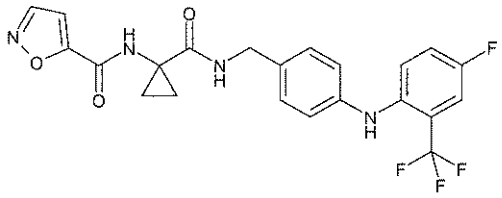
RP-HPLC-MS (method 3). The eluate was made alkaline with conc. Ammonia and the acetonitrile was distilled off. The aqueous mixture was extracted with ethyl acetate and the organic phase was dried on sodium sulphate and evaporated to dryness in vacuo.

Yield: 44% of theory

$C_{21}H_{18}F_7N_3O_2$ (477.38)

R_t= 2.85 min. method 3

Example 31: N-(1-(4-(4-fluoro-2-(trifluoromethyl)phenylamine)benzylcarbamoyl)-cyclopropyl)isoxazole-5-carboxamide

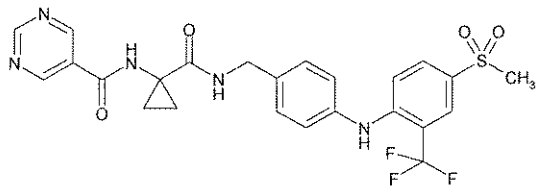


Analogously to method (30a) the title compound was prepared starting from 1-amino-N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide (from 29c) and isoxazole-5-carbonyl chloride.

$C_{22}H_{18}F_4N_4O_3$ (462.4)

R_t= 2.79 min. method 3

Example 32: pyrimidine-5-carboxylic acid- N-(1-(4-(4-(methylsulphonyl)-2-(trifluoromethyl)phenylamine)benzylcarbamoyl)cyclopropyl)amide



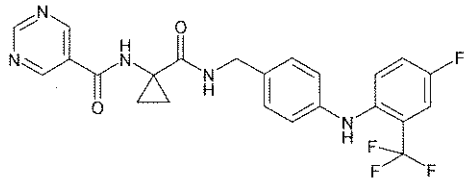
34 mg (0.2 mmol) 3-chloroperoxybenzoic acid were added to 66 mg (0.13 mmol) pyrimidine-5-carboxylic acid-N-(1-(4-(4-(methylthio)-2-(trifluoromethyl)-phenylamino)benzylcarbamoyl)cyclopropyl)amide (from 28b), dissolved in 5 mL dichloromethane, and the mixture was left at ambient temperature overnight with stirring. Then the mixture was added to saturated sodium hydrogen carbonate solution and extracted with dichloromethane. The organic phase was dried through a phase separation cartridge and the filtrate was evaporated to dryness in vacuo.

Yield: 40% of theory

$C_{24}H_{22}F_3N_5O_4S$ (533.52)

R_t= 1.84 min. method 2

Example 33: pyrimidine-5-carboxylic acid-N-(1-(4-(4-fluoro-2-(trifluoromethyl)phenylamine)benzylcarbamoyl)cyclopropyl)amide

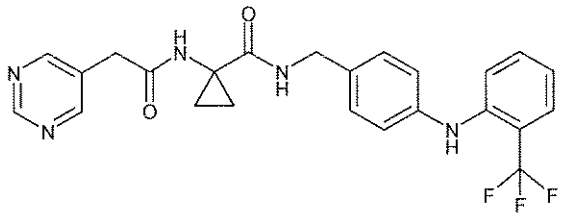


Analogously to method (1d) the title compound was prepared starting from 1-amino-N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide (from 29c) and pyrimidine-5-carboxylic acid.

$C_{23}H_{19}F_4N_5O_2$ (473.42)

R_t= 2.09 min. method 2

Example 34: 1-(2-(pyrimidin-5-yl)acetamido)-N-(4-(2-(trifluoromethyl)phenylamino)-benzyl)cyclopropanecarboxamide

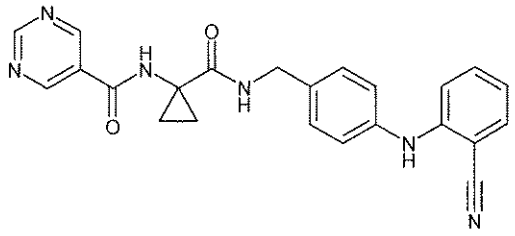


Analogously to method (1d) the title compound was prepared starting from 1-amino-N-(4-(4-fluoro-2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide (from 29c) and pyrimidine-5-carboxylic acid.

$C_{24}H_{22}F_3N_5O_2$ (469.46)

R_t= 2.21 min. method 6

Example 35: pyrimidine-5-carboxylic acid-N-(1-(4-(2-cyanphenylamine)benzylcarbamoyl)cyclopropyl)amide



35a) tert-butyl-4-aminobenzylcarbamate

92.65 g (424.5 mmol) di-tert-butyl-dicarbonate were added to 61.85 g (424.4 mmol) 4-aminomethyl-aniline dissolved in 850 mL chloroform and the mixture was stirred at ambient temperature until no more educt was present. The mixture was evaporated to dryness in vacuo and the residue was recrystallised from ethyl acetate/hexane (approx. 3 mL/g).

Yield:	66% of theory
$C_{12}H_{18}N_2O_2$	(222.28)
R_f= 0.49	hexane : ethyl acetate (1/1)

35b) tert-butyl-4-(2-cyanophenylamino)benzylcarbamate

The reaction was carried out under protective gas (nitrogen). 8 mg (0.01 mmol) of tris(dibenzylideneacetone)dipalladium and 17 mg (0.04 mmol) Xantphos were added to 100 mg (0.45 mmol) tert-butyl-4-aminobenzylcarbamate, 138 mg (0.63 mmol) potassium sulphate and 98 mg (0.54 mmol) 2-bromobenzonitrile in 5 mL toluene. The mixture was stirred overnight at 110°C and then the inorganic salts were filtered off. The filtrate was evaporated to dryness in vacuo and the residue was purified through an RP column with a solvent gradient (water/acetonitrile + 0.1%trifluoroacetic acid).

Yield:	82% of theory
$C_{19}H_{21}N_3O_2$	(323.39)
R_t= 2.57 min.	method 2

35c) 2-(4-(aminomethyl)phenylamino)benzonitrile-2,2,2-trifluoroacetate

119 mg (0.37 mmol) tert-butyl 4-(2-cyanophenylamino)benzylcarbamate were dissolved in 5 mL dichloromethane and combined with 1 mL (13.06 mmol) trifluoroacetic acid. The reaction was stirred overnight at ambient temperature and then evaporated to dryness in vacuo.

Yield: 99% of theory

$C_{14}H_{13}N_3*C_2HF_3O_2$ (337.3)

R_t= 1.30 min. method 2

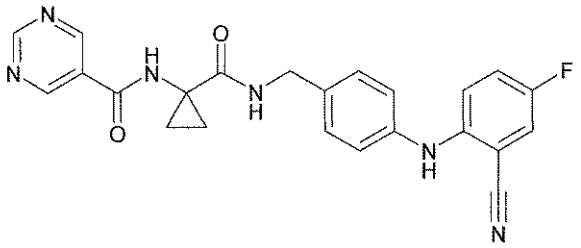
35d) pyrimidine-5-carboxylic acid-N-(1-(4-(2-cyanophenylamine)benzylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared starting from 2-(4-(aminomethyl)phenylamino)benzonitrile 2,2,2-trifluoroacetate (from 35c) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{23}H_{20}N_6O_2$ (412.44)

R_t= 1.84 min. method 2

Example 36: pyrimidine-5-carboxylic acid-N-(1-(4-(2-cyano-4-fluorophenylamine)benzylcarbamoyl)cyclopropyl)amide



36a) Tert-butyl-4-(2-cyano-4-fluorophenylamino)benzylcarbamate

Analogously to method (35b) the title compound was prepared starting from tert-butyl-4-aminobenzylcarbamate (from 35a), potassium sulphate, 2-bromo-5-fluorobenzonitrile, tris(dibenzylideneacetone)dipalladium and Xantphos.

$C_{19}H_{20}FN_6O_2$ (341.38)

R_t= 2.61 min. method 2

36b) 2-(4-(aminomethyl)phenylamino)-5-fluorobenzonitrile 2,2,2-trifluoroacetate

Analogously to method (35c) the title compound was prepared starting from tert-butyl-4-(2-cyano-4-fluorophenylamino)benzylcarbamate and trifluoroacetic acid.

$C_{14}H_{12}FN_3*C_2HF_3O_2$ (355.29)

R_t= 1.39 min. method 2

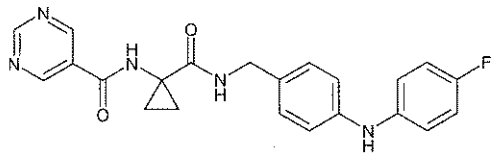
36c) pyrimidine-5-carboxylic acid-N-(1-(4-(2-cyano-4-fluorophenylamine)benzylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared from 2-(4-(aminomethyl)phenylamino)-5-fluorobenzonitrile 2,2,2-trifluoroacetate (from 36b) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{23}H_{19}FN_6O_2$ (430.43)

R_t= 1.91 min. method 2

Example 37: pyrimidine-5-carboxylic acid-N-(1-(4-(4-fluorophenylamino)benzylcarbamoyl)cyclopropyl)amide



37a) 4-(aminomethyl)-N-(4-fluorophenyl)aniline

Analogously to method (1c) the title compound was prepared starting from 2-bromo-4-fluoro-aniline, 4-fluorobenzonitrile and Raney nickel.

$C_{13}H_{13}FN_2$ (216.25)

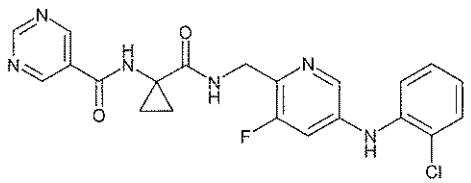
37b) pyrimidine-5-carboxylic acid-N-(1-(4-(4-fluorophenylamino)benzylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared from 4-(aminomethyl)-N-(4-fluorophenyl)aniline (from 37a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{22}H_{20}FN_5O_2$ (405.43)

mass spectroscopy $[M+H]^+$ = 406

Example 38: pyrimidine-5-carboxylic acid-N-(1-((5-(2-chlorophenylamino)-3-fluoropyridin-2-yl)methylcarbamoyl)cyclopropyl)amide



38a) 6-(aminomethyl)-N-(2-chlorophenyl)-5-fluoropyridin-3-amine

Analogously to method (1c) the title compound was prepared starting from 2-chloro-aniline, 2-cyano-3,5-difluoropyridine and Raney nickel.

$C_{12}H_{11}FN_3$ (251.69)

R_t= 1.295 min. method 1

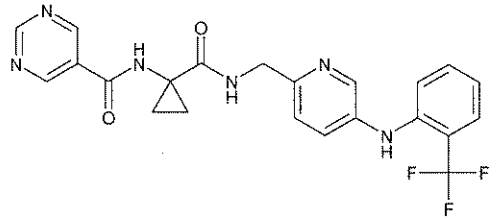
38b) pyrimidine-5-carboxylic acid- N-(1-((5-(2-chlorophenylamino)-3-fluoropyridin-2-yl)-methylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(2-chlorophenyl)-5-fluoropyridin-3-amine (from 38a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{21}H_{18}FN_6O_2$ (440.86)

R_t= 1.73 min. method 1

Example 39: pyrimidine-5-carboxylic acid-N-(1-((5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide



39a) 6-(aminomethyl)-N-(2-(trifluoromethyl)phenyl)pyridin-3-amine

Analogously to method (1c) the title compound was prepared starting from 2-(trifluoromethyl)aniline, 5-fluoro-picolinic acid nitrile and Raney nickel.

$C_{13}H_{12}F_3N_3$ (267.25)

R_t= 1.29 min. method 1

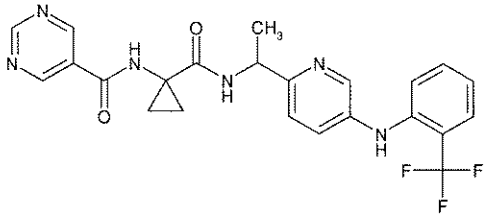
39b) pyrimidine-5-carboxylic acid-N-(1-((5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)-methylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(2-(trifluoromethyl)phenyl)pyridin-3-amine (from 39a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{22}H_{19}F_3N_6O_2$ (456.42)

R_t= 1.39 min. method 1

Example 40: pyrimidine-5-carboxylic acid-N-(1-(1-(5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethylcarbamoyl)cyclopropyl)amide



40a) 5-(2-(trifluoromethyl)phenylamino)picolinic acid nitrile

820 mg (6.72 mmol) 5-fluoropicolinic acid nitrile and 0.84 mL (6.72 mmol) 2-(trifluoromethyl)aniline in 10 mL DMSO were combined with 1.51 g (13.43 mmol) potassium-tert-butoxide and stirred for 2 hours at ambient temperature. The mixture was poured onto an aqueous sodium chloride solution and extracted with tert-butylmethylether. The organic phase was evaporated to dryness in vacuo and the crude product thus obtained was purified by HPLC (method 2).

Yield: 54% of theory

$C_{13}H_8F_3N_3$ (263.22)

40b) 1-(5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone

The reaction was carried out under protective gas (nitrogen). 860 mg (3.27 mmol) 5-(2-(trifluoromethyl)phenylamino)picolinic acid nitrile in 5 mL diethyl ether at -10°C were added dropwise to 9.34 mL (13.07 mmol) of a 1.4 molar solution of methylmagnesium bromide in toluene/THF (3:1) and the mixture was left for 15 minutes at this temperature with stirring. The reaction mixture was combined with saturated ammonium chloride solution, neutralised with 1 molar aqueous hydrochloric acid at -5°C and extracted with tert-butylmethylether. The organic phase was evaporated to dryness in vacuo.

Yield: 96% of theory

$C_{14}H_{11}F_3N_2O$ (280.25)

R_t= 1.97 min. method 1

40c) (Z)-1-(5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone-oxime

0.73 mL (12.42 mmol) of a 50% aqueous hydroxylamine solution were added to 870 mg (3.1 mmol) 1-(5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone in 5 mL ethanol. The mixture was stirred for 2 hours at 100°C and then the solvents were distilled off.

Yield: 98% of theory

$C_{14}H_{12}F_3N_3O$ (295.26)

R_t= 1.75 min. method 1

40d) 6-(1-aminoethyl)-N-(2-(trifluoromethyl)phenyl)pyridin-3-amine

900 mg (3.05 mmol) (Z)-1-(5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone-oxime and 100 mg Raney nickel in 25 mL methanolic ammonia were hydrogenated for 1.5 days at ambient temperature and 50 psi hydrogen pressure. The reaction mixture was filtered, evaporated to dryness and then further reacted directly.

Yield: 96% of theory

$C_{14}H_{14}F_3N_3$ (281.28)

R_t= 1.33 min. method 1

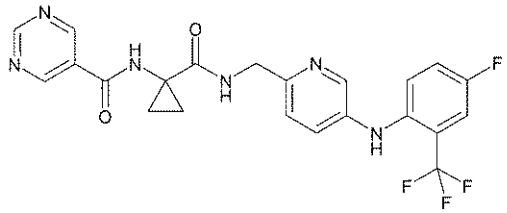
40e) pyrimidine-5-carboxylic acid-N-(1-(1-(5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared from 6-(1-aminoethyl)-N-(2-(trifluoromethyl)phenyl)pyridin-3-amine (from 40d) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{23}H_{21}F_3N_6O_2$ (470.45)

R_t= 1.46 min. method 1

Example 41: pyrimidine-5-carboxylic acid- N-(1-((5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide



41a) 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine

Analogously to method (1c) the title compound was prepared starting from 2-trifluoromethyl-4-fluoro-aniline, 2-cyano-5-fluoropyridine and Raney nickel.

$C_{13}H_{11}F_4N_3$ (285.24)

R_t= 1.50 min. method 9

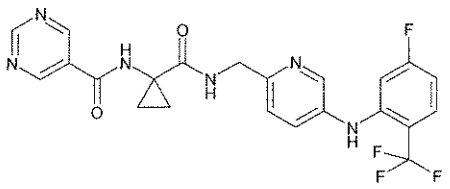
41b) pyrimidine-5-carboxylic acid- N-(1-((5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

Analogously to Example (1d) the title compound was prepared from 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 41a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{22}H_{18}F_4N_6O_2$ (474.41)

R_t= 2.96 min. method 7

Example 42: pyrimidine-5-carboxylic acid-N-(1-((5-(5-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide



42a) 6-(aminomethyl)-N-(5-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine

Analogously to method (1c) the title compound was prepared starting from 2-fluoro-6-(trifluoromethyl)aniline, 2-cyano-5-fluoropyridine and Raney nickel.

$C_{13}H_{11}F_4N_3$ (281.24)

R_t= 1.95 min. method 8

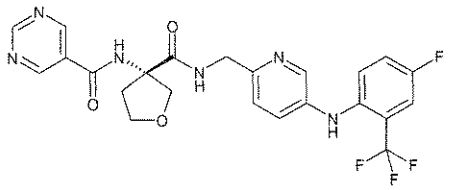
42b) pyrimidine-5-carboxylic acid-N-(1-((5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared starting from 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 41a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{22}H_{18}F_4N_6O_2$ (474.41)

R_t= 3.10 min. method 7

Example 43: (S)-pyrimidine-5-carboxylic acid-N-(3-((5-(4-fluoro-2-(trifluoromethyl)phenyl-amino)pyridin-2-yl)methylcarbamoyl)tetrahydrofuran-3-yl)amide



43a) (S)-phenethyl-3-aminotetrahydrofuran-3-carboxylate

19.37 g (50 mmol) (S)-phenethyl-3-aminotetrahydrofuran-3-carboxylate (S)-2-hydroxy-2-phenylacetate were suspended in 75 mL THF and 75 mL water, combined with 6.3 g (75 mmol) sodium hydrogen carbonate and stirred for 3 hours at ambient temperature. The mixture was extracted twice with dichloromethane. The organic phases were washed with 14% sodium chloride solution, dried on sodium sulphate and evaporated to dryness in vacuo. The crude product thus obtained was further reacted directly.

Yield:	85% of theory
$C_{13}H_{17}NO_3$	(235.28)
R_t= 1.19 min.	method 1

43b) (S)-phenethyl-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylate

4.43 mL (40.3 mmol) N-methylmorpholine and 5.69 g (17.7 mmol) TBTU were added to a solution of 2 g (16.1 mmol) pyrimidine-5-carboxylic acid in 50 mL DMF. The mixture was left for 30 minutes at ambient temperature with stirring and then combined with 3.8 g (16.16 mmol) (S)-phenethyl-3-aminotetrahydrofuran-3-carboxylate. The mixture was stirred overnight at ambient temperature and then evaporated to dryness. The crude product thus obtained was purified by HPLC (method 2).

Yield:	93% of theory
$C_{18}H_{19}N_3O_4$	(341.36)
R_t= 1.60 min.	method 1

43c) (S)-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylic acid

60.24 mL (60.24 mmol) of a 1 molar sodium hydroxide solution were added to a solution of 5.14 g (15.1 mmol) (S)-phenethyl 3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylate in 97 mL ethanol. The mixture was stirred for 1 hour at ambient temperature and then acidified with 4 molar hydrochloric acid. The purification was carried out by HPLC (method 2).

Yield: 93% of theory

$C_{10}H_{11}N_3O_4$ (237.21)

R_t= 0.87 min. method 1

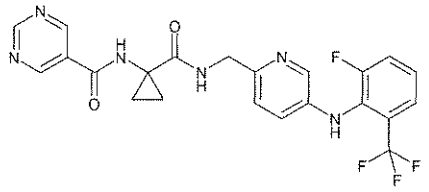
43d) pyrimidine-5-carboxylic acid-(S)-N-(3-((5-(4-fluoro-2-(trifluoromethyl)phenylamino)-pyridin-2-yl)methylcarbamoyl)tetrahydrofuran-3-yl)amide

Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 41a) and (S)-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylic acid (from 43c).

$C_{23}H_{20}F_4N_6O_3$ (504.44)

R_t= 2.86 min. method 7

Example 44: pyrimidine-5-carboxylic acid-N-(1-((5-(2-fluoro-6-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide



44a) 6-(aminomethyl)-N-(2-fluoro-6-(trifluoromethyl)phenyl)pyridin-3-amine

Analogously to method (1c) the title compound was prepared starting from 2-trifluoromethyl-5-fluoro-aniline, 2-cyano-5-fluoropyridine and Raney nickel.

$C_{13}H_{11}F_4N_3$ (285.24)

R_t= 1.95 min. method 8

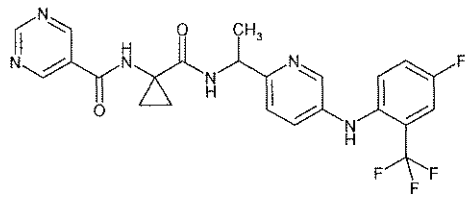
44b) pyrimidine-5-carboxylic acid-N-(1-((5-(2-fluoro-6-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared starting from 6-(aminomethyl)-N-(2-fluoro-6-(trifluoromethyl)phenyl)pyridin-3-amine (from 44a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{22}H_{18}F_4N_6O_2$ (474.41)

R_t=2.71 min. method 7

Example 45: pyrimidine-5-carboxylic acid-N-(1-(1-(5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethylcarbamoyl)cyclopropyl)amide



45a) 5-(4-fluoro-2-(trifluoromethyl)phenylamino)picolinic acid nitrile

Analogously to method (40a) the title compound was prepared starting from 5-fluoro-picolinic acid nitrile, 4-fluoro-2-(trifluoromethyl)aniline and potassium-tert-butoxide in DMSO.

$C_{13}H_8F_3N_3$ (281.21)

R_t= 1.40 min. method 4

45b) 1-(5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone

Analogously to method (40b) the title compound was prepared from methylmagnesium bromide and 5-(4-fluoro-2-(trifluoromethyl)phenylamino)picolinic acid nitrile.

$C_{14}H_{11}F_4N_2O$ (298.24)

R_t= 1.43 min. method 4

45c) (E)-1-(5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone-oxime

Analogously to method (40c) the title compound was prepared starting from 1-(5-(2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone and a 50% aqueous hydroxylamine solution.

$C_{14}H_{11}F_4N_3O$ (313.25)

R_t= 1.31 min. method 4

45d) 6-(1-aminoethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine

Analogously to method (40d) the title compound was prepared starting from (E)-1-(5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethanone-oxime and Raney nickel.

$C_{14}H_{14}F_4N_3$ (299.27)

R_t= 1.65 min. method 9

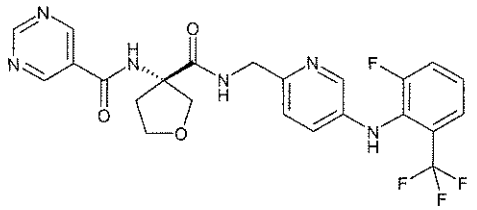
45e) pyrimidine-5-carboxylic acid-N-(1-(1-(5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) 6-(1-aminoethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 45d) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b) were reacted to form the title compound.

$C_{23}H_{20}F_4N_6O_2$ (488.44)

R_t= 3.01 min. method 7

Example 46: (S)-pyrimidine-5-carboxylic acid-N-(3-((5-(2-fluoro-6-(trifluoromethyl)phenyl-amino)pyridin-2-yl)methylcarbamoyl)tetrahydrofuran-3-yl)amide

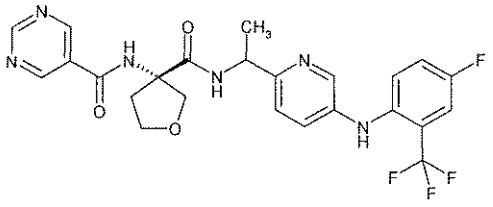


Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 41a) and (S)-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylic acid (from 43c).

$C_{23}H_{20}F_4N_6O_3$ (504.44)

R_t= 2.74 min. method 7

Example 47: (S)-pyrimidine-5-carboxylic acid-N-(-3-(1-(5-(4-fluoro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)ethylcarbamoyl)tetrahydrofuran-3-yl)amide

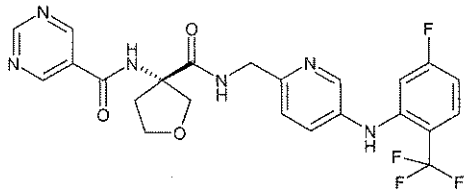


Analogously to method (1d) the title compound was prepared from 6-(1-aminoethyl)-N-(4-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 45d) and (S)-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylic acid (from 43c).

$C_{24}H_{22}F_4N_6O_3$ (518.46)

R_t= 3.00 min. method 7

Example 48: (S)-pyrimidine-5-carboxylic acid-N-(3-((5-(5-fluoro-2-(trifluoromethyl)phenyl-amino)pyridin-2-yl)methylcarbamoyl)tetrahydrofuran-3-yl)amide

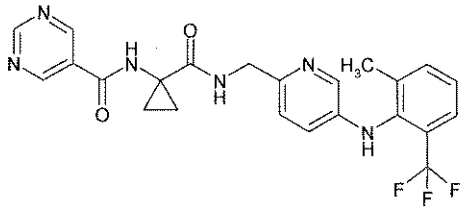


Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(5-fluoro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 42a) and (S)-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylic acid (from 43c).

$C_{23}H_{20}F_4N_6O_3$ (504.44)

R_t= 3.15 min. method 7

Example 49: pyrimidine-5-carboxylic acid-N-(1-((5-(2-methyl-6-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide



49a) 6-(aminomethyl)-N-(2-methyl-6-(trifluoromethyl)phenyl)pyridin-3-amine

Analogously to method (1c) the title compound was prepared from 2-methyl-6-(trifluoromethyl)-aniline and 2-cyano-5-fluoropyridine with Raney nickel as catalyst.

$C_{14}H_{14}F_3N_3$ (281.28)

R_t= 1.52 min. method 2

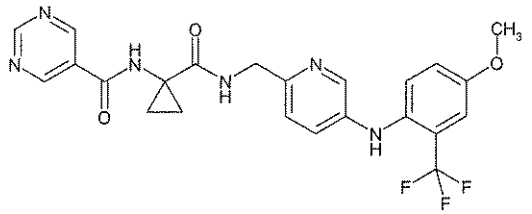
49b) pyrimidine-5-carboxylic acid-N-(1-((5-(2-methyl-6-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(2-methyl-6-(trifluoromethyl)phenyl)pyridin-3-amine (from 49a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{22}H_{18}F_4N_6O_2$ (470.45)

R_t=1.57 min. method 2

Example 50: pyrimidine-5-carboxylic acid-N-(1-((5-(4-methoxy-2-(trifluoromethyl)phenyl-amino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide



50a) 6-(aminomethyl)-N-(4-methoxy-2-(trifluoromethyl)phenyl)pyridin-3-amine

Analogously to method (1c) the title compound was prepared starting from 2-amino-5-methoxybenzotrifluoride and 2-cyano-5-fluoropyridine with Raney nickel as catalyst.

$C_{14}H_{14}F_3N_3O$ (297.28)

R_f= 0.21 ethyl acetate / methanol / ammonia = 9:1:0.1

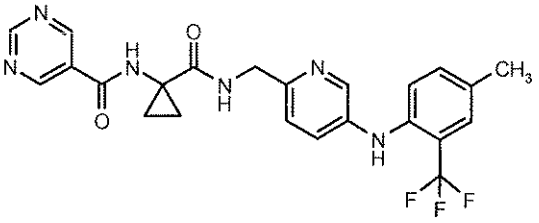
50b) pyrimidine-5-carboxylic acid- N-(1-((5-(4-methoxy-2-(trifluoromethyl)phenylamino)-pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(4-methoxy-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 50a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{23}H_{21}F_3N_6O_3$ (486.45)

R_t=2.82 min. method 7

Example 51: pyrimidine-5-carboxylic acid- N-(1-((5-(4-methyl-2-(trifluoromethyl)phenyl-amino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide



51a) 6-(aminomethyl)-N-(4-methyl-2-(trifluoromethyl)phenyl)pyridin-3-amine

Analogously to method (1c) the title compound was prepared from 2-amino-5-methylbenzotrifluoride and 2-cyano-5-fluoropyridine using Raney nickel.

$C_{14}H_{14}F_3N_3$ (281.28)

R_t= 1.63 min. method 2

51b) pyrimidine-5-carboxylic acid-N-(1-((5-(4-methyl-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

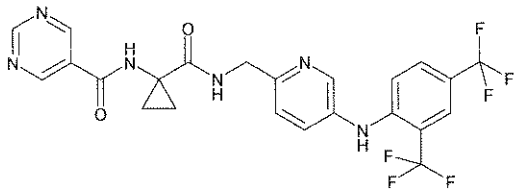
0.1 mL (0.56 mmol) DIPEA and 87 mg (0.27 mmol) O-[(ethoxycarbonyl)cyanomethyleneamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate, dissolved in 0.5 mL DMF, were added to a solution of 50 mg (0.24 mmol) 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b) in 2 mL THF. The mixture was left for 15 minutes at ambient temperature with stirring and then 82 mg (0.29 mmol) of 6-(aminomethyl)-N-(4-methyl-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 51a) in 0.5 mL DMF were added. The mixture was stirred overnight at ambient temperature and then purified by HPLC (Microsorb C18; 41.4 x 250 mm with acetonitrile/water/trifluoroacetic acid = 10/90/0.1 => 100/0/0.1).

Yield: 33% of theory

$C_{23}H_{21}F_3N_6O_2$ (470.45)

R_t= 1.63 min. method 2

Example 52: pyrimidine-5-carboxylic acid-N-(1-((5-(2,4-bis(trifluoromethyl)phenylamino)-pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide



52a) 6-(aminomethyl)-N-(2,4-bis(trifluoromethyl)phenyl)pyridin-3-amine

Analogously to method (1c) the title compound was prepared from 2,4-bis(trifluoromethyl)aniline and 2-cyano-5-fluoropyridine using Raney nickel.

$C_{14}H_{11}F_6N_3$ (335.25)

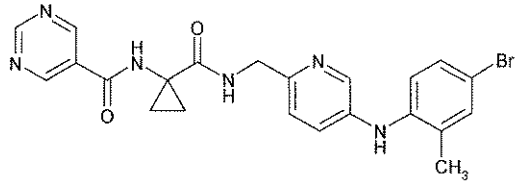
52b) pyrimidine-5-carboxylic acid-N-(1-((5-(2,4-bis(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(2,4-bis(trifluoromethyl)phenyl)pyridin-3-amine (from 52a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{23}H_{18}F_6N_6O_2$ (524.42)

R_t= 3.63 min. method 10

Example 53: pyrimidine-5-carboxylic acid-N-(1-((5-(4-bromo-2-methylphenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide



53a) 5-(4-bromo-2-(trifluoromethyl)phenylamino)picolinonitrile

Analogously to method (40a) the title compound was prepared starting from 2-cyano-5-fluoropyridine, 2-amino-5-bromo-benzotrifluoride and potassium-tert-butoxide with DMSO as solvent.

$C_{13}H_7BrF_3N_3$ (342.11)

R_t=2.50 min. method 2

53b-1) 6-(aminomethyl)-N-(4-bromo-2-methylphenyl)pyridin-3-amine 2,2,2-trifluoroacetate

1.65 mL (3.3 mmol) 2 molar lithium aluminium hydride solution in THF were added to a solution of 564 mg (1.65 mmol) 5-(4-bromo-2-(trifluoromethyl)phenylamino)picolinic acid nitrile in 5 mL THF. The reaction mixture was stirred for 30 minutes at ambient temperature and then mixed with water. The salts were suction filtered and the filtrate was evaporated down in vacuo. The residue was purified by HPLC (with solvent gradient, acetonitrile and water with 0.1% trifluoroacetic acid). 2 products are formed.

Yield: 65% of theory

$C_{13}H_{14}BrN_3*C_2HF_3O_2$ (406.2)

R_t=1.63 min. method 2

53b-2) 6-(aminomethyl)-N-(4-bromo-2-(trifluoromethyl)phenyl)pyridin-3-amine

Yield: 11% of theory

$C_{13}H_{11}Br_FF_3N_3$ (346.15)

R_t=1.72 min. method 2

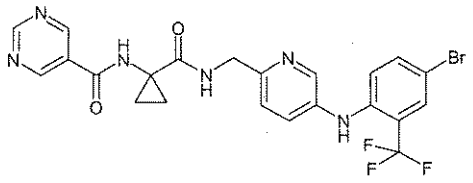
53c) pyrimidine-5-carboxylic acid-N-(1-((5-(4-bromo-2-methylphenylamino)pyridin-2-yl)-methylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared starting from 6-(aminomethyl)-N-(4-bromo-2-methylphenyl)pyridin-3-amine 2,2,2-trifluoroacetate (from 53b-1) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{22}H_{21}BrN_6O_2$ (481.35)

R_t = 1.61 min. method 2

Example 54: pyrimidine-5-carboxylic acid-N-(1-((5-(4-bromo-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

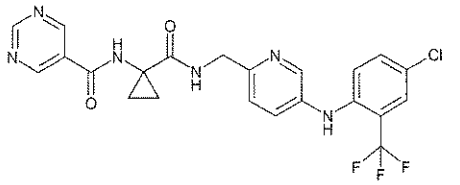


Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(4-bromo-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 53b-2) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{22}H_{18}BrF_3N_6O_2$ (535.32)

R_t = 1.82 min. method 2

Example 55: pyrimidine-5-carboxylic acid-N-(1-((5-(4-chloro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide



55a) 5-(4-chloro-2-(trifluoromethyl)phenylamino)picolinonitrile

The reaction took place under protective gas (nitrogen). 21 mg (0.04 mmol) Xantphos and 10 mg (0.01 mmol) tris(dibenzylideneacetone)dipalladium were added to a solution of 100 mg (0.55 mmol) 5-bromo-2-cyanopyridine, 93 µL (0.66 mmol) 2-amino-5-chlorobenzotrifluoride and 167 mg (0.77 mmol) potassium phosphate in 5 mL toluene. The mixture was stirred overnight at 110°C, the salts were filtered off and the filtrate was evaporated to dryness in vacuo. The residue was purified by HPLC (with eluant gradient, acetonitrile and water with 0.1% trifluoroacetic acid).

Yield: 68% of theory

$C_{13}H_7ClF_3N_3$ (297.66)

R_t = 2.53 min. method 2

55b) 6-(aminomethyl)-N-(4-chloro-2-(trifluoromethyl)phenyl)pyridin-3-amine

Analogously to method (53b) the title compound was prepared starting from 5-(4-chloro-2-(trifluoromethyl)phenylamino)picolinic acid nitrile and 2 molar lithium aluminium hydride solution.

$C_{13}H_{11}ClF_3N_3$ (301.69)

R_t = 1.72 min. method 2

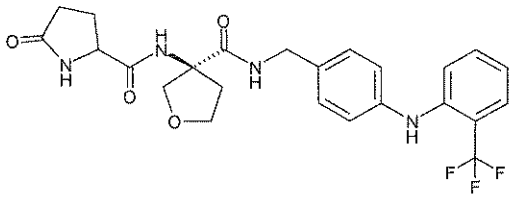
55c) pyrimidine-5-carboxylic acid-N-(1-((5-(4-chloro-2-(trifluoromethyl)phenylamino)pyridin-2-yl)methylcarbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared from 6-(aminomethyl)-N-(4-chloro-2-(trifluoromethyl)phenyl)pyridin-3-amine (from 55b) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 1b).

$C_{22}H_{18}ClF_3N_6O_2$ (490.87)

R_t = 1.76 min. method 2

Example 56: 5-oxo-N-((S)-3-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)-tetrahydrofuran-3-yl)pyrrolidine-2-carboxamide



56a) (S)-phenethyl-3-(tert-butoxycarbonylamino)tetrahydrofuran-3-carboxylate

2 g (9.18 mmol) di-tert-butyldicarbonate and 11.29 mL (9.18 mmol) TEA were added to a solution of 1.8 g (7.65 mmol) (S)-phenethyl 3-aminotetrahydrofuran-3-carboxylate (from 43a) in 30 mL dichloromethane. The mixture was stirred overnight at ambient temperature and then more di-tert-butyldicarbonate and 50 mg dimethylaminopyridine were added. The reaction mixture was evaporated to dryness in vacuo and the residue was taken up in 50 mL dioxane and stirred for 6 hours at 60°C. The solvent was distilled off and the residue was divided between ethyl acetate and 0.5 molar potassium hydrogen sulphate solution. The organic phase was washed with sodium hydrogen sulphate solution, dried on sodium sulphate and evaporated to dryness in vacuo. The residue was purified on silica gel with petroleum ether/ethyl acetate in the ratio 4:1.

Yield: 63% of theory

$C_{18}H_{25}NO_5$ (335.39)

R_t = 2.05 min. method 1

56b) (S)-3-tert-butoxycarbonylamino)tetrahydrofuran-3-carboxylic acid

8.94 mL (17.89 mmol) 2 molar sodium hydroxide solution were added to a solution of 1.5 g (4.47 mmol) (S)-phenethyl-3-(tert-butoxycarbonylamino)tetrahydrofuran-3-carboxylate in 20 mL ethanol. The mixture was stirred for 2 hours at ambient temperature and then 8.94 mL (17.89 mmol) 2 molar hydrochloric acid were added thereto. The mixture was evaporated down, the residue was suspended in ethanol and the salts were suction filtered. The filtrate was freed from the solvent and further reacted in crude form.

Yield: 100% of theory

$C_{10}H_{17}NO_5$ (231.25)

R_t = 1.53 min. method 1

56c) (S)-tert-butyl-3-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)-tetrahydrofuran-3-ylcarbamate

Analogously to method (1d) the title compound was prepared from N-(4-(aminomethyl)phenyl)-2-(trifluoromethyl)aniline (from 4a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid (from 56b).

$C_{24}H_{28}F_3N_3O_4$ (479.49)

56d) (S)-3-amino-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)tetrahydrofuran-3-carboxamide

2 g (4.17 mmol) (S)-tert-butyl-3-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)-tetrahydrofuran-3-ylcarbamate were stirred in 15 mL of a 1:1 mixture of dichloromethane and trifluoroacetic acid for 30 minutes at ambient temperature. After evaporation of the reaction mixture the residue was dissolved in dichloromethane, made basic with 4 molar sodium hydroxide solution and added to a phase separation cartridge. The filtrate was freed from the solvent and the crude product was chromatographed on silica gel with cyclohexane / ethyl acetate in the ratio 1:1 and then a second time with dichloromethane / methanol in the ratio 9:1.

Yield: 77% of theory

$C_{19}H_{20}F_3N_3O_2$ (379.38)

R_t = 1.97 min. method 6

56e) (S)-5-oxo-N-(-3-(4-(2-(trifluoromethyl)phenylamino)benzylcarbamoyl)tetrahydro-furan-3-yl)pyrrolidine-2-carboxamide

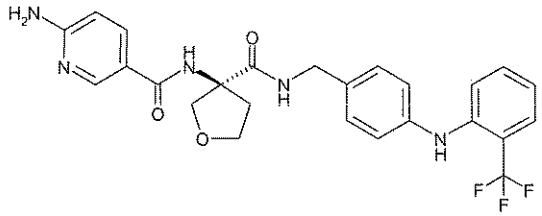
Analogously to method (1d) the title compound was prepared starting from (S)-3-amino-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)tetrahydrofuran-3-carboxamide (from 56d) and 5-oxopyrrolidine-2-carboxylic acid.

$C_{24}H_{25}F_3N_4O_4$ (490.49)

R_t = 1.84 min. method 5

Examples 57 to 107 that follow were prepared analogously to the method (1d) from (S)-3-amino-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)tetrahydrofuran-3-carboxamide and the corresponding acids.

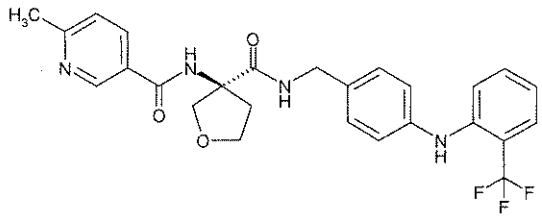
Example 57: (S)-6-amino-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl}-nicotinamide



$C_{25}H_{24}F_3N_5O_3$ (499.5)

R_t = 1.66 min. method 5

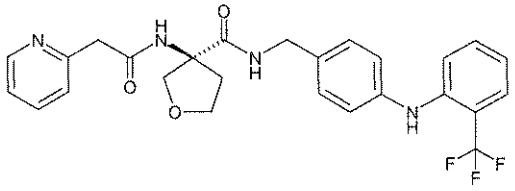
Example 58: (S)-6-methyl-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl}-nicotinamide



$C_{26}H_{25}F_3N_4O_3$ (498.5)

R_t = 1.69 min. method 5

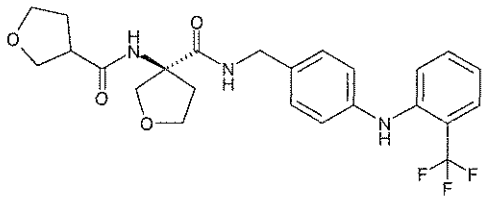
Example 59: 3-(2-pyridin-2-yl-acetylamino)-tetrahydro-furan-3-carboxylic acid 4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{26}H_{25}F_3N_4O_3$ (498.5)

R_t = 1.64 min. method 5

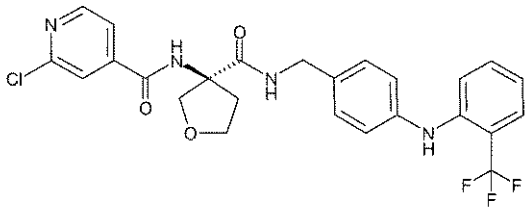
Example 60: (S)-3-[(tetrahydro-furan-3-carbonyl)-amino]-tetrahydro-furan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{24}H_{26}F_3N_3O_4$ (477.5)

R_t = 1.96 min. method 5

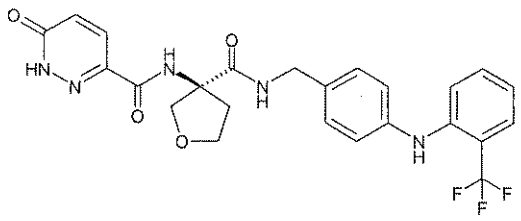
Example 61: (S)-2-chloro-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl}-isonicotinamide



$C_{25}H_{22}ClF_3N_4O_3$ (518.9)

R_t = 2.15 min. method 5

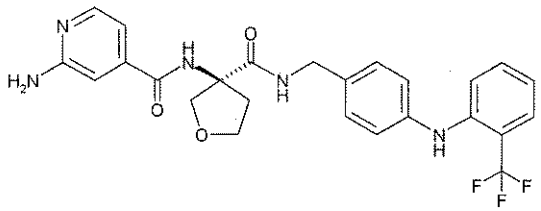
Example 62: (S)-6-oxo-1,6-dihydro-pyridazine-3-carboxylic acid {3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl}-amide



$C_{24}H_{22}F_3N_5O_4$ (501.5)

R_t = 1.91 min. method 5

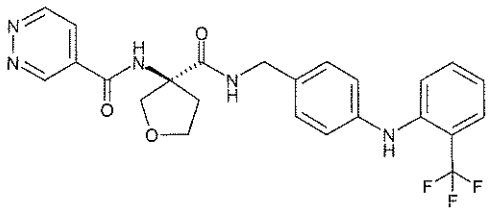
Example 63: (S)-2-amino-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl}-isonicotinamide



$C_{25}H_{24}F_3N_5O_3$ (499.5)

R_t = 1.64 min. method 5

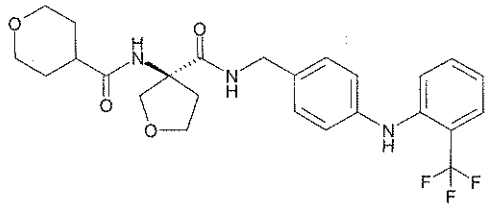
Example 64: (S)-pyridazine-4-carboxylic acid {3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl}-amide



$C_{24}H_{22}F_3N_5O_3$ (485.5)

R_t = 1.92 min. method 5

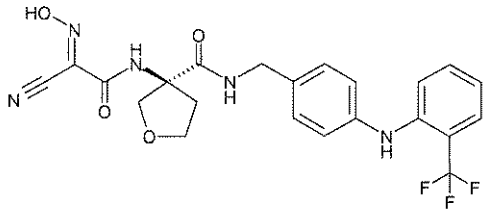
Example 65: (S)-tetrahydropyran-4-carboxylic acid {3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{25}H_{28}F_3N_3O_4$ (491.5)

R_t = 1.97 min. method 5

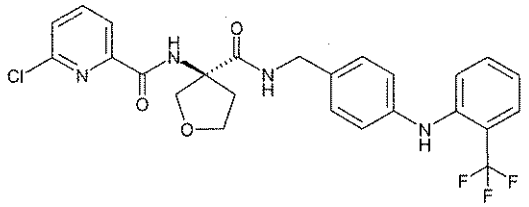
Example 66: (S)-3-(2-cyano-2-hydroxyimino-acetylamino)-tetrahydro-furan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{22}H_{20}F_3N_5O_4$ (475.4)

R_t = 2.07 min. method 5

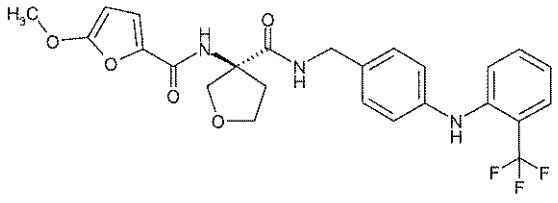
Example 67: (S)-6-chloro-pyridine-2-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl}-amide



$C_{25}H_{22}ClF_3N_4O_3$ (518.9)

R_t = 2.25 min. method 5

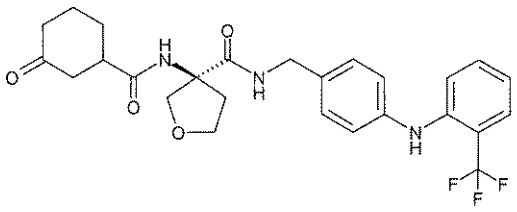
Example 68: (S)-5-methoxy-furan-2-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{25}H_{24}F_3N_3O_5$ (503.5)

R_t = 2.12 min. method 5

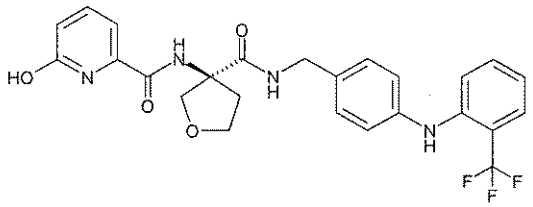
Example 69: (S)-3-[(3-oxo-cyclohexanecarbonyl)-amino]-tetrahydro-furan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{26}H_{28}F_3N_3O_4$ (503.5)

R_t = 2.00 min. method 5

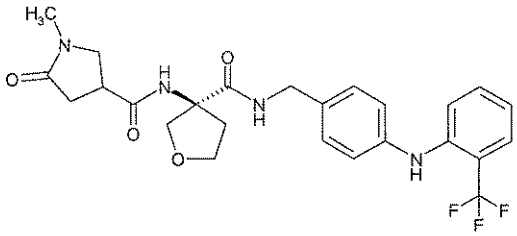
Example 70: (S)-6-hydroxy-pyridine-2-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{25}H_{23}F_3N_4O_4$ (500.5)

R_t = 1.94 min. method 5

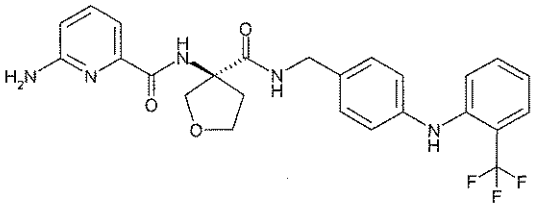
Example 71: (S)-1-methyl-5-oxo-pyrrolidine-3-carboxylic acid {3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{25}H_{27}F_3N_4O_4$ (504.5)

R_t = 1.85 min. method 5

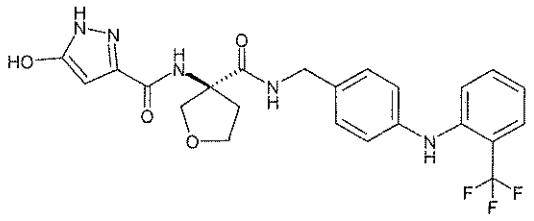
Example 72: (S)-6-amino-pyridine-2-carboxylic acid {3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{25}H_{24}F_3N_5O_3$ (499.5)

R_t = 1.72 min. method 5

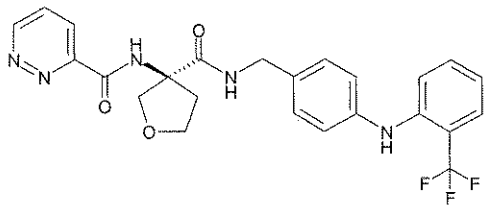
Example 73: (S)-5-hydroxy-1H-pyrazole-3-carboxylic acid {3-[4-(2-trifluoromethyl-phenyl-amino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{23}H_{22}F_3N_5O_4$ (489.5)

R_t = 1.89 min. method 5

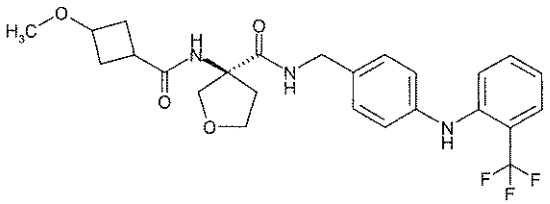
Example 74: (S)-pyridazine-3-carboxylic acid {3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{24}H_{22}F_3N_5O_3$ (485.5)

R_t = 2.02 min. method 5

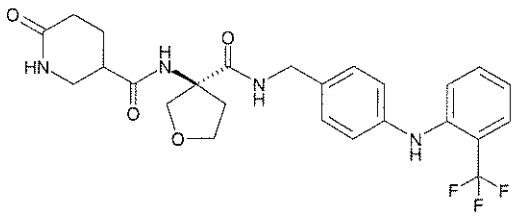
Example 75: (S)-3-[(3-methoxy-cyclobutanecarbonyl)-amino]-tetrahydro-furan-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{25}H_{28}F_3N_3O_4$ (491.5)

R_t = 2.02 min. method 5

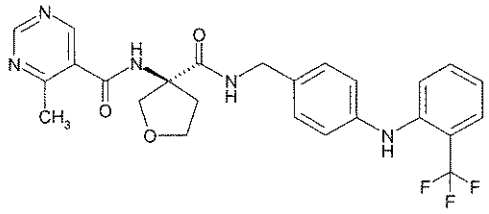
Example 76: (S)-6-oxo-piperidine-3-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{25}H_{27}F_3N_4O_4$ (504.5)

R_t = 1.81 min. method 5

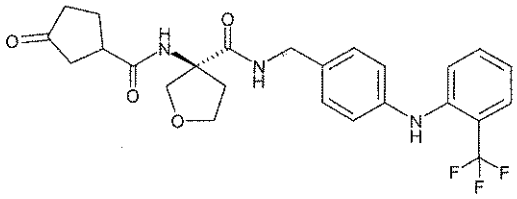
Example 77: (S)-4-methyl-pyrimidine-5-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{25}H_{24}F_3N_5O_3$ (499.5)

R_t = 1.96 min. method 5

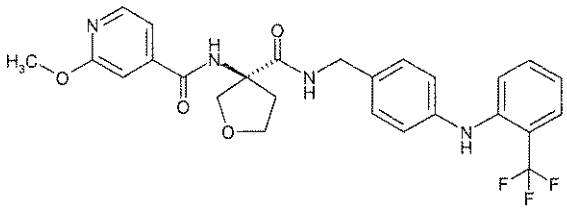
Example 78: (S)-3-[(3-oxo-cyclopentanecarbonyl)-amino]-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{25}H_{26}F_3N_3O_4$ (489.5)

R_t = 1.97 min. method 5

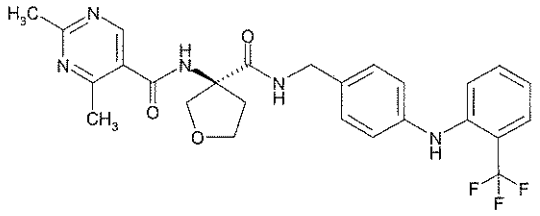
Example 79: (S)-2-methoxy-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-isonicotinamide



$C_{26}H_{25}F_3N_4O_4$ (514.5)

R_t = 2.11 min. method 5

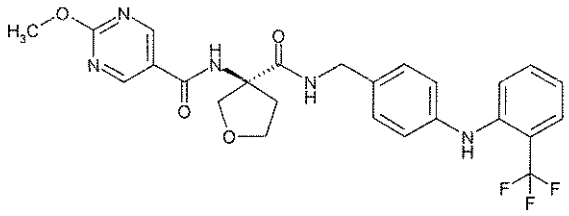
Example 80: (S)-2,4-dimethyl-pyrimidine-5-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{26}H_{26}F_3N_5O_3$ (513.5)

R_t = 1.95 min. method 5

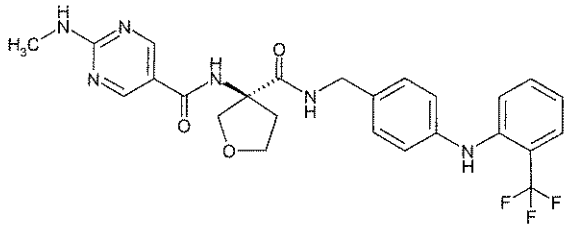
Example 81: (S)-2-methoxy-pyrimidine-5-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{25}H_{24}F_3N_5O_4$ (515.5)

R_t = 2.04 min. method 5

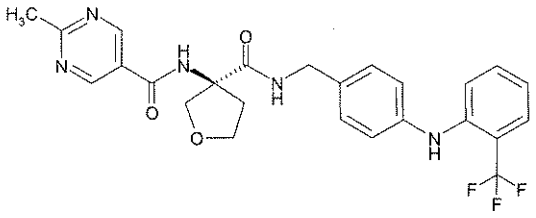
Example 82: (S)-2-methylamino-pyrimidine-5-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{25}H_{25}F_3N_6O_3$ (514.5)

R_t = 1.91 min. method 5

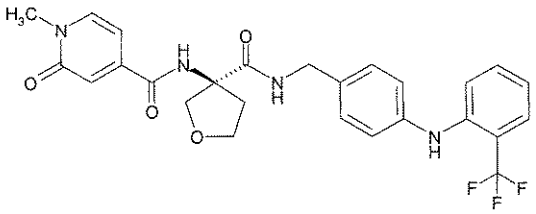
Example 83: (S)-2-methyl-pyrimidine-5-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{25}H_{24}F_3N_5O_3$ (499.5)

R_t = 1.97 min. method 5

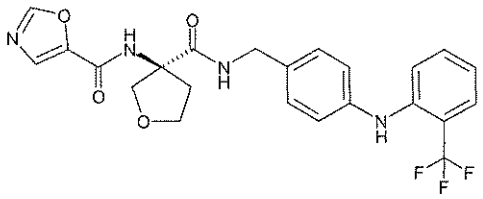
Example 84: (S)-1-methyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{26}H_{25}F_3N_4O_4$ (514.5)

R_t = 1.90 min. method 5

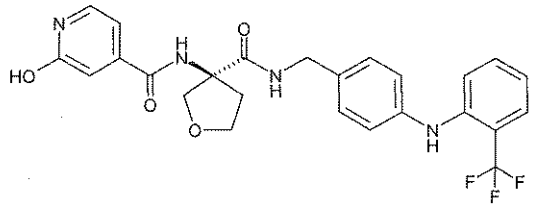
Example 85: (S)-oxazole-5-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{23}H_{21}F_3N_4O_4$ (474.4)

R_t = 1.97 min. method 5

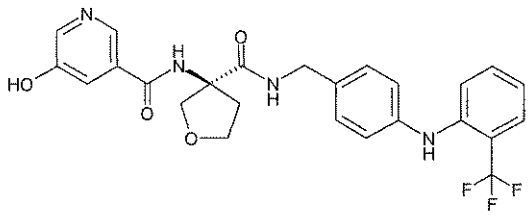
Example 86: (S)-2-hydroxy-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-isonicotinamide



$C_{25}H_{23}F_3N_4O_4$ (500.5)

R_t = 1.85 min. method 5

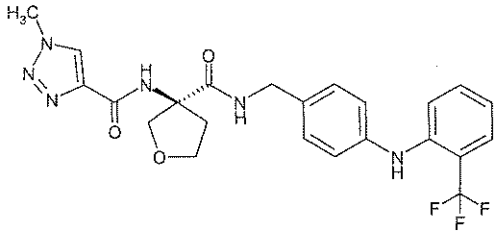
Example 87: (S)-5-hydroxy-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-nicotinamide



$C_{25}H_{23}F_3N_4O_4$ (500.5)

R_t = 1.72 min. method 5

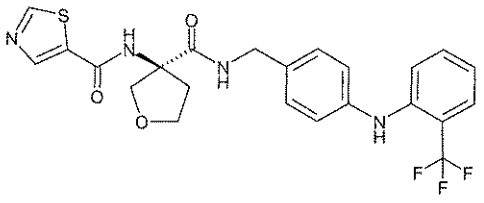
Example 88: (S)-1-methyl-1H-[1.2.3]triazole-4-carboxylic acid {3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{23}H_{23}F_3N_6O_3$ (488.5)

R_t = 1.99 min. method 5

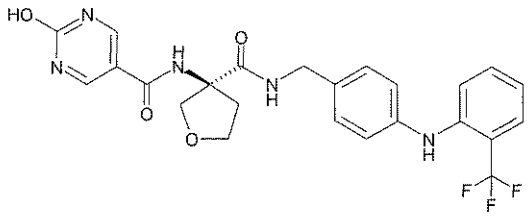
Example 89: (S)-thiazole-5-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydro-furan-3-yl}-amide



$C_{23}H_{21}F_3N_4O_3S$ (490.5)

R_t = 2.01 min. method 5

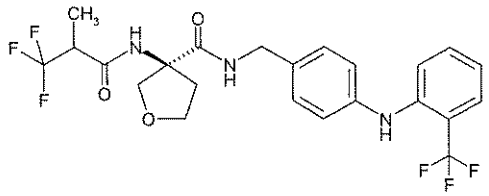
Example 90: (S)-2-hydroxy-pyrimidine-5-carboxylic acid-{3-[4-(2-trifluoromethyl-phenyl-amino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{24}H_{22}F_3N_5O_4$ (501.5)

R_t = 1.79 min. method 5

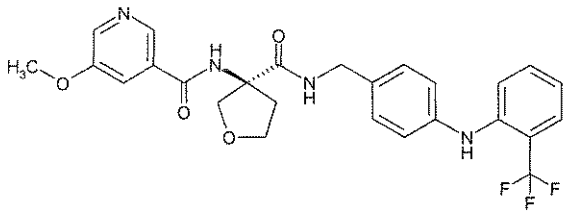
Example 91: (S)-3-(3,3,3-trifluoro-2-methyl-propionylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{23}H_{23}F_6N_3O_3$ (503.4)

R_t = 2.18 min. method 5

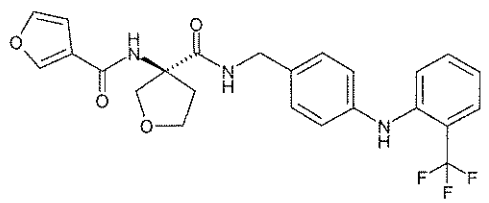
Example 92: (S)-5-methoxy-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-nicotinamide



$C_{26}H_{25}F_3N_4O_4$ (514.5)

R_t = 1.85 min. method 5

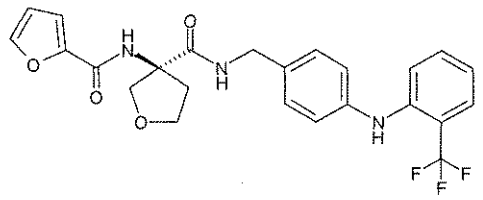
Example 93: (S)-furan-3-carboxylic acid {3-[4-(2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{24}H_{22}F_3N_3O_4$ (473.4)

R_t = 2.09 min. method 5

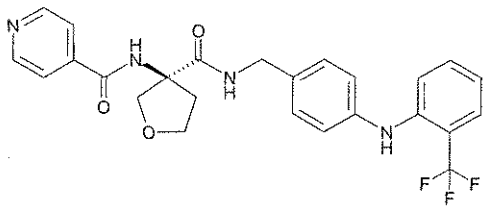
Example 94: (S)-furan-2-carboxylic acid {3-[4-(2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{24}H_{22}F_3N_3O_4$ (473.4)

R_t = 2.08 min. method 5

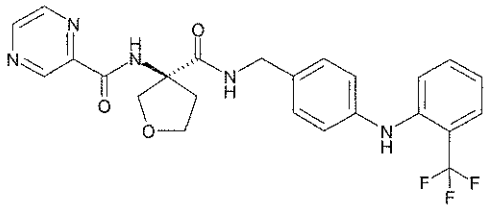
Example 95: (S)-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl}-isonicotinamide



$C_{25}H_{23}F_3N_4O_3$ (484.5)

R_t = 1.71 min. method 5

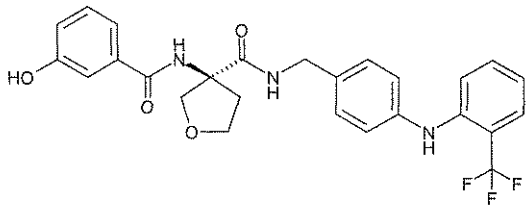
Example 96: (S)-pyrazine-2-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{24}H_{22}F_3N_5O_3$ (485.5)

R_t = 2.06 min. method 5

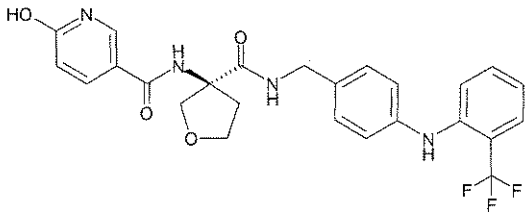
Example 97: (S)-3-(3-hydroxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{26}H_{24}F_3N_3O_4$ (499.5)

R_t = 2.03 min. method 5

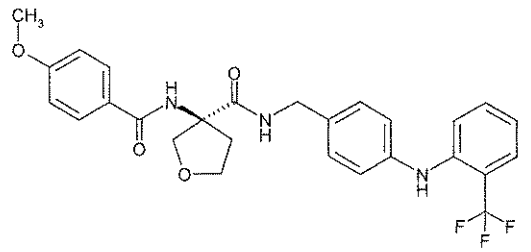
Example 98: (S)-6-hydroxy-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-nicotinamide



$C_{25}H_{23}F_3N_4O_4$ (500.5)

R_t = 1.84 min. method 5

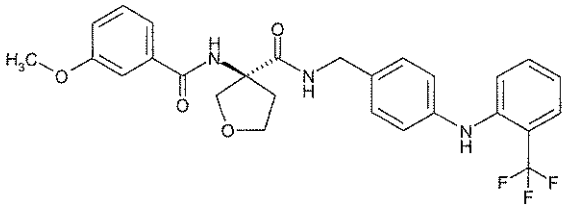
Example 99: (S)-3-(4-methoxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{27}H_{26}F_3N_3O_4$ (513.5)

R_t = 2.16 min. method 5

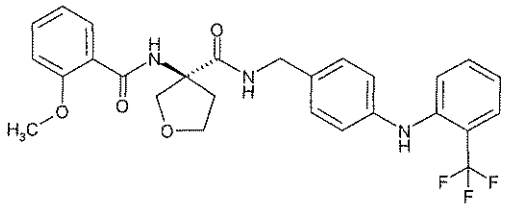
Example 100: (S)-3-(3-methoxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{27}H_{26}F_3N_3O_4$ (513.5)

R_t = 2.18 min. method 5

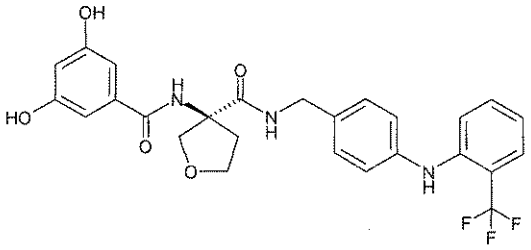
Example 101: (S)-3-(2-methoxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{27}H_{26}F_3N_3O_4$ (513.5)

R_t = 2.22 min. method 5

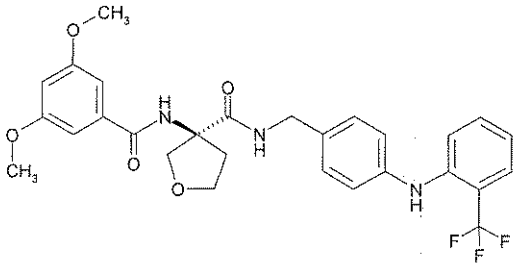
Example 102: (S)-3-(3,5-dihydroxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{26}H_{24}F_3N_3O_5$ (515.5)

R_t = 1.93 min. method 5

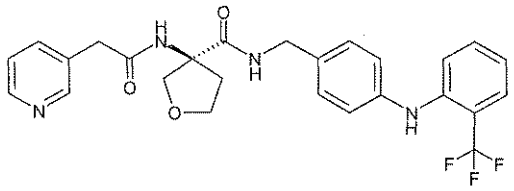
Example 103: (S)-3-(3,5-dimethoxy-benzoylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{28}H_{28}F_3N_3O_5$ (543.5)

R_t = 2.20 min. method 5

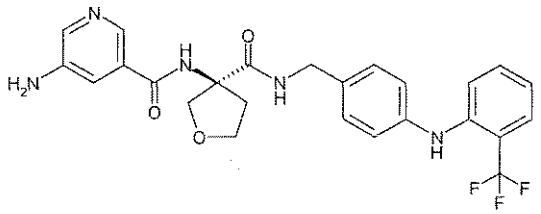
Example 104: (S)-3-(2-pyridin-3-yl-acetylamino)-tetrahydrofuran-3-carboxylic acid-4-(2-trifluoromethyl-phenylamino)-benzylamide



$C_{26}H_{25}F_3N_4O_3$ (498.5)

R_t = 1.64 min. method 5

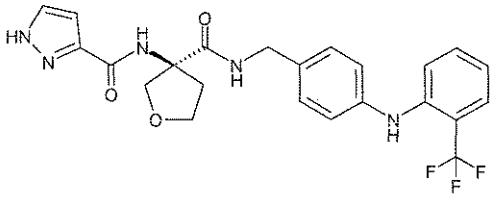
Example 105: (S)-5-amino-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-nicotinamide



$C_{25}H_{24}F_3N_5O_3$ (499.5)

R_t = 1.65 min. method 5

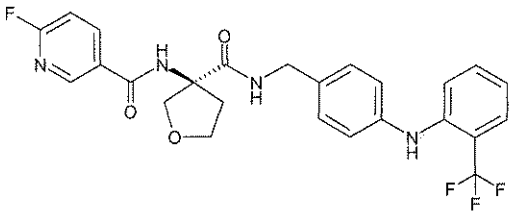
Example 106: (S)-1H-pyrazole-3-carboxylic acid {3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



$C_{23}H_{22}F_3N_5O_3$ (473.5)

R_t = 1.96 min. method 5

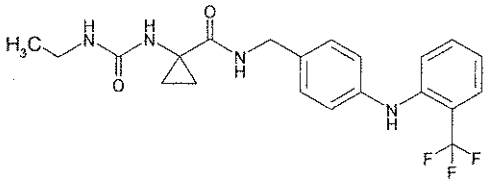
Example 107: (S)-6-fluoro-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-nicotinamide



$C_{25}H_{22}F_4N_4O_3$ (502.5)

R_t = 2.10 min. method 5

Example 108: 1-(3-ethylureido)-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)cyclopropanecarboxamide



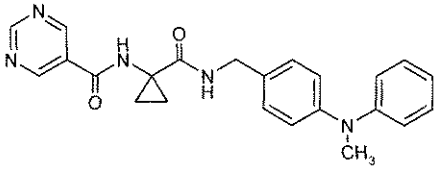
A solution of 55 mg (0.16 mmol) 1-amine-N-(4-(2-(trifluoromethyl)phenylamino)benzyl)-cyclopropanecarboxamide (from 5a) in 2 mL dichloromethane was combined with 68 µL (0.49 mmol) TEA and 16 µL (0.2 mmol) ethylisocyanate and stirred overnight at ambient temperature. Then ethylisocyanate was added another three times and the mixture was stirred at ambient temperature or at 60°C. Then the reaction mixture was evaporated to dryness in vacuo and purified by RP-HPLC-MS with an eluant gradient (water/acetonitrile = 1:1 to 1:20 + 0.1% trifluoroacetic acid).

Yield: 79% of theory

$C_{21}H_{23}F_3N_4O_2$ (420.43)

R_t = 2.27 min. method 5

Example 109: pyrimidine-5-carboxylic acid-N-(1-(4-(methyl(phenyl)amino)benzylcarbamoyl)cyclopropyl)amide



109a) 4-(aminomethyl)-N-methyl-N-phenylaniline

Analogously to method (1c) the title compound was prepared from N-methylaniline and 4-fluorobenzonitrile.

$C_{14}H_{16}N_2$ (212.3)

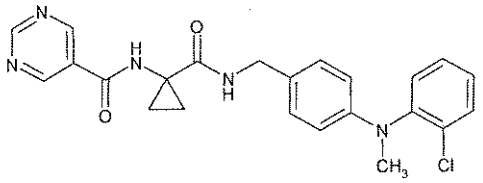
109b) pyrimidine-5-carboxylic acid-N-(1-(4-(methyl(phenyl)amino)benzylcarbamoyl)-cyclopropyl)amide

Analogously to method (1d) the title compound was prepared starting from 4-(aminomethyl)-N-methyl-N-phenylaniline (from 109a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropane-carboxylic acid (from 1b).

$C_{23}H_{23}N_5O_2$ (401.47)

R_t= 2.87 min. method 5

Example 110: pyrimidine-5-carboxylic acid- N-(1-(4-((2-chlorophenyl)(methyl)amino)-benzylcarbamoyl)cyclopropyl)amide



110a) N-(4-(aminomethyl)phenyl)-2-chloro-N-methylaniline

Analogously to Example (1c) the title compound was prepared starting from 2-chloro-N-methylaniline and 4-fluorobenzonitrile.

$C_{14}H_{15}ClN_2$ (246.74)

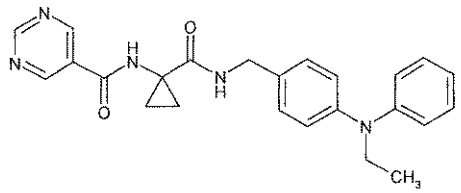
110b) pyrimidine-5-carboxylic acid-N-(1-(4-((2-chlorophenyl)(methyl)amino)benzylcarbamoyl)cyclopropyl)amide

Analogously to Example (1d) the title compound was prepared starting from N-(4-(aminomethyl)phenyl)-2-chloro-N-methylaniline (from 110a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropane-carboxylic acid (from 1b).

$C_{23}H_{22}ClN_5O_2$ (435.91)

R_t = 2.23 min. method 11

Example 111: pyrimidine-5-carboxylic acid-N-(1-(4-(ethyl(phenyl)amino)benzylcarbamoyl)cyclopropyl)amide



111a) 4-(aminomethyl)-N-ethyl-N-phenylaniline

Analogously to method (1c) the title compound was prepared starting from N-ethylaniline and 4-fluorobenzonitrile.

$C_{15}H_{18}N_2$ (226.32)

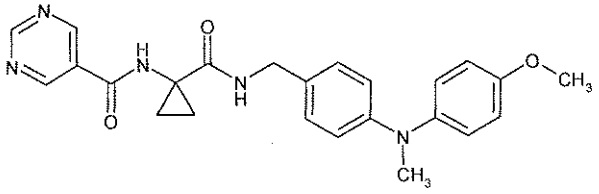
111b) pyrimidine-5-carboxylic acid-N-(1-(4-(ethyl(phenyl)amino)benzylcarbamoyl)-cyclopropyl)amide

Analogously to method (1d) the title compound was prepared from 4-(aminomethyl)-N-ethyl-N-phenylaniline (from 111a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropane-carboxylic acid (from 1b).

$C_{24}H_{25}N_5O_2$ (415.49)

R_t = 2.26 min. method 11

Example 112: pyrimidine-5-carboxylic acid-N-(1-(4-((4-methoxyphenyl)(methyl)amino)benzylcarbamoyl)cyclopropyl)amide



111a) 4-(aminomethyl)-N-(4-methoxyphenyl)-N-methylaniline

Analogously to method (1c) the title compound was prepared starting from 4-methoxy-N-methylaniline and 4-fluorobenzonitrile using Raney nickel.

$C_{15}H_{18}N_2O$ (242.32)

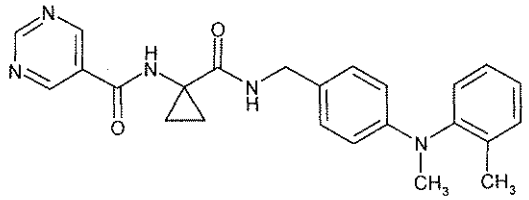
112b) pyrimidine-5-carboxylic acid-N-(1-(4-((4-methoxyphenyl)(methyl)amino)benzyl-carbamoyl)cyclopropyl)amide

Analogously to method (1d) the title compound was prepared starting from 4-(aminomethyl)-N-(4-methoxyphenyl)-N-methylaniline (from 112a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropane-carboxylic acid (from 1b).

$C_{24}H_{25}N_5O_3$ (431.49)

R_t = 2.13 min. method 11

Example 113: pyrimidine-5-carboxylic acid-N-(1-(4-(methyl(o-tolyl)amino)benzylcarbamoyl)cyclopropyl)amide



113a) N-(4-(aminomethyl)phenyl)-2-chloro-N-methylaniline

Analogously to method (1c) N-methyl-o-toluidine and 4-fluorobenzonitrile were reacted using Raney nickel to obtain the title compound.

$C_{15}H_{18}N_2$ (226.32)

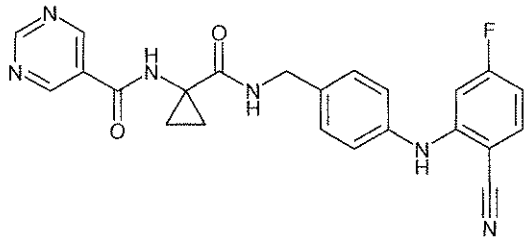
113b) pyrimidine-5-carboxylic acid-N-(1-(4-(methyl(o-tolyl)amino)benzylcarbamoyl)-cyclopropyl)amide

Analogously to method (1d) the title compound was prepared from N-(4-(aminomethyl)phenyl)-2-chloro-N-methylaniline (from 113a) and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropane-carboxylic acid (from 1b).

$C_{24}H_{25}N_5O_2$ (415.49)

R_t = 2.26 min. method 11

Example 114: pyrimidine-5-carboxylic acid-{1-[4-(2-cyano-5-fluoro-phenylamino)-benzyl-carbamoyl]-cyclopropyl}-amide



114a) tert-butyl [4-(2-cyano-5-fluoro-phenylamino)-benzyl]-carbamate

Prepared analogously to the method in (55a) from 2-bromo-4-fluoro-benzonitrile and tert-butyl (4-amino-benzyl)-carbamate.

Yield: 60% of theory

$C_{19}H_{20}FN_3O_2$ (341.38)

R_t = 2.65 min. method 12

114b) 2-(4-aminomethyl-phenylamino)-4-fluoro-benzonitrile di-trifluoroacetate

92 mg (0.27 mmol) tert-butyl [4-(2-cyano-5-fluoro-phenylamino)-benzyl]-carbamate were stirred in 1 mL trifluoroacetic acid and 5 mL dichloromethane for 1 hour at ambient temperature. Then the reaction mixture was evaporated to dryness in vacuo.

Yield: 96% of theory

$C_{14}H_{12}FN_3 * 2\ C_2HF_3O_2$ (469.31)

R_t = 1.41 min. method 12

114c) pyrimidine-5-carboxylic acid {1-[4-(2-cyano-5-fluoro-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide

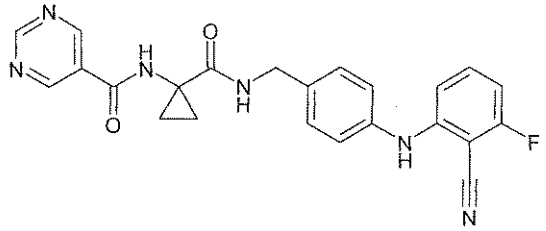
83 mg (0.21 mmol) TBTU, 146 µL (1.0 mmol) triethylamine and 122 mg (0.21 mmol) 2-(4-aminomethyl-phenylamino)-4-fluoro-benzonitrile di-trifluoroacetate were added to a solution of 54 mg (0.26 mmol) 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid in 5 mL DMF. The mixture was stirred overnight at ambient temperature and then the solvents were distilled off in vacuo. The residue was purified by chromatography (RP with eluant gradient, acetonitrile and water with 0.1% trifluoroacetic acid).

Yield: 69% of theory

$C_{23}H_{19}FN_6O_2$ (430.44)

R_t = 1.91 min. method 12

Example 115: pyrimidine-5-carboxylic acid {1-[4-(2-cyano-3-fluoro-phenylamino)-benzyl-carbamoyl]-cyclopropyl}-amide



115a) tert-butyl 4-(2-cyano-3-fluoro-phenylamino)-benzyl]-carbamate

The title compound was obtained from 2-bromo-6-fluoro-benzonitrile and tert-butyl (4-amino-benzyl)-carbamate analogously to method (55a).

$C_{19}H_{20}FN_3O_2$ (341.38)

R_t = 2.65 min. method 12

115b) 2-(4-aminomethyl-phenylamino)-6-fluoro-benzonitrile di-trifluoroacetate

The title compound was prepared from tert-butyl [4-(2-cyano-3-fluoro-phenylamino)-benzyl]-carbamate analogously to method (114b).

$C_{14}H_{12}FN_3 * 2\ C_2HF_3O_2$ (469.31)

R_t = 1.46 min. method 12

115c) pyrimidine-5-carboxylic acid-{1-[4-(2-cyano-3-fluoro-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide

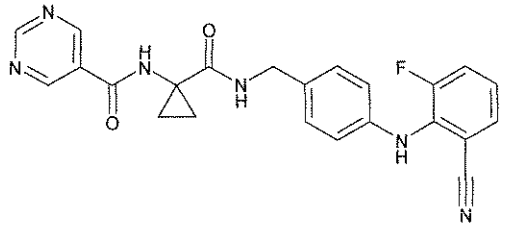
The title compound was obtained analogously to method (114c) from 2-(4-aminomethyl-phenylamino)-6-fluoro-benzonitrile di-trifluoroacetate and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid.

Yield: 44% of theory

$C_{23}H_{19}FN_6O_2$ (430.44)

R_t = 1.94 min. method 12

Example 116: pyrimidine-5-carboxylic acid-{1-[4-(2-cyano-6-fluoro-phenylamino)-benzyl-carbamoyl]-cyclopropyl}-amide



116a) tert-butyl [4-(2-cyano-6-fluoro-phenylamino)-benzyl]-carbamidate

The title compound was prepared from 2-bromo-3-fluoro-benzonitrile and tert-butyl (4-amino-benzyl)-carbamate according to method (55a).

$C_{19}H_{20}FN_3O_2$ (341.38)

R_t = 2.50 min. method 12

116b) 2-(4-aminomethyl-phenylamino)-3-fluoro-benzonitrile di-trifluoroacetate

Preparation of the title compound from tert-butyl [4-(2-cyano-6-fluoro-phenylamino)-benzyl]-carbamate analogously to method (114b).

$C_{14}H_{12}FN_3 * 2\ C_2HF_3O_2$ (469.31)

R_t = 1.27 min. method 12

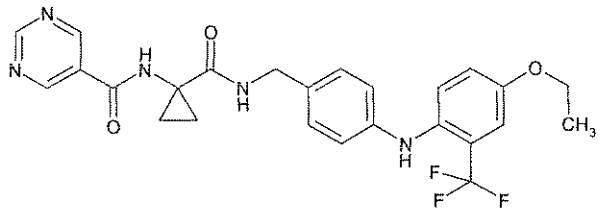
116c) pyrimidine-5-carboxylic acid {1-[4-(2-cyano-6-fluoro-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide

The title compound was prepared analogously to method (114c) from 2-(4-aminomethyl-phenylamino)-3-fluoro-benzonitrile di-trifluoroacetate and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid.

$C_{23}H_{19}FN_6O_2$ (430.44)

R_t = 1.78 min. method 12

Example 117: pyrimidine-5-carboxylic acid {1-[4-(4-ethoxy-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



117a) 4-(4-ethoxy-2-trifluoromethyl-phenylamino)-benzonitrile

276 mg (2.28 mmol) 4-fluoro-benzonitrile and 550 mg (2.28 mmol) 4-ethoxy-2-trifluoromethyl-phenylamine-hydrochloride were dissolved in 10 mL DMSO and combined with 639 mg (5.69 mmol) potassium-tert-butoxide while cooling with ice. The reaction mixture was stirred overnight at ambient temperature, diluted with water and extracted with diethyl ether. The organic phase was dried on sodium sulphate and evaporated down. The residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 9:1).

Yield: 20% of theory

$C_{16}H_{13}F_3N_2O$ (306.28)

mass spectroscopy $[M+H]^+$ = 307

117b) (4-aminomethyl-phenyl)-(4-ethoxy-2-trifluoromethyl-phenyl)-amine

140 mg (0.46 mmol) 4-(4-ethoxy-2-trifluoromethyl-phenylamino)-benzonitrile in 10 mL methanolic ammonia were hydrogenated with Raney nickel as catalyst at 50 psi hydrogen pressure. The catalyst was filtered off and the filtrate was freed from the solvent.

$C_{16}H_{17}F_3N_2O$ (310.31)

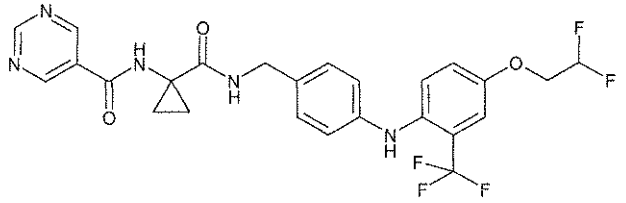
117c) pyrimidine-5-carboxylic acid {1-[4-(4-ethoxy-2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-cyclopropyl}-amide

1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid and (4-aminomethyl-phenyl)-(4-ethoxy-2-trifluoromethyl-phenyl)-amine were refluxed analogously to method (1d). After the end of the reaction the solvent was distilled off and the residue was combined with ethyl acetate, extracted with sodium hydrogen carbonate solution and dried on sodium sulphate. The solution was evaporated down in vacuo and the residue was purified on a silica gel column (dichloromethane/ethanol = 19:1)

$C_{25}H_{24}F_3N_5O_3$ (499.49)

mass spectroscopy $[M+H]^+ = 500$

Example 118: pyrimidine-5-carboxylic acid (1-{4-[4-(2,2-difluoro-ethoxy)-2-trifluoromethyl-phenylamino]-benzylcarbamoyl}-cyclopropyl)-amide hydrochloride



118a) 4-[4-(2,2-difluoro-ethoxy)-2-trifluoromethyl-phenylamino]-benzonitrile

The title compound was obtained analogously to method (117a) from 4-fluoro-benzonitrile and 4-(2,2-difluoro-ethoxy)-2-trifluoromethyl-phenylamine.

Yield: 32% of theory

$C_{16}H_{11}F_5N_2O$ (342.26)

mass spectroscopy $[M+H]^+ = 343$

118b) (4-aminomethyl-phenyl)-[4-(2,2-difluoro-ethoxy)-2-trifluoromethyl-phenyl]-amine

The title compound was prepared analogously to method (117b) from 4-[4-(2,2-difluoro-ethoxy)-2-trifluoromethyl-phenylamino]-benzonitrile.

$C_{16}H_{15}F_5N_2O$ (346.30)

mass spectroscopy $[M+H-NH_3]^+ = 330$

118c) pyrimidine-5-carboxylic acid (1-{4-[4-(2,2-difluoro-ethoxy)-2-trifluoromethylphenylamino]-benzylcarbamoyl}-cyclopropyl)-amide hydrochloride

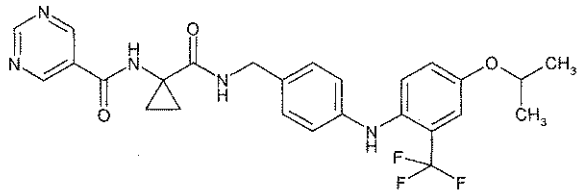
(4-aminomethyl-phenyl)-[4-(2,2-difluoro-ethoxy)-2-trifluoromethyl-phenyl]-amine and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid were refluxed analogously to method (1d). The reaction mixture was then purified by chromatography (RP, acetonitrile/water + 0.15% formic acid). The fractions containing product were evaporated down, made alkaline with aqueous ammonia solution and extracted with ethyl acetate. Then the organic phases were evaporated down, the residue was dissolved in ethyl acetate, an acid pH was created with hydrochloric acid and the solvent was distilled off.

Yield: 56% of theory

$C_{25}H_{22}F_5N_5O_3$ * HCl (571.93)

R_t = 3.96 min method 10

Example 119: Pyrimidine-5-carboxylic acid-{1-[4-(4-isopropoxy-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



119a) 4-(4-isopropoxy-2-trifluoromethyl-phenylamino)-benzonitrile

Prepared analogously to method (117a) from 4-fluoro-benzonitrile and 4-isopropoxy-2-trifluoromethyl-phenylamine.

Yield: 37% of theory

$C_{17}H_{15}F_3N_2O$ (320.31)

mass spectroscopy $[M+H]^+$ = 321

119b) (4-aminomethyl-phenyl)-(4-isopropoxy-2-trifluoromethyl-phenyl)-amine

The title compound was obtained according to method (117b) from 4-(4-isopropoxy-2-trifluoromethyl-phenylamino)-benzonitrile.

$C_{17}H_{19}F_3N_2O$ (324.34)

mass spectroscopy $[M+H-NH_3]^+$ = 308

119c) pyrimidine-5-carboxylic acid {1-[4-(4-isopropoxy-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide

(4-aminomethyl-phenyl)-(4-isopropoxy-2-trifluoromethyl-phenyl)-amine and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid were reacted analogously to method (1d).

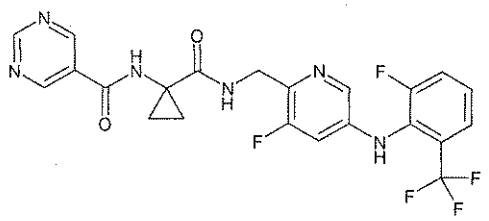
After the chromatographic purification (RP, acetonitrile/water + 0.15% formic acid) of the reaction mixture the hydrochloride was prepared as described in method (118c).

Yield: 28% of theory

$C_{26}H_{26}F_3N_5O_3$ * HCl (549.97)

R_t = 2.72 min method 14

Example 120: pyrimidine-5-carboxylic acid-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



120a) 3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile

While cooling with ice 7.21 g (64.2 mmol) potassium-tert-butoxide were added to a solution of 6.00 g (42.8 mmol) 3,5-difluoro-pyridine-2-carbonitrile and 7.67 g (42.8 mmol) 2-fluoro-6-trifluoromethyl-phenylamine in 240 mL DMSO. The reaction mixture was stirred for 2 hours at ambient temperature, mixed with water and extracted with diethyl ether. The organic phases were dried on sodium sulphate and evaporated down. The residue was purified by chromatography (silica gel, petroleum ether with 0-15% ethyl acetate).

120b) (6-aminomethyl-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine

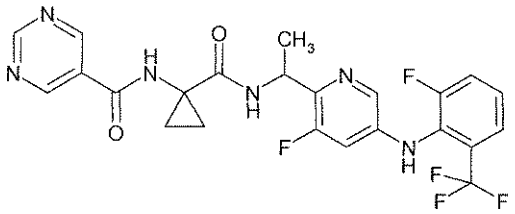
3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile was hydrogenated analogously to method (1c). The product obtained was further reacted directly.

120c) pyrimidine-5-carboxylic acid (1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

(6-aminomethyl-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid were reacted analogously to method (1d). For working up solvent was distilled off. Then the residue was mixed with water, made alkaline with potassium carbonate solution and extracted with ethyl acetate. The organic phases were washed with water, dried on sodium sulphate and evaporated down. The crude product remaining was purified by chromatography.

$C_{22}H_{17}F_5N_6O_2$ (492.40)
mass spectroscopy $[M+H]^+ = 493$

Example 121: pyrimidine-5-carboxylic acid-(1-{1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide



121a) 1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone
At -25°C a solution of 2.70 g (9.02 mmol) (6-aminomethyl-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine in 50 mL diethyl ether was added dropwise to 12 mL of a 3 molar methylmagnesium bromide solution in 50 mL diethyl ether. The reaction mixture was heated to 5°C and then while being cooled combined with 1 molar aqueous hydrochloric acid. Then the organic phase was separated off, dried on sodium sulphate and evaporated down. The residue was used in the next reaction without any further purification.
$C_{14}H_9F_5N_2O$ (316.23)
mass spectroscopy $[M+H]^+ = 317$

121b) 1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxime
1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone was reacted analogously to method (40c). For working up the reaction mixture was evaporated down, mixed with water and extracted with ethyl acetate. The organic phases were washed with water and sodium chloride solution and dried on sodium sulphate. After the solvent has been distilled off the residue was purified by chromatography (silica gel, dichloromethane with 2-6% methanol).
$C_{14}H_{10}F_5N_3O$ (331.24)
mass spectroscopy $[M+H]^+ = 332$

121c) 6-(1-amino-ethyl)-5-fluoro-pyridin-3-yl]-(2-fluoro-6-trifluoromethyl-phenyl)-amine

The reaction of 1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxime was carried out analogously to method (40d). The crude product was purified by chromatography (silica gel, ethyl acetate with 0-10% methanol/ammonia = 9:1).

$C_{14}H_{12}F_5N_3$ (317.26)

mass spectroscopy $[M+H]^+ = 318$

121d) pyrimidine-5-carboxylic acid-(1-{1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide

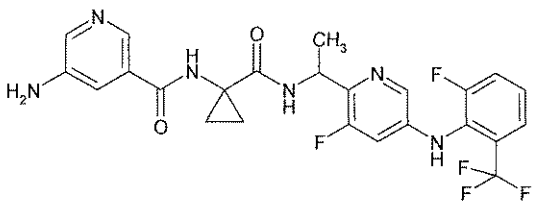
6-(1-amino-ethyl)-5-fluoro-pyridin-3-yl]-(2-fluoro-6-trifluoromethyl-phenyl)-amine and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid were reacted analogously to method (1d). For working up the reaction mixture was evaporated down and made alkaline with potassium carbonate solution. The solid was filtered off, washed with water and dried. Then the residue was purified by chromatography on a silica gel column and the fractions containing product were freed from the solvent. The hydrochloride was obtained by dissolving the residue in an amount of ethyl acetate and combining it with ethereal hydrochloric acid.

$C_{23}H_{19}F_5N_6O_2 * 2\ HCl$ (579.35)

mass spectroscopy $[M+H]^+ = 507$

The (R)- and (S)-enantiomer of Example 121 were obtained by chiral HPLC (SFC) from the racemic compound (column: Daicel AD-H, 250 x 20 mm, eluant: 80% supercritical carbon dioxide and 20% isopropanol with 0.2% diethylamine, flow rate: 70 mL/min).

Example 122: 5-amino-N-(1-{1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-nicotinamide



122a) tert-butyl (1-{1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-carbamate

1-tert-butoxycarbonylamino-cyclopropanecarboxylic acid and 6-(1-amino-ethyl)-5-fluoro-pyridin-3-yl]-(2-fluoro-6-trifluoromethyl-phenyl)-amine were reacted and worked up as

described in method (121d). In the final chromatographic purification a silica gel column was used (petroleum ether with 30-50% ethyl acetate).

122b) 1-amino-cyclopropanecarboxylic acid-{1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl}-amide

400 mg (0.80 mmol) tert-butyl (1-{1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-carbamate in 10 mL dichloromethane were combined with 3 mL of 4 molar hydrochloric acid in dioxane and stirred for two hours at ambient temperature. Then the solvents were distilled off. The residue was further reacted directly.

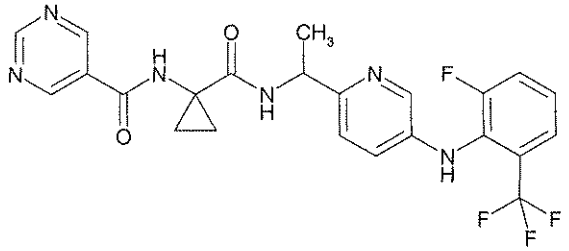
122c) 5-amino-N-(1-{1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-nicotinamide

1-amino-cyclopropanecarboxylic acid {1-[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl}-amide dihydrochloride and 5-amino-nicotinic acid were reacted and worked up as described in method (121d). During the chromatographic purification through silica gel dichloromethane with 0-15% methanol was used as eluant.

$C_{24}H_{21}F_5N_6O_2$ * 2 HCl (593.38)

mass spectroscopy $[M+H]^+$ = 521

Example 123: pyrimidine-5-carboxylic acid-(1-{1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide



123a) 1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone

39.7 mL of a 1.4 molar methylmagnesium bromide solution in toluene/THF (3:1) and 200 mL diethyl ether were taken and cooled to -30°C. Then 3.90 g (13.9 mmol) 5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile in 100 mL diethyl ether were added and the reaction mixture was left overnight with heating to ambient temperature and with stirring. The reaction mixture was mixed with 1 molar aqueous hydrochloric acid and

stirred for some time. The organic phase was separated off, dried on sodium sulphate and evaporated down. The crude product was used in the next reaction without any further purification.

$C_{14}H_{10}F_4N_2O_2$ (298.24)

mass spectroscopy $[M+H]^+ = 299$

123b) 1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxime

1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone was reacted and worked up analogously to method (121b). During the subsequent column chromatography on silica gel dichloromethane/ethanol 50:1 was used as eluant.

$C_{14}H_{11}F_4N_3O$ (313.25)

123c) [6-(1-amino-ethyl)-pyridin-3-yl]-(2-fluoro-6-trifluoromethyl-phenyl)-amine

1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxime was hydrogenated analogously to method (40d). The crude product was purified by chromatography (silica gel, dichloromethane with 2 to 5% methanol/ammonia 10:1).

$C_{14}H_{13}F_4N_3$ (299.27))

R_t = 2.76 min. method 7

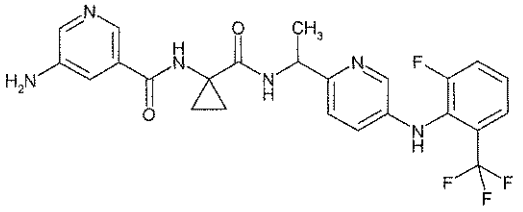
123d) pyrimidine-5-carboxylic acid (1-{1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide

[6-(1-amino-ethyl)-pyridin-3-yl]-(2-fluoro-6-trifluoromethyl-phenyl)-amine and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid were reacted analogously to method (1d). For working up the reaction mixture was evaporated down, combined with ethyl acetate and washed with sodium hydrogen carbonate solution. The organic phase was dried on sodium sulphate and the solvent was distilled off. The residue was purified by chromatography (silica gel, dichloromethane/ethanol = 50:1).

$C_{23}H_{20}F_4N_6O_2$ (488.44)

mass spectroscopy $[M+H]^+ = 489$

Example 124: 5-amino-N-(1-{1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-nicotinamide



124a) tert-butyl (1-{1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-carbamate

1-tert-butoxycarbonylamino-cyclopropanecarboxylic acid and [6-(1-amino-ethyl)-pyridin-3-yl]-(2-fluoro-6-trifluoromethyl-phenyl)-amine were reacted and worked up as described in method (123d). The crude product was used in the next reaction without being purified by column chromatography.

$C_{23}H_{26}F_4N_4O_3$ (482.47)

mass spectroscopy $[M+H]^+ = 483$

124b) 1-amino-cyclopropanecarboxylic acid {1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl}-amide hydrochloride

Reaction of tert-butyl (1-{1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl-carbamoyl}-cyclopropyl)-carbamate analogously to method (122b).

$C_{18}H_{18}F_4N_4O * HCl$ (418.82)

mass spectroscopy $[M+H]^+ = 383$

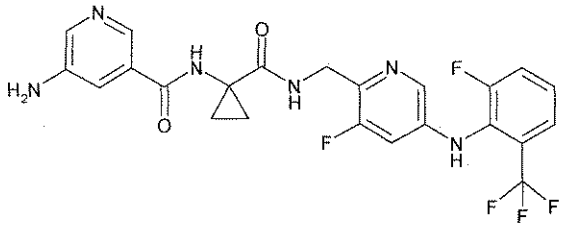
124c) 5-amino-N-(1-{1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl-carbamoyl}-cyclopropyl)-nicotinamide

1-amino-cyclopropanecarboxylic acid {1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl}-amide hydrochloride and 5-aminonicotinic acid were reacted analogously to method (1d). For working up the reaction mixture was evaporated down, combined with ethyl acetate and washed with sodium hydrogen carbonate solution. The organic phase was dried on sodium sulphate and the solvent was distilled off. The residue was purified by chromatography (silica gel, dichloromethane/ethanol = 9:1).

$C_{24}H_{22}F_4N_6O_2$ (502.46)

mass spectroscopy $[M+H]^+ = 503$

Example 125: 5-amino-N-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide



125a) tert-butyl (1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-carbamate

Reaction of (6-aminomethyl-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine and 1-tert-butoxycarbonylamino-cyclopropanecarboxylic acid analogously to method (1d). After the end of the reaction the solution was evaporated down and made alkaline with potassium carbonate solution. The precipitate was filtered off, washed with water and dried.

$C_{22}H_{23}F_5N_4O_3$ (486.44)

125b) 1-amino-cyclopropanecarboxylic acid-{1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl}-amide

Tert-butyl (1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-carbamate was reacted analogously to method (122b).

$C_{17}H_{15}F_5N_4O$ * 2 HCl (459.24)

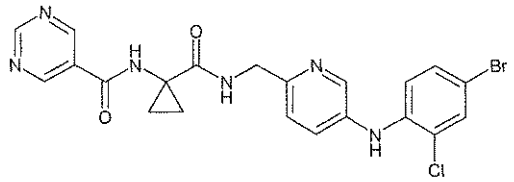
125c) 5-amino-N-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

5-amino-nicotinic acid and 1-amino-cyclopropanecarboxylic acid {1-[5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethyl}-amide were reacted as described in method (121d). During the chromatographic purification through silica gel dichloromethane and 0 to 15% methanol were used as eluant.

$C_{23}H_{19}F_5N_6O_2$ * 2 HCl (579.35)

mass spectroscopy $[M+H]^+ = 507$

Example 126: pyrimidine-5-carboxylic acid-(1-{[5-(4-bromo-2-chloro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



126a) 5-(4-bromo-2-chloro-phenylamino)-pyridine-2-carbonitrile

250 mg (2.0 mmol) 5-fluoro-pyridine-2-carbonitrile were added at ambient temperature to a solution of 423 mg (2.0 mmol) 4-bromo-2-chloroaniline and 459 mg (4.0 mmol) potassium-tert-butoxide in 4 mL DMSO. The reaction mixture was stirred overnight, then combined with sodium chloride solution and extracted with tert-butyl-methylether. The organic phases were dried on sodium sulphate and evaporated down.

$C_{12}H_7BrClN_3$ (308.56)

mass spectroscopy $[M+H]^+ = 308$

126b) (6-aminomethyl-pyridin-3-yl)-(4-bromo-2-chloro-phenyl)-amine

A solution of 250 mg 5-(4-bromo-2-chloro-phenylamino)-pyridine-2-carbonitrile in 4 mL THF was added dropwise to 0.8 mL of a 2 molar solution of lithium aluminium hydride in THF at ambient temperature. Then the reaction mixture was refluxed for 20 minutes. It was carefully hydrolysed with water and extracted with THF. The organic phases were washed with sodium chloride solution, dried on sodium sulphate and evaporated down. The residue was purified by chromatography (RP, eluant: acetonitrile and water with 0.1 % trifluoroacetic acid).

$C_{12}H_{11}BrClN_3$ (312.59)

mass spectroscopy $[M+H]^+ = 311$

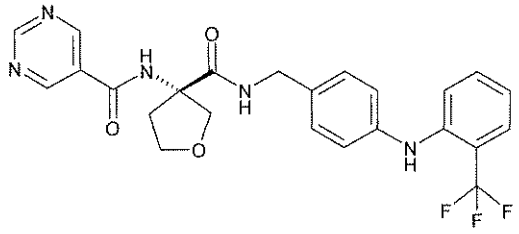
126c) pyrimidine-5-carboxylic acid-(1-{[5-(4-bromo-2-chloro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

Prepared analogously to method (51b) from (6-aminomethyl-pyridin-3-yl)-(4-bromo-2-chloro-phenyl)-amine and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid.

$C_{21}H_{18}BrClN_6O_2$ (501.76)

mass spectroscopy $[M+H]^+ = 501$

Example 127: (S)-pyrimidine-5-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl}-amide

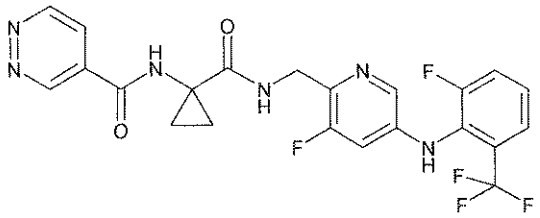


(S)-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylic acid and N-(4-(aminomethyl)phenyl)-2-(trifluoromethyl)aniline were reacted analogously to method (51b). The final purification was carried out by chromatography (RP, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

$C_{24}H_{22}F_3N_5O_3$ (485.46)

mass spectroscopy (ESI): $[M+H]^+ = 486$

Example 128: pyridazine-4-carboxylic acid-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



128a) tert-butyl (1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-carbamate

Reaction of tert-butyl (1-carbamoyl-cyclopropyl)-carbamate and (6-aminomethyl-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine analogously to method (1d). For working up the reaction mixture was evaporated down and made alkaline with potassium carbonate solution. The product precipitated was filtered off, washed with water and dried.

$C_{22}H_{23}F_5N_4O_3$ (486.44)

R_t = 2.30 min. method 12

128b) 1-amino-cyclopropanecarboxylic acid [3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide dihydrochloride

Tert-butyl (1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-carbamate was reacted as described in method (122b).

$C_{17}H_{15}F_5N_4O * 2\ HCl$ (459.24)

R_t = 1.50 min. method 12

128c) pyridazine-4-carboxylic acid-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

1-amino-cyclopropanecarboxylic acid [3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide dihydrochloride and pyridazine-4-carboxylic acid were reacted analogously to method (1d) and then purified by chromatography (RP, eluant: acetonitrile and water with 0.1% trifluoroacetic acid).

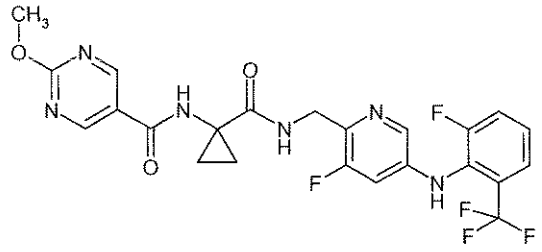
Yield: 47% of theory

$C_{22}H_{17}F_5N_6O_2$ (492.40)

mass spectroscopy (ESI): $[M+H]^+ = 493$

The following Examples 129 to 137 were prepared analogously to method (128c) from 1-amino-cyclopropanecarboxylic acid [3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide dihydrochloride and the corresponding carboxylic acid.

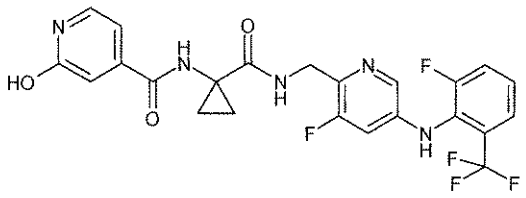
Example 129: 2-methoxy-pyrimidine-5-carboxylic acid-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



$C_{23}H_{19}F_5N_6O_3 * C_2HF_3O_2$ (636.45)

mass spectroscopy (ESI): $[M+H]^+ = 523$

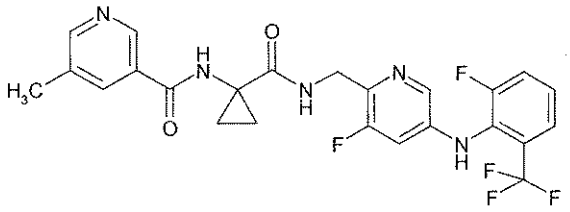
Example 130: N-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-2-hydroxy-isonicotinamide



$C_{23}H_{18}F_5N_5O_3$ (507.41)

mass spectroscopy (ESI): $[M+H]^+ = 508$

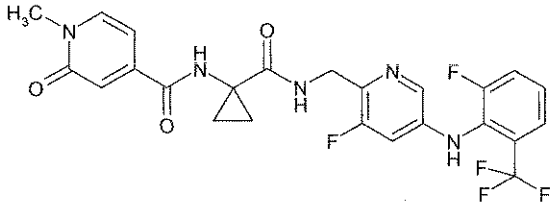
Example 131: N-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-methyl-nicotinamide



$C_{24}H_{20}F_5N_5O_2$ (505.44)

mass spectroscopy (ESI): $[M+H]^+ = 506$

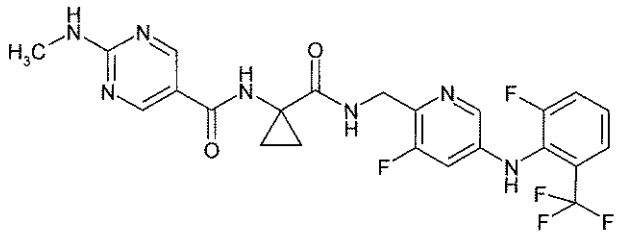
Example 132: 1-methyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



$C_{24}H_{20}F_5N_5O_3$ (521.44)

mass spectroscopy (ESI): $[M+H]^+ = 522$

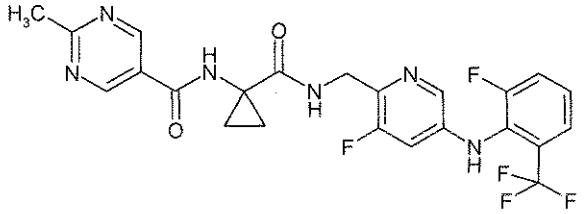
Example 133: 2-methylamino-pyrimidine-5-carboxylic acid-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



$C_{23}H_{20}F_5N_7O_2$ (521.44)

mass spectroscopy (ESI): $[M+H]^+ = 522$

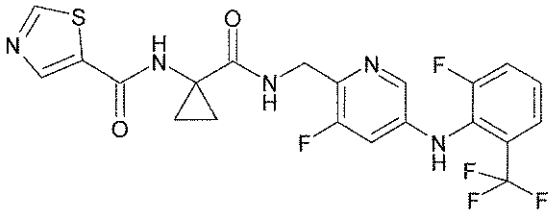
Example 134: 2-methyl-pyrimidine-5-carboxylic acid-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



$C_{23}H_{19}F_5N_6O_2$ (506.43)

mass spectroscopy (ESI): $[M+H]^+ = 507$

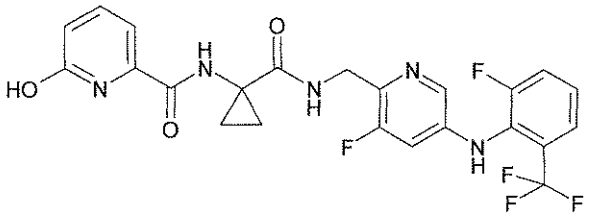
Example 135: thiazole-5-carboxylic acid-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



$C_{21}H_{16}F_5N_5O_2S$ (497.44)

mass spectroscopy (ESI): $[M+H]^+ = 498$

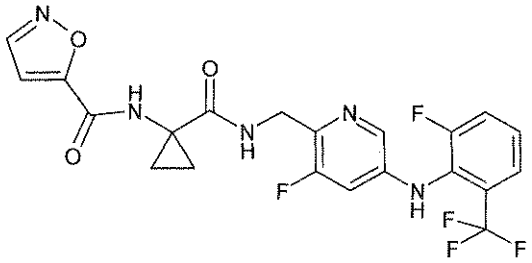
Example 136: 6-hydroxy-pyridine-2-carboxylic acid-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



$C_{23}H_{18}F_5N_5O_3$ (507.41)

mass spectroscopy (ESI): $[M+H]^+ = 508$

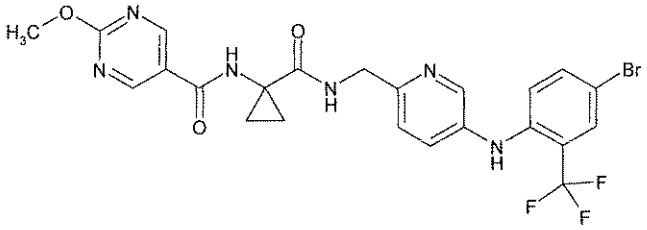
Example 137: isoxazole-5-carboxylic acid-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



$C_{21}H_{16}F_5N_5O_3$ (481.38)

mass spectroscopy (ESI): $[M+H]^+ = 482$

Example 138: 2-methoxy-pyrimidine-5-carboxylic acid (1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



138a) tert-butyl (1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-carbamate

Reaction of (6-aminomethyl-pyridin-3-yl)-(4-bromo-2-trifluoromethyl-phenyl)-amine and 1-tert-butoxycarbonylamino-cyclopropanecarboxylic acid analogously to method (1d). Then the reaction mixture was evaporated down and the residue was chromatographed (RP, eluant: acetonitrile and water with 0.1% trifluoroacetic acid)

$C_{22}H_{24}BrF_3N_4O_3$ (529.35)

mass spectroscopy (ESI): $[M+H]^+ = 529$

138b) 1-amino-cyclopropanecarboxylic acid [5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide trifluoroacetate

150 mg (0.28 mmol) tert-butyl (1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-carbamate in 2.5 mL dichloromethane were combined with 1 mL trifluoroacetic acid and stirred for one hour at ambient temperature. The solvent was distilled off and the residue was further reacted directly.

Yield: 100% of theory

$C_{17}H_{16}BrF_3N_4O * C_2HF_3O_2$ (543.26)

R_t = 1.59 min. method 12

138c) 2-methoxy-pyrimidine-5-carboxylic acid-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

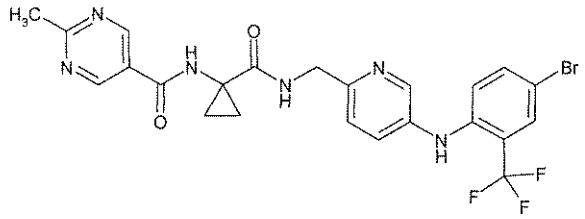
The product was prepared according to method (1d) from 1-amino-cyclopropanecarboxylic acid [5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide trifluoroacetate and 2-methoxy-pyrimidine-5-carboxylic acid.

$C_{23}H_{20}BrF_3N_6O_3$ (565.34)

mass spectroscopy (ESI): $[M+H]^+$ = 565

The following Examples 139 to 141 were prepared from 1-amino-cyclopropanecarboxylic acid [5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide trifluoroacetate and the corresponding carboxylic acid according to method (1d).

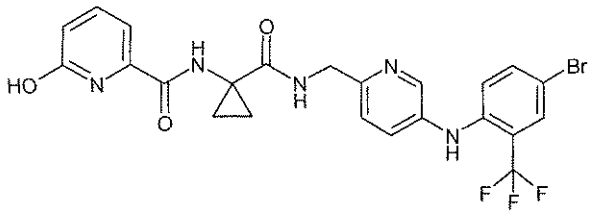
Example 139: 2-methyl-pyrimidine-5-carboxylic acid-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



$C_{23}H_{20}BrF_3N_6O_2$ (549.34)

mass spectroscopy (ESI): $[M+H]^+$ = 549

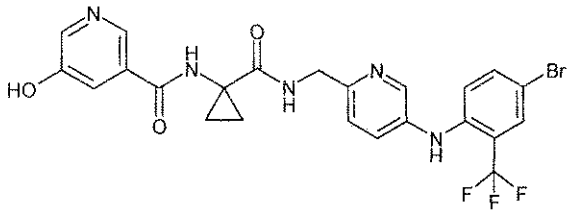
Example 140: 6-hydroxy-pyridine-2-carboxylic acid-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



$C_{23}H_{19}BrF_3N_5O_3$ (550.33)

mass spectroscopy (ESI): $[M+H]^+ = 550$

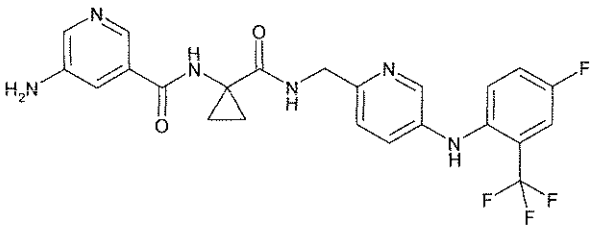
Example 141: N-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-hydroxy-nicotinamide



$C_{23}H_{19}BrF_3N_5O_3$ (550.33)

mass spectroscopy (ESI): $[M+H]^+ = 550$

Example 142: 5-amino-N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide



142a) benzyl 1-[(5-amino-pyridine-3-carbonyl)-amino]-cyclopropanecarboxylate

5-amino-nicotinic acid and benzyl 1-amino-cyclopropanecarboxylate hydrochloride were coupled according to method (1d). For working up the reaction mixture was evaporated down, combined with potassium carbonate solution and extracted with ethyl acetate. The organic phases were washed with water, dried on sodium sulphate and freed from the solvent in vacuo. The residue was chromatographed on a silica gel column (eluant: dichloromethane with 0-10% methanol).

142b) 1-[(5-amino-pyridine-3-carbonyl)-amino]-cyclopropanecarboxylic acid

1.90 g (6.1 mmol) benzyl 1-[(5-amino-pyridine-3-carbonyl)-amino]-cyclopropanecarboxylate were dissolved in 70 mL methanol and hydrogenated with palladium on charcoal (10%) as catalyst at 3 bar hydrogen pressure. The catalyst was filtered off and the filtrate was evaporated down. For purification the residue was stirred with diethyl ether, filtered and dried.

Yield: 85% of theory

$C_{10}H_{11}N_3O_3$ (221.21)

mass spectroscopy (ESI): $[M+H]^+ = 222$

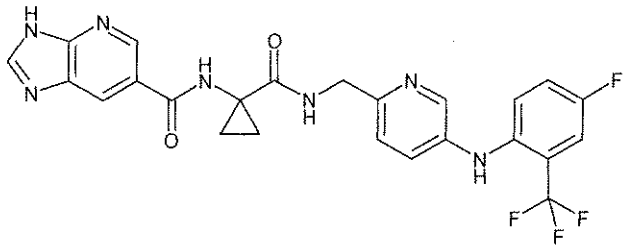
142c) 5-amino-N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

1-[(5-amino-pyridine-3-carbonyl)-amino]-cyclopropanecarboxylic acid and (6-aminomethyl-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine were reacted analogously to method (1d). Following the chromatographic purification (RP, eluant: acetonitrile and water with 0.15% formic acid) the fractions containing product were made alkaline with potassium carbonate solution. Then the acetonitrile was distilled off and extracted with ethyl acetate. The organic phases were dried on sodium sulphate, freed from the solvent and triturated with diisopropylether.

$C_{23}H_{20}F_4N_6O_2$ (488.44)

mass spectroscopy (ESI): $[M+H]^+ = 489$

Example 143: 3H-imidazo[4,5-b]pyridine-6-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



143a) benzyl 1-[(3H-imidazo[4,5-b]pyridine-6-carbonyl)-amino]-cyclopropanecarboxylate

Prepared from 3H-imidazo[4,5-b]pyridine-6-carboxylic acid and benzyl 1-amino-cyclopropanecarboxylate hydrochloride analogously to method (142a).

$C_{18}H_{16}N_4O_3$ (336.35)

mass spectroscopy (ESI): $[M+H]^+ = 337$

143b) 1-[(3H-imidazo[4,5-b]pyridine-6-carbonyl)-amino]-cyclopropanecarboxylic acid

Obtained from the reaction of benzyl 1-[(3H-imidazo[4,5-b]pyridine-6-carbonyl)-amino]-cyclopropanecarboxylate according to method (142b).

$C_{11}H_{10}N_4O_3$ (246.22)

R_t = 1.64 min. method 10

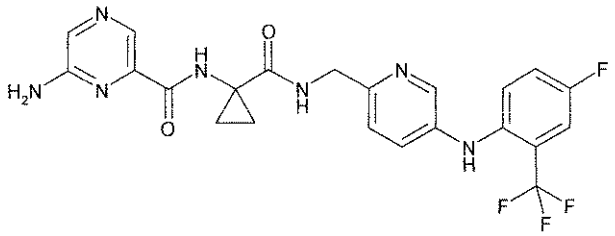
143c) 3H-imidazo[4,5-b]pyridine-6-carboxylic acid (1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

The compound was obtained by reacting 1-[(3H-imidazo[4,5-b]pyridine-6-carbonyl)-amino]-cyclopropanecarboxylic acid and (6-aminomethyl-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine analogously to (142c).

$C_{24}H_{19}F_4N_7O_2$ (513.45)

mass spectroscopy (ESI): $[M+H]^+ = 514$

Example 144: 6-amino-pyrazine-2-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



144a) tert-butyl (1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-carbamate

1-tert-butoxycarbonylamino-cyclopropanecarboxylic acid and (6-aminomethyl-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine were coupled with TBTU analogously to method (1d). The reaction mixture was evaporated down, combined with ethyl acetate and washed with sodium hydrogen carbonate solution. Then the organic phase was dried on sodium sulphate and freed from the solvent. The residue was purified on a silica gel column with dichloromethane/ethanol as eluant in the ratio 1:50 to 1:20.

$C_{22}H_{24}F_4N_4O_3$ (468.45)
mass spectroscopy (ESI): $[M+H]^+ = 469$

144b) 1-amino-cyclopropanecarboxylic acid [5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide hydrochloride

1.00 g (2.14 mmol) tert-butyl (1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-carbamate were dissolved in 30 mL dioxane and after the addition of 3.2 mL 4 molar hydrochloride solution in dioxane stirred overnight at ambient temperature. The solvent was distilled off in vacuo and the residue was further reacted directly.

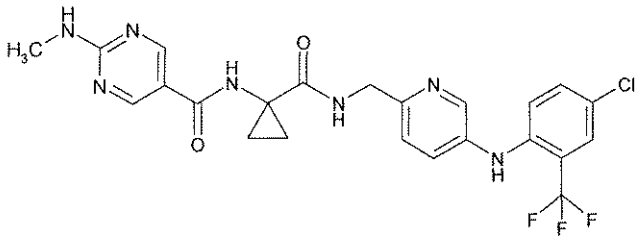
$C_{17}H_{16}F_4N_4O \cdot HCl$ (404.79)
mass spectroscopy (ESI): $[M+H]^+ = 369$

144c) 6-amino-pyrazine-2-carboxylic acid (1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

Obtained analogously to method (142c) from 1-amino-cyclopropanecarboxylic acid [5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide hydrochloride and 6-amino-pyrazine-2-carboxylic acid.

$C_{22}H_{19}F_4N_7O_2$ (489.43)
mass spectroscopy (ESI): $[M+H]^+ = 490$

Example 145: 2-methylamino-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



145a) tert-butyl (1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-carbamate

1-(tert-butoxycarbonyl-amino)-cyclopropanecarboxylic acid and (6-aminomethyl-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine were coupled as described in method (1d). For working up the reaction mixture was mixed with water and extracted with

dichloromethane. The organic phases were dried on sodium sulphate and evaporated down.

$C_{22}H_{24}ClF_3N_4O_3$ (484.90)

R_t = 2.23 min. method 12

145b) 1-amino-cyclopropanecarboxylic acid-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide trifluoroacetate

906 mg (1.40 mmol) tert-butyl (1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-carbamate in 5 mL dichloromethane were combined with 2 mL trifluoroacetic acid and stirred for one hour at ambient temperature. Then the solvent was distilled off in vacuo and the residue was reacted without any further purification.

$C_{17}H_{16}ClF_3N_4O * C_2HF_3O_2$ (498.81)

R_t = 1.54 min. method 12

145c) 2-methylamino-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

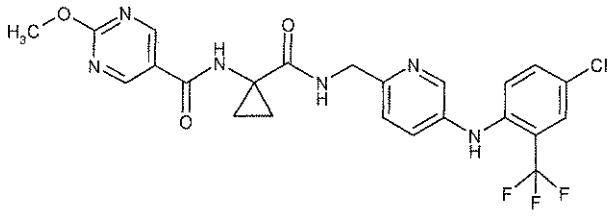
1-amino-cyclopropanecarboxylic acid [5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide trifluoroacetate and 2-methylamino-pyrimidine-5-carboxylic acid were reacted analogously to method (1d). Then the reaction mixture was purified by chromatography (RP, eluant: acetonitrile and water with 0.1% trifluoroacetic acid).

$C_{23}H_{21}ClF_3N_7O_2$ (519.91)

mass spectroscopy (ESI): $[M+H]^+$ = 520

Examples 146 to 149 were prepared analogously from 1-amino-cyclopropanecarboxylic acid [5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide and the corresponding carboxylic acid.

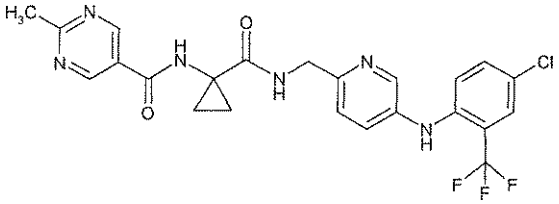
Example 146: 2-methoxy-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



$C_{23}H_{20}ClF_3N_6O_3$ (520.89)

mass spectroscopy (ESI): $[M+H]^+ = 521$

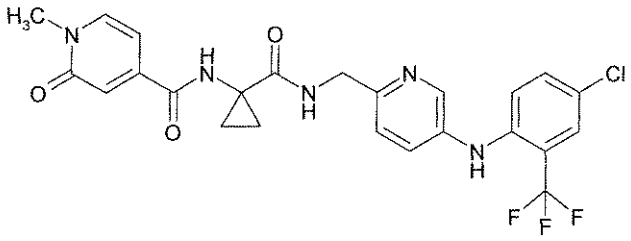
Example 147: 2-methyl-pyrimidine-5-carboxylic acid (1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



$C_{23}H_{20}ClF_3N_6O_2$ (504.89)

mass spectroscopy (ESI): $[M+H]^+ = 505$

Example 148: 1-methyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid (1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

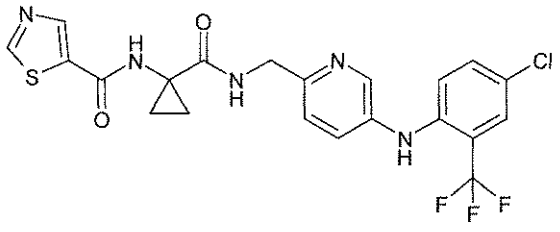


$C_{24}H_{21}ClF_3N_5O_3$ (519.90)

mass spectroscopy (ESI): $[M+H]^+ = 520$

$R_t = 1.74$ min. method 13

Example 149: thiazole-5-carboxylic acid (1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

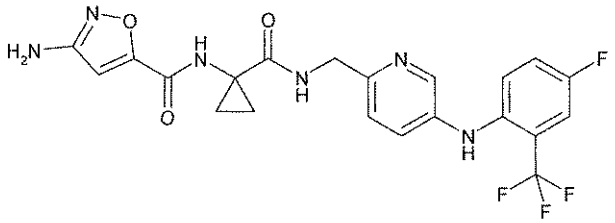


$C_{21}H_{17}ClF_3N_5O_2S$ (495.91)

mass spectroscopy (ESI): $[M+H]^+ = 496$

R_t = 1.84 min. method 13

Example 150: 3-amino-isoxazole-5-carboxylic acid (1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

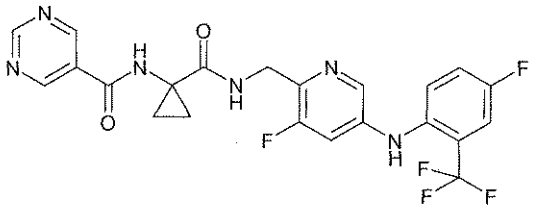


Prepared according to method (142c) from 1-amino-cyclopropanecarboxylic acid [5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide hydrochloride and 3-amino-isoxazole-5-carboxylic acid.

$C_{21}H_{18}F_4N_6O_3$ (478.40)

mass spectroscopy (ESI): $[M+H]^+ = 479$

Example 151: pyrimidine-5-carboxylic acid (1-{[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide dihydrochloride



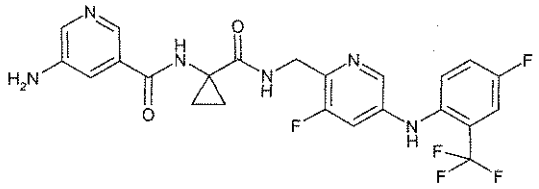
1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid and (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine were reacted analogously to method (1d). The reaction mixture was evaporated down, combined with potassium carbonate solution and extracted with ethyl acetate. The organic phases were washed with water and sodium chloride solution, dried on sodium sulphate and freed from the

solvent. After the chromatographic purification of the residue (RP, eluant: water and acetonitrile with formic acid) the fractions containing product were made alkaline with ammonia, the acetonitrile was distilled off and the remainder was extracted with ethyl acetate. The product was precipitated from the organic solution with ethereal hydrochloride solution after drying with sodium sulphate.

$C_{22}H_{17}F_5N_6O_2 * 2$ HCl (565.32)

mass spectroscopy (ESI): $[M+H]^+ = 493$

Example 152: 5-amino-N-(1-{[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide dihydrochloride

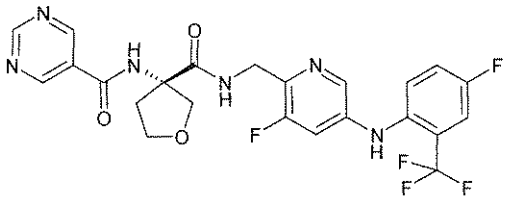


Obtained analogously to the method of Example 147 from 5-amino-nicotinic acid and 1-amino-cyclopropanecarboxylic acid-[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide. In the chromatographic purification, however, a silica gel column was used (eluant: dichloromethane with 5 to 12% methanol).

$C_{23}H_{19}F_5N_6O_2 * 2$ HCl (579.35)

mass spectroscopy (ESI): $[M+H]^+ = 507$

Example 153: (S)-pyrimidine-5-carboxylic acid (3-{[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydro-furan-3-yl)-amide dihydrochloride

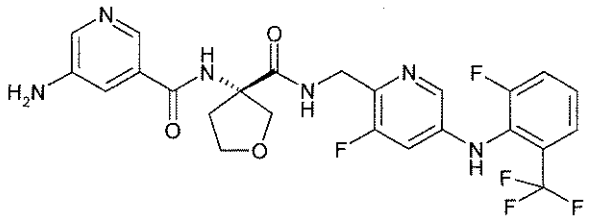


Prepared from (S)-3-(pyrimidine-5-carboxamido)tetrahydrofuran-3-carboxylic acid and (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine analogously to Example 150. The column chromatographic purification used a silica gel column and dichloromethane with 0 to 7% methanol as eluant.

$C_{23}H_{19}F_5N_6O_3 * 2$ HCl (595.35)

mass spectroscopy (ESI): $[M+H]^+ = 523$

Example 154: (S)-5-amino-N-(3-{[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide



154a) butyl (S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylate

5-amino-nicotinic acid and butyl (S)-3-amino-tetrahydrofuran-3-carboxylate were coupled with TBTU analogously to method (1d). For working up the reaction mixture was evaporated down, combined with potassium carbonate solution and extracted with ethyl acetate. The organic phases were washed with water and sodium chloride solution, dried on sodium sulphate and freed from the solvent. The residue was chromatographed on a silica gel column (eluant: dichloromethane with 5 to 10% methanol).

$C_{15}H_{21}N_3O_4$ (307.35)

mass spectroscopy (ESI): $[M+H]^+ = 308$

154b) (S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydro-furan-3-carboxylic acid

2.45 g (7.97 mmol) butyl (S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylate in 50 mL methanol were combined with 16 mL 1 molar sodium hydroxide solution and stirred for one hour at ambient temperature. After the addition of 16 mL of 1 molar hydrochloric acid the solvents were distilled off in vacuo. The residue was dissolved in ethanol and the inorganic salts were filtered off. Then the filtrate was evaporated down.

Yield: 99% of theory

$C_{11}H_{13}N_3O_4$ (251.24)

mass spectroscopy (ESI): $[M+H]^+ = 252$

154c) (S)-5-amino-N-(3-{[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide-dihydrochloride

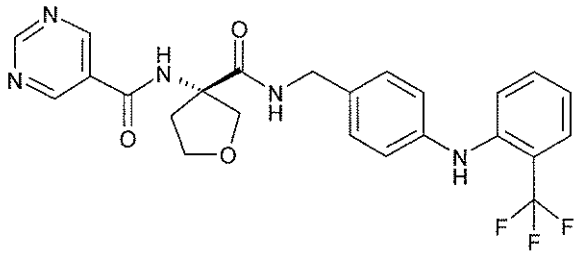
(S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid and (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine were reacted

and purified as described in method (154a). Following the chromatographic purification the product was dissolved in ethyl acetate and precipitated with ethereal hydrochloride solution.

$C_{24}H_{21}F_5N_6O_3$ * 2 HCl (609.38)

mass spectroscopy (ESI): $[M+H]^+$ = 537

Example 155: (S)-pyrimidine-5-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide



A solution of 64 mg (0.27 mmol) (S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid, 93 mg (0.28 mmol) O-[(ethoxycarbonyl)cyanomethyleneamino]-N,N,N',N'-tetramethyluronium-tetrafluoroborate (TOTU) and 139 µL (0.81 mmol) DIPEA in 1 mL DMF was stirred for 1 hour at ambient temperature, then combined with 144 mg (0.41 mmol) N-(4-(aminomethyl)phenyl)-2-(trifluoromethyl)aniline and left to stand overnight. Then the mixture was purified by chromatography (RP with gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

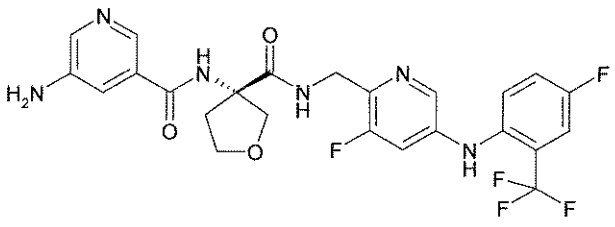
Yield: 18% of theory

$C_{24}H_{22}F_3N_5O_3$ (485.46)

mass spectroscopy (ESI): $[M+H]^+$ = 486

R_t = 2.15 min. method 12

Example 156: (S)-5-amino-N-(3-{[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide dihydrochloride

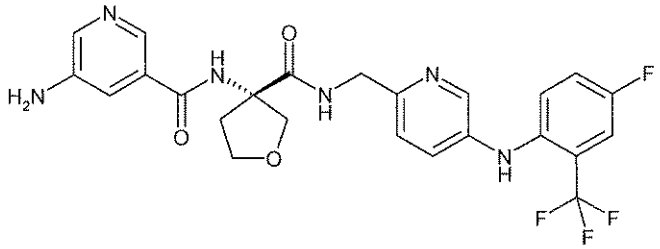


(S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid and (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine were reacted and purified as described in method (154a). Following the chromatographic purification the product was dissolved in ethyl acetate and precipitated with ethereal hydrochloride solution.

$C_{24}H_{21}F_5N_6O_3$ * 2 HCl (609.38)

mass spectroscopy (ESI): $[M+H]^+$ = 537

Example 157: (S)-5-amino-N-(3-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

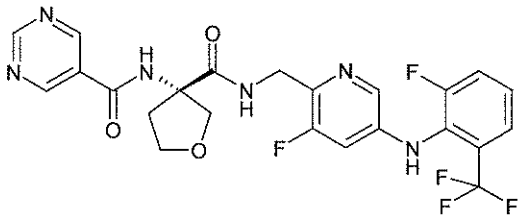


Obtained from (S)-3-[(5-amino-pyridine-3-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid and (6-aminomethyl-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine according to method (142c).

$C_{24}H_{22}F_4N_6O_3$ (518.46)

mass spectroscopy (ESI): $[M+H]^+$ = 519

Example 158: (S)-pyrimidine-5-carboxylic acid-(3-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide dihydrochloride

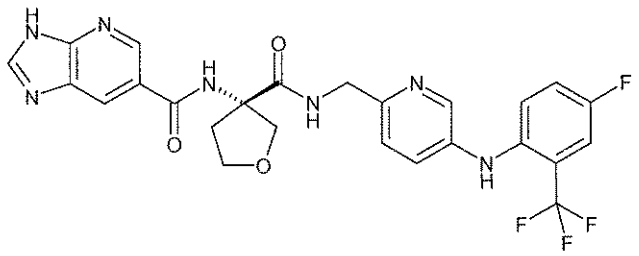


Prepared analogously to method (154a) from (S)-3-[(pyrimidine-5-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid and (6-aminomethyl-5-fluoro-pyridin-3-yl)-(2-fluoro-6-trifluoromethyl-phenyl)-amine.

$C_{23}H_{19}F_5N_6O_3$ * 2 HCl (595.35)

mass spectroscopy (ESI): $[M+H]^+$ = 523

Example 159: (S)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid-(3-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydro-furan-3-yl)-amide



159a) butyl (S)-3-[(3H-imidazo[4,5-b]pyridine-6-carbonyl)-amino]-tetrahydro-furan-3-carboxylate

Prepared from 3H-imidazo[4,5-b]pyridine-6-carboxylic acid and butyl (S)-3-amino-tetrahydrofuran-3-carboxylate as described in method (154a), with no chromatographic purification.

$C_{16}H_{20}N_4O_4$ (332.36)

R_t = 1.99 min. method 13

159b) (S)-3-[(3H-imidazo[4,5-b]pyridine-6-carbonyl)-amino]-tetrahydro-furan-3-carboxylic acid

400 mg (1.20 mmol) butyl (S)-3-[(3H-imidazo[4,5-b]pyridine-6-carbonyl)-amino]-tetrahydrofuran-3-carboxylate were dissolved in 10 mL THF and 5 mL ethanol, combined with 1.2 mL 2 molar lithium hydroxide solution and stirred overnight at ambient temperature. Then the solvents were distilled off and the residue was combined with 2.4 mL 1 molar aqueous hydrochloric acid. The mixture was evaporated down in vacuo and residual water was eliminated by repeated azeotropic distillation with ethanol.

$C_{12}H_{12}N_4O_4$ (276.25)

mass spectroscopy (ESI): $[M-H]^+ = 275$

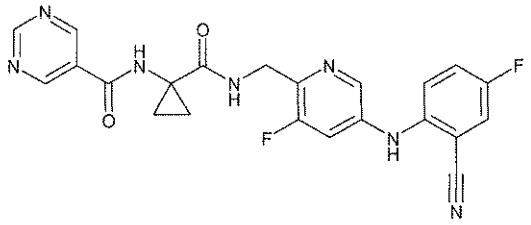
159c) (S)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid (3-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

Prepared from (S)-3-[(3H-imidazo[4,5-b]pyridine-6-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid and (6-aminomethyl-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine analogously to method (154a).

$C_{25}H_{21}F_4N_7O_3$ (543.47)

mass spectroscopy (ESI): $[M+H]^+ = 544$

Example 160: pyrimidine-5-carboxylic acid-(1-{[5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



160a) tert-butyl (5-bromo-3-fluoro-pyridin-2-ylmethyl)-carbamate

581 mg (2.41 mmol) C-(5-bromo-3-fluoro-pyridin-2-yl)-methylamine were dissolved in 5 mL triethylamine and 1.5 mL water and while the mixture was being cooled with the ice bath 630 mg (2.89 mmol) di-tert-butyl-dicarbonate were added. Then the reaction mixture was stirred overnight. The solvent was distilled off and the residue was purified by chromatography (RP with eluant gradient, eluant: acetonitrile and water with 0.2 % trifluoroacetic acid). The fractions containing product were neutralised with triethylamine and evaporated down.

Yield: 40% of theory

$C_{11}H_{14}BrFN_2O_2$ (305.14)

R_t = 2.29 min. method 12

160b) tert-butyl [5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamate

132 mg (0.97 mmol) 2-amino-5-fluorobenzonitrile and 295 mg (0.97 mmol) tert-butyl (5-bromo-3-fluoro-pyridin-2-ylmethyl)-carbamate were reacted and worked up analogously to method (55a).

Yield: 15% of theory

$C_{18}H_{18}F_2N_4O_2$ (360.36)

R_t = 2.35 min. method 12

160c) 2-(6-aminomethyl-5-fluoro-pyridin-3-ylamino)-5-fluoro-benzonitrile-trifluoroacetate

51 mg (0.14 mmol) tert-butyl [5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamate were stirred with 1.5 mL trifluoroacetic acid and 2.5 mL dichloromethane for 3 hours at ambient temperature. Then the reaction mixture was evaporated down in vacuo and further reacted directly.

Yield: 94% of theory

$C_{13}H_{10}F_2N_4 * C_2HF_3O_2$ (374.27)

R_t = 1.17 min. method 12

160d) pyrimidine-5-carboxylic acid-(1-{[5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

28 mg (0.13 mmol) 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid and 50 mg (0.13 mmol) 2-(6-aminomethyl-5-fluoro-pyridin-3-ylamino)-5-fluoro-benzonitrile were reacted with TBTU using DMF as solvent analogously to method (1d).

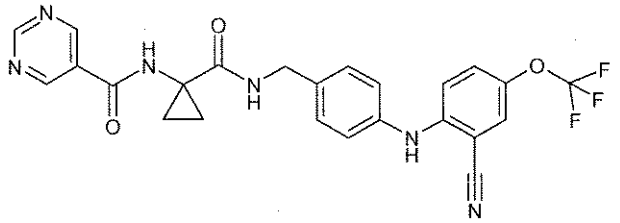
Yield: 50% of theory

$C_{22}H_{17}F_2N_7O_2$ (449.13)

mass spectroscopy (ESI): $[M+H]^+$ = 450

R_t = 1.67 min. method 12

Example 161: pyrimidine-5-carboxylic acid {1-[4-(2-cyano-4-trifluoromethoxy-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



161a) tert-butyl (4-bromo-benzyl)-carbamate

2.35 g (11 mmol) di-tert-butyl-dicarbonate in 20 mL dichloromethane were added dropwise to a solution of 2.00 g (8.99 mmol) 4-bromobenzylamine hydrochloride and 6.26 mL triethylamine in 30 mL dichloromethane while being cooled with the ice bath. Then the mixture was stirred overnight and then evaporated down. The residue was dissolved in ethyl acetate, acidified with citric acid and then washed with water and sodium hydrogen carbonate solution. The organic phase was dried on sodium sulphate and freed from the solvent.

Yield: 96% of theory

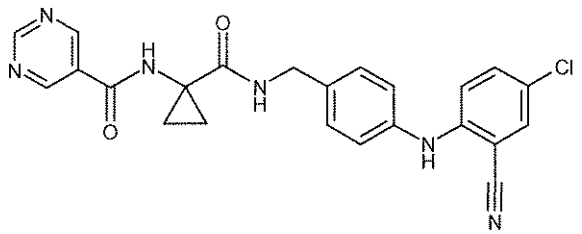
$C_{12}H_{16}BrNO_2$ (286.17)
mass spectroscopy (ESI): $[M+H]^+ = 286$

161b) tert-butyl [4-(2-cyano-4-trifluoromethoxy-phenylamino)-benzyl]-carbamate
Tert-butyl (4-bromo-benzyl)-carbamate and 2-amino-5-trifluoromethoxy-benzonitrile were reacted analogously to method (55a).
$C_{20}H_{20}F_3N_3O_3$ (407.39)
mass spectroscopy (ESI): $[M+H]^+ = 408$
R_t = 4.63 min. method 13

161c) 2-(4-aminomethyl-phenylamino)-5-trifluoromethoxy-benzonitrile-trifluoroacetate
To cleave the protective group tert-butyl [4-(2-cyano-4-trifluoromethoxy-phenylamino)-benzyl]-carbamate was treated with trifluoroacetic acid in dichloromethane. Then the solvent was distilled off and the residue was chromatographed (RP with eluant gradient, eluant: acetonitrile and water with 0.2 % trifluoroacetic acid).
$C_{15}H_{12}F_3N_3O * C_2HF_3O_2$ (421.29)
mass spectroscopy (ESI): $[M+H]^+ = 308$
R_t = 2.45 min. method 13

161d) pyrimidine-5-carboxylic acid-{1-[4-(2-cyano-4-trifluoromethoxy-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide
166 mg (0.39 mmol) of 2-(4-aminomethyl-phenylamino)-5-trifluoromethoxy-benzonitrile-trifluoroacetate and 82 mg (0.39 mmol) 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid were coupled analogously to method (1d).
Yield: 33% of theory
$C_{24}H_{19}F_3N_6O_3$ (496.44)
mass spectroscopy (ESI): $[M+H]^+ = 497$
R_t = 2.24 min. method 13

Example 162: pyrimidine-5-carboxylic acid {1-[4-(4-chloro-2-cyano-phenylamino)-benzyl-carbamoyl]-cyclopropyl}-amide



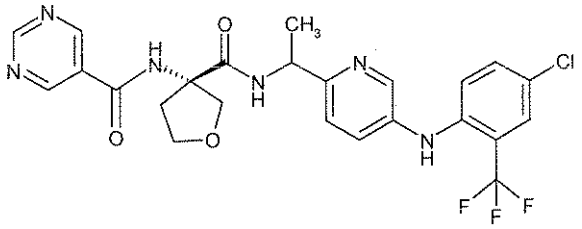
Prepared by the same reaction sequence (Buchwald reaction, cleaving of protective group, amide linking) as in Example 161 starting from tert-butyl (4-bromobenzyl)-carbamate.

$C_{23}H_{19}ClN_6O_2$ (446.89)

mass spectroscopy (ESI): $[M+H]^+ = 447$

R_t = 2.10 min. method 13

Example 163: (S)-pyrimidine-5-carboxylic acid (3-{1-[5-(4-chloro-2-trifluoromethyl-phenyl-amino)-pyridin-2-yl]-ethylcarbamoyl}-tetrahydrofuran-3-yl)-amide



163a) 1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone

500 mg (1.68 mmol) 5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile in 5 mL diethyl ether were added dropwise at -5°C to a solution of 2.2 mL of 3 molar methylmagnesium bromide in diethyl ether. The reaction mixture was hydrolysed with ammonium chloride solution and combined with 1 molar hydrochloric acid and tert-butylmethylether. The organic phase was separated off, dried on sodium sulphate and evaporated down

Yield: 50% of theory

$C_{14}H_{10}ClF_3N_2O$ (314.69)

mass spectroscopy (ESI): $[M+H]^+ = 315$

163b) 1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxime

266 mg (0.85 mmol) 1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone, 73 mg (1.04 mmol) hydroxylamine-hydrochloride and 238 µL (1.69 mmol) triethylamine were refluxed overnight in 15 mL acetonitrile with stirring. Then the reaction mixture was

mixed with water and extracted with dichloromethane. The organic phase was dried on sodium sulphate and evaporated down. The residue was used in the next reaction without any further purification.

Yield: 79% of theory

$C_{14}H_{11}ClF_3N_3O$ (329.71)

R_t = 2.27 min. method 12

163c) [6-(1-amino-ethyl)-pyridin-3-yl]-(4-chloro-2-trifluoromethyl-phenyl)-amine

220 mg (0.67 mmol) 1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxime in 1 mL methanol were mixed batchwise with 50 mg zinc powder and 1.1 mL of 4 molar hydrochloric acid in methanol and then refluxed for 3 hours with stirring. Then water was added to the mixture and it was extracted with dichloromethane. The organic phases were dried on sodium sulphate and evaporated down.

Yield: 62% of theory

$C_{14}H_{13}ClF_3N_3$ (315.72)

R_t = 1.76 min. method 12

163d) (S)-pyrimidine-5-carboxylic acid-(3-{1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-tetrahydrofuran-3-yl)-amide

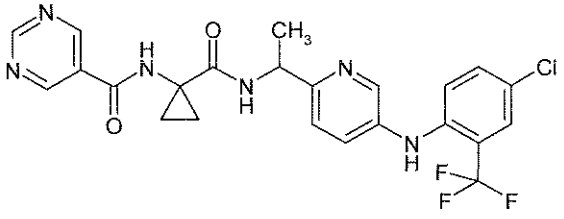
The compound was obtained from (S)-3-[(pyrimidine-5-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid and [6-(1-amino-ethyl)-pyridin-3-yl]-(4-chloro-2-trifluoromethyl-phenyl)-amine analogously to method (51b).

$C_{24}H_{22}ClF_3N_6O_3$ (534.93)

mass spectroscopy (ESI): $[M+H]^+$ = 535

R_t = 1.86 min. method 12

Example 164: pyrimidine-5-carboxylic acid (1-{1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide trifluoroacetate



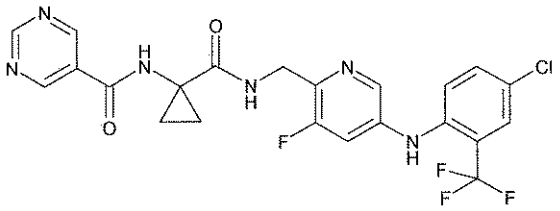
Obtained analogously to method (1d) from [6-(1-amino-ethyl)-pyridin-3-yl]-(4-chloro-2-trifluoromethyl-phenyl)-amine and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid.

$C_{23}H_{20}ClF_3N_6O_2 * C_2HF_3O_2$ (618.92)

mass spectroscopy (ESI): $[M+H]^+ = 505$

$R_t = 1.84$ min. method 12

Example 165: tert-butyl [5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamate



165a) tert-butyl [5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamate

Prepared analogously to method (55a) from tert-butyl (5-bromo-3-fluoro-pyridin-2-ylmethyl)-carbamate and 4-chloro-2-trifluoromethyl-phenylamine.

$C_{18}H_{18}ClF_4N_3O_2$ (419.80)

mass spectroscopy (ESI): $[M+H]^+ = 420$

165b) (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine hydrochloride

50 mg (0.12 mmol) tert-butyl [5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamate in 3 mL dioxane were combined with 2 mL of semi-concentrated hydrochloric acid and stirred for two hours at 60°C. After evaporation of the reaction mixture residual water was eliminated by azeotropic distillation with toluene.

$R_t = 1.73$ min. method 12

165c) tert-butyl [5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamate

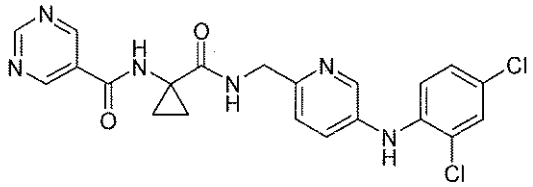
Prepared from (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-chloro-2-trifluoromethyl-phenyl)-amine hydrochloride and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid analogously to method (1d).

$C_{22}H17ClF_4N_6O_2$ (508.86)

mass spectroscopy (ESI): $[M+H]^+ = 509$

R_t = 2.12 min. method 12

Example 166: pyrimidine-5-carboxylic acid-(1-{[5-(2,4-dichloro-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-cyclopropyl)-amide



166a) 5-(2,4-dichloro-phenylamino)-pyridine-2-carbonitrile

1.33 g (8.2 mmol) 2,4-dichloroaniline in 30 mL DMSO were combined with 1.38 g (12.3 mmol) potassium-tert-butoxide and stirred for one hour at ambient temperature. Then 1.00 g (8.2 mmol) of 2-cyano-5-fluoropyridine in 20 mL DMSO was added and the mixture was stirred for a further six hours. It was diluted with dichloromethane, washed with sodium chloride solution, dried on sodium sulphate and evaporated down. The residue was chromatographed on a silica gel column (eluant: petroleum ether/ethyl acetate = 4:1).

Yield: 44% of theory

$C_{12}H_7Cl_2N_3$ (264.11)

R_t = 2.46 min. method 12

166b) (6-aminomethyl-pyridin-3-yl)-(2,4-dichloro-phenyl)-amine

3.56 mL of a 2 molar solution of lithium aluminium hydride in THF were added at -10°C to 0.94 g (3.6 mmol) 5-(2,4-dichloro-phenylamino)-pyridine-2-carbonitrile in 60 mL THF. The mixture was stirred for 30 minutes at ambient temperature, then mixed with water and filtered. The solid was washed with THF and the filtrate was evaporated to dryness.

$C_{12}H_{11}Cl_2N_3$ (268.14)

mass spectroscopy (ESI): $[M+H]^+ = 268$

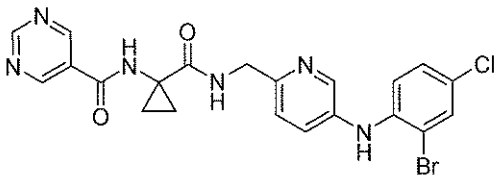
166c) pyrimidine-5-carboxylic acid-(1-{[5-(2,4-dichloro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

Obtained from (6-aminomethyl-pyridin-3-yl)-(2,4-dichloro-phenyl)-amine and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid analogously to method (1d).

$C_{21}H_{18}Cl_2N_6O_2$ (457.31)

mass spectroscopy (ESI): $[M+H]^+ = 457$

Example 167: pyrimidine-5-carboxylic acid (1-{[5-(2-bromo-4-chloro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



167a) 5-(2-bromo-4-chloro-phenylamino)-pyridine-2-carbonitrile

Prepared from 2-bromo-4-chloroaniline and 2-cyano-5-fluoropyridine analogously to (166a).

$C_{12}H_7BrClN_3$ (308.56)

mass spectroscopy (ESI): $[M+H]^+ = 308$

167b) (6-aminomethyl-pyridin-3-yl)-(2-bromo-4-chloro-phenyl)-amine-trifluoroacetate

5-(2-bromo-4-chloro-phenylamino)-pyridine-2-carbonitrile was reduced analogously to method (166b) with lithium aluminium hydride. The subsequent purification, however, was carried out by chromatography (RP with eluant gradient, eluant: acetonitrile and water with 0.1% trifluoroacetic acid).

$C_{12}H_{11}BrClN_3$ (312.59)

mass spectroscopy (ESI): $[M+H]^+ = 312$

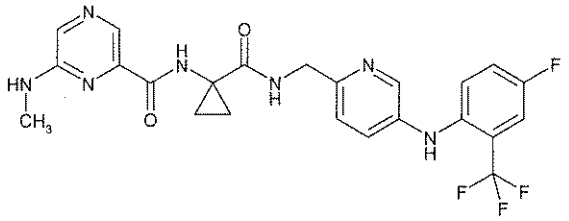
167c) pyrimidine-5-carboxylic acid-(1-{[5-(2-bromo-4-chloro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

Prepared analogously to method (1d) from (6-aminomethyl-pyridin-3-yl)-(2-bromo-4-chloro-phenyl)-amine-trifluoroacetate and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid.

$C_{21}H_{18}BrClN_6O_2$ (501.76)

mass spectroscopy (ESI): $[M+H]^+ = 501$

Example 168: 6-methylamino-pyrazine-2-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



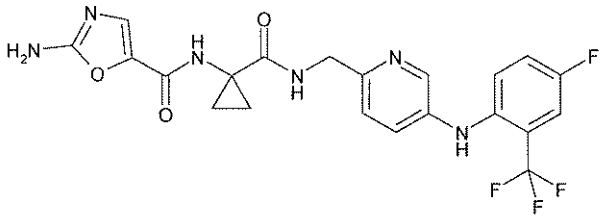
61 mg (0.40 mmol) 6-methylamino-pyrazine-2-carboxylic acid, 162 mg (0.40 mmol) 1-amino-cyclopropanecarboxylic acid [5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide hydrochloride and 167 µL (1.20 mmol) triethylamine were placed in 7 mL THF and 1 mL DMF, combined with 154 mg (0.48 mmol) TBTU and then stirred for 4 days at ambient temperature. The THF was distilled off and the residue was purified by chromatography (RP with eluant gradient, eluant: water and acetonitrile with formic acid). Then the fractions containing product were made alkaline with potassium carbonate solution. The acetonitrile was distilled off and the residue was extracted with ethyl acetate. The organic phases were dried on sodium sulphate, freed from the solvent and triturated with diisopropylether.

Yield: 34% of theory

$C_{23}H_{21}F_4N_7O_2$ (503.45)

mass spectroscopy (ESI): $[M+H]^+ = 504$

Example 169: 2-amino-oxazole-5-carboxylic acid (1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



169a) tert-butyl [5-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropylcarbamoyl)-oxazol-2-yl]-carbamate

Obtained from 2-tert-butoxycarbonylamino-oxazole-5-carboxylic acid and 1-amino-cyclopropanecarboxylic acid [5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide hydrochloride analogously to the method for Example 168. However, in the working up, no chromatographic purification was carried out.

$C_{26}H_{26}F_4N_6O_5$ (578.52)

R_t = 3.19 min. method 14

169b) 2-amino-oxazole-5-carboxylic acid (1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

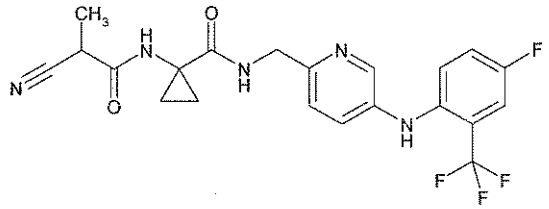
The protective group of the compound tert-butyl [5-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropylcarbamoyl)-oxazol-2-yl]-carbamate was cleaved using the method described for intermediate step (144b).

$C_{21}H_{18}F_4N_6O_3$ (478.40)

mass spectroscopy (ESI): $[M+H]^+ = 479$

$R_t = 2.71$ min. method 7

Example 170: 1-(2-cyano-2-methyl-acetylamino)-cyclopropanecarboxylic acid [5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide



Reaction of 40 mg (0.40 mmol) cyanomethyl-acetic acid and 162 mg (0.40 mmol) 1-amino-cyclopropanecarboxylic acid [5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide hydrochloride analogously to the method for Example 168.

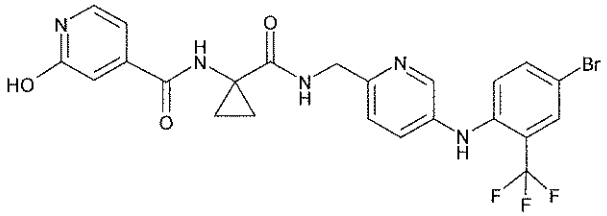
Yield: 28% of theory

$C_{21}H_{19}F_4N_5O_2$ (449.40)

mass spectroscopy (ESI): $[M+H]^+ = 450$

$R_t = 3.03$ min. method 7

Example 171: N-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-2-hydroxy-isonicotinamide



150 mg (0.165 mmol) of 1-amino-cyclopropanecarboxylic acid [5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide tri-trifluoroacetate were added to a

solution of 23 mg (0.165 mmol) 2-hydroxyisonicotinic acid, 56 mg (0.174 mmol) TBTU and 114 µL (0.661 mol) DIPEA in 0.5 mL DMF after 5 minutes stirring at ambient temperature. Then the reaction mixture was left to stand overnight and then chromatographed (RP with gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

Yield: 69% of theory

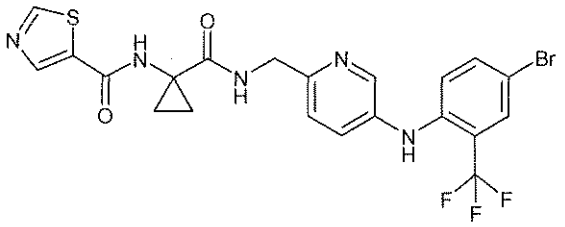
$C_{23}H_{19}BrF_3N_5O_3$ (550.33)

mass spectroscopy (ESI): $[M+H]^+ = 550$

R_t = 1.73 min. method 12

The following Examples 172 to 179 were prepared analogously from 1-amino-cyclopropanecarboxylic acid-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide tri-trifluoroacetate and the corresponding acids.

Example 172: thiazole-5-carboxylic acid-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



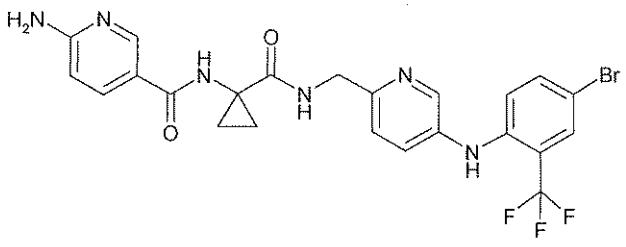
Yield: 94% of theory

$C_{21}H_{17}BrF_3N_5O_2S$ (540.36)

mass spectroscopy (ESI): $[M+H]^+ = 540$

R_t = 1.88 min. method 12

Example 173: 6-amino-N-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide trifluoroacetate

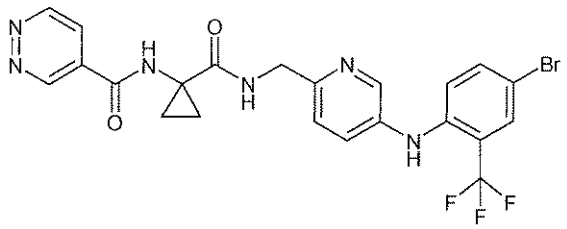


Yield: 89% of theory

$C_{23}H_{20}BrF_3N_6O_2 * C_2HF_3O_2$ (663.37)

mass spectroscopy (ESI): $[M+H]^+$ = 549

Example 174: pyridazine-4-carboxylic acid-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



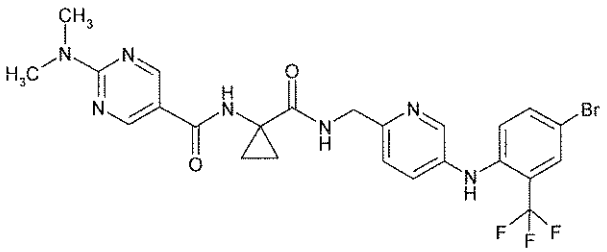
Yield: 71% of theory

$C_{22}H_{18}BrF_3N_6O_2$ (535.32)

mass spectroscopy (ESI): $[M+H]^+$ = 535

R_t = 1.80 min. method 12

Example 175: 2-dimethylamino-pyrimidine-5-carboxylic acid-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



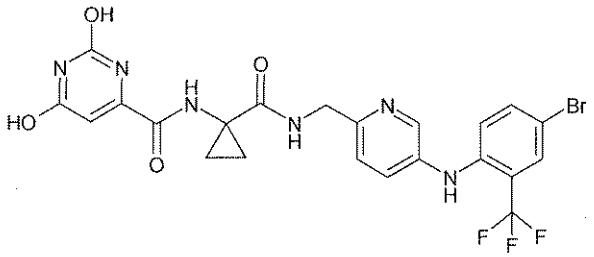
Yield: 67% of theory

$C_{24}H_{23}BrF_3N_7O_2$ (578.39)

mass spectroscopy (ESI): $[M+H]^+$ = 578

R_t = 1.99 min. method 12

Example 176: 2,6-dihydroxy-pyrimidine-4-carboxylic acid-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



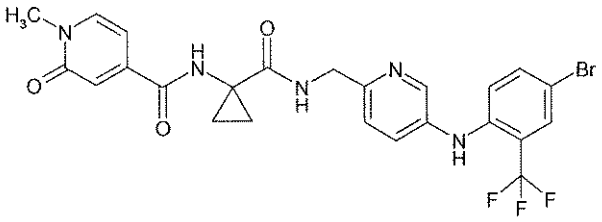
Yield: 46% of theory

$C_{22}H_{18}BrF_3N_6O_4$ (567.32)

mass spectroscopy (ESI): $[M+H]^+ = 567$

R_t = 1.74 min. method 12

Example 177: 1-methyl-2-oxo-1,2-dihydro-pyridine-4-carboxylic acid-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



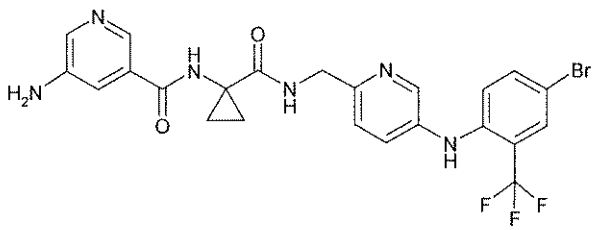
Yield: 71% of theory

$C_{24}H_{21}BrF_3N_5O_3$ (564.36)

mass spectroscopy (ESI): $[M+H]^+ = 564$

R_t = 1.78 min. method 12

Example 178: 5-amino-N-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide



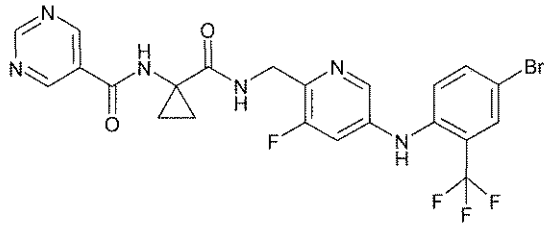
Yield: 99% of theory

$C_{23}H_{20}BrF_3N_6O_2 * C_2HF_3O_2$ (663.37)

mass spectroscopy (ESI): $[M+H]^+ = 549$

R_t = 1.68 min. method 12

Example 179: pyrimidine-5-carboxylic acid (1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



179a) 5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridine-2-carbonitrile

Obtained from 2-cyano-3,5-difluoropyridine and 4-bromo-2-trifluoromethyl-phenylamine analogously to method (40a).

$C_{13}H_6BrF_4N_3$ (360.11)

mass spectroscopy (ESI): $[M+H]^+ = 360$

R_t = 2.68 min. method 12

179b) (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-bromo-2-trifluoromethyl-phenyl)-amine

171 mg (0.48 mmol) 5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridine-2-carbonitrile were dissolved in 3 mL pyridine, 1.5 mL glacial acetic acid and 1.5 mL water and combined with 459 mg (5.22 mmol) sodium hypophosphite and Raney nickel. Then the mixture was hydrogenated for three hours at 55°C and 3 bar hydrogen pressure. The catalyst was filtered off, the filtrate was evaporated to dryness and the residue was purified by chromatography (RP with gradient, eluant: acetonitrile and water with 0.2 % trifluoroacetic acid).

$C_{13}H_{10}BrF_4N_3$ (364.14)

mass spectroscopy (ESI): $[M+H]^+ = 364$

R_t = 1.79 min. method 13

179c) pyrimidine-5-carboxylic acid (1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

54 mg (0.26 mmol) 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid, 36 µL triethylamine and 105 mg (0.31 mmol) TBTU in 4 mL DMF were stirred for 5 minutes at ambient temperature and then combined with another 144 µL triethylamine and 95 mg (0.26 mmol) (6-aminomethyl-5-fluoro-pyridin-3-yl)-(4-bromo-2-trifluoromethyl-phenyl)-amine. The reaction mixture was stirred overnight and then evaporated to dryness. The

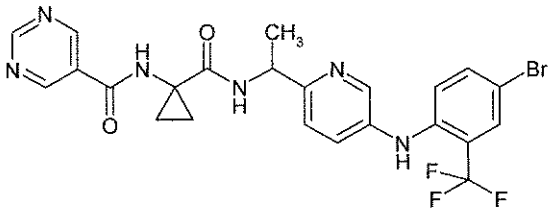
residue was purified by chromatography (RP with gradient, eluant: acetonitrile and water with 0.2 % trifluoroacetic acid).

$C_{22}H_{17}BrF_4N_6O_2$ (553.31)

mass spectroscopy (ESI): $[M+H]^+ = 553$

R_t = 2.20 min. method 13

Example 180: pyrimidine-5-carboxylic acid-(1-{1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide



180a) 1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone

A solution of 3.27 g (9.56 mmol) 5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile in 100 mL diethyl ether was added dropwise to 5.42 mL 3 molar methylmagnesium bromide in diethyl ether while being cooled with the ice bath. Then the reaction mixture was allowed to come up to ambient temperature and stirred for another hour. The mixture was combined with 2.5 mL 1 molar hydrochloric acid and then evaporated to dryness. The residue was purified by chromatography (RP with gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

$C_{14}H_{10}BrF_3N_2O$ (359.14)

R_t = 2.57 min. method 12

180b) 1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxime

702 mg (1.96 mmol) 1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone, 182 mg hydroxylamine-hydrochloride and 549 µl (3.91 mmol) triethylamine in 25 mL acetonitrile were refluxed for 1.5 hours. The solvent was distilled off and the residue was combined with dichloromethane and triethylamine and filtered through silica gel. The filtrate was freed from the solvent and used directly in the next reaction. 870 mg product.

180c) [6-(1-amino-ethyl)-pyridin-3-yl]-(4-bromo-2-trifluoromethyl-phenyl)-amine trifluoroacetate

A solution of 870 mg (approx. 85%, 2.0 mmol) 1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethanone-oxime in 20 mL methanol was combined with 6 mL 10 molar hydrochloric acid in methanol and 567 mg zinc and refluxed for 3 hours. Then the mixture was filtered and the filtrate was freed from the solvent. The residue was purified by chromatography (RP with gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

Yield: 78% over two steps

$C_{14}H_{13}BrF_3N_3$ (360.17)

mass spectroscopy (ESI): $[M+H]^+ = 360$

R_t = 1.83 min. method 12

180d) pyrimidine-5-carboxylic acid-(1-{1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide

Analogously to method (179c) from 190 mg (0.92 mmol) 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid and 330 mg (0.69 mmol) [6-(1-amino-ethyl)-pyridin-3-yl]-(4-bromo-2-trifluoromethyl-phenyl)-amine trifluoroacetate.

Yield: 55% of theory

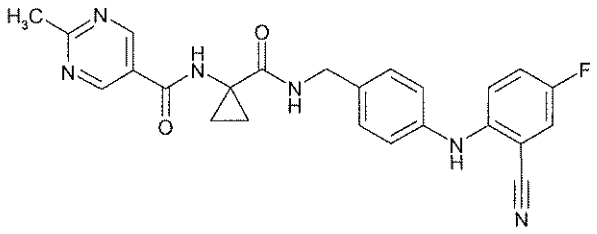
$C_{23}H_{20}BrF_3N_6O_2 \cdot C_2HF_3O_2$ (663.37)

mass spectroscopy (ESI): $[M+H]^+ = 549$

R_t = 1.92 min. method 12

The (R)- and (S)-enantiomer of Example 180 were obtained by chiral HPLC (SFC) from the racemic compound (column: Daicel ASH, 250 mm x 10 mm, flow rate: 10 mL/min, eluant: 70% supercritical carbon dioxide and 30% isopropanol with 0.2% triethylamine).

Example 181: 2-methyl-pyrimidine-5-carboxylic acid {1-[4-(2-cyano-4-fluoro-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



181a) tert-butyl {1-[4-(2-cyano-4-fluoro-phenylamino)-benzylcarbamoyl]-cyclopropyl}-carbamate

877 mg (4.36 mmol) 1-tert-butoxycarbonylamino-cyclopropanecarboxylic acid and 2.58 (60%, 4.36 mmol) 2-(4-aminomethyl-phenylamino)-5-fluoro-benzonitrile trifluoroacetate were coupled analogously to method (179c).

Yield: 30% of theory

$C_{23}H_{25}FN_4O_3$ (424.47)

mass spectroscopy (ESI): $[M-H]^+ = 423$

R_t = 2.39 min. method 13

181b) 1-amino-cyclopropanecarboxylic acid 4-(2-cyano-4-fluoro-phenylamino)-benzylamide trifluoroacetate

560 mg (1.32 mmol) 2-(4-aminomethyl-phenylamino)-5-fluoro-benzonitrile trifluoroacetate in 15 mL dichloromethane were combined with 15 mL trifluoroacetic acid and stirred at ambient temperature. Then the reaction mixture was evaporated to dryness and purified by chromatography (RP with gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

$C_{18}H_{17}FN_4O * C_2HF_3O_2$ (438.38)

mass spectroscopy (ESI): $[M-H]^+ = 325$

R_t = 1.56 min. method 13

181c) 2-methyl-pyrimidine-5-carboxylic acid-{1-[4-(2-cyano-4-fluoro-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide

Prepared analogously to method (179c) from 42 mg (0.29 mmol) 2-methyl-pyrimidine-5-carboxylic acid and 167 mg (75%, 0.29 mmol) 1-amino-cyclopropanecarboxylic acid-4-(2-cyano-4-fluoro-phenylamino)-benzylamide trifluoroacetate.

Yield: 83% of theory

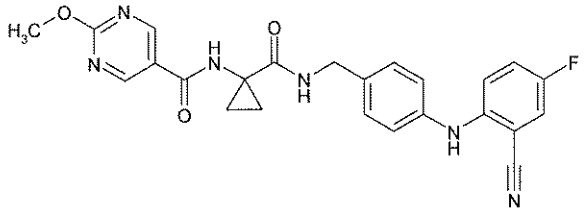
$C_{24}H_{21}FN_6O_2$ (444.46)

mass spectroscopy (ESI): $[M+H]^+ = 445$

R_t = 1.92 min. method 13

Examples 182 and 183 were prepared analogously from 1-amino-cyclopropanecarboxylic acid-4-(2-cyano-4-fluoro-phenylamino)-benzylamide trifluoroacetate and the corresponding carboxylic acids.

Example 182: 2-methoxy-pyrimidine-5-carboxylic acid-{1-[4-(2-cyano-4-fluoro-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



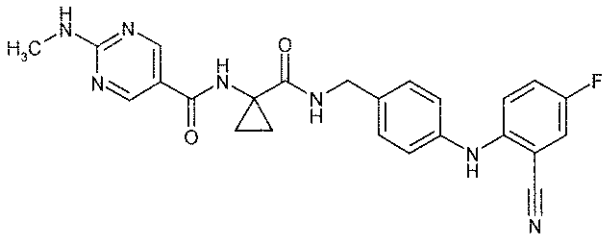
Yield: 28% of theory

$C_{24}H_{21}FN_6O_3$ (460.46)

mass spectroscopy (ESI): $[M+H]^+$ = 461

R_t = 2.03 min. method 13

Example 183: 2-methylamino-pyrimidine-5-carboxylic acid-{1-[4-(2-cyano-4-fluoro-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



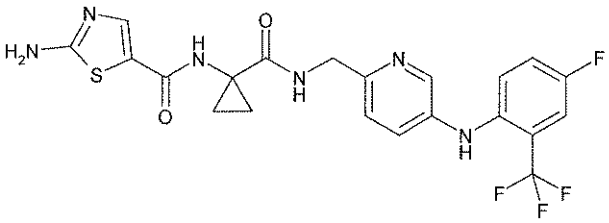
Yield: 58% of theory

$C_{24}H_{22}FN_7O_2$ (459.48)

mass spectroscopy (ESI): $[M+H]^+$ = 460

R_t = 1.91 min. method 13

Example 184: 2-amino-thiazole-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



184a) 2-acetylamino-thiazole-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

Prepared from 1-amino-cyclopropanecarboxylic acid-[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide hydrochloride and 2-acetylamino-thiazole-5-carboxylic acid analogously to method (142c).

Yield: 51% of theory

$C_{23}H_{20}F_4N_6O_3S$ (536.50)

R_t = 2.96 min. method 7

184b) 2-amino-thiazole-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

110 mg (0.21 mmol) 2-acetylamino-thiazole-5-carboxylic acid (1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide were stirred overnight at 80°C in 5 mL 4 molar hydrochloric acid. Then the reaction mixture was made alkaline with potassium carbonate solution and the precipitated solid was filtered off, washed with water and dried.

Yield: 43% of theory

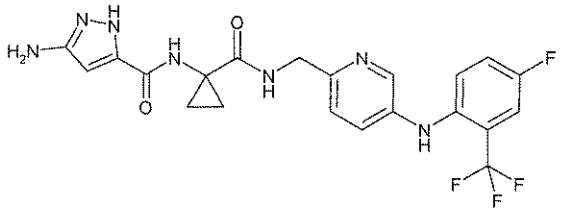
$C_{21}H_{18}F_4N_6O_2S$ (494.47)

mass spectroscopy (ESI): $[M+H]^+$ = 495

R_t = 2.73 min. method 7

Examples 185 and 186 were prepared analogously from 1-amino-cyclopropanecarboxylic acid-[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide hydrochloride and the corresponding acetylamino-carboxylic acid.

Example 185: 5-amino-2H-pyrazole-3-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

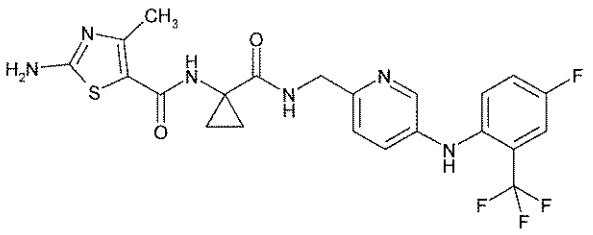


$C_{21}H_{19}F_4N_7O_2$ (477.42)

mass spectroscopy (ESI): $[M+H]^+$ = 478

R_t = 2.69 min. method 7

Example 186: 2-amino-4-methyl-thiazole-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

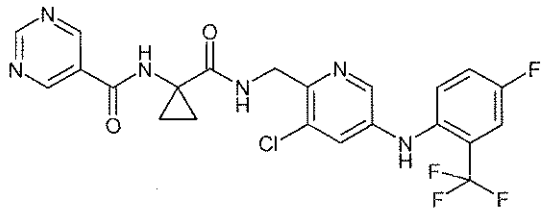


$C_{22}H_{20}F_4N_6O_2S$ (508.49)

mass spectroscopy (ESI): $[M+H]^+ = 509$

R_t = 2.67 min. method 7

Example 187: pyrimidine-5-carboxylic acid (1-{[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide dihydrochloride



187a) 3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile

A solution of 5.00 g (28.9 mmol) 3,5-dichloro-pyridine-2-carbonitrile and 5.18 g (28.9 mmol) 4-fluoro-2-trifluoromethyl-phenylamine in 75 mL DMSO was combined with 5.05 g (45.0 mmol) potassium-tert-butoxide while being cooled and then stirred for 30 minutes at ambient temperature. The reaction mixture was stirred into water and then extracted with diethyl ether. The organic phases were washed with water and sodium chloride solution, dried on sodium sulphate and evaporated down. The residue was purified by chromatography through a silica gel column (petroleum ether with 5 to 15% ethyl acetate).

Yield: 45% of theory

187b) (6-aminomethyl-5-chloro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine

A solution of 100 mg (0.32 mmol) 3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile in 3 mL THF was combined at ambient temperature with 31 µL borane-dimethylsulphide complex and then stirred overnight. Methanol was then added

carefully and the mixture was evaporated to dryness. The residue was used in the next reaction without any further purification.

187c) pyrimidine-5-carboxylic acid (1-{[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide dihydrochloride

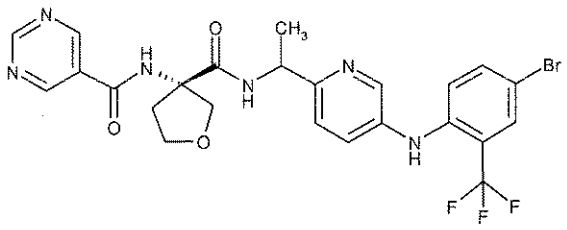
Prepared from (6-aminomethyl-5-chloro-pyridin-3-yl)-(4-fluoro-2-trifluoromethyl-phenyl)-amine and 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid analogously to the method for Example 151.

$C_{22}H_{17}ClF_4N_6O_2$* 2 HCl (581.78)

mass spectroscopy (ESI): $[M+H]^+$ = 509

R_t = 3.68 min. method 10

Example 188: pyrimidine-5-carboxylic acid-(3-{1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-(S)-tetrahydro-furan-3-yl)-amide



A solution of 59 mg (0.25 mmol) (S)-3-[(pyrimidine-5-carbonyl)-amino]-tetrahydrofuran-3-carboxylic acid and 48 mg (0.30 mmol) N,N'-carbonyldiimidazole in 5 mL DMF was stirred for one hour at 50°C and then combined with 89 mg (0.25 mmol) [6-(1-amino-ethyl)-pyridin-3-yl]-(4-bromo-2-trifluoromethyl-phenyl)-amine and 45 µL (0.26 mmol) DIPEA. It was then stirred for another hour at ambient temperature. The reaction mixture was purified by chromatography (RP with eluant gradient, eluant: acetonitrile and water with 0.2 % trifluoroacetic acid).

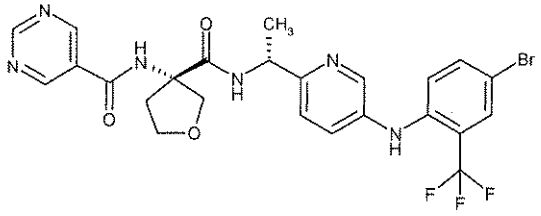
Yield: 41% of theory

$C_{24}H_{22}BrF_3N_6O_3$ (579.37)

mass spectroscopy (ESI): $[M+H]^+$ = 579

R_t = 1.93 min. method 12

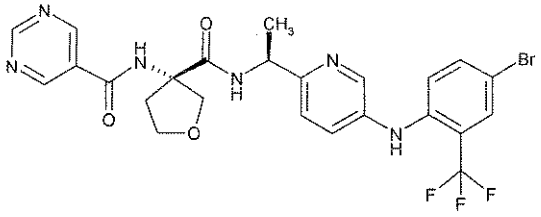
Example 188a: pyrimidine-5-carboxylic acid-(3-{1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-tetrahydrofuran-3-yl)-amide



Separation of diastereomers by chiral HPLC (column: Daicel ASH; 250 x 4.6 mm; 5 µm; 25°C; eluant CO_2 / (isopropanol + 0.2% diethylamine) 80:20; flow: 10 mL/min)

R_t = 5.32 – 7.15 minutes

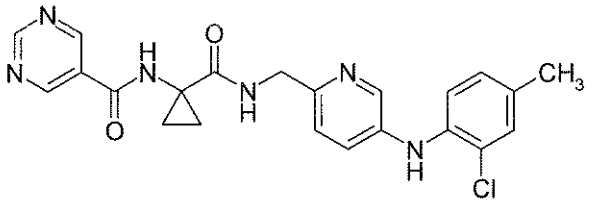
Example 188b: pyrimidine-5-carboxylic acid (3-{1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl]-ethylcarbamoyl}-tetrahydrofuran-3-yl)-amide



Separation of diastereomers by chiral HPLC (column: Daicel ASH; 250 x 4.6 mm; 5 µm; 25°C; eluant CO_2 / (isopropanol + 0.2% diethylamine) 80:20; flow: 10 mL/min)

R_t = 8.23 – 10.51 minutes

Example 189: pyrimidine-5-carboxylic acid (1-{[5-(2-chloro-4-methyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



Analogously to Example 1d) the product was prepared by amide coupling from 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid and (6-aminomethyl-pyridin-3-yl)-(2-chloro-4-methyl-phenyl)-amine using TBTU as coupling reagent and diisoproylethylamine as base.

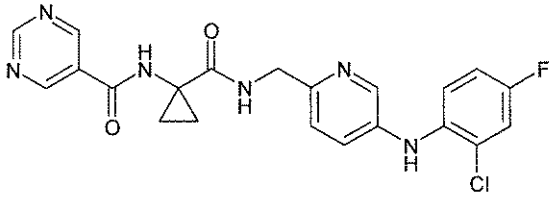
$C_{22}H_{21}ClN_6O_2$ (436.90)

Mass spectrum (ESI): $[M+H]^+$ = 437

$M-H]^-$ = 435

R_t = 1.59 min (method 2)

Example 190: pyrimidine-5-carboxylic acid (1-{[5-(2-chloro-4-fluoro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



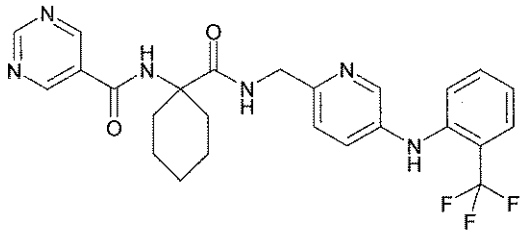
Analogously to Example 1d) the product was prepared by amide coupling from 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropane-carboxylic acid and (6-aminomethyl-pyridin-3-yl)-(2-chloro-4-fluoro-phenyl)-amine, using TBTU as coupling reagent and diisoproylethylamine as base.

$C_{21}H_{16}ClFN_6O_2$ (440.86)

Mass spectrum (ESI): $[M+H]^+$ = 441

R_t = 1.50 min (method 2)

Example 191: pyrimidine-5-carboxylic acid (1-{[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclohexyl)-amide



191a) 1-amino-cyclohexanecarboxylic acid [5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

61 mg (0.25 mmol) 1-*tert*-butoxycarbonylamino-cyclohexanecarboxylic acid, 80 mg (0.25 mmol) TBTU and 53 µL (0.38 mmol) triethylamine in 2 mL DMF were stirred for 5 minutes at ambient temperature and then mixed with 67 mg (0.25 mmol) (6-aminomethyl-pyridin-3-yl)-(2-trifluoromethyl-phenyl)-amine. The reaction mixture was then stirred overnight and purified by chromatography (RP with eluting gradient, eluant: acetonitrile and water with 0.1% trifluoroacetic acid). 93 mg of the isolated Boc-protected amine were stirred for 2 hours at ambient temperature in 5 mL of a 1:1 mixture of dichloromethane and

trifluoroacetic acid. The reaction mixture was evaporated to dryness and then purified by chromatography (RP with eluting gradient, eluant: acetonitrile and water with 0.1% trifluoroacetic acid).

Yield: 68% of theory (as trifluoroacetate)

mass spectroscopy $[M+H]^+$ = 393

R_t = 1.70 min method 6

191b) pyrimidine-5-carboxylic acid-(1-{[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclohexyl)-amide

Prepared from 1-amino-cyclohexanecarboxylic acid [5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide and pyrimidine-5-carboxylic acid analogously to method 191a).

Yield: 37% of theory

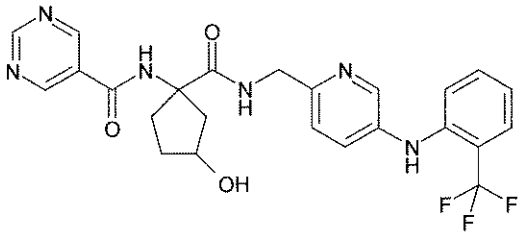
$C_{25}H_{25}F_3N_6O_2$ (498.51)

Mass spectrum (ESI): $[M+H]^+$ = 499

$[M-H]^-$ = 497

R_t = 1.84 min (method 5)

Example 192: pyrimidine-5-carboxylic acid (3-hydroxy-1-{[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopentyl)-amide



192a) 1-amino-3-hydroxy-cyclopentanecarboxylic acid [5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

1-*tert*-butoxycarbonylamino-3-hydroxy-cyclopentanecarboxylic acid and (6-aminomethyl-pyridin-3-yl)-(2-trifluoromethyl-phenyl)-amine were reacted analogously to method 191a).

Yield: 49% of theory (as trifluoroacetate)

mass spectroscopy $[M+H]^+$ = 395

R_t = 1.62 min method 6

192b) pyrimidine-5-carboxylic acid (3-hydroxy-1-{[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopentyl)-amide

The target compound was prepared from 1-amino-3-hydroxy-cyclopentanecarboxylic acid [5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide and pyrimidine-5-carboxylic acid analogously to method 191a).

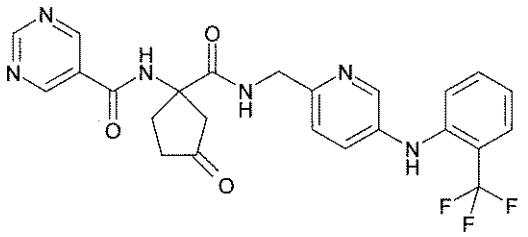
Yield: 55% of theory

$C_{24}H_{23}F_3N_6O_3$ (500.48)

Mass spectrum (ESI): $[M+H]^+ = 501$

R_t = 1.66 min (method 5)

Example 193: pyrimidine-5-carboxylic acid (3-oxo-1-{[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopentyl)-amide



10 mg pyrimidine-5-carboxylic acid (3-hydroxy-1-{[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopentyl)-amide in 1 mL acetonitrile were mixed with 8 mg Dess-Martin-Periodinane reagent and stirred for 1 hour at ambient temperature. Then the reaction mixture was purified by chromatography (RP with eluting gradient, eluant: acetonitrile and water with 0.1% trifluoroacetic acid).

Yield: 90% of theory

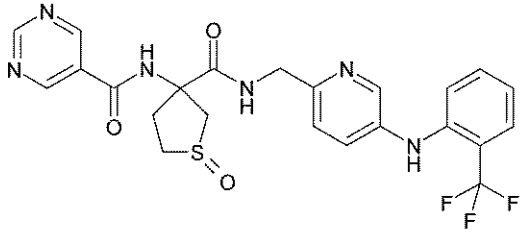
$C_{24}H_{21}F_3N_6O_3$ (498.46)

Mass spectrum (ESI): $[M+H]^+ = 499$

$[M-H]^- = 497$

R_t = 1.73 min (method 5)

Example 194: pyrimidine-5-carboxylic acid (1-oxo-3-{[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydro-1lambda*4*-thiophen-3-yl)-amide



194a) 3-amino-1-oxo-tetrahydrothiophene-3-carboxylic acid [5-(2-trifluoromethyl-phenyl-amino)-pyridin-2-ylmethyl]-amide

The product was obtained from 3-*tert*-butoxycarbonylamino-1-oxo-tetrahydro-thiophene-3-carboxylic acid and (6-aminomethyl-pyridin-3-yl)-(2-trifluoromethyl-phenyl)-amine analogously to method 191a).

Yield: 96% of theory (as trifluoroacetate)

mass spectroscopy $[M+H]^+ = 413$

$R_t = 1.62$ min method 6

194b) pyrimidine-5-carboxylic acid (1-oxo-3-{[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydro-thiophen-3-yl)-amide

Prepared from 3-amino-1-oxo-tetrahydro-thiophene-3-carboxylic acid-[5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide and pyrimidine-5-carboxylic acid analogously to method 191a).

Yield: 58% of theory

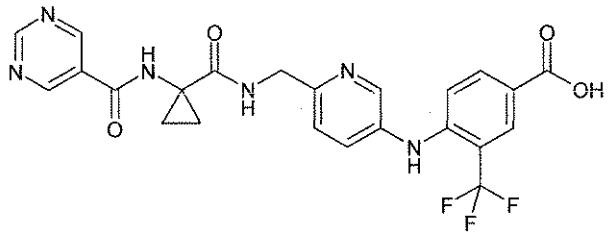
$C_{23}H_{21}F_3N_6O_3S$ (518.52)

Mass spectrum (ESI): $[M+H]^+ = 519$

$[M+H]^+ = 517$

$R_t = 1.66$ min (method 5)

Example 195: 4-{6-[({1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarbonyl}-amino)-methyl]-pyridin-3-ylamino}-3-trifluoromethyl-benzoic acid



469 (0.91 mmol) methyl 4-{6-[({1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarbonyl}-amino)-methyl]-pyridin-3-ylamino}-3-trifluoromethyl-benzoate were stirred overnight in 5 mL of 1N aqueous sodium hydroxide solution and 20 mL ethanol at ambient temperature. Then the reaction mixture was neutralised with 1N aqueous hydrochloric acid and evaporated to dryness. The residue was dissolved in methanol and DMF, filtered and then chromatographed (RP with eluting gradient, eluant: acetonitrile and water with 0.2 % trifluoroacetic acid).

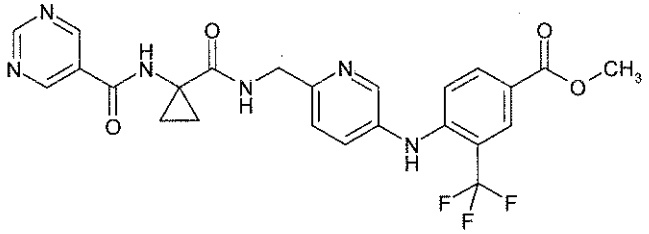
Yield: 69% of theory

$C_{23}H_{19}F_3N_6O_4$ (500.44)

Mass spectrum (ESI): $[M+H]^+ = 501$

$[M-H]^- = 499$

Example 196: methyl 4-{6-[({1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarbonyl}-amino)-methyl]-pyridin-3-ylamino}-3-trifluoromethyl-benzoate



196a) methyl 4-(6-cyano-pyridin-3-ylamino)-3-trifluoromethyl-benzoate

1190 mg (3.48 mmol) 5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridine-2-carbonitrile, 221 µL (1.6 mmol) triethylamine and 97 mg (0.13 mmol) $Pd(ddpf)Cl_2$ in 10 mL methanol and 2 mL DMF were heated to 50°C in an autoclave under a carbon monoxide pressure of 5 bar for 60 hours. After removal of the solvents by distillation the residue was dissolved in acetonitrile and methanol and filtered. The filtrate was then evaporated down and purified by chromatography (1st column: RP with eluting gradient, eluant: acetonitrile and water with 0.1% trifluoroacetic acid; 2nd column: silica gel, eluant: dichloromethane).

Yield: 78% of theory

mass spectroscopy $[M+H]^+ = 322$

196b) methyl 4-(6-aminomethyl-pyridin-3-ylamino)-3-trifluoromethyl-benzoate

860 mg (2.7 mmol) methyl 4-(6-cyano-pyridin-3-ylamino)-3-trifluoromethyl-benzoate in 30 mL methanolic ammonia were hydrogenated at ambient temperature under a hydrogen pressure of 50 psi in the presence of 100 mg Raney nickel. The catalyst was filtered off and the filtrate was freed from solvent.

Yield: 76% of theory

mass spectroscopy $[M+H]^+ = 326$

196c) methyl 4-{6-[({1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarbonyl}-amino)-methyl]-pyridin-3-ylamino}-3-trifluoromethyl-benzoate

191 mg (0.92 mmmol) 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid, 305 mg (0.95 mmol) TBTU and 203 µL (1.85 mmol) N-methylmorpholine in 3 mL DMF were stirred for 5 minutes at ambient temperature. The solution was combined with 300 mg (0.92 mmol) methyl 4-(6-aminomethyl-pyridin-3-ylamino)-3-trifluoromethyl-benzoate and left to stand over the weekend. Then the reaction mixture was purified by chromatography (RP with eluting gradient, eluant: acetonitrile and water with 0.2 % trifluoroacetic acid).

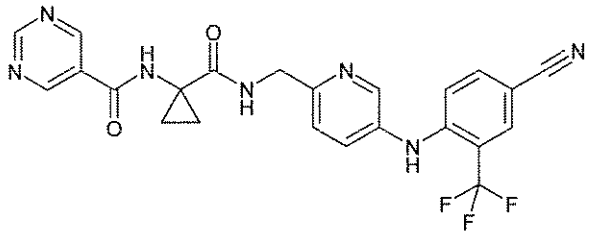
Yield: 62% of theory

$C_{24}H_{21}F_3N_6O_4$ (514.46)

Mass spectrum (ESI): $[M+H]^+ = 515$

R_t = 1.73 min (method 12)

Example 197: pyrimidine-5-carboxylic acid (1-{[5-(4-cyano-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



55 mg (0.18 mmol) pyrimidine-5-carboxylic acid {1-[(5-amino-pyridin-2-ylmethyl)-carbamoyl]-cyclopropyl}-amide, 33 mg (0.18 mmol) 4-fluoro-3-(trifluoromethyl)benzonitrile and 42 mg (0.35 mg) potassium-*tert*-butoxide in 5 mL DMSO were stirred for 1 h at 50°C. The reaction mixture was filtered and the filtrate was purified by chromatography (RP with eluting gradient, eluant: acetonitrile and water with 0.2 % trifluoroacetic acid).

Yield: 23% of theory

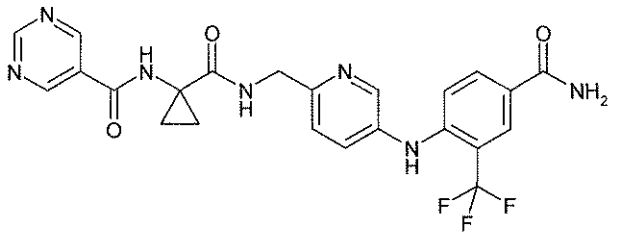
$C_{23}H_{18}F_3N_7O_2$ (481.44)

Mass spectrum (ESI): $[M+H]^+ = 482$

$[M-H]^- = 480$

R_t = 1.69 min (method 12)

Example 198: pyrimidine-5-carboxylic acid (1-{[5-(4-carbamoyl-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



A solution of 50 mg (0.10 mmol) 4-{6-[({1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarbonyl}-amino)-methyl]-pyridin-3-ylamino}-3-trifluoromethyl-benzoic acid, 33 mg (0.10 mmol) TBTU and 12 µL (0.11 mmol) N-methylmorpholine in 0.5 mL DMF was stirred for 3 minutes at ambient temperature, then combined with 17 µL (0.11 mmol) 2,4-dimethoxybenzylamine, stirred for a further 10 minutes and left to stand overnight. In order to cleave the benzyl group the mixture was combined with 10 mL dichloromethane and 10 mL trifluoroacetic acid, left to stand overnight and evaporated to dryness. The residue was filtered and then purified by chromatography (RP with eluting gradient, eluant: acetonitrile and water with 0.2% trifluoroacetic acid).

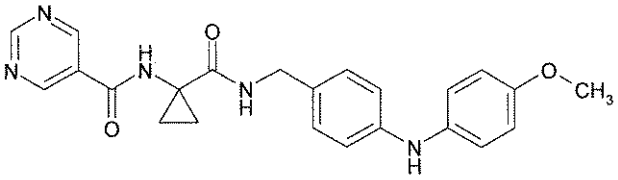
Yield: 6% of theory

$C_{23}H_{20}F_3N_7O_3$ (499.45)

Mass spectrum (ESI): $[M+H]^+ = 500$

$[M-H]^- = 498$

Example 199: pyrimidine-5-carboxylic acid {1-[4-(4-methoxy-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



Obtained from 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid and (4-aminomethyl-phenyl)-(4-methoxy-phenyl)-amine analogously to method 191a).

Yield: 37% of theory

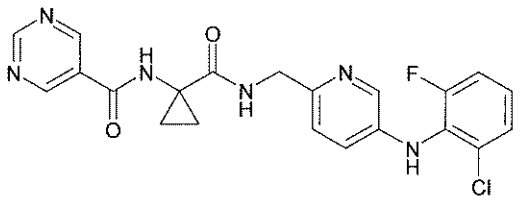
$C_{23}H_{23}N_5O_3$ (417.47)

Mass spectrum (ESI): $[M+H]^+ = 418$

$[M-H]^- = 416$

R_t = 1.83 min (method 12)

Example 200: pyrimidine-5-carboxylic acid (1-{[5-(2-chloro-6-fluoro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



Coupling of 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid and (6-aminomethyl-pyridin-3-yl)-(2-chloro-6-fluoro-phenyl)-amine trifluoroacetate with TBTU analogously to method 191a).

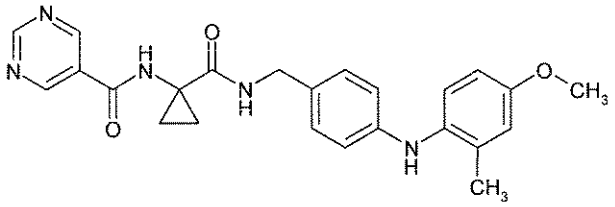
$C_{21}H_{18}ClFN_6O_2$ (440.86)

Mass spectrum (ESI): $[M+H]^+$ = 441

$[M-]^-$= 439

R_t = 1.38 min (method 2)

Example 201: pyrimidine-5-carboxylic acid {1-[4-(4-methoxy-2-methyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide



Prepared from 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid and (4-aminomethyl-phenyl)-(4-methoxy-2-methyl-phenyl)-amine according to method 191a).

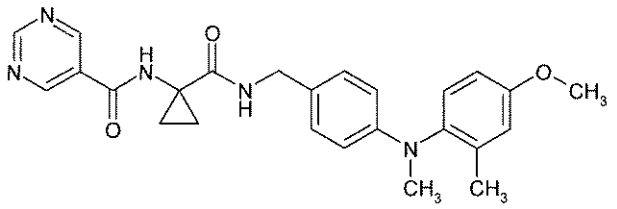
$C_{24}H_{25}N_5O_3$ (431.49)

Mass spectrum (ESI): $[M+H]^+$ = 432

$[M+H]^+$ = 430

R_t = 1.97 min (method 12)

Example 202: pyrimidine-5-carboxylic acid (1-{4-[(4-methoxy-2-methyl-phenyl)-methyl-amino]-benzylcarbamoyl}-cyclopropyl)-amide



73 mg (0.35 mmol) of 1-[(pyrimidine-5-carbonyl)-amino]-cyclopropanecarboxylic acid and 57 mg (0.35 mmol) CDI were stirred for 30 minutes at 50°C in 5 mL DMF. 90 mg (0.35 mmol) (4-aminomethyl-phenyl)-(4-methoxy-2-methyl-phenyl)-methyl-amine and 101 µL diisopropylethylamine were added at ambient temperature and the mixture was left overnight with stirring. The solvent was distilled off and the residue was dissolved in methanol and purified by chromatography (RP with eluting gradient, eluant: acetonitrile and water with 0.2 % trifluoroacetic acid).

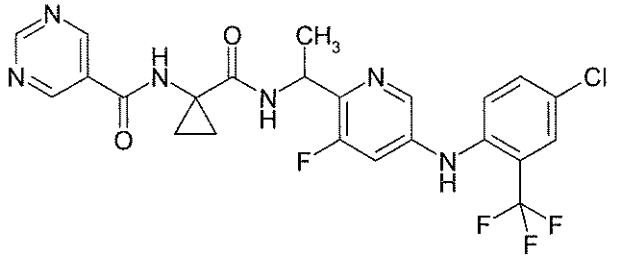
Yield: 19% of theory

$C_{25}H_{27}N_5O_3$ (445.52)

Mass spectrum (ESI): $[M+H]^+$ = 446

R_t = 2.16 min (method 12)

Example 203: pyrimidine-5-carboxylic acid-(1-{1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide



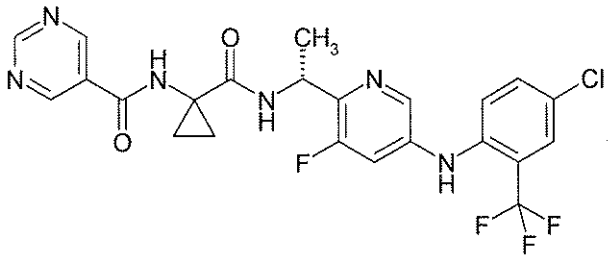
Prepared from intermediates A1 and B1 according to AAV1

$C_{23}H_{19}ClF_4N_6O_2$ (522.89)

R_t = 2.30 minutes method 2

The racemate was separated into the enantiomers by chiral HPLC (column: Daicel AD-H 250 x 20 mm; 5 µm; 25°C; eluant CO_2 / isopropanol (+0.2% diethylamine) 80:20; flow: 10 mL/min).

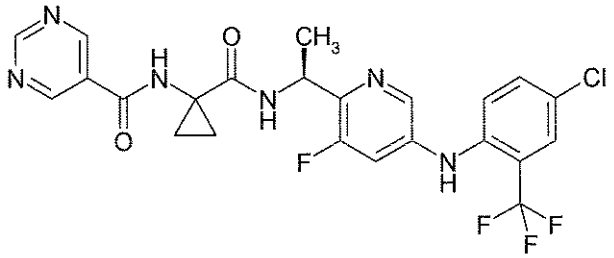
Example 203a: (*R*)-pyrimidine-5-carboxylic acid-(1-{1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide



Analytical chiral HPLC (column: Daicel AD-H; 250 x 4.6 mm; 5 µm; 25°C; eluant CO_2 / isopropanol 80:20; flow: 4 mL/min)

R_t = 1.62 minutes

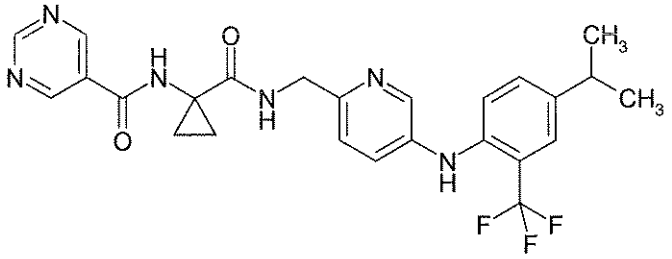
Example 203b: (*S*)-pyrimidine-5-carboxylic acid-(1-{1-[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide



Analytical chiral HPLC (column: Daicel AD-H; 250 x 4.6 mm; 5 µm; 25°C; eluant CO_2 / isopropanol 80:20; flow: 4 mL/min)

R_t = 2.29 minutes

Example 204: pyrimidine-5-carboxylic acid(1-{[5-(4-isopropyl-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

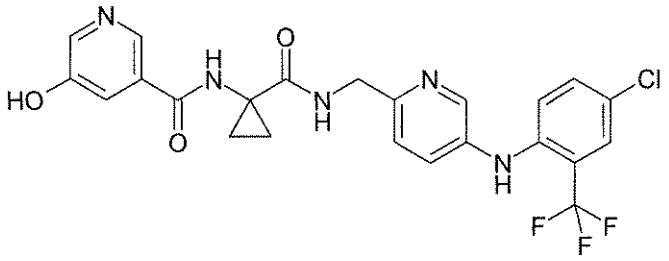


Prepared from intermediates A2 and B1 according to AAV1

$C_{25}H_{25}F_3N_6O_2$ (498.51)

R_t = 1.95 minutes (method 2)

Example 205: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-hydroxy-nicotinamide

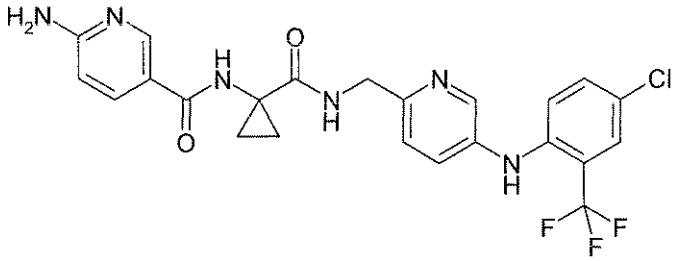


Prepared from intermediate C1 and 5-hydroxynicotinic acid according to AAV1

$C_{23}H_{19}ClF_3N_5O_3$ (505.88)

R_t = 1.74 minutes (method 13)

Example 206: 6-amino-N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

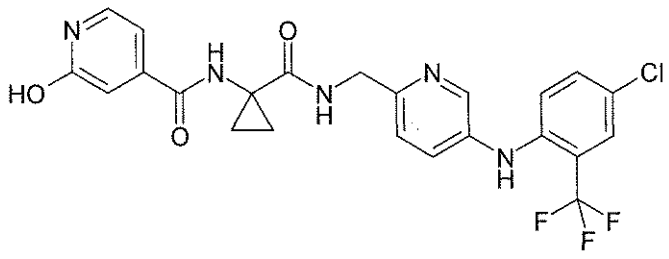


Prepared from intermediate C1 and 6-aminonicotinic acid according to AAV1

$C_{23}H_{20}ClF_3N_6O_2$ (504.90)

R_t = 1.60 minutes (method 13)

Example 207: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-2-hydroxy-isonicotinamide

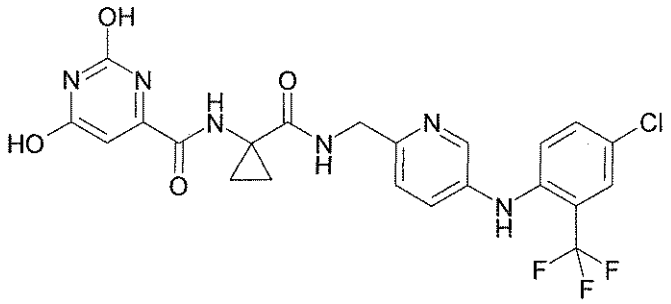


Prepared from intermediate C1 and 2-hydroxy-isonicotinic acid according to AAV1

$C_{23}H_{19}ClF_3N_5O_3$ (505.88)

R_t = 1.69 minutes (method 13)

Example 208: 2,6-dihydroxy-pyrimidine-4-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

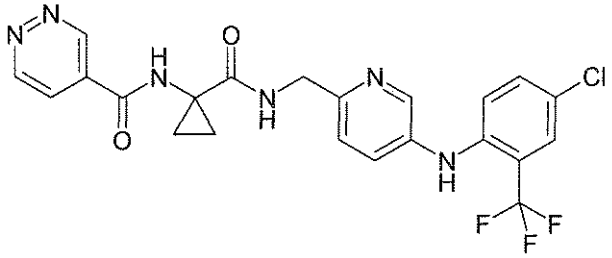


Prepared from intermediate C1 and 2,6-dihydroxy-pyrimidine-4-carboxylic acid according to AAV1

$C_{22}H_{18}ClF_3N_6O_4$ (522.87)

R_t = 1.70 minutes (method 13)

Example 209: pyridazine-4-carboxylic acid (1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

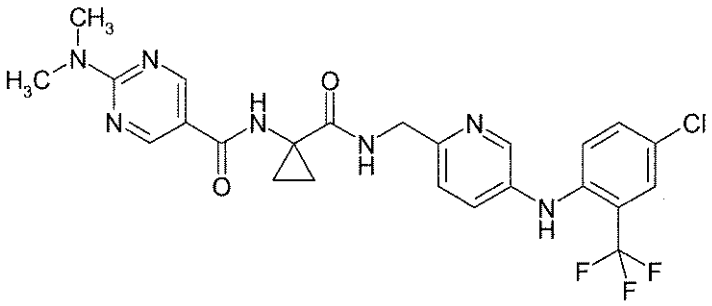


Prepared from intermediate C1 and pyridazine-4-carboxylic acid according to AAV1

$C_{22}H_{18}ClF_3N_6O_2$ (522.87)

R_t = 1.76 minutes (method 13)

Example 210: 2-dimethylamino-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

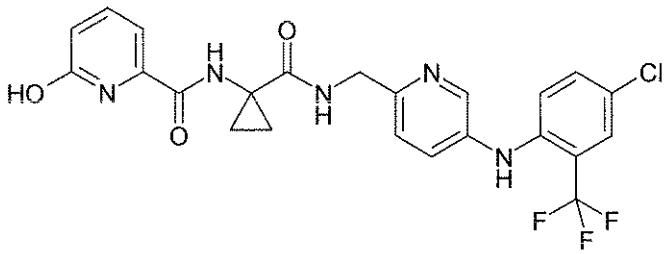


Prepared from intermediate C1 and 2-dimethylamino-pyrimidine-5-carboxylic acid according to AAV1

$C_{24}H_{23}ClF_3N_7O_2$ (533.94)

R_t = 1.94 minutes (method 13)

Example 211: 6-hydroxy-pyridine-2-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

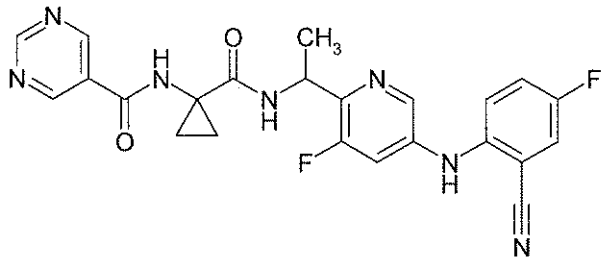


Prepared from intermediate C1 and 6-hydroxy-pyridine-2-carboxylic acid according to AAV1

$C_{23}H_{19}ClF_3N_5O_3$ (505.88)

R_t = 1.75 minutes method 13

Example 212: pyrimidine-5-carboxylic acid-(1-{1-[5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide



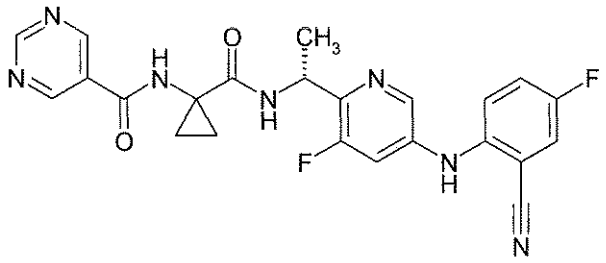
Prepared from intermediates A4 and B1 according to AAV1

$C_{23}H_{19}F_2N_7O_2$ (463.45)

R_t = 1.81 minutes method 2

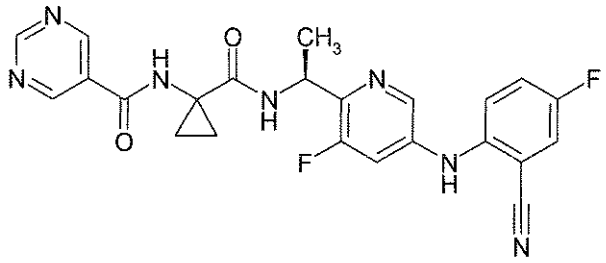
The racemate was separated into the enantiomers by chiral HPLC (column: Daicel AD-H 250 x 20mm; 5 µm; 25°C; eluant CO_2 / isopropanol (+0.2% diethylamine) 80:20; flow: 10 mL/min):

Example 212a: (*R*)-pyrimidine-5-carboxylic acid-(1-{1-[5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide



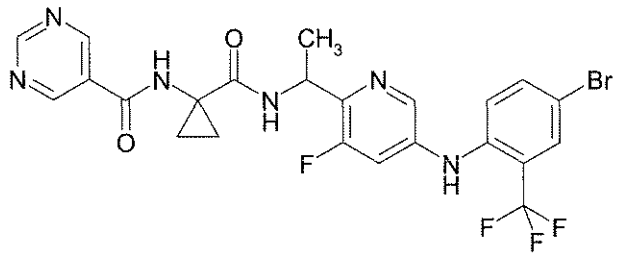
R_t = 2.75 minutes

Example 212b: (*S*)-pyrimidine-5-carboxylic acid-(1-{1-[5-(2-cyano-4-fluoro-phenylamino)-3-fluoro-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide



R_t = 5.12 minutes

Example 213: pyrimidine-5-carboxylic acid-(1-{1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide



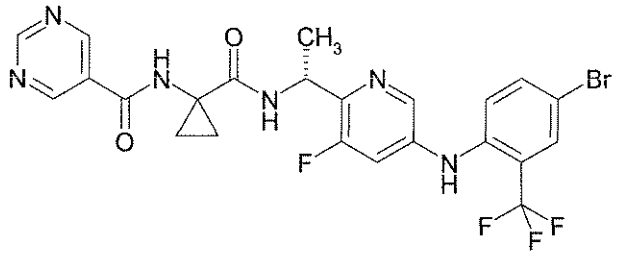
Prepared from intermediates A5 and B1 according to AAV1

$C_{23}H_{19}BrF_4N_6O_2$ (567.34)

R_t = 2.34 minutes (method 2)

The racemate was separated into the enantiomers by chiral HPLC:

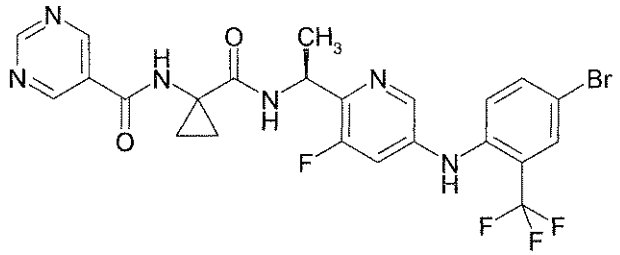
Example 213a: (*R*)-pyrimidine-5-carboxylic acid-(1-{1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide



Analytical chiral HPLC (column: Daicel AD-H; 250 x 4.6 mm; 5 µm; 25°C; eluant CO_2 / isopropanol 80:20; flow: 4mL/min)

R_t = 1.78 minutes

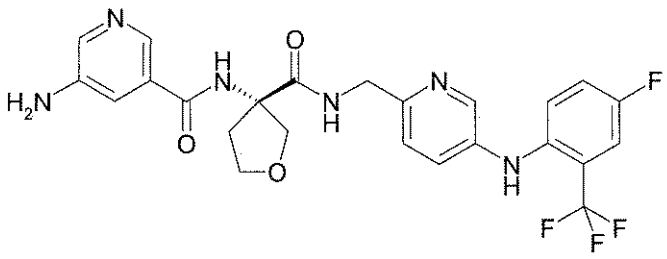
Example 213b: (*S*)-pyrimidine-5-carboxylic acid-(1-{1-[5-(4-bromo-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl]-ethylcarbamoyl}-cyclopropyl)-amide



Analytical chiral HPLC (column: Daicel AD-H; 250 x 4.6 mm; 5 µm; 25°C; eluant CO_2 / isopropanol 80:20; flow: 4mL/min)

R_t = 2.55 minutes

Example 214: (*S*)-5-amino-N-(3-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

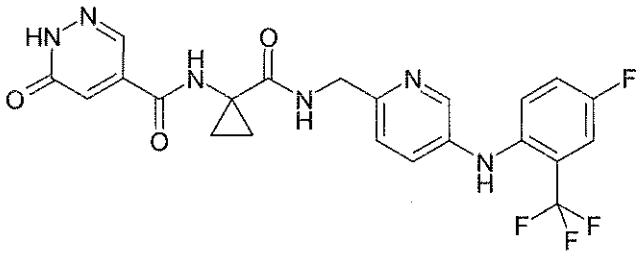


Prepared from intermediates A6 and B2 according to AAV1

$C_{25}H_{23}F_4N_5O_3$ (517.48)

R_t = 3.33 minutes (method 7)

Example 215: 6-oxo-5,6-dihydro-pyridazine-4-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

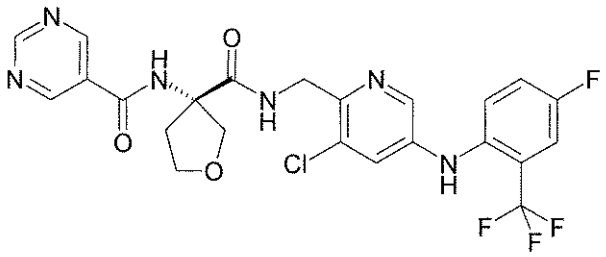


Prepared from intermediate C2 and 6-oxo-5,6-dihydro-pyridazine-4-carboxylic acid according to AAV1

$C_{22}H_{18}F_4N_6O_3$ (490.42)

R_t = 2.80 minutes (method 7)

Example 216: (*S*)-pyrimidine-5-carboxylic acid-(3-{[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

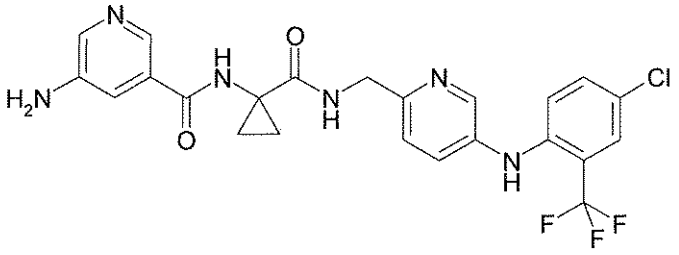


Prepared from intermediates A8 and B3 according to AAV1

$C_{23}H_{19}ClF_4N_6O_3$ (538.89)

R_t = 3.86 minutes (method 7)

Example 217: 5-amino-N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

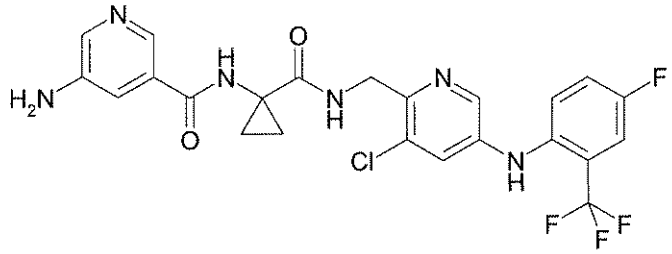


Prepared from intermediate C1 and 5-aminonicotinic acid according to AAV1.

$C_{23}H_{20}ClF_3N_6O_2$ (504.90)

R_t = 2.01 minutes (method 2)

Example 218: 5-amino-N-(1-{[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

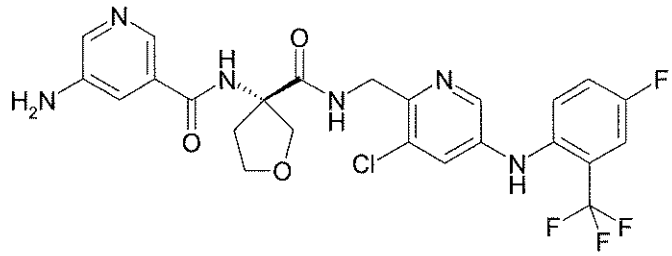


Prepared from intermediates A8 and B4 according to AAV1

$C_{23}H_{19}ClF_4N_6O_2$ (522.89)

R_t = 3.21 minutes (method 7)

Example 219: (*S*)-5-amino-N-(3-{[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

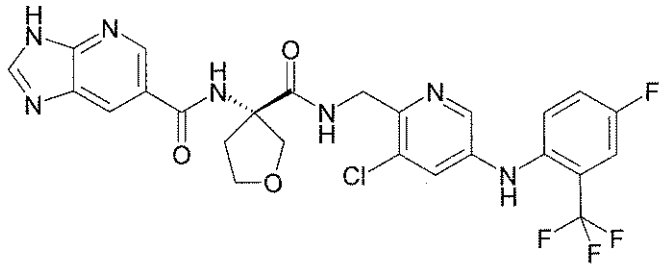


Prepared from intermediates A8 and B2 according to AAV1

$C_{24}H_{21}ClF_4N_6O_3$ (552.91)

R_t = 3.22 minutes (method 7)

Example 220: (*S*)-3H-imidazo[4,5-b]pyridine-6-carboxylic acid-(3-{[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

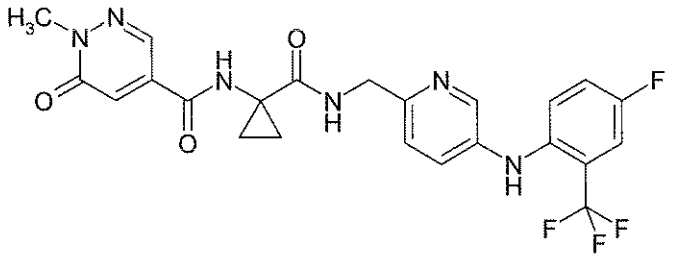


Prepared from intermediates A8 and B5 according to AAV1

$C_{25}H_{20}ClF_4N_7O_3$ (577.92)

R_t = 3.62 minutes (method 7)

Example 221: 1-methyl-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

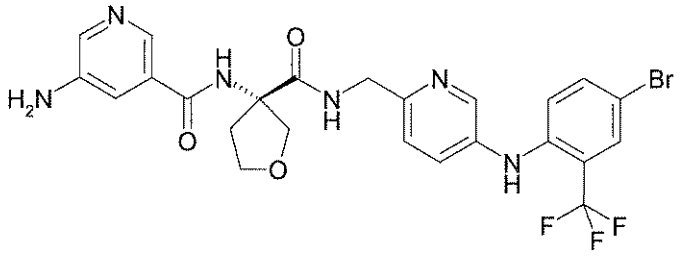


Prepared from intermediate C2 and 1-methyl-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid according to AAV1

$C_{23}H_{20}F_4N_6O_3$ (504.44)

R_t = 2.95 minutes (method 7)

Example 222: (*S*)-5-amino-N-(3-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

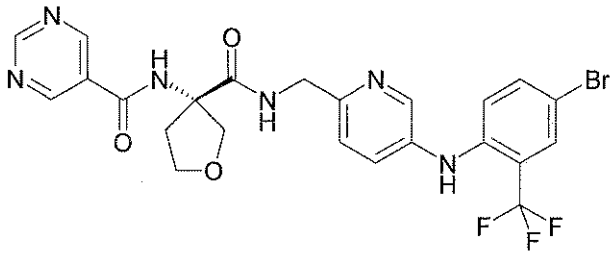


Prepared from intermediates A9 and B2 according to AAV1

$C_{24}H_{22}BrF_3N_6O_3$ (579.37)

R_t = 1.88 minutes (method 2)

Example 223: (*S*)-pyrimidine-5-carboxylic acid-(3-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

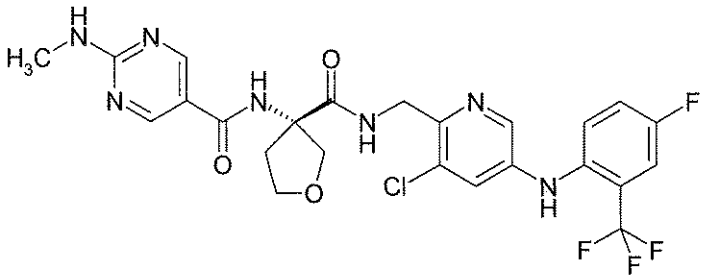


Prepared from intermediates A9 and B3 according to AAV1

$C_{23}H_{20}BrF_3N_6O_3$ (565.35)

R_t = 1.74 minutes (method 2)

Example 224: (*S*)-2-methylamino-pyrimidine-5-carboxylic acid-(3-{[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

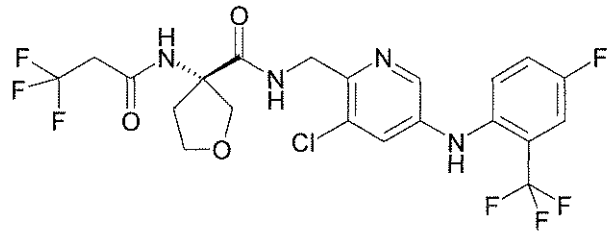


Prepared from intermediate C3 and 2-methylamino-pyrimidine-5-carboxylic acid according to AAV1

$C_{24}H_{22}ClF_4N_7O_3$ (567.93)

R_t = 3.89 minutes (method 7)

Example 225: (*S*)-3-(3,3,3-trifluoro-propionylamino)-tetrahydrofuran-3-carboxylic acid-[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

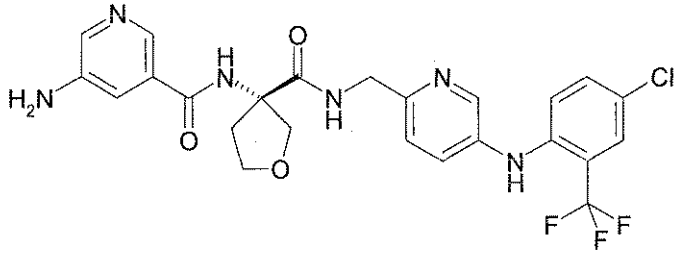


Prepared from intermediate C3 and 3,3,3-trifluoro-propionic acid according to AAV1

$C_{21}H_{18}ClF_7N_4O_3$ (542.84)

R_t = 4.18 minutes (method 7)

Example 226: (*S*)-5-amino-N-(3-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

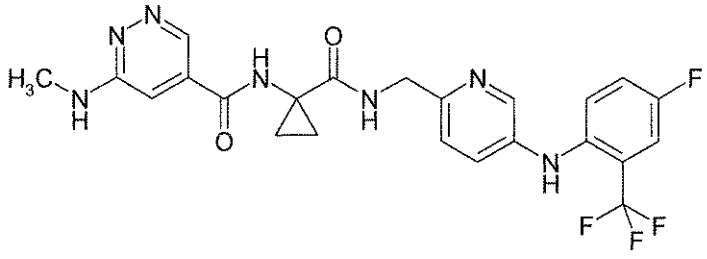


Prepared from intermediates A3 and B2 according to AAV1

$C_{24}H_{22}ClF_3N_6O_3$ (534.92)

R_t = 1.57 minutes (method 2)

Example 227: 6-methylamino-pyridazine-4-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

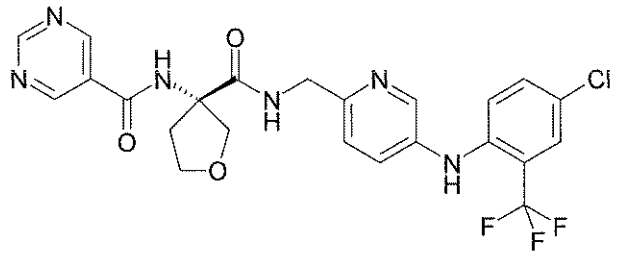


Prepared from intermediate C2 and 6-methylamino-pyridazine-4-carboxylic acid according to AAV1

$C_{23}H_{21}F_4N_7O_2$ (503.46)

R_t = 1.55 minutes (method 5)

Example 228: (*S*)-pyrimidine-5-carboxylic acid-(3-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

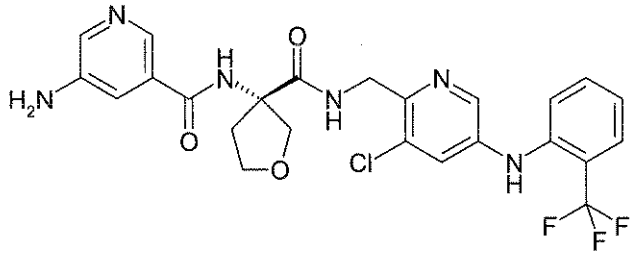


Prepared from intermediates A3 and B3 according to AAV1

$C_{23}H_{20}ClF_3N_6O_3$ (520.90)

R_t = 1.74 minutes (method 2)

Example 229: (*S*)-5-amino-N-(3-{[3-chloro-5-(2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

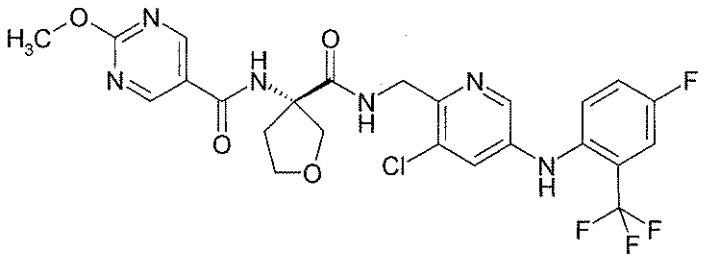


Prepared from intermediates A10 and B2 according to AAV1

$C_{24}H_{22}ClF_3N_6O_3$ (534.92)

R_t = 3.19 minutes (method 7)

Example 230: (*S*)-2-methoxy-pyrimidine-5-carboxylic acid-(3-{[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

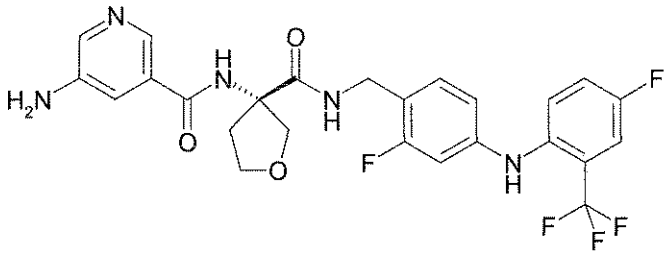


Prepared from intermediate C3 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1

$C_{24}H_{21}ClF_4N_6O_4$ (568.91)

R_t = 4.01 minutes (method 7)

Example 231: (*S*)-5-amino-N-{3-[2-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-nicotinamide

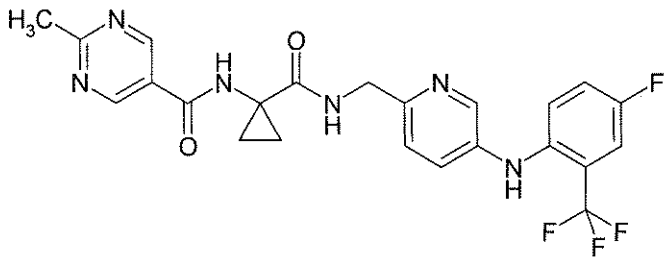


Prepared from intermediates A11 and B2 according to AAV1

$C_{25}H_{22}F_5N_5O_3$ (535.47)

R_t = 1.23 minutes (method 2)

Example 232: 2-methyl-pyrimidine-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

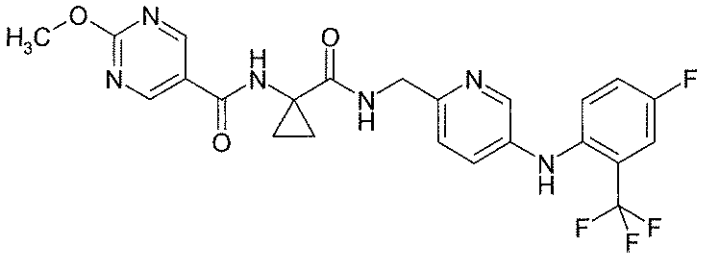


Prepared from intermediate C2 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1

$C_{23}H_{20}F_4N_6O_2$ (488.44)

R_t = 1.94 minutes (method 2)

Example 233: 2-methoxy-pyrimidine-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

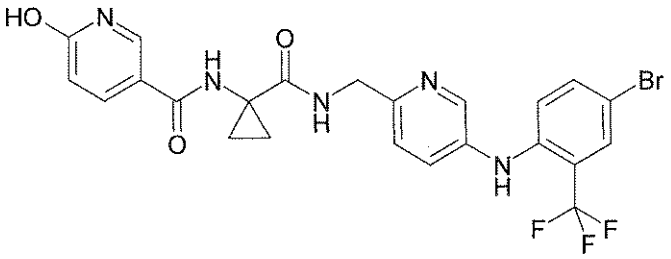


Prepared from intermediate C2 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1

$C_{23}H_{20}F_4N_6O_3$ (504.44)

R_t = 2.00 minutes (method 2)

Example 234: N-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-hydroxy-nicotinamide

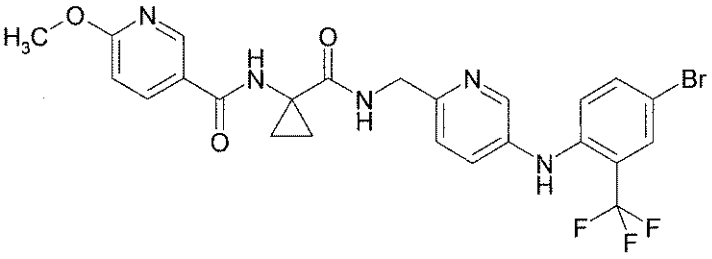


Prepared from intermediate C4 and 6-hydroxy-nicotinic acid according to AAV1

$C_{23}H_{19}BrF_3N_5O_3$ (550.33)

R_t = 1.79 minutes (method 2)

Example 235: N-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-methoxy-nicotinamide

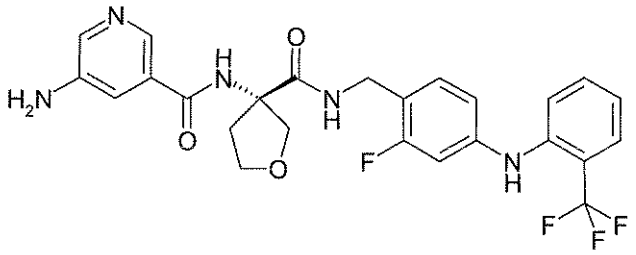


Prepared from intermediate C4 and 6-methoxy-nicotinic acid according to AAV1

$C_{24}H_{21}BrF_3N_5O_3$ (564.36)

R_t = 1.84 minutes (method 2)

Example 236: (*S*)-5-amino-N-{3-[2-fluoro-4-(2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydrofuran-3-yl}-nicotinamide

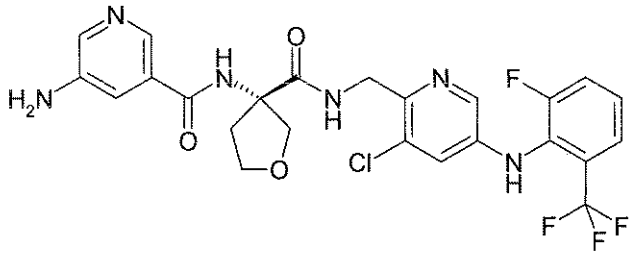


Prepared from intermediates A12 and B2 according to AAV1

$C_{25}H_{23}F_4N_5O_3$ (517.48)

R_t = 3.07 minutes (method 3)

Example 237: (*S*)-5-amino-N-(3-{[3-chloro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

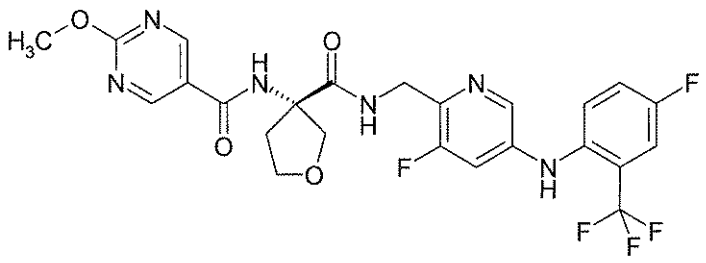


Prepared from intermediate C5 and 5-aminonicotinic acid according to AAV1

$C_{24}H_{21}ClF_4N_6O_3$ (552.91)

R_t = 3.28 minutes (method 3)

Example 238: (*S*)-2-methoxy-pyrimidine-5-carboxylic acid-(3-{[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

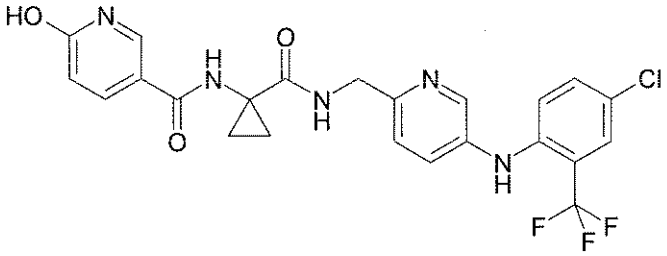


Prepared from intermediate C6 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1

$C_{24}H_{21}F_5N_6O_4$ (552.46)

R_t = 3.62 minutes (method 3)

Example 239: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-hydroxy-nicotinamide

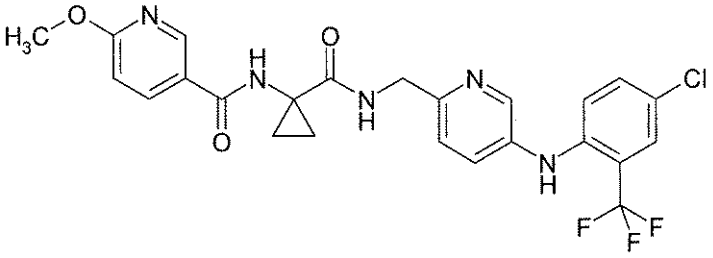


Prepared from intermediate C1 and 6-hydroxy-nicotinic acid according to AAV1

$C_{23}H_{19}ClF_3N_5O_3$ (505.88)

R_t = 1.71 minutes (method 2)

Example 240: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-methoxy-nicotinamide

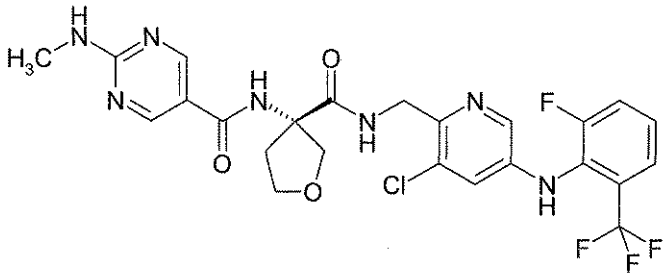


Prepared from intermediate C1 and 6-methoxy-nicotinic acid according to AAV1

$C_{24}H_{21}ClF_3N_5O_3$ (519.91)

R_t = 1.75 minutes (method 2)

Example 241: (*S*)-2-methylamino-pyrimidine-5-carboxylic acid-(3-{[3-chloro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

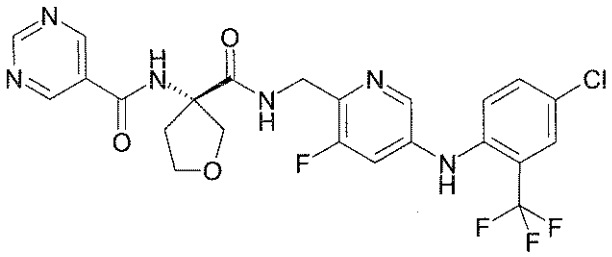


Prepared from intermediate C5 and 2-methylamino-pyrimidine-5-carboxylic acid according to AAV1

$C_{24}H_{22}ClF_4N_7O_3$ (567.93)

R_t = 4.64 minutes (method 3)

Example 242: (*S*)-pyrimidine-5-carboxylic acid-(3-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

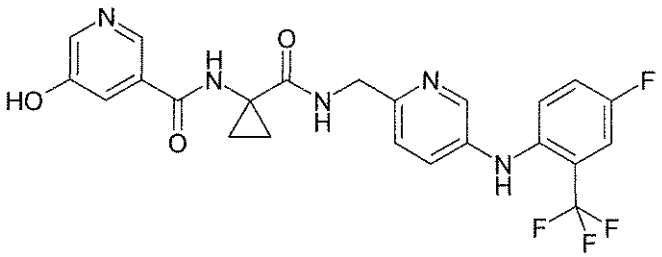


Prepared from intermediates A15 and B3 according to AAV1

$C_{23}H_{19}ClF_4N_6O_3$ (538.89)

R_t = 2.15 minutes (method 2)

Example 243: N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-hydroxy-nicotinamide



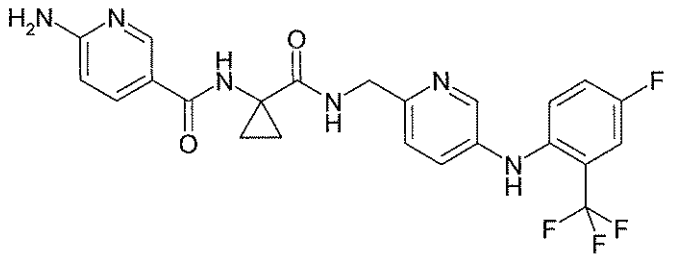
Prepared from intermediate C2 and 5-hydroxynicotinic acid according to AAV1

$C_{23}H_{19}F_4N_5O_3$ (489.43)

mass spectroscopy (ESI): [M+H]+ = 490

[M-H]- = 488

Example 244: 6-amino-N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide



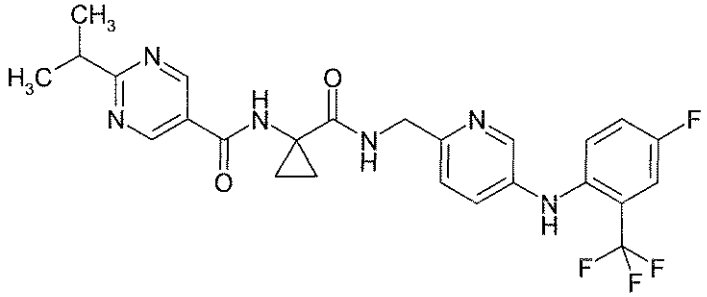
Prepared from intermediate C2 and 6-aminonicotinic acid according to AAV1

$C_{23}H_{20}F_4N_6O_2$ (488.44)

mass spectroscopy (ESI): [M+H]+ = 489

[M-H]- = 487

Example 245: 2-isopropyl-pyrimidine-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

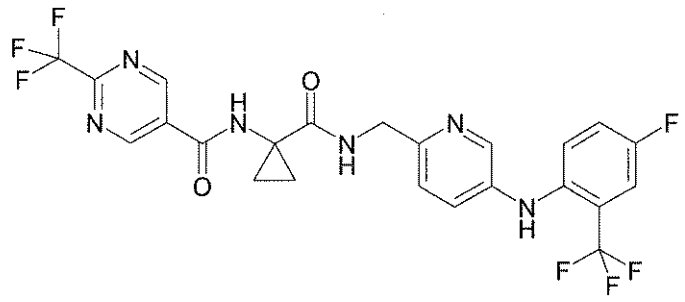


Prepared from intermediate C2 and 2-isopropyl-pyrimidine-5-carboxylic acid according to AAV1

$C_{25}H_{24}F_4N_6O_2$ (516.50)

mass spectroscopy (ESI): [M+H]+ = 517

Example 246: 2-trifluoromethyl-pyrimidine-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

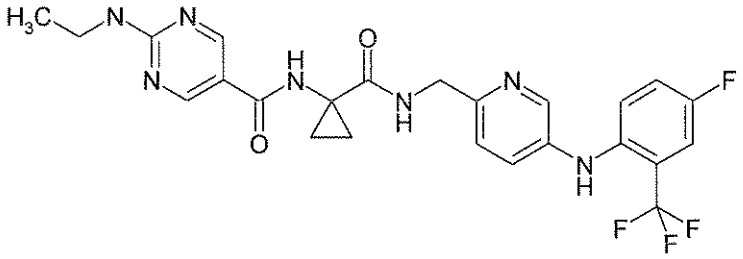


Prepared from intermediate C2 and 2-trifluoromethyl-pyrimidine-5-carboxylic acid according to AAV1

$C_{23}H_{17}F_7N_6O_2$ (542.41)

mass spectroscopy (ESI): [M+H]+ = 543

Example 247: 2-ethylamino-pyrimidine-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide



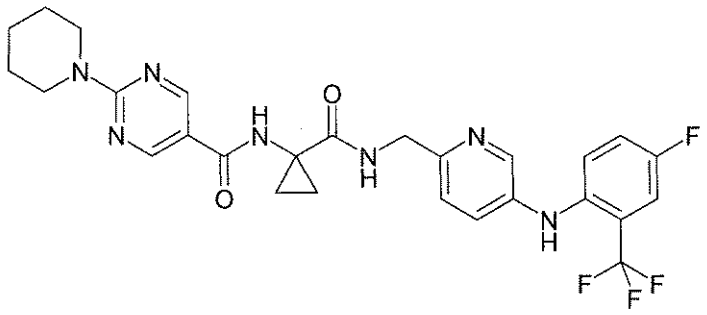
Prepared from intermediate C2 and 2-ethylamino-pyrimidine-5-carboxylic acid according to AAV1

$C_{24}H_{23}F_4N_7O_2$ (517.48)

mass spectroscopy (ESI): [M+H]+ = 518

R_t = 1.58 minutes (method 5)

Example 248: 2-piperidin-1-yl-pyrimidine-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

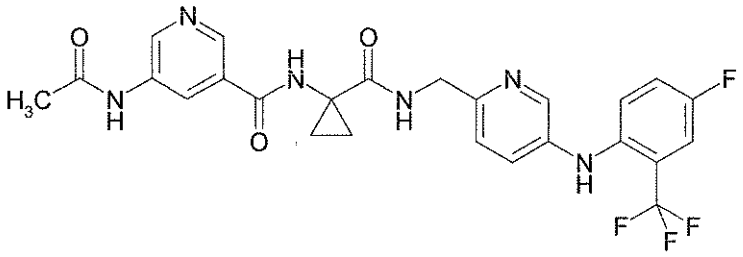


Prepared from intermediate C2 and 2-piperidin-1-yl-pyrimidine-5-carboxylic acid according to AAV1

$C_{27}H_{27}F_4N_7O_2$ (557.55)

mass spectroscopy (ESI): [M+H]+ = 558

Example 249: 5-acetylamino-N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

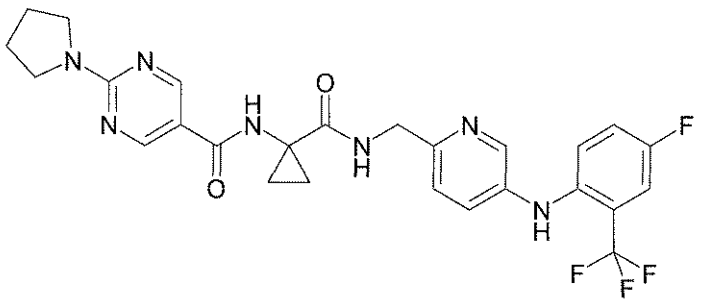


Prepared from intermediate C2 and 5-acetylaminonicotinic acid according to AAV1

$C_{25}H_{22}F_4N_6O_3$ (530.48)

mass spectroscopy (ESI): [M+H]+ = 531

Example 250: 2-pyrrolidin-1-yl-pyrimidine-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

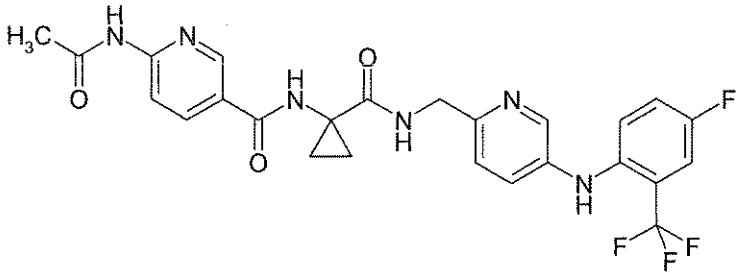


Prepared from intermediate C2 and 2-pyrrolidin-1-yl-pyrimidine-5-carboxylic acid according to AAV1

$C_{26}H_{25}F_4N_7O_2$ (543.52)

mass spectroscopy (ESI): [M+H]+ = 544

Example 251: 6-acetylamino-N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

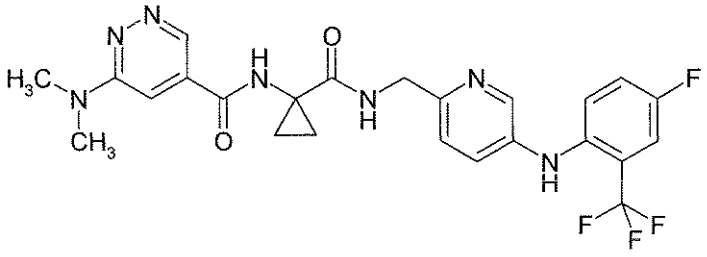


Prepared from intermediate C2 and 6-acetylamino-nicotinic acid according to AAV1

$C_{25}H_{22}F_4N_6O_3$ (530.48)

mass spectroscopy (ESI): [M+H]+ = 531

Example 252: 6-dimethylamino-pyridazine-4-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

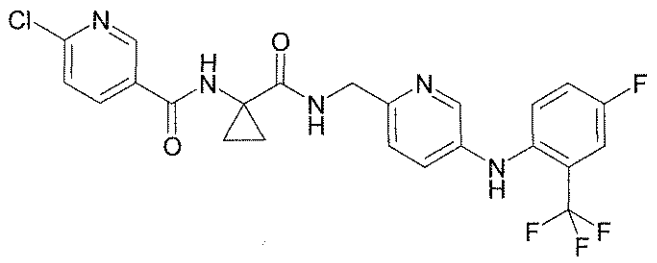


Prepared from intermediate C2 and 6-dimethylamino-pyridazine-4-carboxylic acid according to AAV1

$C_{24}H_{23}F_4N_7O_2$ (517.48)

mass spectroscopy (ESI): [M+H]+ = 518

Example 253: 6-chloro-N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

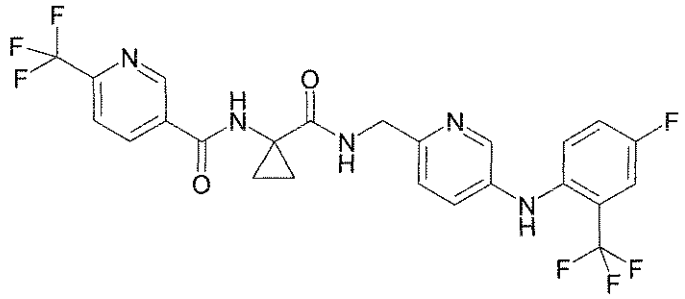


Prepared from intermediate C2 and 6-chloro-nicotinic acid according to AAV1

$C_{23}H_{18}ClF_4N_5O_2$ (507.87)

mass spectroscopy (ESI): [M+H]+ = 508

Example 254: N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-trifluoromethyl-nicotinamide

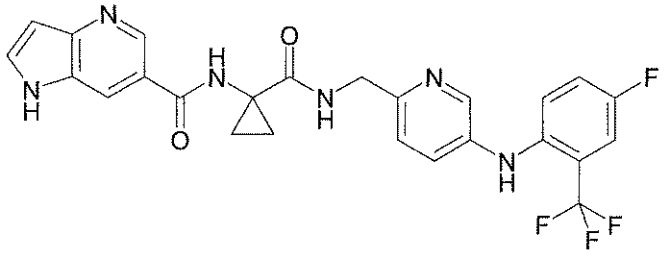


Prepared from intermediate C2 and 6-trifluoromethyl-nicotinic acid according to AAV1

$C_{24}H_{18}F_7N_5O_2$ (541.43)

mass spectroscopy (ESI): [M+H]+ = 542

Example 255: 1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

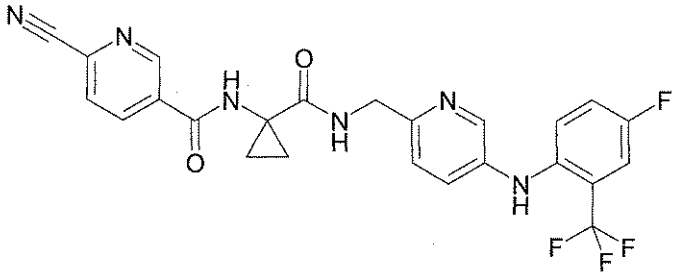


Prepared from intermediate C2 and 1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid according to AAV1

$C_{25}H_{20}F_4N_6O_2$ (512.47)

mass spectroscopy (ESI): [M+H]+ = 513

Example 256: 6-cyano-N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

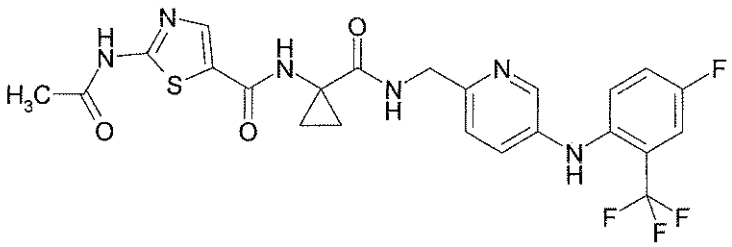


Prepared from intermediate C2 and 6-cyano-nicotinic acid according to AAV1

$C_{24}H_{18}F_4N_6O_2$ (498.44)

mass spectroscopy (ESI): [M+H]+ = 499

Example 257: 2-acetylamino-thiazole-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

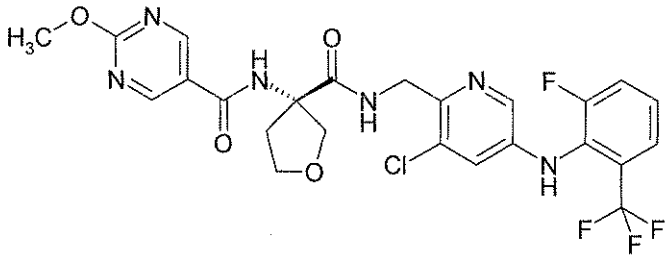


Prepared from intermediate C2 and 2-acetylamino-thiazole-5-carboxylic acid according to AAV1

$C_{23}H_{20}F_4N_6O_3S$ (536.51)

mass spectroscopy (ESI): [M+H]+ = 537

Example 258: (S)-2-methoxy-pyrimidine-5-carboxylic acid-(3-{[3-chloro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

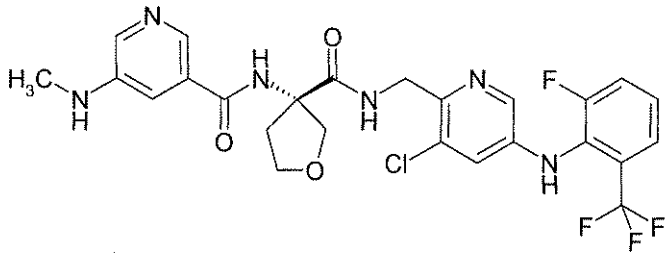


Prepared from intermediate C3 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1

$C_{24}H_{21}ClF_4N_6O_4$ (568.91)

R_t = 3.99 minutes (method 3)

Example 259: (*S*)-N-(3-{[3-chloro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-5-methylamino-nicotinamide

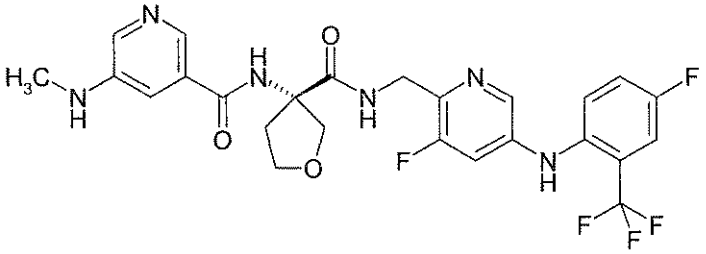


Prepared from intermediate C3 and 5-methylamino-nicotinic acid according to AAV1

$C_{25}H_{23}ClF_4N_6O_3$ (566.94)

R_t = 3.59 minutes (method 3)

Example 260: (*S*)-N-(3-{[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-5-methylamino-nicotinamide

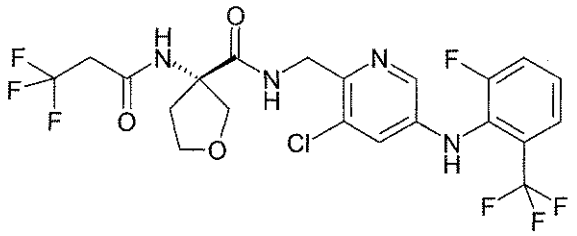


Prepared from intermediate C6 and 5-methylamino-nicotinic acid according to AAV1

$C_{25}H_{23}F_5N_6O_3$ (550.49)

R_t = 3.81 minutes (method 3)

Example 261: (S)-3-(3,3,3-trifluoro-propionylamino)-tetrahydrofuran-3-carboxylic acid-[3-chloro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

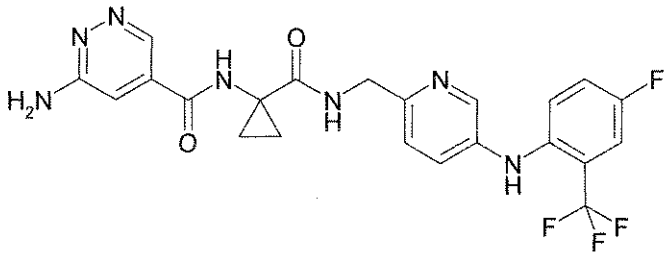


Prepared from intermediate C5 and 3,3,3-trifluorpropionic acid according to AAV1

$C_{21}H_{18}ClF_7N_4O_3$ (542.84)

R_t = 4.11 minutes (method 3)

Example 262: 6-amino-pyridazine-4-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

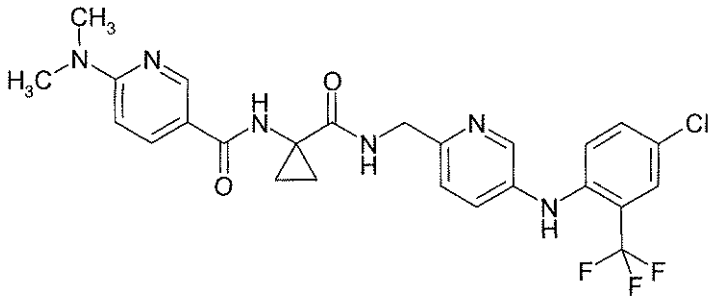


Prepared from intermediate C2 and 6-amino-pyridazine-4-carboxylic acid according to AAV1

$C_{22}H_{19}F_4N_7O_2$ (489.43)

R_t = 1.81 minutes (method 6)

Example 263: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-dimethylamino-nicotinamide

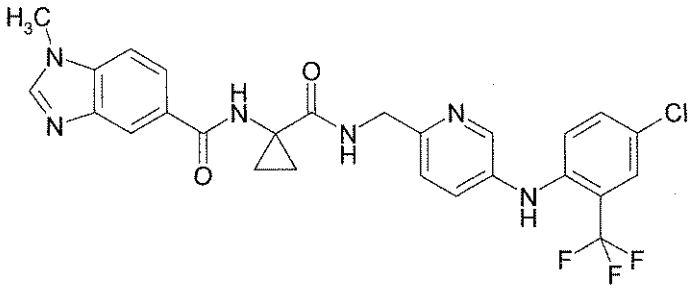


Prepared from intermediate C1 and 6-dimethylamino-nicotinic acid according to AAV1

$C_{25}H_{24}ClF_3N_6O_2$ (532.95)

R_t = 1.90 minutes (method 2)

Example 264: 1-methyl-1H-benzimidazole-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

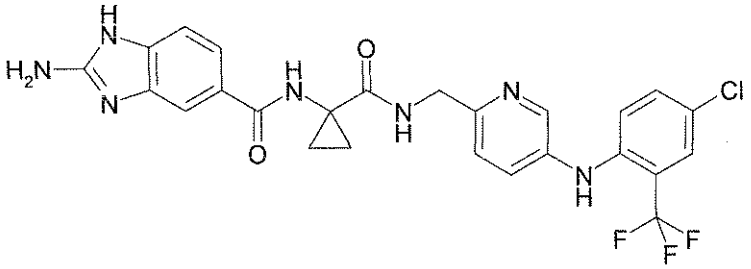


Prepared from intermediate C1 and 1-methyl-1H-benzimidazole-5-carboxylic acid according to AAV1

$C_{26}H_{22}ClF_3N_6O_2$ (542.95)

R_t = 1.72 minutes (method 2)

Example 265: 2-amino-1H-benzimidazole-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

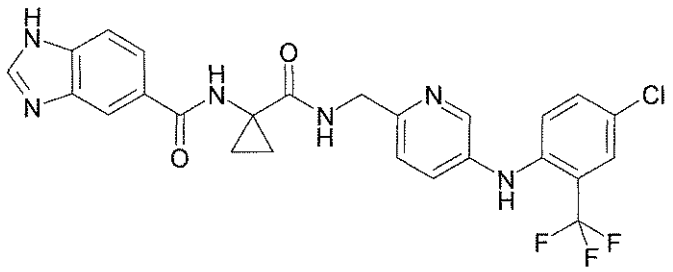


Prepared from intermediate C1 and 2-amino-1H-benzimidazole-5-carboxylic acid according to AAV1

$C_{25}H_{21}ClF_3N_7O_2$ (543.93)

mass spectroscopy (ESI): [M+H]+ = 544

Example 266: 1H-benzimidazole-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

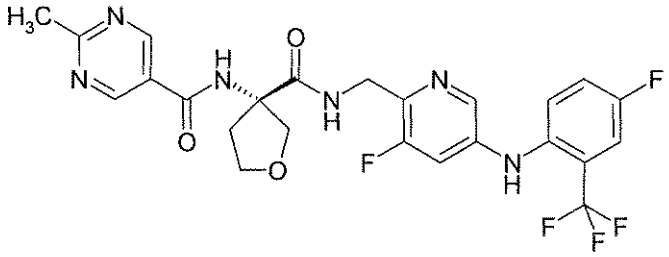


Prepared from intermediate C1 and 1H-benzimidazole-5-carboxylic acid according to AAV1

$C_{25}H_{20}ClF_3N_6O_2$ (528.92)

R_t = 1.79 minutes (method 2)

Example 267: (S)-2-methyl-pyrimidine-5-carboxylic acid-(3-{[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

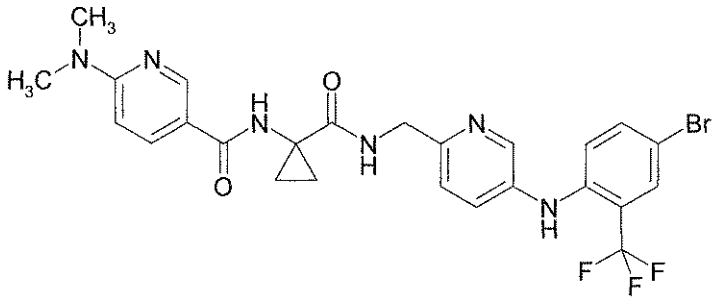


Prepared from intermediate C6 and (S)-2-methyl-pyrimidine-5-carboxylic acid according to AAV1

$C_{24}H_{21}F_5N_6O_3$ (536.46)

R_t = 3.91 minutes (method 3)

Example 268: N-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-dimethylamino-nicotinamide

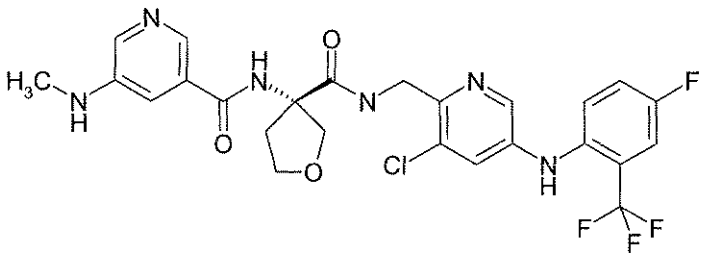


Prepared from intermediate C4 and 6-dimethylamino-nicotinic acid according to AAV1

$C_{25}H_{24}BrF_3N_6O_2$ (577.40)

R_t = 2.09 minutes (method 2)

Example 269: (*S*)-N-(3-{[3-chloro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-5-methylamino-nicotinamide

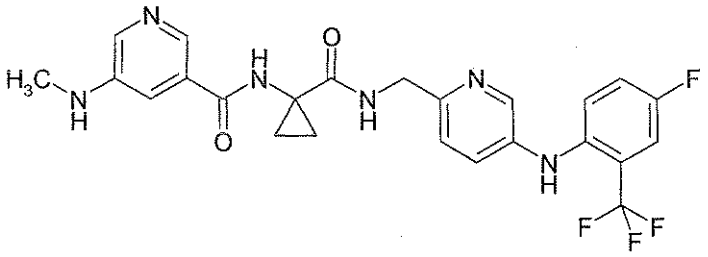


Prepared from intermediate C3 and 5-methylaminonicotinic acid according to AAV1

$C_{25}H_{23}ClF_4N_6O_3$ (566.94)

R_t = 3.66 minutes (method 3)

Example 270: N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-methylamino-nicotinamide

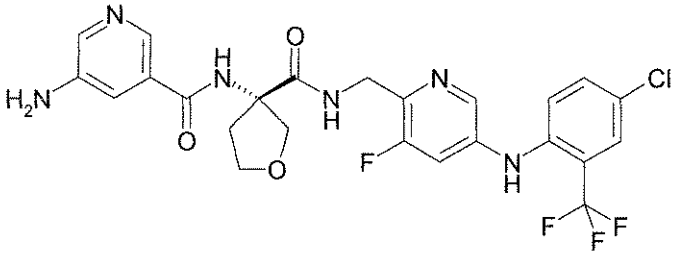


Prepared from intermediate C2 and 5-methylaminonicotinic acid according to AAV1

$C_{24}H_{22}F_4N_6O_2$ (502.47)

R_t = 1.97 minutes (method 2)

Example 271: (*S*)-5-amino-N-(3-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

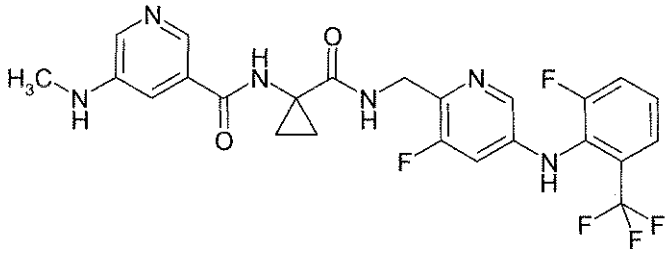


Prepared from intermediates A15 and B2 according to AAV1

$C_{24}H_{21}ClF_4N_6O_3$ (552.91)

R_t = 2.48 minutes (method 2)

Example 272: N-(1-{[3-fluoro-5-(2-fluoro-6-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-methylamino-nicotinamide

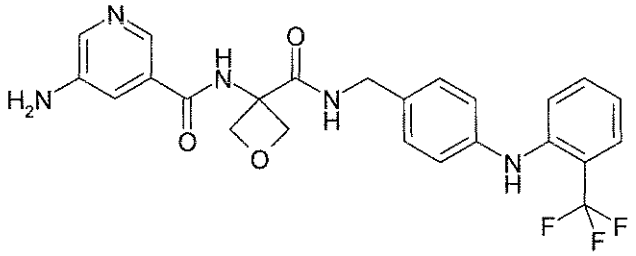


Prepared from intermediate C7 and 5-methylaminonicotinic acid according to AAV1

$C_{24}H_{21}F_5N_6O_3$ (520.46)

R_t = 1.87 minutes (method 2)

Example 273: 5-amino-N-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-oxetan-3-yl}-nicotinamide

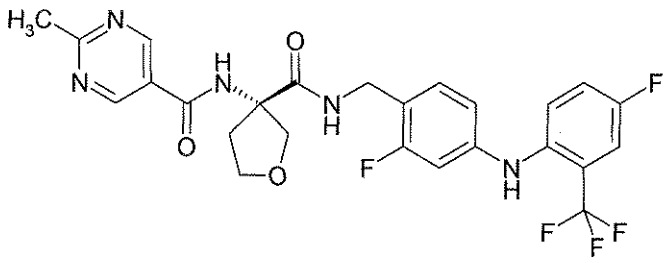


Prepared from intermediate C8 and 5-aminonicotinic acid according to AAV1

$C_{24}H_{22}F_3N_5O_3$ (485.46)

R_t = 2.17 minutes (method 6)

Example 274: (*S*)-2-methyl-pyrimidine-5-carboxylic acid-{3-[2-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

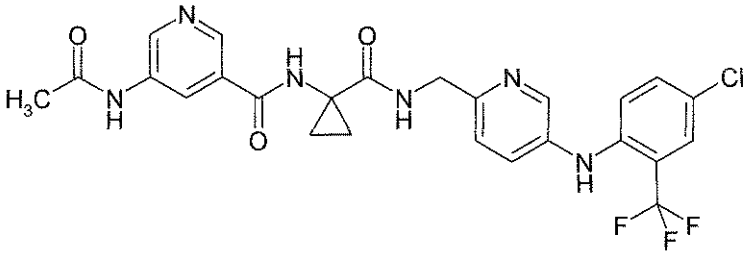


Prepared from intermediate C9 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1

$C_{25}H_{22}F_5N_5O_3$ (535.47)

R_t = 3.61 minutes (method 3)

Example 275: 5-acetylamino-N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

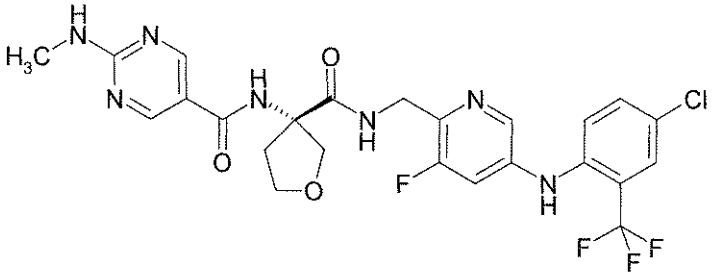


Prepared from intermediate C1 and 5-acetylamino-nicotinic acid according to AAV1

$C_{25}H_{22}ClF_3N_6O_3$ (546.93)

R_t = 1.78 minutes (method 2)

Example 276: (*S*)-2-methylamino-pyrimidine-5-carboxylic acid-(3-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

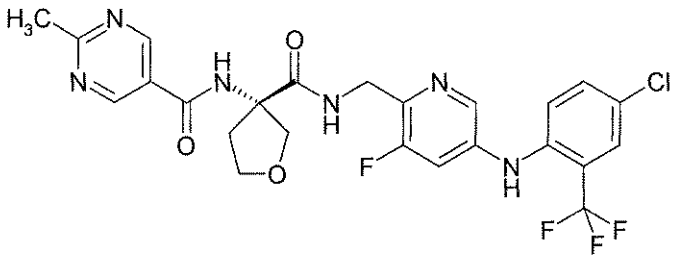


Prepared from intermediates A15 and B6 according to AAV1

$C_{24}H_{22}ClF_4N_7O_3$ (567.93)

R_t = 2.16 minutes (method 2)

Example 277: (S)-2-methyl-pyrimidine-5-carboxylic acid-(3-{[5-(4-chloro-2-trifluoromethylphenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

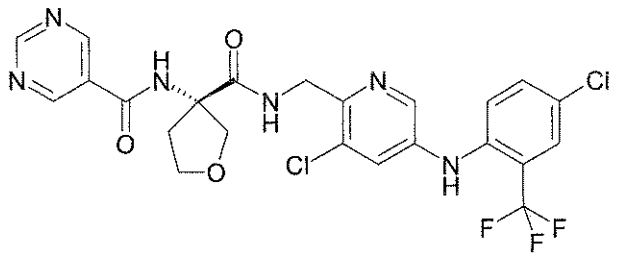


Prepared from intermediates A15 and B7 according to AAV1

$C_{24}H_{21}ClF_4N_6O_3$ (552.91)

R_t = 2.50 minutes (method 2)

Example 278: (*S*)-pyrimidine-5-carboxylic acid-(3-{[3-chloro-5-(4-chloro-2-trifluoromethylphenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

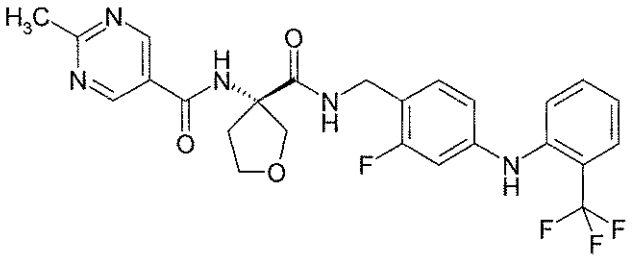


Prepared from intermediates A18 and B3 according to AAV1

$C_{23}H_{19}Cl_2F_3N_6O_3$ (555.34)

R_t = 2.56 minutes (method 2)

Example 279: (S)-2-methyl-pyrimidine-5-carboxylic acid-{3-[2-fluoro-4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

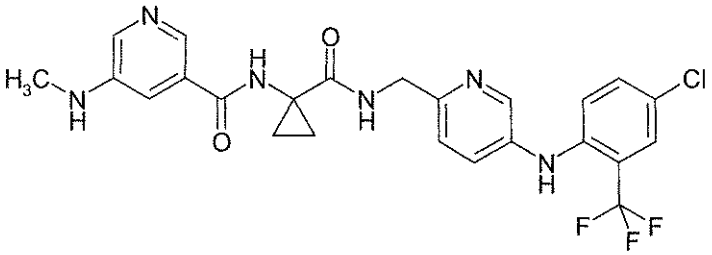


Prepared from intermediate C22 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1

$C_{25}H_{23}F_4N_5O_3$ (517.48)

R_t = 1.97 minutes (method 7)

Example 280: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-methylamino-nicotinamide

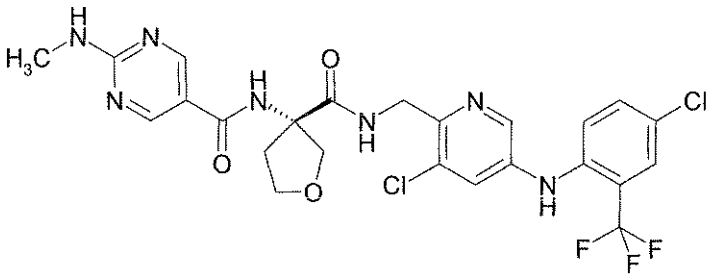


Prepared from intermediate C1 and 5-methylaminonicotinic acid according to AAV1

$C_{24}H_{22}ClF_3N_6O_2$ (518.92)

R_t = 1.96 minutes (method 2)

Example 281: (*S*)-2-methylamino-pyrimidine-5-carboxylic acid-(3-{[3-chloro-5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

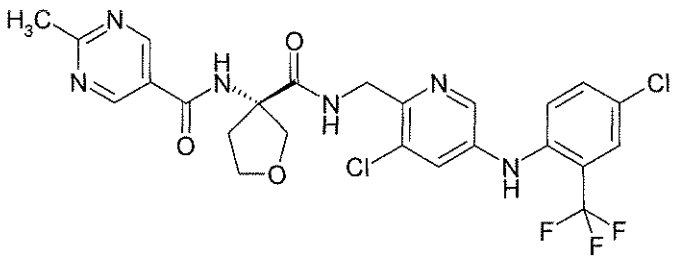


Prepared from intermediates A18 and B6 according to AAV1

$C_{24}H_{22}Cl_2F_3N_7O_3$ (584.38)

R_t = 2.56 minutes (method 2)

Example 282: (*S*)-2-methyl-pyrimidine-5-carboxylic acid-(3-{[3-chloro-5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

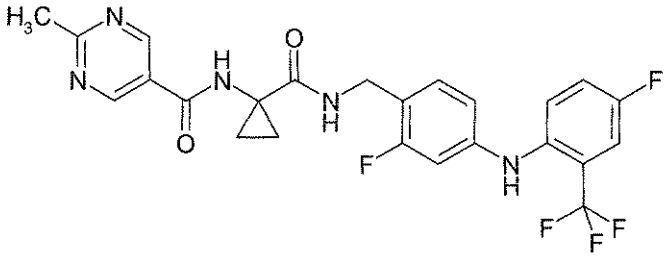


Prepared from intermediates A18 and B7 according to AAV1

$C_{24}H_{21}Cl_2F_3N_6O_3$ (569.37)

R_t = 2.59 minutes (method 2)

Example 283: 2-methyl-pyrimidine-5-carboxylic acid-{1-[2-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide

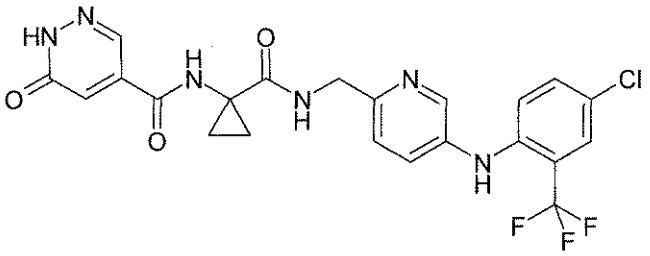


Prepared from intermediate C10 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1

$C_{24}H_{20}F_5N_5O_2$ (505.44)

R_t = 1.33 minutes (method 7)

Example 284 6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

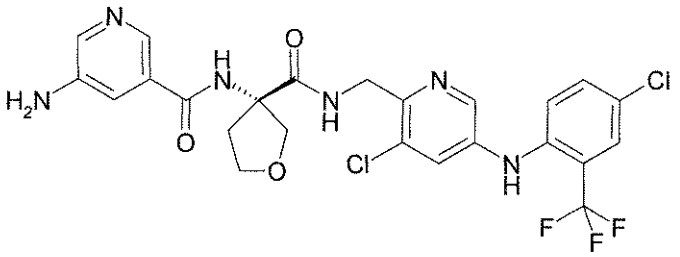


Prepared from intermediate C1 and 6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid according to AAV1

$C_{22}H_{18}ClF_3N_6O_3$ (506.87)

R_t = 2.13 minutes (method 2)

Example 285: (S)-5-amino-N-(3-{[3-chloro-5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

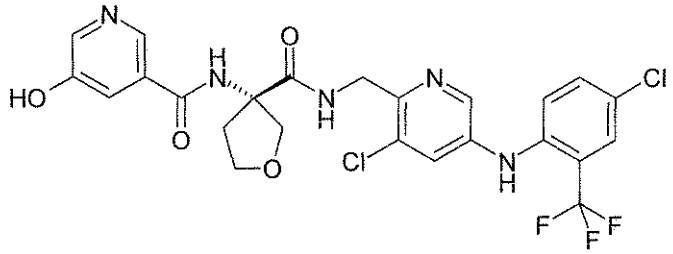


Prepared from intermediates A18 and B2 according to AAV1

$C_{24}H_{21}Cl_2F_3N_6O_3$ (569.37)

R_t = 2.34 minutes (method 2)

Example 286: (*S*)-N-(3-{[3-chloro-5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-5-hydroxy-nicotinamide



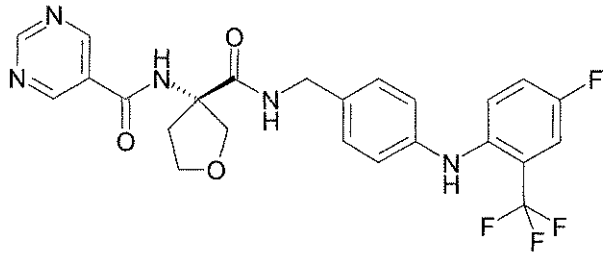
Prepared from intermediates A18 and B8 according to AAV 1

$C_{24}H_{20}Cl_2F_3N_5O_4$ (570.35)

R_t = 2.52 minutes (method 2)

mass spectroscopy (ESI): [M+H]+ = 570; [M-H]- = 568

Example 287: (*S*)-pyrimidine-5-carboxylic acid-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

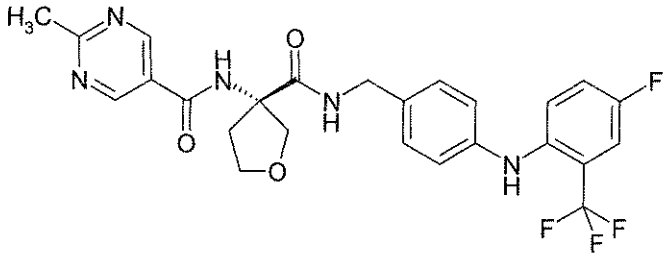


Prepared from intermediates A6 and B3 according to AAV1

$C_{24}H_{21}F_4N_5O_3$ (503.45)

R_t = 2.43 minutes (method 2)

Example 288: (*S*)-2-methyl-pyrimidine-5-carboxylic acid-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

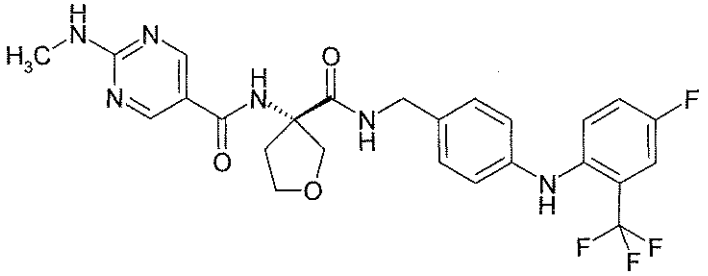


Prepared from intermediates A6 and B7 according to AAV1

$C_{25}H_{23}F_4N_5O_3$ (517.48)

R_t = 2.64 minutes (method 2)

Example 289: (S)-2-methylamino-pyrimidine-5-carboxylic acid-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

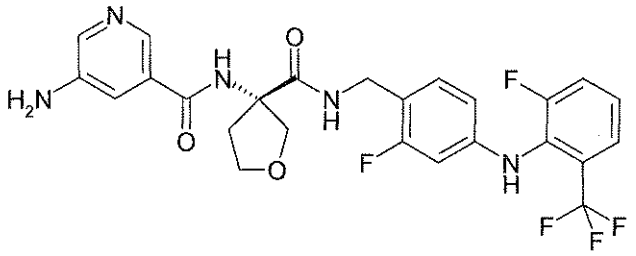


Prepared from intermediates A6 and B6 according to AAV1

$C_{25}H_{24}F_4N_6O_3$ (532.50)

R_t = 2.44 minutes (method 2)

Example 290: (*S*)-5-amino-N-{3-[2-fluoro-4-(2-fluoro-6-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-nicotinamide

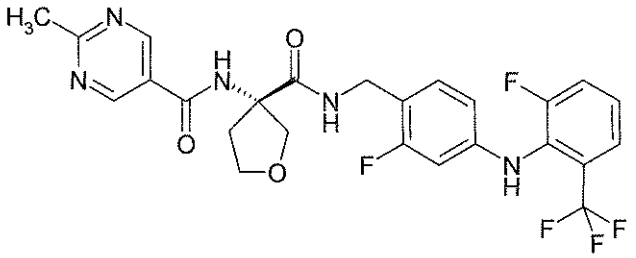


Prepared from intermediate C11 and 5-aminonicotinic acid according to AAV1

$C_{25}H_{22}F_5N_5O_3$ (535.47)

R_t = 1.63 minutes (method 7)

Example 291: (*S*)-2-methyl-pyrimidine-5-carboxylic acid-{3-[2-fluoro-4-(2-fluoro-6-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

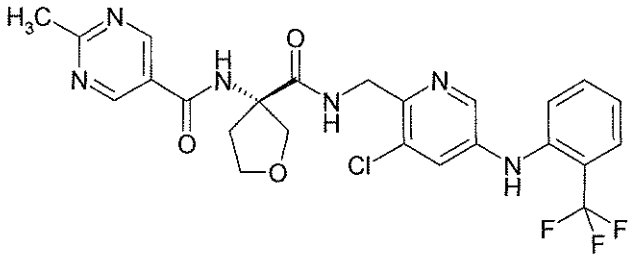


Prepared from intermediate C11 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1

$C_{25}H_{22}F_5N_5O_3$ (535.47)

R_t = 1.83 minutes (method 7)

Example 292: (*S*)-2-methyl-pyrimidine-5-carboxylic acid-(3-{[3-chloro-5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

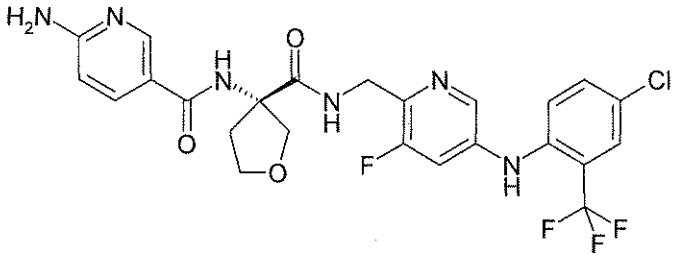


Prepared from intermediates A10 and B7 according to AAV1

$C_{24}H_{22}ClF_3N_6O_3$ (534.92)

R_t = 1.78 minutes (method 7)

Example 293: (*S*)-6-amino-N-(3-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

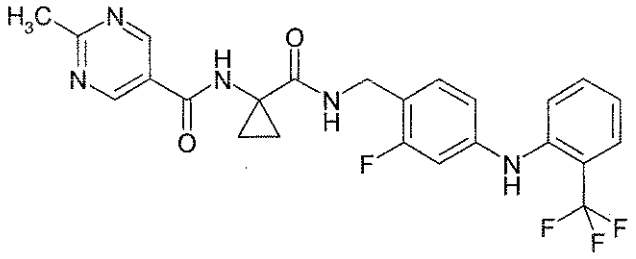


Prepared from intermediates A15 and B9 according to AAV1

$C_{24}H_{21}ClF_4N_6O_3$ (552.91)

R_t = 2.14 minutes (method 2)

Example 294: 2-methyl-pyrimidine-5-carboxylic acid-{1-[2-fluoro-4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-cyclopropyl}-amide

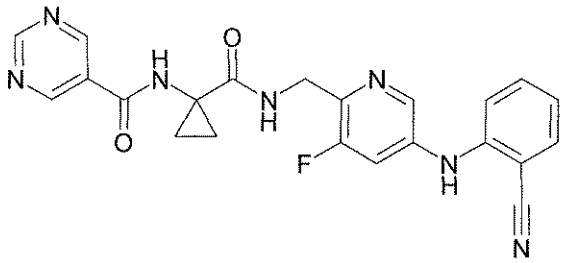


Prepared from intermediate C12 and 2-methylpyrimidine-5-carboxylic acid according to AAV1

$C_{24}H_{21}F_4N_5O_2$ (487.45)

R_t = 1.91 minutes (method 7)

Example 295: pyrimidine-5-carboxylic acid-(1-{[5-(2-cyano-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

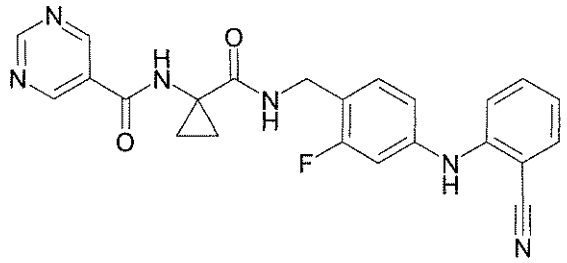


Prepared from intermediates A20 and B1 according to AAV1

$C_{22}H_{18}FN_7O_2$ (431.43)

R_t = 1.62 minutes (method 2)

Example 296: pyrimidine-5-carboxylic acid-{1-[4-(2-cyano-phenylamino)-2-fluoro-benzyl-carbamoyl]-cyclopropyl}-amide

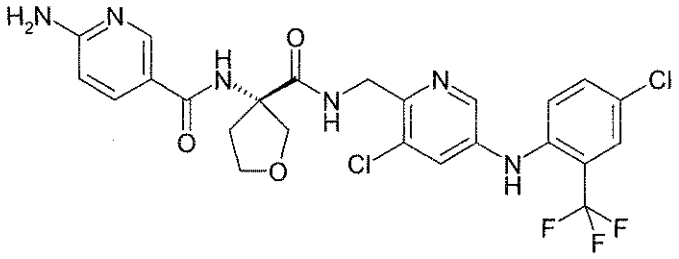


Prepared from intermediates A30 and B1 according to AAV1

$C_{23}H_{19}FN_6O_2$ (430.44)

R_t = 1.88 minutes (method 2)

Example 297: (*S*)-6-amino-N-(3-{[3-chloro-5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

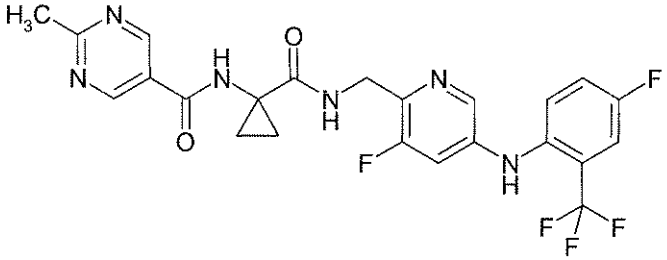


Prepared from intermediates A18 and B9 according to AAV1

$C_{24}H_{21}Cl_2F_3N_6O_3$ (569.37)

R_t = 2.46 minutes (method 2)

Example 298: 2-methyl-pyrimidine-5-carboxylic acid-(1-{[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

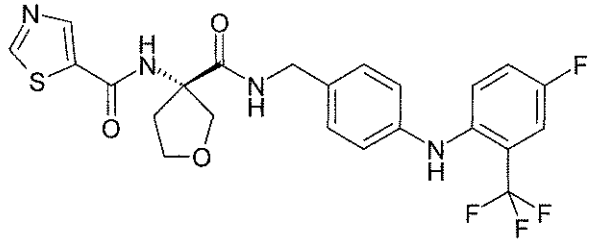


Prepared from intermediate C13 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1

$C_{23}H_{19}F_5N_6O_2$ (506.43)

R_t = 1.74 minutes (method 7)

Example 299: (*S*)-thiazole-5-carboxylic acid-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

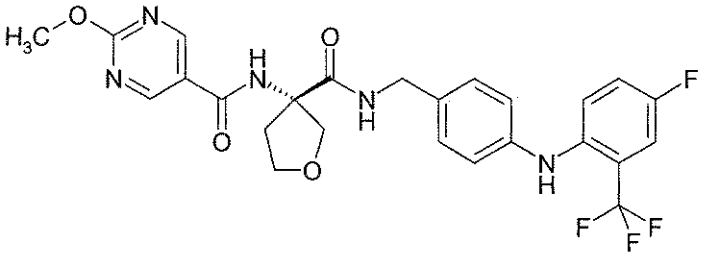


Prepared from intermediate C14 and thiazole-5-carboxylic acid according to AAV1

$C_{23}H_{20}F_4N_4O_3S$ (508.49)

R_t = 2.43 minutes (method 2)

Example 300: (*S*)-2-methoxy-pyrimidine-5-carboxylic acid-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

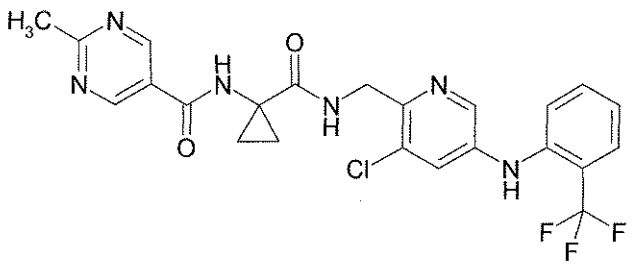


Prepared from intermediate C14 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1

$C_{25}H_{23}F_4N_5O_4$ (533.48)

R_t = 2.61 minutes (method 2)

Example 301: 2-methyl-pyrimidine-5-carboxylic acid-(1-{[3-chloro-5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

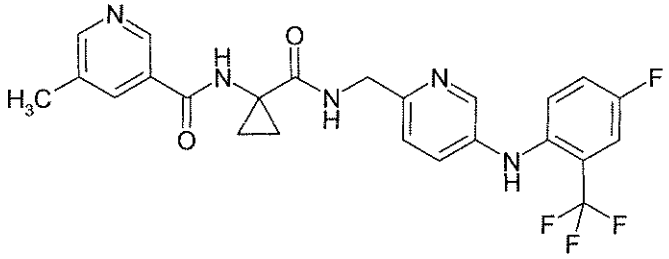


Prepared from intermediate C15 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1

$C_{23}H_{20}ClF_3N_6O_2$ (504.90)

R_t = 1.79 minutes (method 7)

Example 302: N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-methyl-nicotinamide

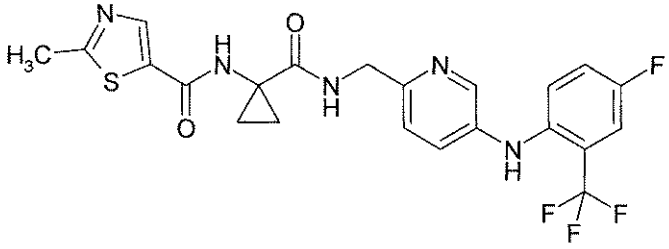


Prepared from intermediate C2 and 5-methyl-nicotinic acid according to AAV1

$C_{24}H_{21}F_4N_5O_2$ (487.45)

R_t = 1.96 minutes (method 2)

Example 303: 2-methyl-thiazole-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenyl-amino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

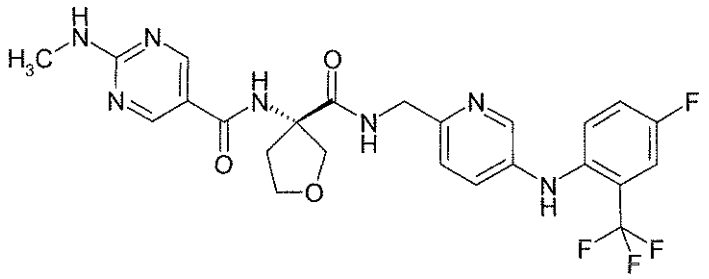


Prepared from intermediate C2 and 2-methyl-thiazole-5-carboxylic acid according to AAV1

$C_{22}H_{19}F_4N_5O_2S$ (493.48)

R_t = 2.07 minutes (method 2)

Example 304: (*S*)-2-methylamino-pyrimidine-5-carboxylic acid-(3-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

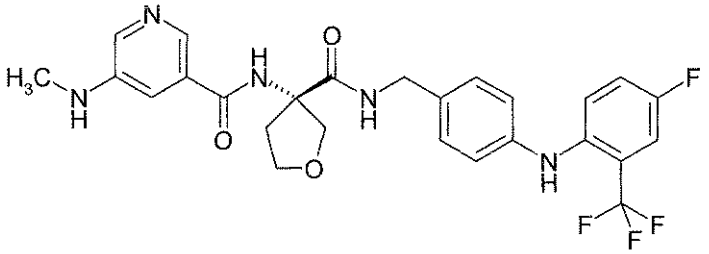


Prepared from intermediates A7 and B6 according to AAV1

$C_{24}H_{23}F_4N_7O_3$ (533.48)

R_t = 1.88 minutes (method 2)

Example 305: (*S*)-N-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-5-methylamino-nicotinamide

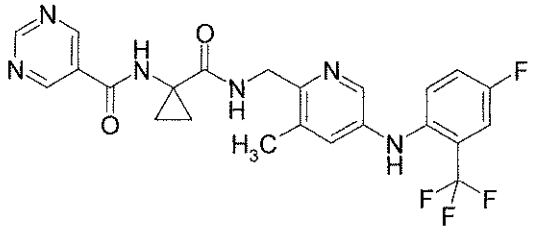


Prepared from intermediate C14 and 5-methylaminonicotinic acid according to AAV1

$C_{26}H_{25}F_4N_5O_3$ (531.51)

R_t = 1.83 minutes (method 7)

Example 306: pyrimidine-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

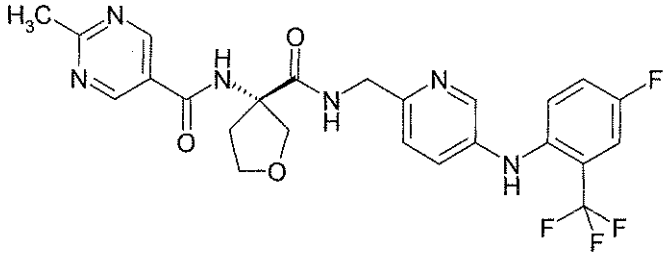


Prepared from intermediates A21 and B1 according to AAV1

$C_{23}H_{20}F_4N_6O_2$ (488.44)

R_t = 1.81 minutes (method 2)

Example 307: (*S*)-2-methyl-pyrimidine-5-carboxylic acid-(3-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

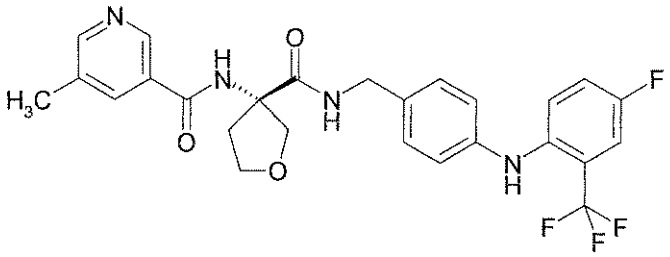


Prepared from intermediates A7 and B7 according to AAV1

$C_{24}H_{22}F_4N_6O_3$ (518.47)

R_t = 2.32 minutes (method 2)

Example 308: (*S*)-N-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-5-methyl-nicotinamide

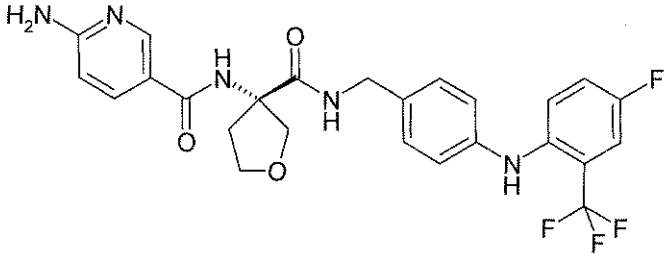


Prepared from intermediates C14 and 5-methylnicotinic acid according to AAV1

$C_{26}H_{24}F_4N_4O_3$ (516.49)

R_t = 2.45 minutes (method 2)

Example 309: (*S*)-6-amino-N-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydrofuran-3-yl}-nicotinamide

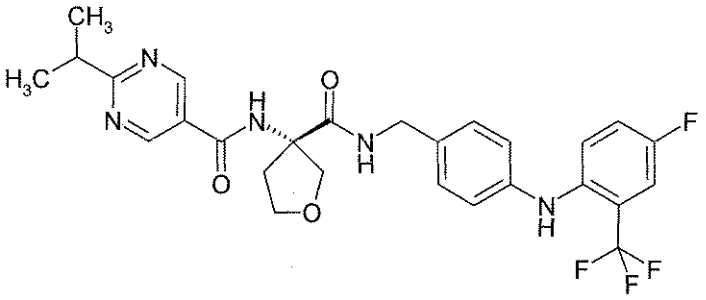


Prepared from intermediates C14 and 6-aminonicotinic acid according to AAV1

$C_{25}H_{23}F_4N_5O_3$ (517.48)

R_t = 2.09 minutes (method 2)

Example 310: (*S*)-2-isopropyl-pyrimidine-5-carboxylic acid-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

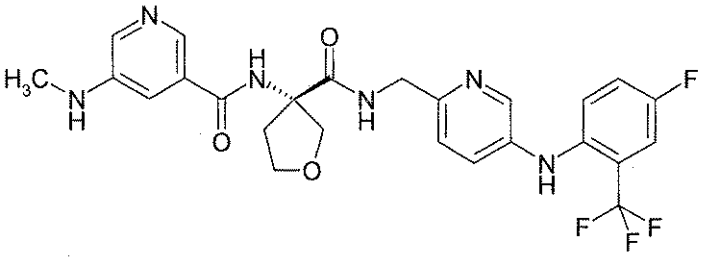


Prepared from intermediates C14 and 2-isopropyl-pyrimidine-5-carboxylic acid according to AAV1

$C_{27}H_{27}F_4N_5O_3$ (545.53)

R_t = 2.60 minutes (method 2)

Example 311: (*S*)-N-(3-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-5-methylamino-nicotinamide

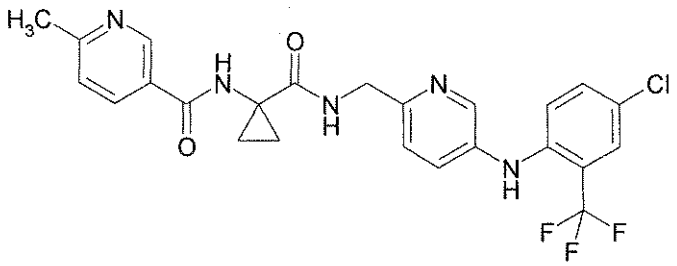


Prepared from intermediates C16 and 5-methylamino-nicotinic acid according to AAV1

$C_{25}H_{24}F_4N_6O_3$ (532.50)

R_t = 2.22 minutes (method 2)

Example 312: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-methyl-nicotinamide

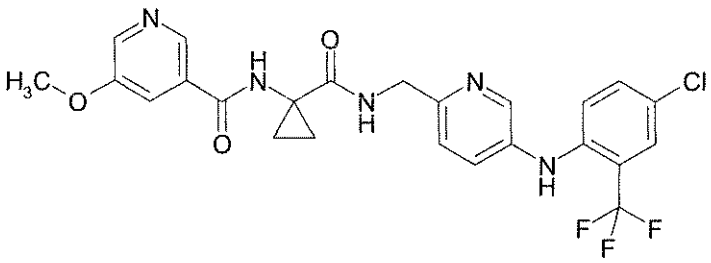


Prepared from intermediates C1 and 6-methyl-nicotinic acid according to AAV1

$C_{24}H_{21}ClF_3N_5O_2$ (503.91)

R_t = 2.17 minutes (method 2)

Example 313: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-methoxy-nicotinamide

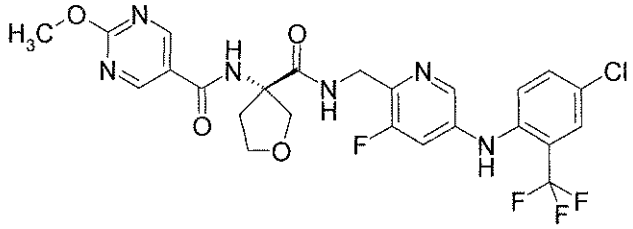


Prepared from intermediates C1 and 5-methoxy-nicotinic acid according to AAV1

$C_{24}H_{21}ClF_3N_5O_3$ (519.91)

R_t = 2.29 minutes (method 2)

Example 314: (*S*)-2-methoxy-pyrimidine-5-carboxylic acid-(3-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

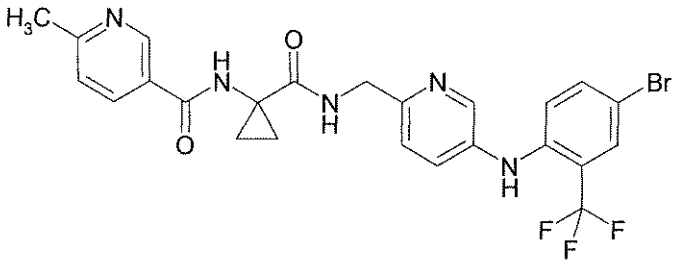


Prepared from intermediates C17 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1

$C_{24}H_{21}ClF_4N_6O_4$ (568.91)

R_t = 2.53 minutes (method 2)

Example 315: N-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-methyl-nicotinamide

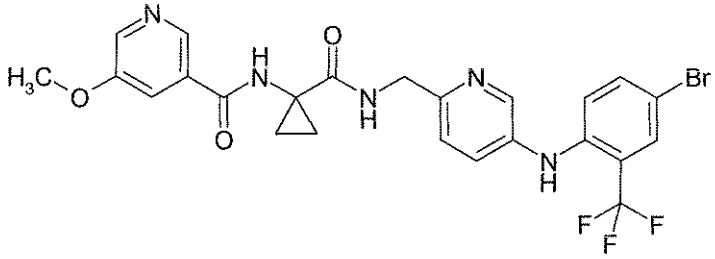


Prepared from intermediates C4 and 6-methyl-nicotinic acid according to AAV1

$C_{24}H_{21}BrF_3N_5O_2$ (548.36)

R_t = 2.24 minutes (method 2)

Example 316: N-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-methoxy-nicotinamide

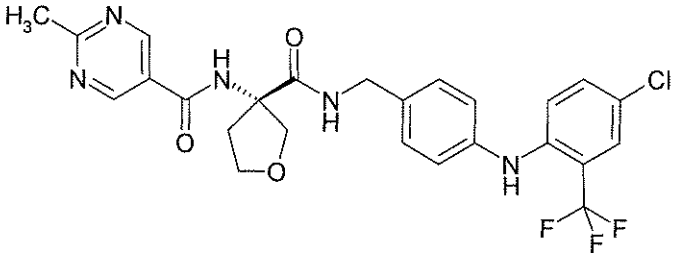


Prepared from intermediates C4 and 5-methoxy-nicotinic acid according to AAV1

$C_{24}H_{21}BrF_3N_5O_3$ (564.36)

R_t = 2.34 minutes (method 2)

Example 317: (*S*)-2-methyl-pyrimidine-5-carboxylic acid-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

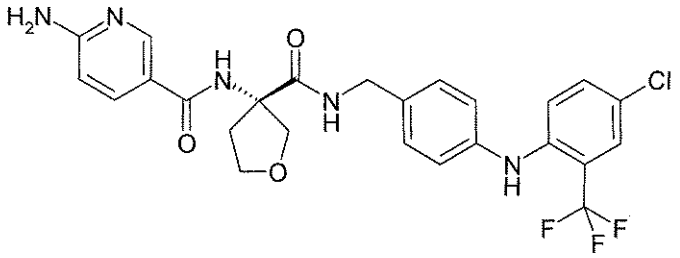


Prepared from intermediates A22 and B7 according to AAV1

$C_{25}H_{23}ClF_3N_5O_3$ (533.94)

R_t = 2.60 minutes (method 2)

Example 318: (*S*)-6-amino-N-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydrofuran-3-yl}-nicotinamide

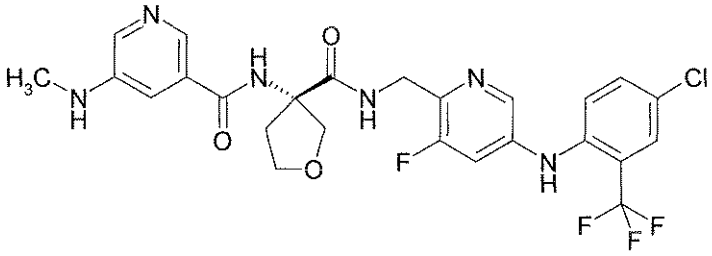


Prepared from intermediates A22 and B9 according to AAV1

$C_{25}H_{23}ClF_3N_5O_3$ (533.94)

R_t = 2.25 minutes (method 2)

Example 319: (*S*)-N-(3-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-5-methylamino-nicotinamide

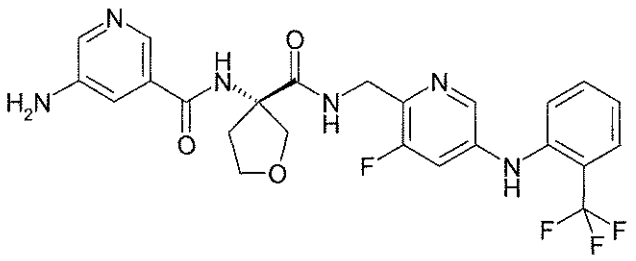


Prepared from intermediates C17 and 5-methylamino-nicotinic acid according to AAV1

$C_{25}H_{23}ClF_4N_6O_3$ (566.94)

R_t = 2.21 minutes (method 2)

Example 320: (*S*)-5-amino-N-(3-{[3-fluoro-5-(2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

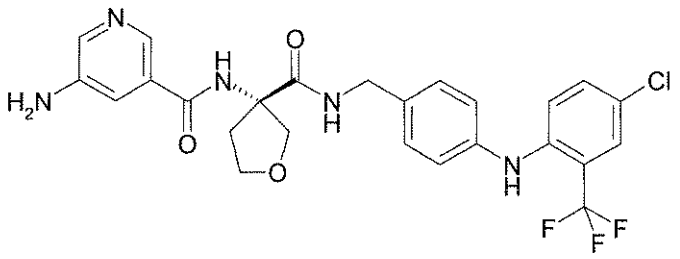


Prepared from intermediates A23 and B2 according to AAV1

$C_{24}H_{22}F_4N_6O_3$ (518.47)

R_t = 1.52 minutes (method 7)

Example 321: (*S*)-5-amino-N-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzyl-carbamoyl]-tetrahydrofuran-3-yl}-nicotinamide

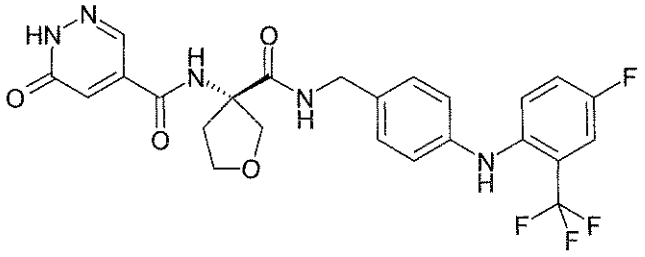


Prepared from intermediates A22 and B2 according to AAV1

$C_{25}H_{23}ClF_3N_5O_3$ (533.94)

R_t = 2.36 minutes (method 2)

Example 322: (*S*)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

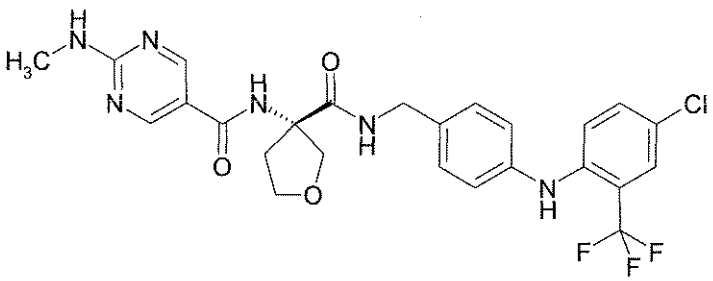


Prepared from intermediates C14 and 6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid according to AAV1

$C_{24}H_{21}F_4N_5O_4$ (519.45)

R_t = 2.39 minutes (method 2)

Example 323: (*S*)-2-methylamino-pyrimidine-5-carboxylic acid-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

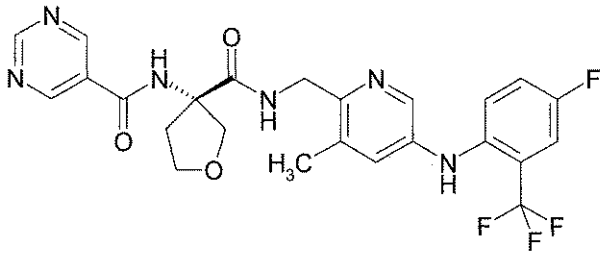


Prepared from intermediates A22 and B6 according to AAV1

$C_{25}H_{24}ClF_3N_6O_3$ (548.95)

R_t = 2.57 minutes (method 2)

Example 324: (*S*)-pyrimidine-5-carboxylic acid-(3-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide



Prepared from intermediates A21 and B3 according to AAV1.

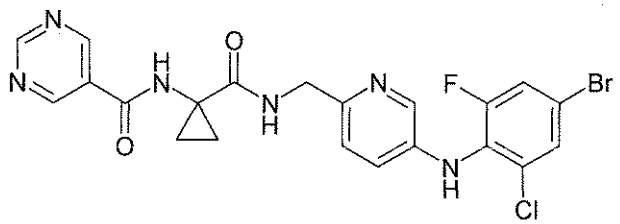
$C_{24}H_{22}F_4N_6O_3$ (518.47)

R_t = 1.80 minutes (method 2)

mass spectroscopy (ESI): [M+H]+ = 519

[M-H]- = 517

Example 325: pyrimidine-5-carboxylic acid-(1-{[5-(4-bromo-2-chloro-6-fluoro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

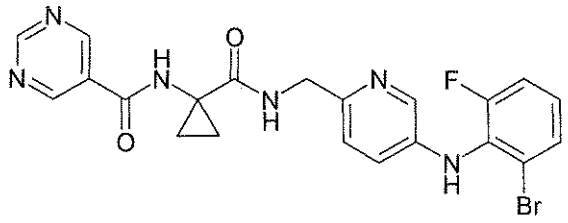


Prepared from intermediates A24 and B1 according to AAV1.

$C_{21}H_{17}BrClFN_6O_2$ (519.76)

R_t = 2.01 minutes (method 2)

Example 326: pyrimidine-5-carboxylic acid-(1-{[5-(2-bromo-6-fluoro-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

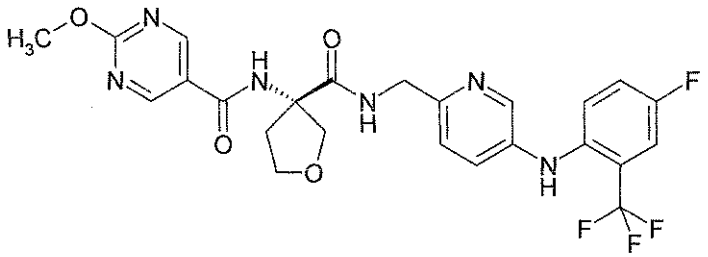


Prepared from intermediates A25 and B1 according to AAV1.

$C_{21}H_{18}BrFN_6O_2$ (485.32)

R_t = 1.64 minutes (method 2)

Example 327: (*S*)-2-methoxy-pyrimidine-5-carboxylic acid-(3-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

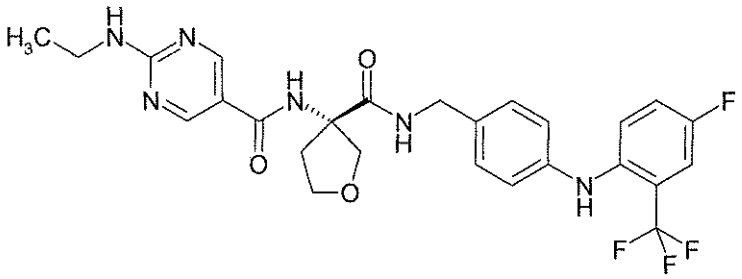


Prepared from intermediates C16 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1.

$C_{24}H_{22}F_4N_6O_4$ (534.47)

R_t = 1.98 minutes (method 2)

Example 328: (*S*)-2-ethylamino-pyrimidine-5-carboxylic acid-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

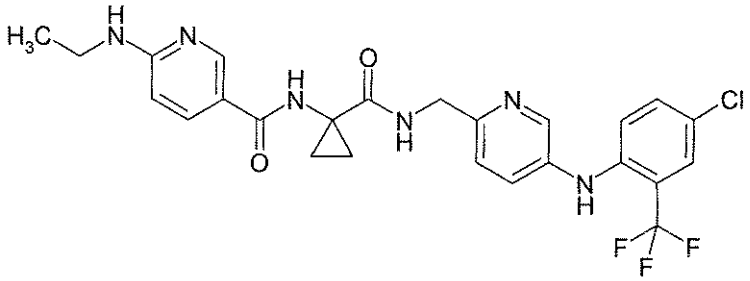


Prepared from intermediates C14 and 2-ethylamino-pyrimidine-5-carboxylic acid according to AAV1.

$C_{26}H_{26}F_4N_6O_3$ (546.52)

R_t = 2.62 minutes (method 2)

Example 329: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-ethylamino-nicotinamide

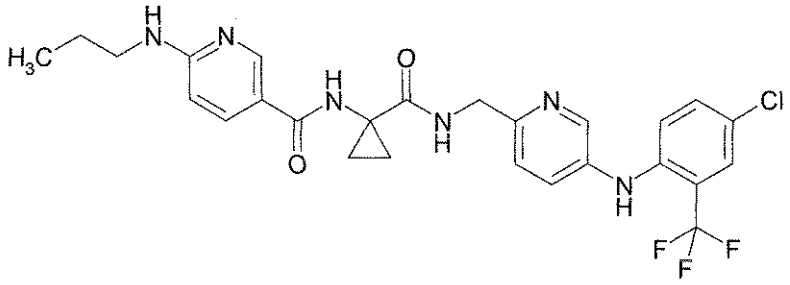


Prepared from intermediates C1 and 6-ethylamino-nicotinic acid according to AAV1.

$C_{25}H_{24}ClF_3N_6O_2$ (532.95)

R_t = 2.32 minutes (method 2)

Example 330: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-propylamino-nicotinamide

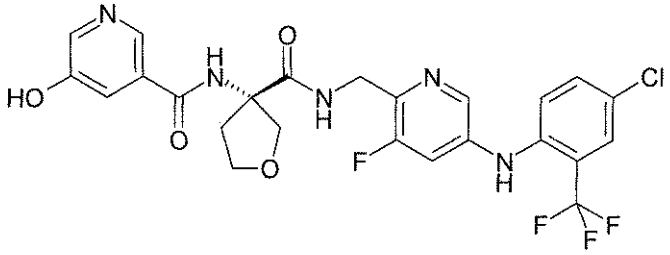


Prepared from intermediates C1 and 6-propylamino-nicotinic acid according to AAV1.

$C_{26}H_{26}ClF_3N_6O_2$ (546.98)

R_t = 2.04 minutes (method 2)

Example 331: (*S*)-N-(3-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-fluoro-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-5-hydroxy-nicotinamide

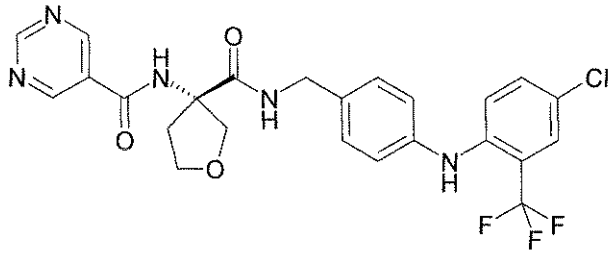


Prepared from intermediates A15 and B8 according to AAV1.

$C_{24}H_{20}ClF_4N_5O_4$ (553.90)

R_t = 2.48 minutes (method 2)

Example 332: (*S*)-pyrimidine-5-carboxylic acid-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

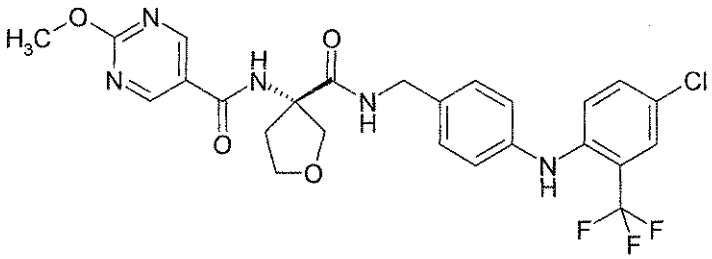


Prepared from intermediates C18 and pyrimidine-5-carboxylic acid according to AAV1.

$C_{24}H_{21}ClF_3N_5O_3$ (519.91)

R_t = 2.57 minutes (method 2)

Example 333: (*S*)-2-methoxy-pyrimidine-5-carboxylic acid-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

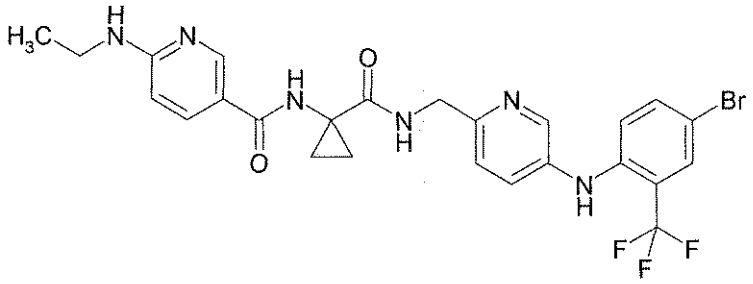


Prepared from intermediates C18 and 2-methoxy-pyrimidine-5-carboxylic acid according to AAV1.

$C_{25}H_{23}ClF_3N_5O_4$ (549.93)

R_t = 2.72 minutes (method 2)

Example 334: N-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-ethylamino-nicotinamide

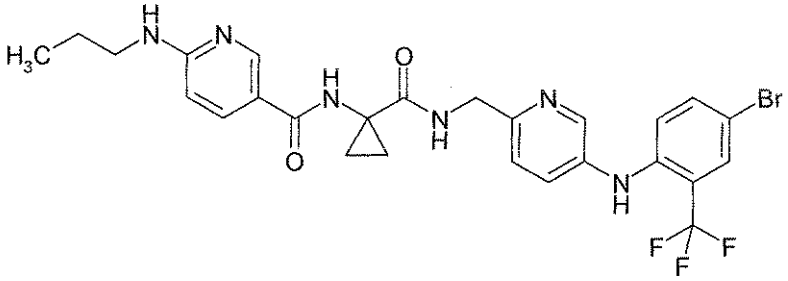


Prepared from intermediates C4 and 6-ethylamino-nicotinic acid according to AAV1.

$C_{25}H_{24}CBrF_3N_6O_2$ (577.40)

R_t = 2.01 minutes (method 2)

Example 335: N-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-propylamino-nicotinamide

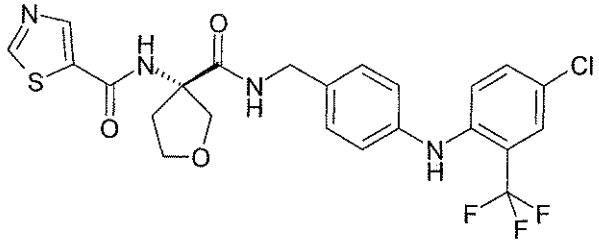


Prepared from intermediates C4 and 6-propylamino-nicotinic acid according to AAV1.

$C_{26}H_{26}BrF_3N_6O_2$ (591.43)

R_t = 2.12 minutes (method 2)

Example 336: (*S*)-thiazole-5-carboxylic acid-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

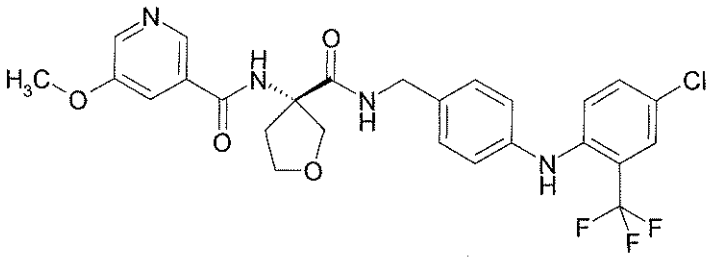


Prepared from intermediates C18 and thiazole-5-carboxylic acid according to AAV1.

$C_{23}H_{20}ClF_3N_4O_3S$ (524.95)

R_t = 2.58 minutes (method 2)

Example 337: (*S*)-N-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-5-methoxy-nicotinamide

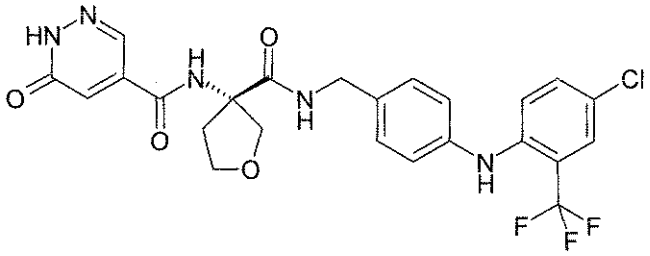


Prepared from intermediates C18 and 5-methoxy-nicotinic acid according to AAV1.

$C_{26}H_{24}ClF_3N_4O_4$ (548.95)

R_t = 2.62 minutes (method 2)

Example 338: (*S*)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

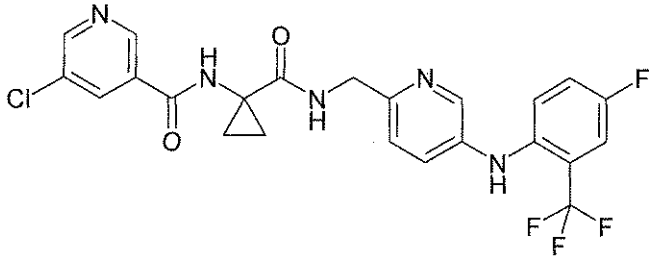


Prepared from intermediates A22 and B10 according to AAV1.

$C_{24}H_{21}ClF_3N_5O_4$ (535.91)

R_t = 2.28 minutes (method 2)

Example 339: 5-chloro-N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

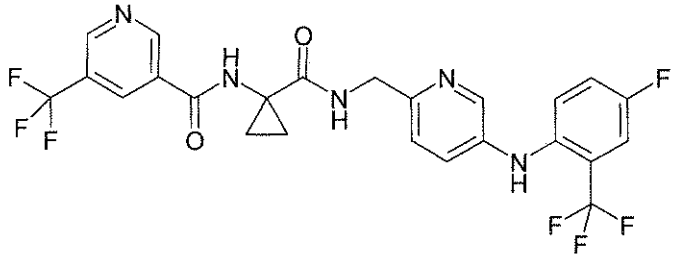


Prepared from intermediates C2 and 5-chloro-nicotinic acid according to AAV1.

$C_{23}H_{18}ClF_4N_5O_2$ (507.87)

R_t = 2.18 minutes (method 2)

Example 340: N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-trifluoromethyl-nicotinamide

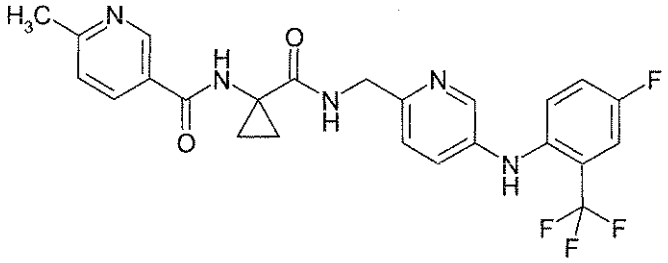


Prepared from intermediates C2 and 5-trifluoromethyl-nicotinic acid according to AAV1.

$C_{24}H_{18}F_7N_5O_2$ (541.43)

R_t = 2.32 minutes (method 2)

Example 341: N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-methyl-nicotinamide

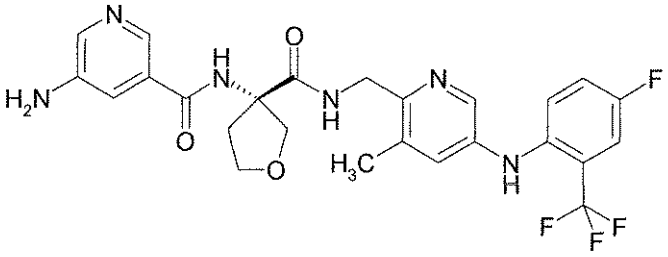


Prepared from intermediates C2 and 6-methyl-nicotinic acid according to AAV1.

$C_{24}H_{21}F_4N_5O_2$ (487.45)

R_t = 1.85 minutes (method 2)

Example 342: (*S*)-5-amino-N-(3-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

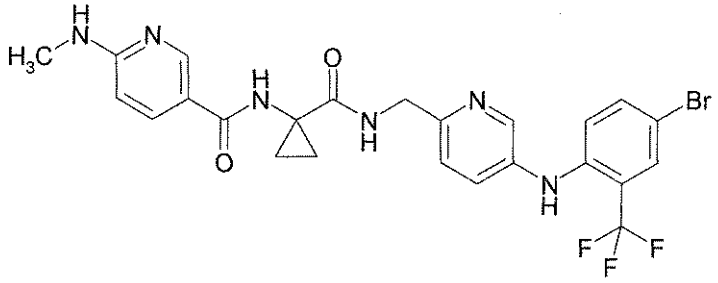


Prepared from intermediates A21 and B2 according to AAV1.

$C_{25}H_{24}F_4N_6O_3$ (487.45)

R_t = 1.85 minutes (method 2)

Example 343: N-(1-{[5-(4-bromo-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-methylamino-nicotinamide

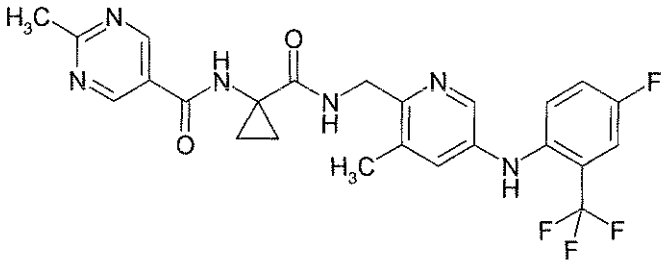


Prepared from intermediates C4 and 6-methylamino-nicotinic acid according to AAV1.

$C_{24}H_{22}BrF_3N_6O_2$ (563.38)

R_t = 2.32 minutes (method 2)

Example 344: 2-methyl-pyrimidine-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

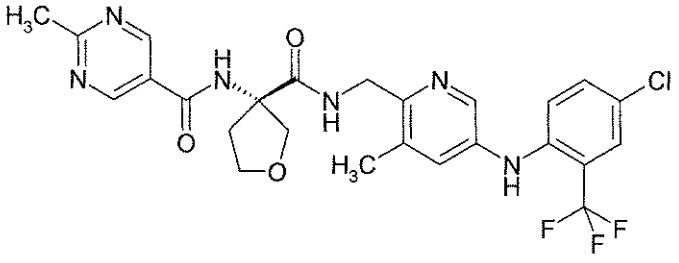


Prepared from intermediates C19 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1.

$C_{24}H_{22}F_4N_6O_2$ (502.47)

R_t = 1.84 minutes (method 2)

Example 345: (*S*)-2-methyl-pyrimidine-5-carboxylic acid-(3-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

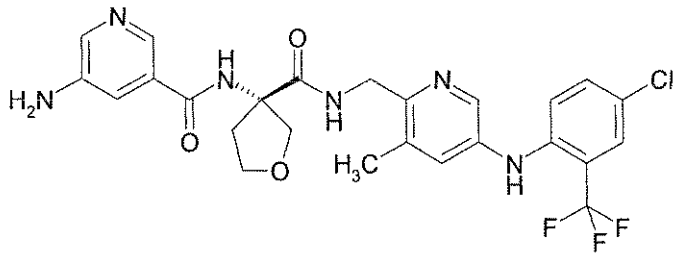


Prepared from intermediates A26 and B7 according to AAV1.

$C_{25}H_{24}ClF_3N_6O_3$ (548.95)

R_t = 2.16 minutes (method 2)

Example 346: (*S*)-5-amino-N-(3-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

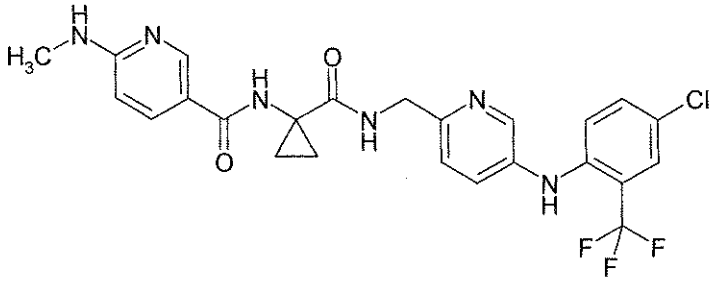


Prepared from intermediates A26 and B2 according to AAV1.

$C_{25}H_{24}ClF_3N_6O_3$ (548.95)

R_t = 2.23 minutes (method 2)

Example 347: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-methylamino-nicotinamide

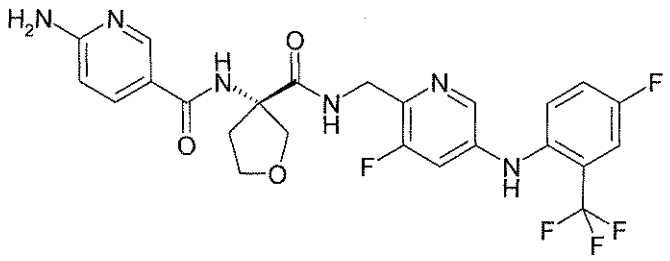


Prepared from intermediates C1 and 6-methylamino-nicotinic acid according to AAV1.

$C_{24}H_{22}ClF_3N_6O_2$ (518.92)

R_t = 1.85 minutes (method 2)

Example 348: (*S*)-6-amino-N-(3-{[3-fluoro-5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide



Prepared from intermediates A14 and B9 according to AAV1.

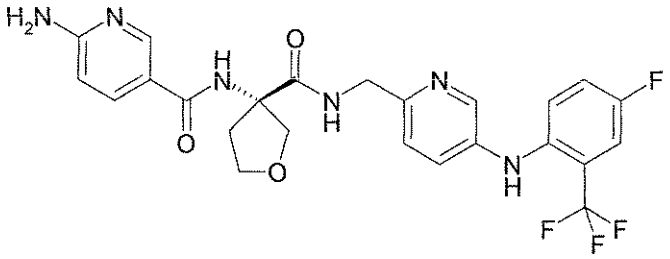
$C_{24}H_{21}F_5N_6O_3$ (536.46)

R_t = 1.96 minutes (method 2)

mass spectroscopy (ESI): [M+H]+ = 537

[M-H]- = 535

Example 349: (*S*)-6-amino-N-(3-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide



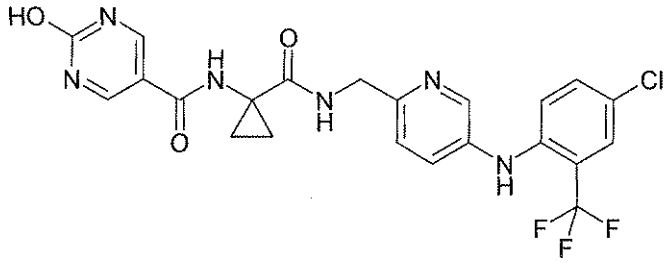
Prepared from intermediates A7 and B9 according to AAV1.

$C_{24}H_{22}F_4N_6O_3$ (518.47)

mass spectroscopy (ESI): [M+H]+ = 519

[M-H]- = 517

Example 350: 2-hydroxy-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

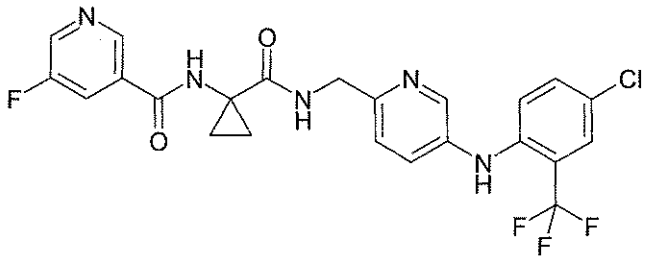


Prepared from intermediates C1 and 2-hydroxy-pyrimidine-5-carboxylic acid according to AAV1.

$C_{22}H_{18}ClF_3N_6O_3$ (506.87)

R_t = 2.42 minutes (method 2)

Example 351: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-fluoro-nicotinamide

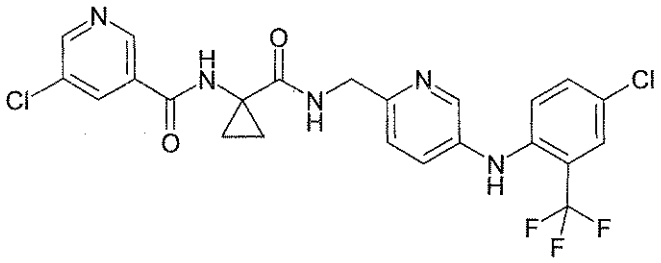


Prepared from intermediates C1 and 5-fluoro-nicotinic acid according to AAV1.

$C_{23}H_{18}ClF_4N_5O_2$ (507.87)

R_t = 1.96 minutes (method 2)

Example 352: 5-chloro-N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

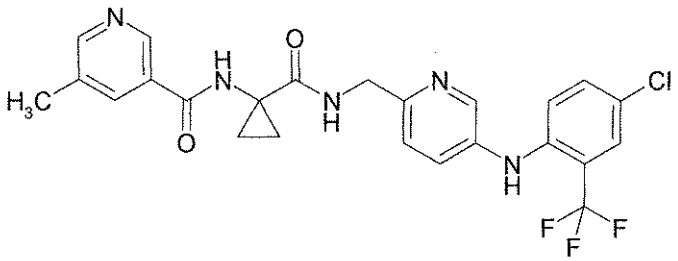


Prepared from intermediates C1 and 5-chloro-nicotinic acid according to AAV1.

$C_{23}H_{18}Cl_2F_3N_5O_2$ (524.33)

R_t = 2.10 minutes (method 2)

Example 353: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-methyl-nicotinamide

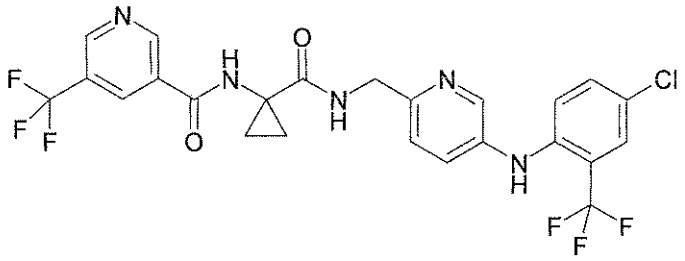


Prepared from intermediates C1 and 5-methyl-nicotinic acid according to AAV1.

$C_{24}H_{21}ClF_3N_5O_2$ (503.91)

R_t = 1.86 minutes (method 2)

Example 354: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-trifluoromethyl-nicotinamide

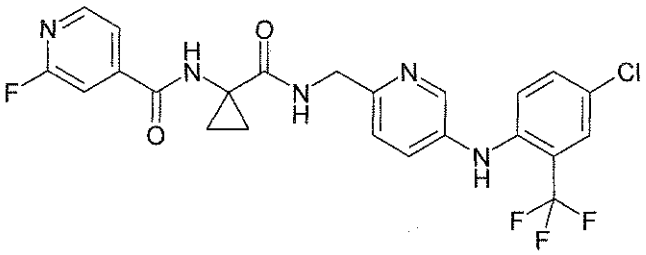


Prepared from intermediates C1 and 5-trifluoromethyl-isonicotinic acid according to AAV1.

$C_{24}H_{18}ClF_6N_5O_2$ (557.88)

R_t = 2.22 minutes (method 2)

Example 355: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-2-fluoro-isonicotinamide

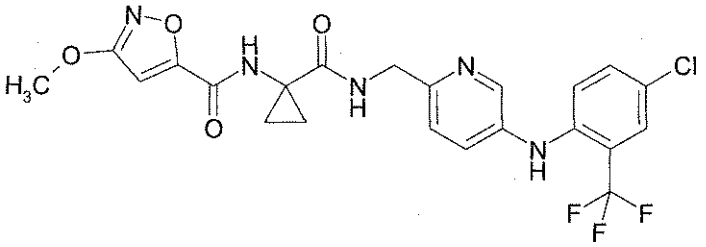


Prepared from intermediates C1 and 2-fluoro-isonicotinic acid according to AAV1.

$C_{23}H_{18}ClF_4N_5O_2$ (507.87)

R_t = 2.02 minutes (method 2)

Example 356: 3-methoxy-isoxazole-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

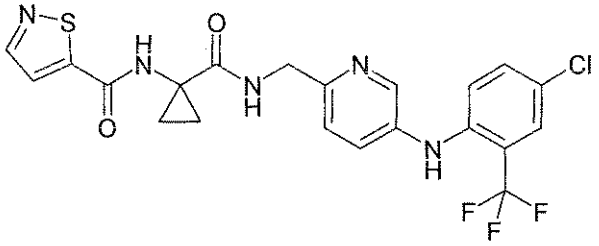


Prepared from intermediates C1 and 3-methoxy-isoxazole-5-carboxylic acid according to AAV1.

$C_{22}H_{19}ClF_3N_5O_4$ (509.87)

R_t = 1.96 minutes (method 2)

Example 357: isothiazole-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

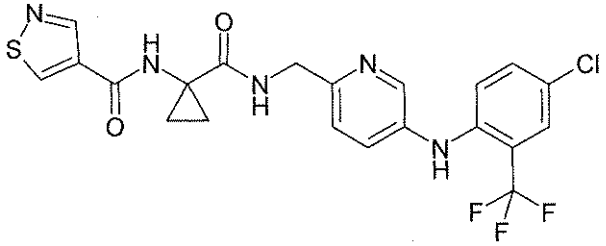


Prepared from intermediates C1 and isothiazole-5-carboxylic acid according to AAV1.

$C_{21}H_{17}ClF_3N_5O_2S$ (495.91)

R_t = 1.88 minutes (method 2)

Example 358: isothiazol-4-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

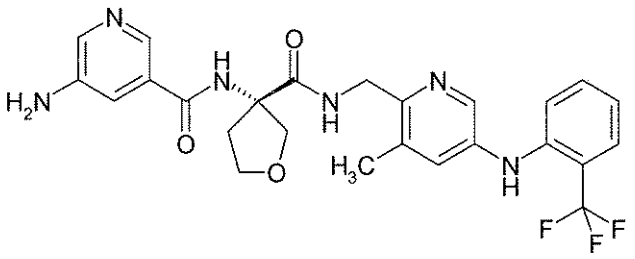


Prepared from intermediates C1 and isothiazole-4-carboxylic acid according to AAV1.

$C_{21}H_{17}ClF_3N_5O_2S$ (495.91)

R_t = 1.84 minutes (method 2)

Example 359: (*S*)-5-amino-N-(3-{[3-methyl-5-(2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-tetrahydrofuran-3-yl)-nicotinamide

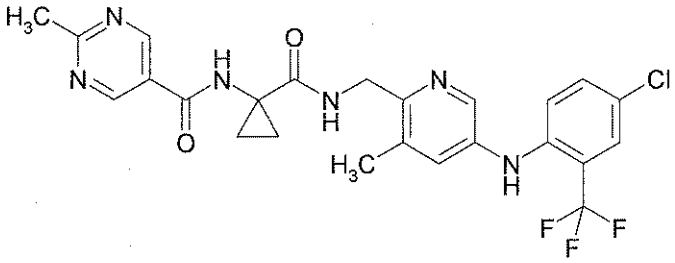


Prepared from intermediates A27 and B2 according to AAV1.

$C_{25}H_{25}F_3N_6O_3$ (514.51)

R_t = 1.51 minutes (method 2)

Example 360: 2-methyl-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

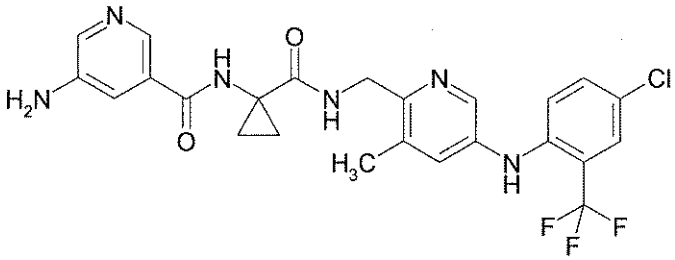


Prepared from intermediates A26 and B11 according to AAV1.

$C_{24}H_{22}ClF_3N_6O_2$ (518.92)

R_t = 2.11 minutes (method 2)

Example 361: 5-amino-N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

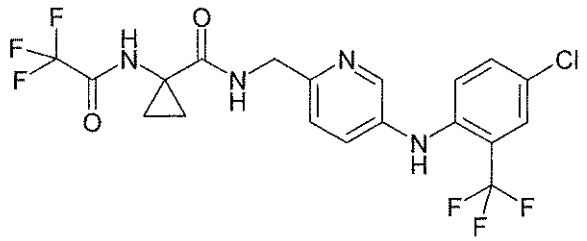


Prepared from intermediates A26 and B4 according to AAV1.

$C_{24}H_{22}ClF_3N_6O_2$ (518.92)

R_t = 1.83 minutes (method 2)

Example 362: 1-(2,2,2-trifluoro-acetylamino)-cyclopropanecarboxylic acid-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

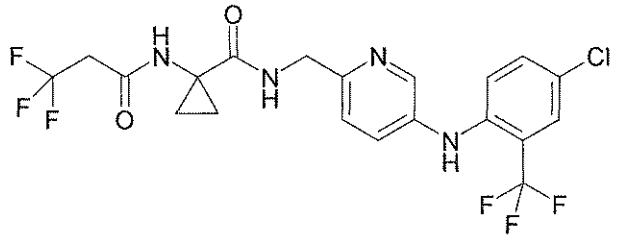


Prepared from intermediates C1 and trifluoroacetic acid according to AAV1

$C_{19}H_{15}ClF_6N_4O_2$ (480.79)

R_t = 2.15 minutes (method 2)

Example 363: 1-(3,3,3-trifluoro-propionylamino)-cyclopropanecarboxylic acid-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

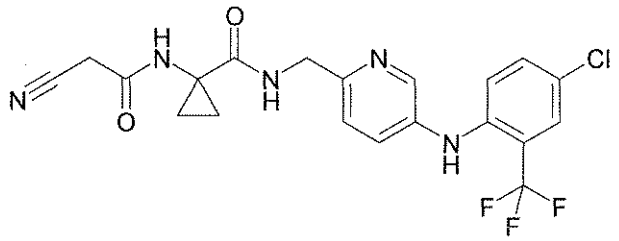


Prepared from intermediates C1 and 3,3,3-trifluoro-propionic acid according to AAV1

$C_{20}H_{17}ClF_6N_4O_2$ (494.82)

R_t = 2.07 minutes (method 2)

Example 364: 1-(2-cyano-acetylamino)-cyclopropanecarboxylic acid-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

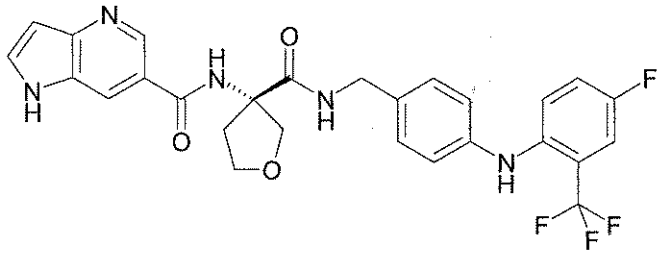


Prepared from intermediates C1 and 2-cyano-acetic acid according to AAV1.

$C_{20}H_{17}ClF_3N_5O_2$ (451.83)

R_t = 1.85 minutes (method 2)

Example 365: (*S*)-1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

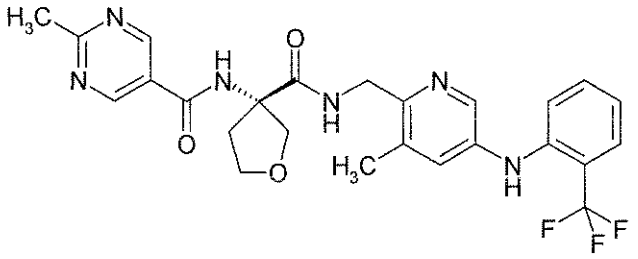


Prepared from intermediates C14 and 1H-pyrrolo[3,2-b]pyridine-6-carboxylic acid according to AAV1.

$C_{27}H_{23}F_4N_5O_3$ (541.50)

R_t = 2.14 minutes (method 2)

Example 366: (*S*)-2-methyl-pyrimidine-5-carboxylic acid-(3-{[3-methyl-5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

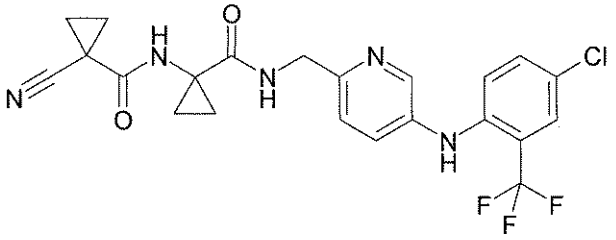


Prepared from intermediates A27 and B7 according to AAV1

$C_{25}H_{25}F_3N_6O_3$ (514.51)

R_t = 1.84 minutes (method 2)

Example 367: 1-cyano-1-(cyclopropanecarbonyl-amino)-cyclopropanecarboxylic acid-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

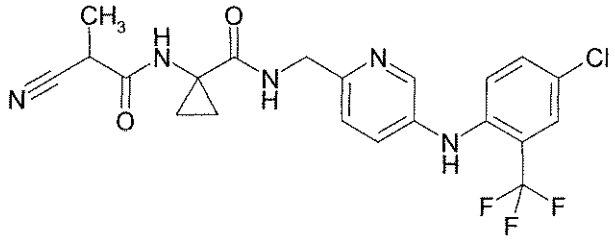


Prepared from intermediates C1 and 1-cyano-1-cyclopropanecarboxylic acid according to AAV1.

$C_{22}H_{19}ClF_3N_5O_2$ (477.87)

R_t = 1.96 minutes (method 2)

Example 368: 1-(2-cyano-2-methyl-acetylamino)-cyclopropanecarboxylic acid-[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-amide

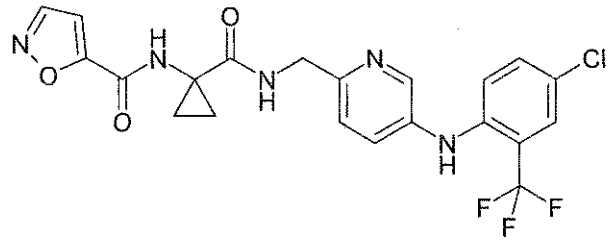


Prepared from intermediates C1 and 2-cyano-2-methyl-acetic acid according to AAV1.

$C_{21}H_{19}ClF_3N_5O_2$ (465.86)

R_t = 1.92 minutes (method 2)

Example 369: isoxazole-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

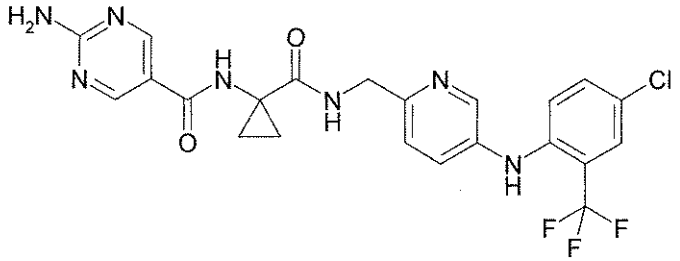


Prepared from intermediates C1 and isoxazole-5-carboxylic acid according to AAV1.

$C_{21}H_{17}ClF_3N_5O_3$ (479.84)

R_t = 1.89 minutes (method 2)

Example 370: 2-amino-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

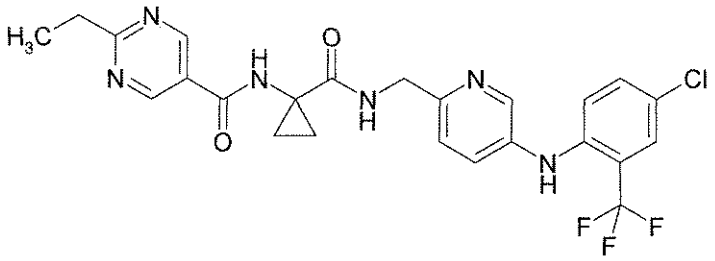


Prepared from intermediates C1 and 2-amino-pyrimidine-5-carboxylic acid according to AAV1.

$C_{22}H_{19}ClF_3N_7O_2$ (505.89)

R_t = 2.11 minutes (method 2)

Example 371: 2-ethyl-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

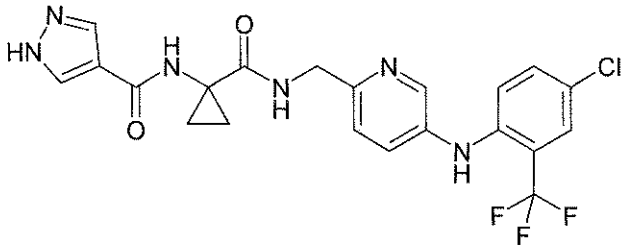


Prepared from intermediates C1 and 2-ethyl-pyrimidine-5-carboxylic acid according to AAV1.

$C_{24}H_{22}ClF_3N_6O_2$ (518.92)

R_t = 2.38 minutes (method 2)

Example 372: 1H-pyrazole-4-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

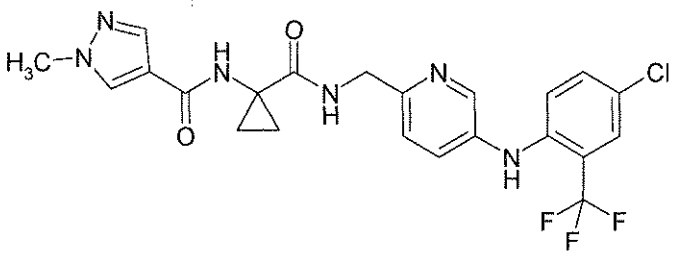


Prepared from intermediates C1 and 1H-pyrazole-4-carboxylic acid according to AAV1.

$C_{21}H_{18}ClF_3N_6O_2$ (478.86)

R_t = 1.69 minutes (method 2)

Example 373: 1-methyl-1H-pyrazole-4-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

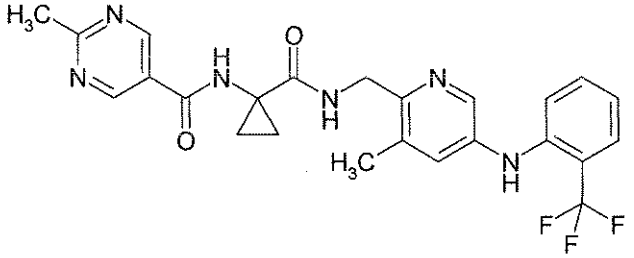


Prepared from intermediates C1 and 1-methyl-1H-pyrazole-4-carboxylic acid according to AAV1.

$C_{22}H_{20}ClF_3N_6O_2$ (492.89)

R_t = 1.74 minutes (method 2)

Example 374: 2-methyl-pyrimidine-5-carboxylic acid-(1-{[3-methyl-5-(2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

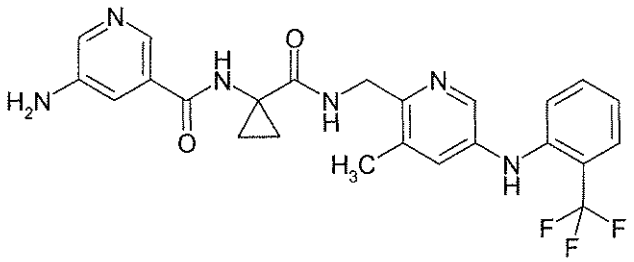


Prepared from intermediates C20 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1.

$C_{24}H_{23}F_3N_6O_2$ (484.48)

R_t = 1.81 minutes (method 2)

Example 375: 5-amino-N-(1-{[3-methyl-5-(2-trifluoromethyl-phenylamino)-pyridin-2-yl-methyl]-carbamoyl}-cyclopropyl)-nicotinamide

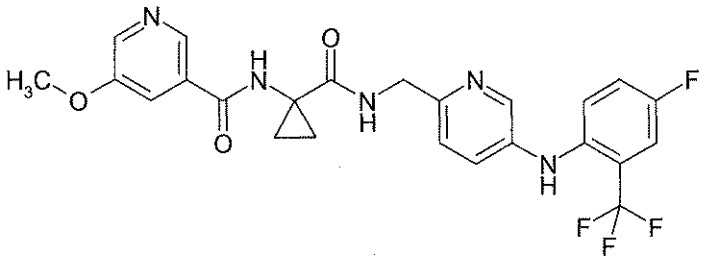


Prepared from intermediates C20 and 5-amino-nicotinic acid according to AAV1.

$C_{24}H_{23}F_3N_6O_2$ (484.48)

R_t = 1.29 minutes (method 2)

Example 376: N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-methoxy-nicotinamide

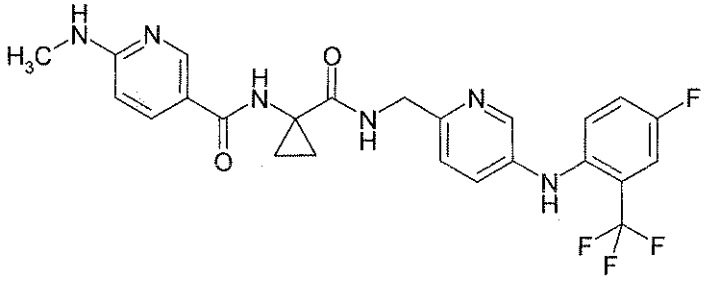


Prepared from intermediates C2 and 5-methoxy-nicotinic acid according to AAV1.

$C_{24}H_{21}F_4N_5O_3$ (503.45)

R_t = 2.02 minutes (method 2)

Example 377: N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-methylamino-nicotinamide

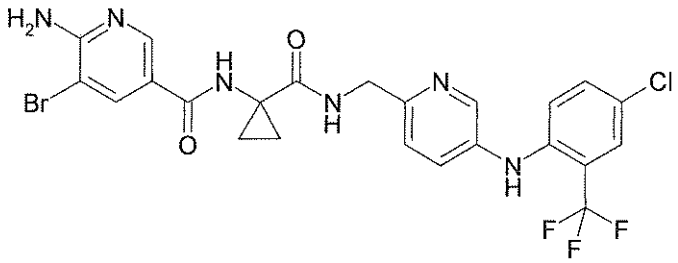


Prepared from intermediates C2 and 6-methylamino-nicotinic acid according to AAV1.

$C_{24}H_{22}F_4N_6O_2$ (502.47)

R_t = 2.01 minutes (method 2)

Example 378: 6-amino-5-bromo-N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-nicotinamide

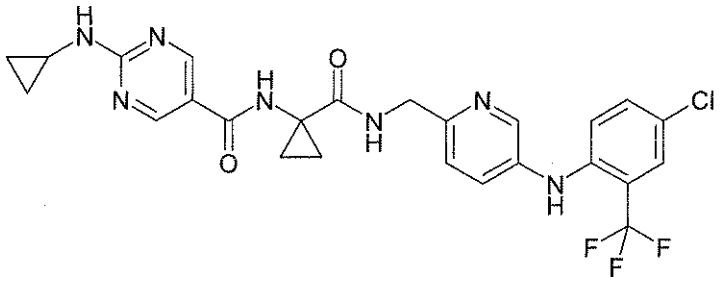


Prepared from intermediates C1 and 6-amino-5-bromo-nicotinic acid according to AAV1.

$C_{23}H_{19}BrClF_3N_6O_2$ (583.79)

R_t = 1.91 minutes (method 2)

Example 379: 2-cyclopropylamino-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

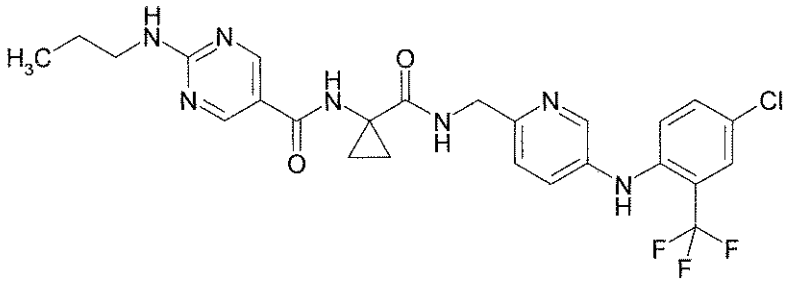


Prepared from intermediates C1 and 2-cyclopropylamino-pyrimidine-5-carboxylic acid according to AAV1.

$C_{25}H_{23}ClF_3N_7O_2$ (545.95)

R_t = 2.29 minutes (method 2)

Example 380: 2-propylamino-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

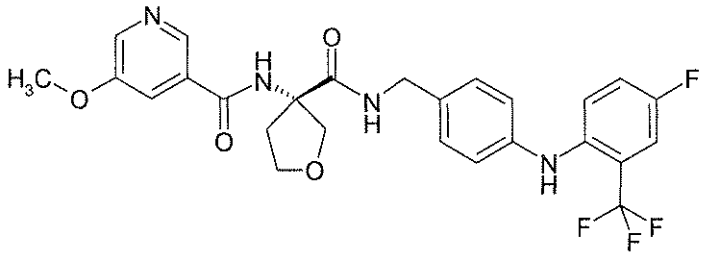


Prepared from intermediates C1 and 2-propylamino-pyrimidine-5-carboxylic acid according to AAV1.

$C_{25}H_{25}ClF_3N_7O_2$ (547.97)

R_t = 2.42 minutes (method 2)

Example 381: (*S*)-N-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-5-methoxy-nicotinamide

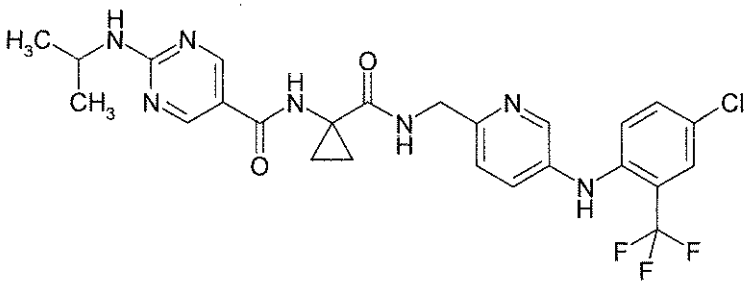


Prepared from intermediates C14 and 5-methoxy-nicotinic acid according to AAV1.

$C_{26}H_{24}F_4N_4O_4$ (532.49)

R_t = 2.50 minutes (method 2)

Example 382: 2-isopropylamino-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

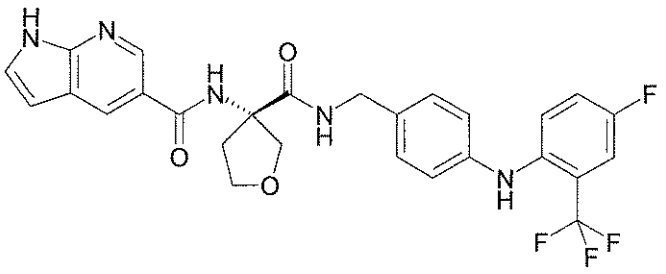


Prepared from intermediates C1 and 2-isopropylamino-pyrimidine-5-carboxylic acid according to AAV1.

$C_{25}H_{25}ClF_3N_7O_2$ (547.97)

R_t = 2.41 minutes (method 2)

Example 383: (*S*)-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid-{3-[4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

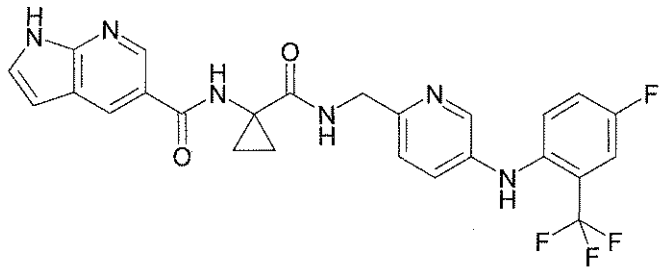


Prepared from intermediates C14 and 1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid according to AAV1.

$C_{27}H_{23}F_4N_5O_3$ (541.50)

R_t = 2.48 minutes (method 2)

Example 384: 1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

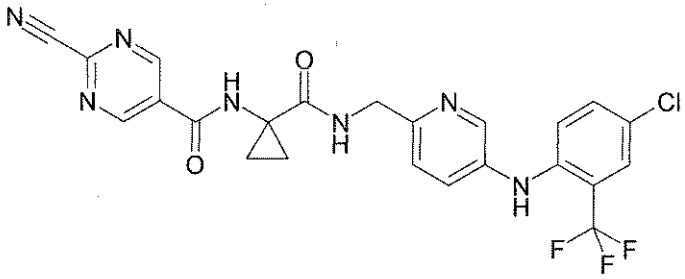


Prepared from intermediates C2 and 1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid according to AAV1.

$C_{25}H_{20}F_4N_6O_2$ (512.47)

R_t = 2.27 minutes (method 2)

Example 385: 2-cyano-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

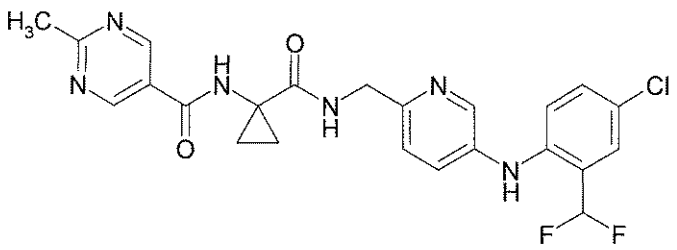


Prepared from intermediates C1 and 2-cyano-pyrimidine-5-carboxylic acid according to AAV1.

$C_{23}H_{17}ClF_3N_7O_2$ (515.88)

R_t = 2.39 minutes (method 2)

Example 386: 2-methyl-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-difluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

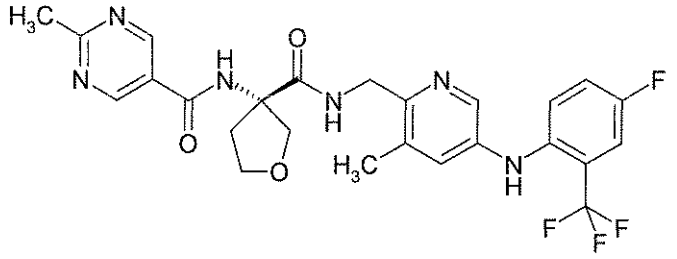


Prepared from intermediates C21 and 2-methyl-pyrimidine-5-carboxylic acid according to AAV1.

$C_{23}H_{21}ClF_2N_6O_2$ (486.91)

R_t = 1.68 minutes (method 2)

Example 387: (*S*)-2-methyl-pyrimidine-5-carboxylic acid-(3-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-3-methyl-pyridin-2-ylmethyl]-carbamoyl}-tetrahydrofuran-3-yl)-amide

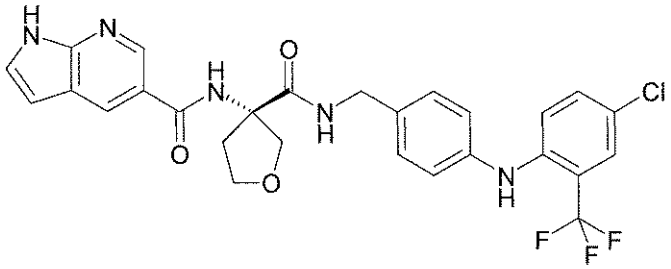


Prepared from intermediates A21 and B7 according to AAV1.

$C_{25}H_{24}F_4N_6O_3$ (532.50)

R_t = 1.86 minutes (method 2)

Example 388: (*S*)-1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

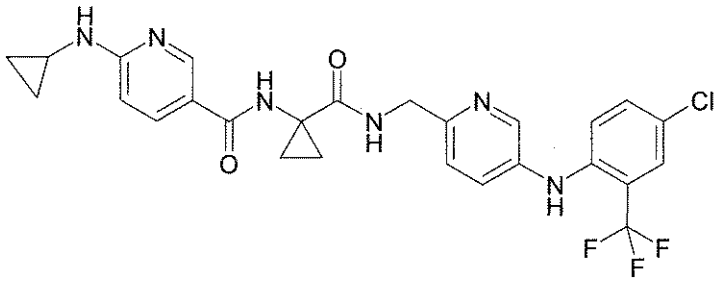


Prepared from intermediates C18 and 1H-pyrrolo[2,3-b]pyridine-5-carboxylic acid according to AAV1.

$C_{27}H_{23}ClF_3N_5O_3$ (557.96)

mass spectroscopy (ESI): [M+H]+ = 558
[M-H]- = 556

Example 389: N-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-6-cyclopropylamino-nicotinamide

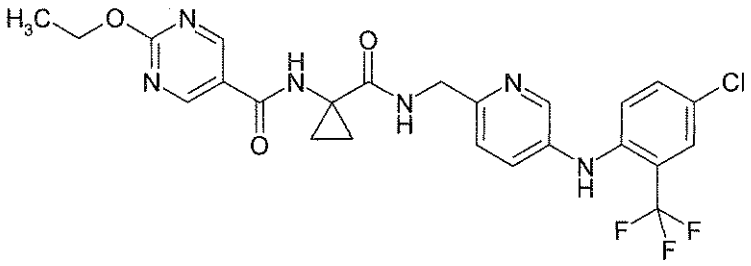


Prepared from intermediates C1 and 6-cyclopropylamino-nicotinic acid according to AAV1.

$C_{28}H_{24}ClF_3N_6O_2$ (544.96)

R_t = 1.67 minutes (method 2)

Example 390: 2-ethoxy-pyrimidine-5-carboxylic acid-(1-{[5-(4-chloro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-amide

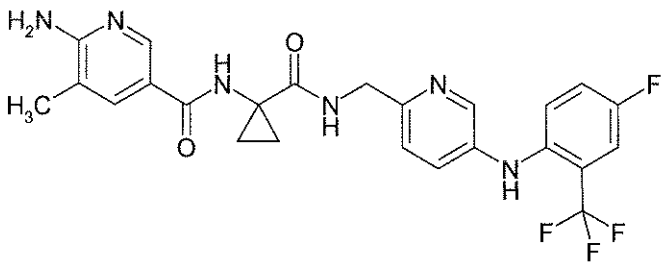


Prepared from intermediates C1 and 2-ethoxy-pyrimidine-5-carboxylic acid according to AAV1.

$C_{24}H_{22}ClF_3N_6O_3$ (534.92)

R_t = 1.99 minutes (method 2)

Example 391: 6-amino-N-(1-{[5-(4-fluoro-2-trifluoromethyl-phenylamino)-pyridin-2-ylmethyl]-carbamoyl}-cyclopropyl)-5-methyl-nicotinamide

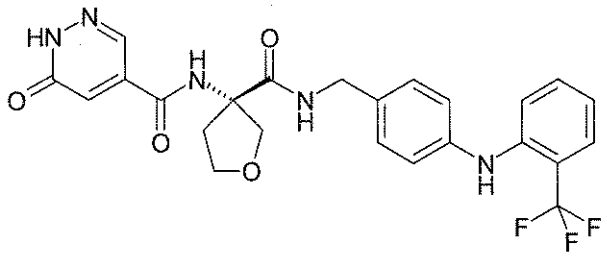


Prepared from intermediates C2 and 6-amino-5-methyl-nicotinic acid according to AAV1.

$C_{24}H_{22}F_4N_6O_2$ (502.47)

R_t = 1.38 minutes (method 2)

Example 392: (*S*)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-{3-[4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

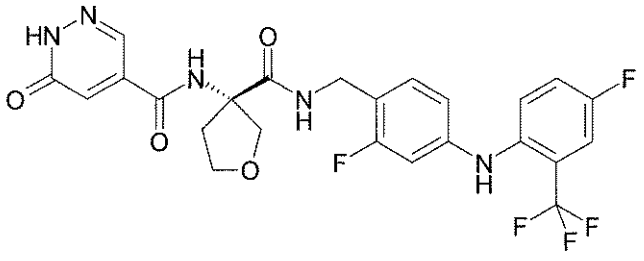


Prepared from intermediates A17 and B10 according to AAV1.

$C_{24}H_{22}F_3N_5O_4$ (501.46)

R_t = 2.09 minutes (method 2)

Example 393: (*S*)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-{3-[2-fluoro-4-(4-fluoro-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

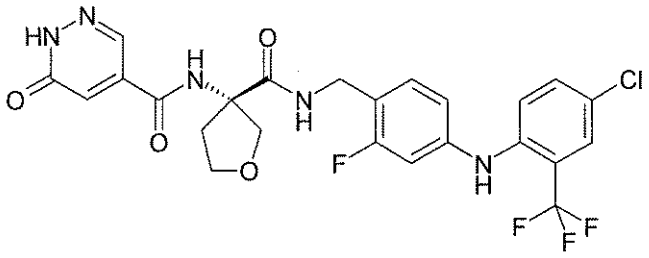


Prepared from intermediates A11 and B10 according to AAV1.

$C_{24}H_{20}F_5N_5O_4$ (537.44)

R_t = 2.15 minutes (method 2)

Example 394: (*S*)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-{3-[4-(4-chloro-2-trifluoromethyl-phenylamino)-2-fluoro-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

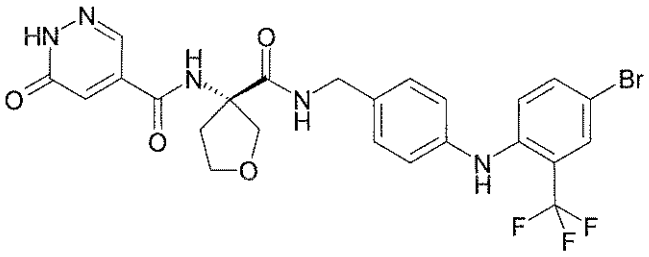


Prepared from intermediates A29 and B10 according to AAV1.

$C_{24}H_{20}ClF_4N_5O_4$ (553.90)

R_t = 2.31 minutes (method 2)

Example 395: (*S*)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid-{3-[4-(4-bromo-2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydrofuran-3-yl}-amide

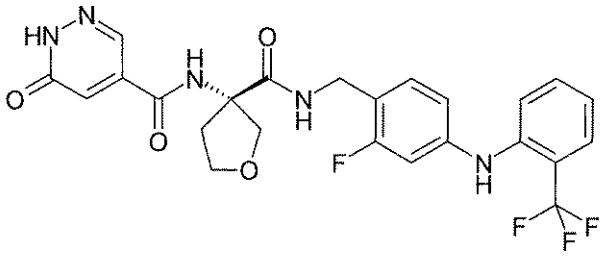


Prepared from intermediates A31 and B10 according to AAV1.

$C_{24}H_{21}BrF_3N_5O_4$ (580.35)

R_t = 2.32 minutes (method 2)

Example 396: (*S*)-6-oxo-1,6-dihydro-pyridazine-4-carboxylic acid {3-[2-fluoro-4-(2-trifluoromethyl-phenylamino)-benzylcarbamoyl]-tetrahydro-furan-3-yl}-amide



Prepared from intermediates A12 and B10 according to AAV1.

$C_{24}H_{21}F_4N_5O_4$ (519.45)

R_t = 1.35 minutes (method 7)

mass spectroscopy (ESI): $[M+H]^+$ = 520

$[M-H]^-$ = 518

The following Examples describe pharmaceutical formulations which contain as active substance any desired compound of general formula I, without restricting the scope of the present invention thereto:

Example I

Dry ampoule with 75 mg of active compound per 10 ml

Composition:

Active compound	75.0 mg
Mannitol	500 mg
Water for injection	ad 10.0 ml

Production:

Active compound and mannitol are dissolved in water. The charged ampoules are freeze dried. Water for injection is used to dissolve to give the solution ready for use.

Example II

Tablet with 50 mg of active compound

Composition:

(1) Active compound	50.0 mg
(2) Lactose	98.0 mg
(3) Maize starch	50.0 mg
(4) Polyvinylpyrrolidone	15.0 mg
(5) Magnesium stearate	2.0 mg
	215.0 mg

Production:

(1), (2) and (3) are mixed and granulated with an aqueous solution of (4). (5) is admixed to the dry granules. Tablets are compressed from this mixture, biplanar with a bevel on both sides and dividing groove on one side.

Diameter of the tablets: 9 mm.

Example III

Tablet with 350 mg of active compound

Composition:

(1) Active compound	350.0 mg
(2) Lactose	136.0 mg
(3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	4.0 mg
	600.0 mg

Production:

(1), (2) and (3) are mixed and granulated with an aqueous solution of (4). (5) is admixed to the dry granules. Tablets are compressed from this mixture, biplanar with a bevel on both sides and dividing groove on one side.

Diameter of the tablets: 12 mm.

Example IV

Capsule with 50 mg of active compound

Composition:

(1) Active compound	50.0 mg
(2) Maize starch dried	58.0 mg
(3) Lactose powdered	50.0 mg
(4) Magnesium stearate	2.0 mg
	160.0 mg

Production:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into hard gelatine two-piece capsules of size 3 in a capsule-filling machine.

Example V

Capsules with 350 mg of active compound

Composition:

(1) Active compound	350.0 mg
(2) Maize starch dried	46.0 mg
(3) Lactose powdered	30.0 mg
(4) Magnesium stearate	4.0 mg
	430.0 mg

Production:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous stirring.

This powder mixture is packed into hard gelatine two-piece capsules of size 0 in a capsule-filling machine.

Example VI

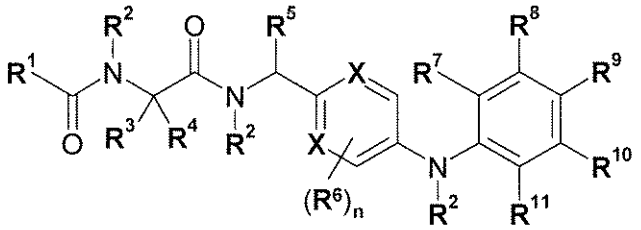
Suppositories with 100 mg of active compound

1 suppository comprises:

Active compound	100.0 mg
Polyethylene glycol (M.W. 1500)	600.0 mg
Polyethylene glycol (M.W. 6000)	460.0 mg
Polyethylene sorbitan monostearate	840.0 mg
	2000.0 mg

PATENT CLAIMS

1. Compounds of general formula **I**



, (I)

wherein

n denotes one of the numbers 0, 1 or 2,

$\mathbf{R^1}$ denotes

(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(c) a substituted C_{3-6}-cycloalkyl group optionally substituted by a group $\mathbf{R^{1.2}}$ wherein a $-CH_2-$ unit may be replaced by a -C(O)- group,

(d) an aryl-C_{0-2}-alkylene group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.3}}$,

(e) a five-membered heteroaryl-C_{0-2}-alkylene group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.4}}$, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms and which may additionally be benzo-condensed,

(f) a six-membered heteroaryl-C_{0-2}-alkylene group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms and which may additionally be benzo-condensed,

(g) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$ substituted, which contains one, two or three N-atoms,

(h) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, in which a $-CH_2-$ unit may be replaced by a -C(O)- group,

(i) $-O-\mathbf{R^{1.1.1}}$,

(j) $-N\mathbf{R^{1.1.3}}\mathbf{R^{1.1.4}}$ or

(k) $-C(=N\mathbf{R^{1.5}})-CN$,

$R^{1.1}$ denotes halogen, $-NO_2$, -CN, C_{3-6}-cycloalkyl, $-OR^{1.1.1}$, $-SR^{1.1.1}$, $-C(O)R^{1.1.1}$, $-S(O)_2-R^{1.1.2}$, $-O-S(O)_2-R^{1.1.1}$, $-CO_2R^{1.1.1}$, $-O-C(O)-R^{1.1.1}$, $-NR^{1.1.3}R^{1.1.4}$, $-NR^{1.1.3}-C(O)-R^{1.1.1}$, $-NR^{1.1.3}-C(O)-R^{1.1.1}$, $-NR^{1.1.3}-CO_2-R^{1.1.1}$ or $-C(O)-NR^{1.1.3}R^{1.1.4}$,

$R^{1.1.1}$ denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) a phenyl group optionally substituted by 1, 2 or 3 groups $R^{1.1.1.1}$,

(e) C_{3-6}-cycloalkyl or

(f) a pyridyl group optionally substituted by 1, 2 or 3 groups $R^{1.1.1.2}$,

$R^{1.1.1.1}$ independently of one another denote

(a) halogen, $-NO_2$, -CN, -OH, $-O-C_{1-4}$-alkyl, C_{3-6}-cycloalkyl, C_{1-4}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$R^{1.1.1.2}$ independently of one another denote halogen or C_{1-4}-alkyl,

$R^{1.1.2}$ denotes

(a) C_{1-4}-alkyl,

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(c) $-O-C_{1-4}$-alkyl or

(d) a phenyl group optionally substituted by 1, 2 or 3 groups $R^{1.1.1.1}$ substituted,

$R^{1.1.3}$,

$R^{1.1.4}$ independently of one another denote

(a) H,

(b) a C_{1-4}-alkyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.1.4.1}}$,

(c) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.1.1.1}}$,

(d) C_{3-6}-cycloalkyl, or

$\mathbf{R^{1.1.3}}$ and $\mathbf{R^{1.1.4}}$ together with the N atom to which they are attached form a 5- or 6-membered heterocyclic ring, which may additionally contain a further heteroatom selected from N, O and S, or

$\mathbf{R^{1.1.3}}$ and $\mathbf{R^{1.1.4}}$ together with the N atom to which they are attached, form a cyclic imide,

$\mathbf{R^{1.1.4.1}}$ independently of one another halogen denote $-NH_2$, $-NH(C_{1-4}\text{-alkyl})$, $-N(C_{1-4}\text{-alkyl})_2$ or $-SO_2\text{-}\mathbf{R^{1.1.2}}$,

$\mathbf{R^{1.2}}$ denotes halogen, $-NO_2$, -CN, OH, $-O-CH_3$ or phenyl,

$\mathbf{R^{1.3}}$ denotes

(a) halogen, $-NO_2$, -CN, $-O\mathbf{R^{1.1.1}}$, $-S\mathbf{R^{1.1.1}}$, $-CO_2\mathbf{R^{1.1.1}}$, C_{1-6}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^{1.4}}$ independently of one another denote

(a) halogen, $-NO_2$, -CN, $-O\mathbf{R^{1.1.1}}$, $-S\mathbf{R^{1.1.1}}$, $-S(O)\text{-}\mathbf{R^{1.1.2}}$, $-S(O)_2\text{-}\mathbf{R^{1.1.2}}$, $-N\mathbf{R^{1.1.3}}\mathbf{R^{1.1.4}}$, $-N(\mathbf{R^{1.4.1}})\text{-}C(O)\text{-}C_{1-4}$-alkyl, C_{1-6}-alkyl,

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, or

(c) an oxo group,

$\mathbf{R^{1.4.1}}$ denotes H or C_{1-4}-alkyl,

$\mathbf{R^{1.5}}$ denotes -OH or $-O\text{-}C_{1-3}$-alkyl,

$\mathbf{R^{2}}$ denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) C_{1-4}-alkyl-C(O)-,

$\mathbf{R^3}$ and $\mathbf{R^4}$ together with the carbon atom to which they are bound denote a C_{3-6}-cycloalkylene group optionally substituted by a group $\mathbf{R^{3.1}}$ wherein a $-CH_2-$ unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO_2,

$\mathbf{R^{3.1}}$ denotes H, -OH,

$\mathbf{R^5}$ denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^6}$ independently of one another denote

(a) H, halogen, -CN, -OH, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, -O-C_{1-4}-alkyl, -O-CF_3, -O-C_{3-6}-cycloalkyl, -N(C_{1-3}-alkyl)$_2$, -C(O)-NH_2, -(SO_2)NH_2, -SO_2-C_{1-3}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^7}$ denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,

(e) -O-C_{1-6}-alkyl,

(f) -O-C_{3-7}-cycloalkyl,

(g) $-NH_2$, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,

(h) -C(O)-$\mathbf{R}^{7.1}$,

(i) -S-C_{1-4}-alkyl, -SO_2-$\mathbf{R}^{7.2}$,

(j) a five-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl, or

(k) a six-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,

$\mathbf{R}^{7.1}$ denotes -NH_2, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, -OH, -O-C_{1-8}-alkyl or -O-C_{3-7}-cycloalkyl,

$\mathbf{R}^{7.2}$ denotes -NH_2, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl or *N*-morpholinyl and

$\mathbf{R}^{8}$ denotes H, halogen, C_{1-4}-alkyl,

$\mathbf{R}^{9}$ denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,

(e) C_{2-4}-alkynyl,

(f) -O-C_{1-6}-alkyl,

(g) -O-C_{3-7}-cycloalkyl,

(h) -NH_2, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,

(i) -C(O)-$\mathbf{R}^{9.1}$,

(j) -S-C_{1-4}-alkyl, -SO-C_{1-4}-alkyl, -SO_2-C_{1-4}-alkyl,

$\mathbf{R}^{9.1}$ denotes -NH_2, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, -OH, -O-C_{1-8}-alkyl or -O-C_{3-7}-cycloalkyl,

$\mathbf{R^{10}}$ denotes H, halogen, C_{1-4}-alkyl,

$\mathbf{R^{11}}$ denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,

(e) -O-C_{1-6}-alkyl,

(f) -O-C_{3-7}-cycloalkyl,

(g) $-NH_2$, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,

(h) -C(O)-$\mathbf{R^{11.1}}$,

(i) -S-C_{1-3}-alkyl, -SO_2-$\mathbf{R^{11.2}}$,

(j) a five-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyrrolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, imidazolyl, pyrazolyl, triazolyl and tetrazolyl, or

(k) a six-membered heteroaryl group optionally substituted by one or two C_{1-3}-alkyl groups which is selected from among pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl and triazinyl,

$\mathbf{R^{11.1}}$ denotes $-NH_2$, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl, *N*-morpholinyl, -OH, -O-C_{1-8}-alkyl or -O-C_{3-7}-cycloalkyl,

$\mathbf{R^{11.2}}$ denotes $-NH_2$, -NH(C_{1-6}-alkyl),-N(C_{1-6}-alkyl)$_2$, *N*-acetidinyl, *N*-pyrrolidinyl, *N*-piperidinyl or *N*-morpholinyl and

X independently of one another denote C-$\mathbf{R^6}$ or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

2. Compounds of general formula **I** according to claim 1, wherein $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, **n** and **X** are defined as in claim 1 and

$\mathbf{R^1}$ denotes

(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(c) a C_{3-6}-cycloalkyl group optionally substituted by a group $\mathbf{R^{1.2}}$ wherein a $-CH_2-$ unit may be replaced by a -C(O)- group,

(d) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.3}}$,

(e) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.4}}$, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,

(f) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms,

(g) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms,

(h) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, in which a $-CH_2-$ unit may be replaced by a -C(O)- group,

(i) $-O-\mathbf{R^{1.1.1}}$ or

(j) $-N\mathbf{R^{1.1.3}}\mathbf{R^{1.1.4}}$,

$\mathbf{R^{1.1}}$ denotes -CN, C_{3-6}-cycloalkyl, $-O\mathbf{R^{1.1.1}}$, $-N\mathbf{R^{1.1.3}}\mathbf{R^{1.1.4}}$,

$\mathbf{R^{1.1.1}}$ denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^{1.1.3}}$,

$\mathbf{R^{1.1.4}}$ independently of one another denote

(a) H,
(b) C_{1-4}-alkyl,
(c) C_{3-6}-cycloalkyl, or

$\mathbf{R^{1.1.3}}$ and $\mathbf{R^{1.1.4}}$ together with the N atom to which they are attached form a 5- or 6-membered heterocyclic ring, which may additionally contain a further heteroatom selected from N, O and S, or

$\mathbf{R^{1.2}}$ denotes halogen, $-NO_2$, -CN, -OH, $-O-CH_3$ or phenyl,

$\mathbf{R^{1.3}}$ independently of one another denote
(a) halogen, $-NO_2$, -CN, $-OR^{1.1.1}$, C_{1-6}-alkyl or
(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^{1.4}}$ independently of one another denote
(a) halogen, $-NO_2$, -CN, $-OR^{1.1.1}$, $-NR^{1.1.3}R^{1.1.4}$, $-N(R^{1.4.1})-C(O)-C_{1-4}$-alkyl, C_{1-6}-alkyl, or
(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$\mathbf{R^{1.4.1}}$ denotes H or C_{1-4}-alkyl,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

3. Compounds of general formula **I** according to claim 1, wherein $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, **n** and **X** are defined as in claim 1 and

$\mathbf{R^1}$ denotes
(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,
(b) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.3}}$,

(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $R^{1.4}$, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,

(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $R^{1.4}$, which contains one, two or three N-atoms,

(e) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups $R^{1.4}$, which contains one, two or three N-atoms,

(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $R^{1.4}$, in which a $-CH_2-$ unit may be replaced by a -C(O)- group,

$R^{1.1}$ denotes -CN, C_{3-6}-cycloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$R^{1.3}$ independently of one another denote

(a) F, Cl, Br, -OH, $-OCH_3$, C_{1-6}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$R^{1.4}$ independently of one another denote

(a) F, Cl, Br, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, $-NHC_{2-3}$-alkyl, $-N(C_{2-3}$-alkyl$)_2$, $-NH-C(O)-C_{1-4}$-alkyl, C_{1-6}-alkyl, or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

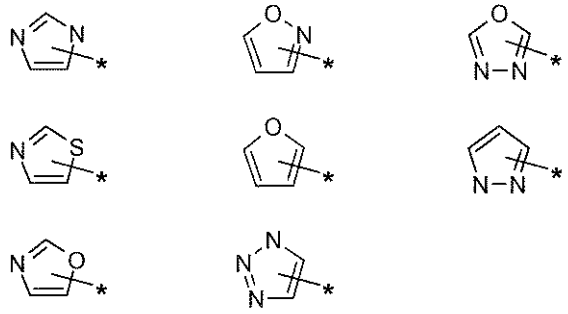
4. Compounds of general formula **I** according to claim 1, wherein R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as in claim 1 and

R^1 denotes

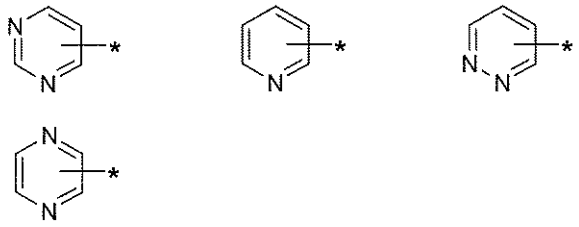
(a) a C_{1-6}-alkyl group optionally substituted by a group $R^{1.1}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $R^{1.3}$,

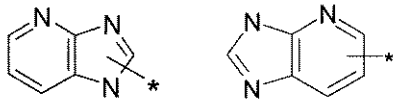
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $\mathbf{R}^{1.4}$, which is selected from among



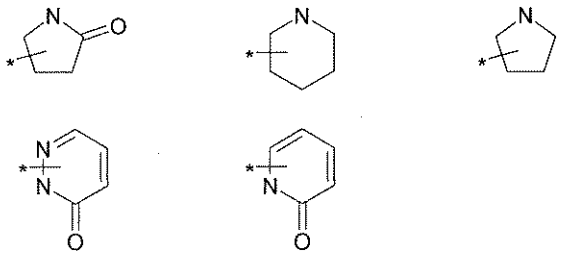
(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R}^{1.4}$ which is selected from among



(e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R}^{1.4}$, which is selected from among



(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R}^{1.4}$, which is selected from among



$\mathbf{R}^{1.1}$ denotes -CN, cyclopropyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$\mathbf{R^{1.3}}$ independently of one another denotes

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, C_{1-4}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$\mathbf{R^{1.4}}$ independently of one another denotes

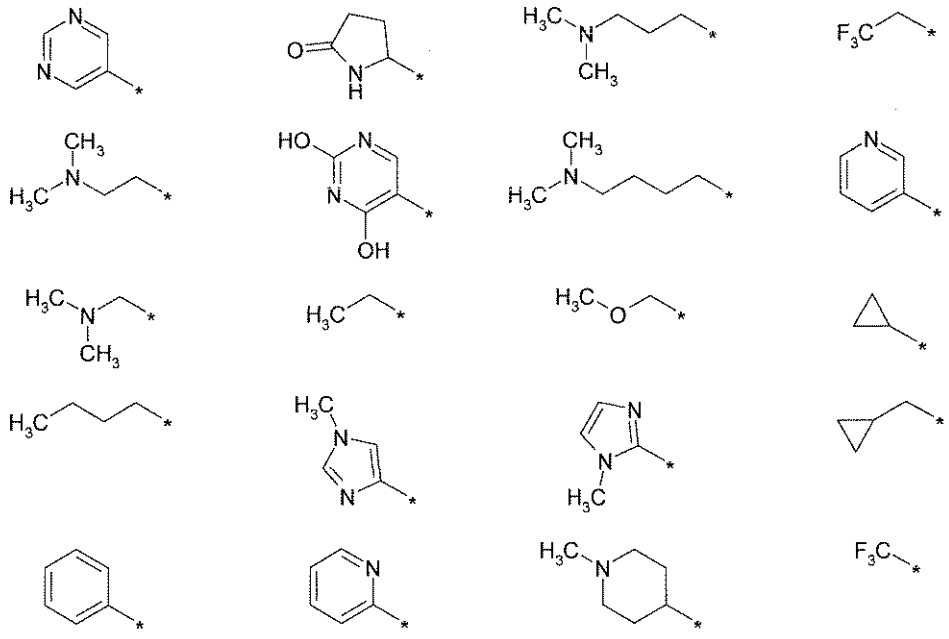
(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, $-NH_2$, $-NH-C_{1-4}$-alkyl, $-N(C_{1-4}\text{-alkyl})_2$, $-NH-C(O)-C_{1-4}$-alkyl, C_{1-6}-alkyl, or

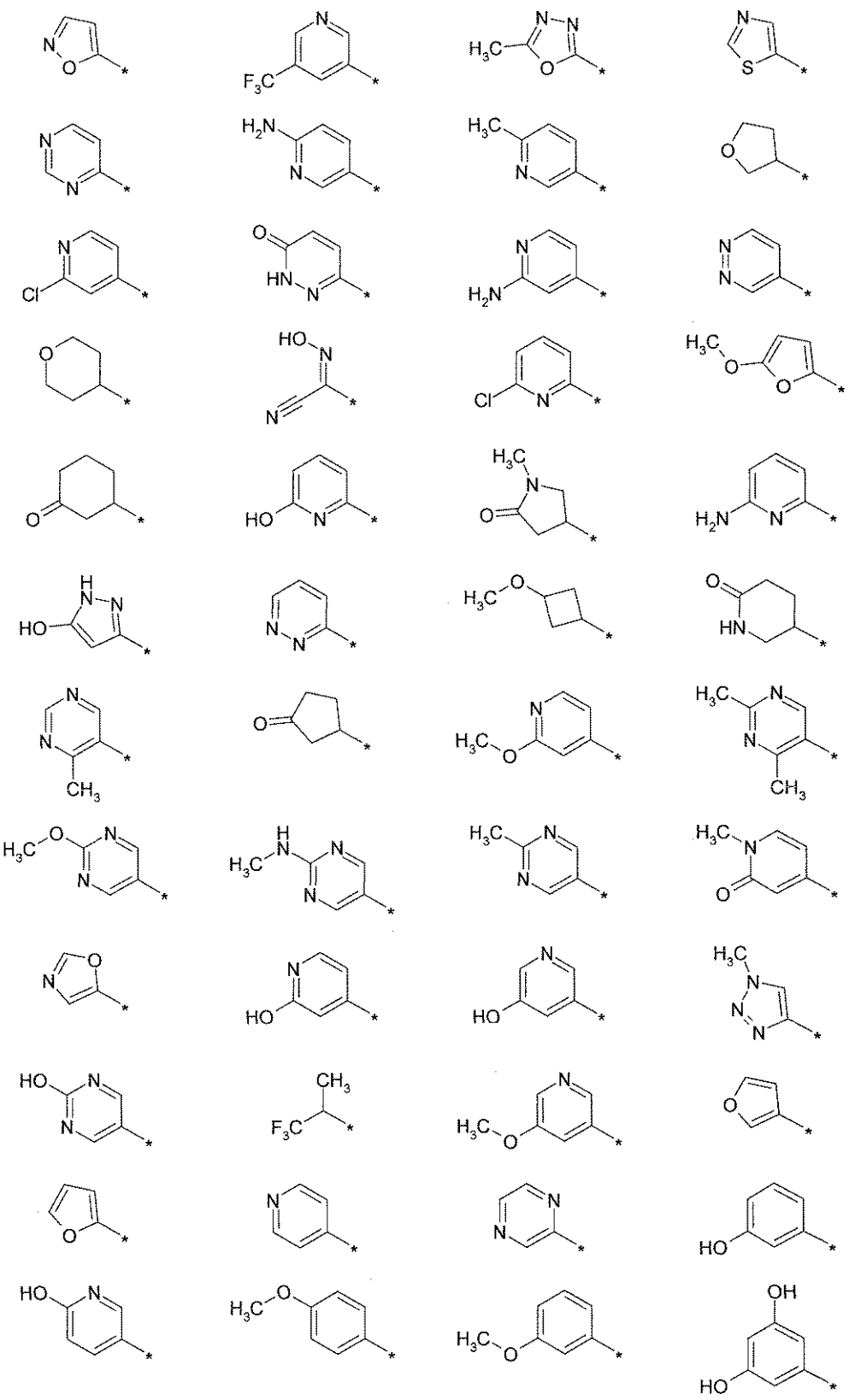
(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

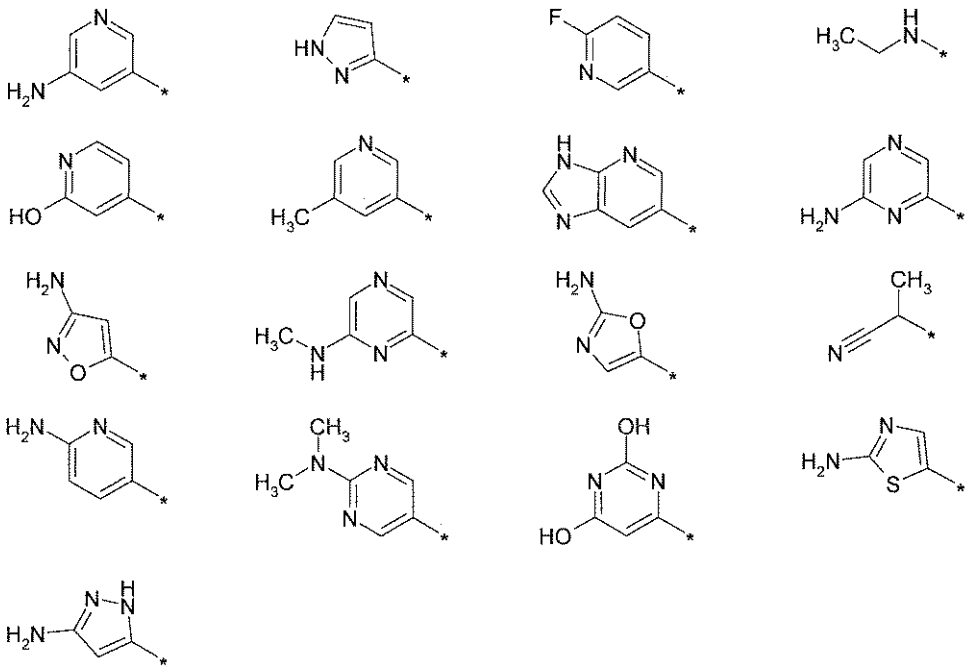
the enantiomers, the diastereomers, the mixtures and the salts thereof.

5. Compounds of general formula **I** according to claim 1, wherein $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, **n** and **X** are defined as in claim 1 and

$\mathbf{R^1}$ is selected from among



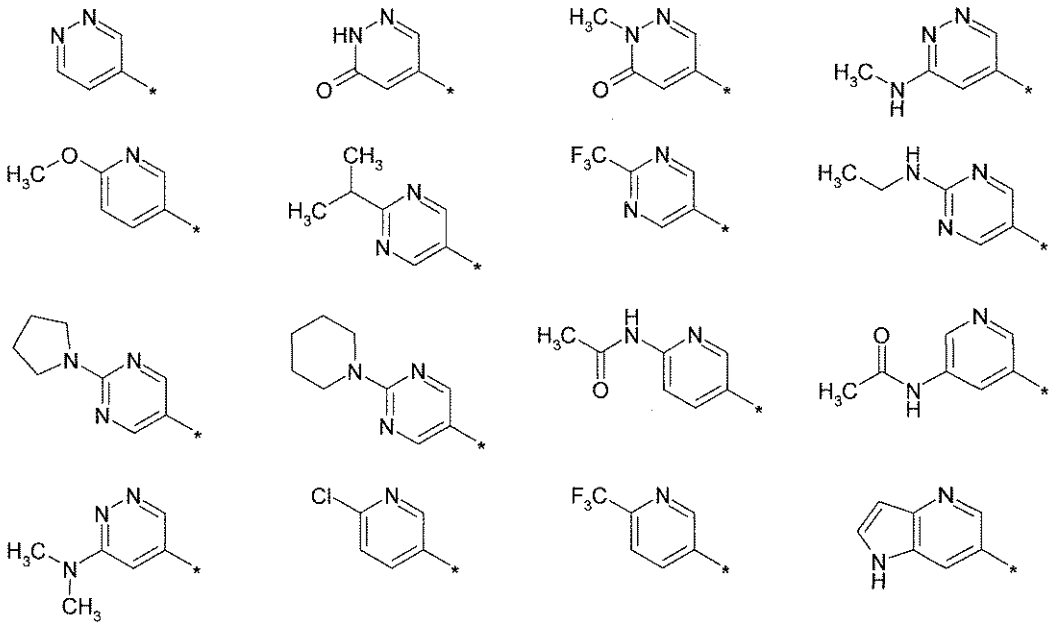


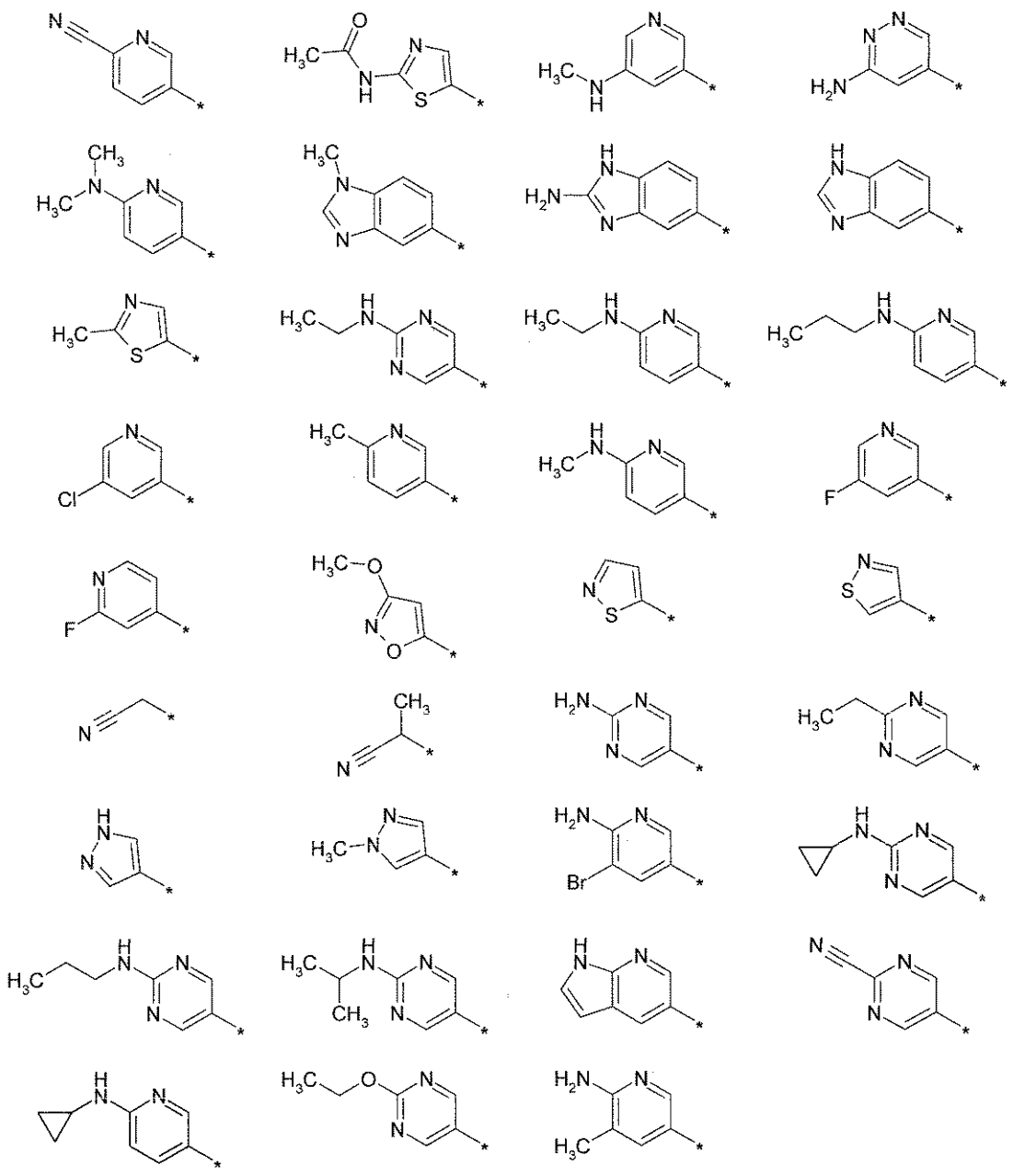


the enantiomers, the diastereomers, the mixtures and the salts thereof.

6. Compounds of general formula **I** according to claim 1, wherein **R^2**, **R^3**, **R^4**, **R^5**, **R^6**, **R^7**, **R^8**, **R^9**, **R^{10}**, **R^{11}**, **n** and **X** are defined as in claim 1 and

R^1 is selected from among





the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

7. Compounds of general formula **I** according to claim 1, wherein $\mathbf{R^1}$ is defined as in claim 1, 2, 3, 4, 5 or 6 and

n denotes one of the numbers 0, 1 or 2,

R^2 denotes

(a) H,

(b) C_{1-4}-alkyl,

R^3 and R^4 together with the carbon atom to which they are bound denote a C_{3-6}-cycloalkylene group optionally substituted by a group $R^{3.1}$ wherein a $-CH_2-$ unit may be replaced by a heteroatom O, N, S or by a group CO, SO or SO_2,

$R^{3.1}$ denotes H, -OH,

R^5 denotes

(a) H,

(b) C_{1-4}-alkyl,

(c) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^6 independently of one another denotes

(a) H, halogen, -CN, -OH, C_{1-6}-alkyl, C_{3-7}-cycloalkyl, -O-C_{1-4}-alkyl, -O-CF_3, -O-C_{3-6}-cycloalkyl, -N(C_{1-3}-alkyl)$_2$, -C(O)-NH_2, -(SO_2)NH_2, -SO_2-C_{1-3}-alkyl, or

(a) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^7 denotes

(a) H, halogen, -CN, -OH,

(b) C_{1-6}-alkyl,

(c) C_{1-3}-alkyl or -O-C_{1-3}-alkyl, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

(d) C_{3-7}-cycloalkyl,

(e) -O-C_{1-6}-alkyl,

(f) -O-C_{3-7}-cycloalkyl,

(g) $-NH_2$, $-NH(C_{1-3}\text{-alkyl})$, $-N(C_{1-3}\text{-alkyl})_2$,
(h) $-C(O)-\mathbf{R^{7.1}}$,
(i) $-S-C_{1-4}\text{-alkyl}$,

$\mathbf{R^{7.1}}$ denotes $-NH_2$, , -OH, $-O-C_{1-8}\text{-alkyl}$,

$\mathbf{R^{8}}$ denotes H, halogen, $C_{1-4}\text{-alkyl}$,

$\mathbf{R^{9}}$ denotes
(a) H, halogen, -CN, -OH,
(b) $C_{1-6}\text{-alkyl}$,
(c) $C_{1-3}\text{-alkyl}$ or $-O-C_{1-3}\text{-alkyl}$, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(d) $C_{3-7}\text{-cycloalkyl}$,
(e) $C_{2-4}\text{-alkynyl}$,
(f) $-O-C_{1-6}\text{-alkyl}$,
(g) $-O-C_{3-7}\text{-cycloalkyl}$,
(h) $-NH_2$, $-NH(C_{1-3}\text{-alkyl})$, $-N(C_{1-3}\text{-alkyl})_2$,
(i) $-C(O)-\mathbf{R^{9.1}}$,
(j) $-S-C_{1-4}\text{-alkyl}$, $-SO-C_{1-4}\text{-alkyl}$, $-SO_2-C_{1-4}\text{-alkyl}$,

$\mathbf{R^{9.1}}$ denotes $-NH_2$, -OH, $-O-C_{1-8}\text{-alkyl}$,

$\mathbf{R^{10}}$ denotes H, halogen, $C_{1-4}\text{-alkyl}$,

$\mathbf{R^{11}}$ denotes
(a) H, halogen, -CN, -OH,
(b) $C_{1-6}\text{-alkyl}$,
(c) $C_{1-3}\text{-alkyl}$ or $-O-C_{1-3}\text{-alkyl}$, wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,
(d) $C_{3-7}\text{-cycloalkyl}$,
(e) $-O-C_{1-6}\text{-alkyl}$,

(f) -O-C_{3-7}-cycloalkyl,

(g) -NH_2, -NH(C_{1-3}-alkyl), -N(C_{1-3}-alkyl)$_2$,

(h) -C(O)-$\mathbf{R^{11.1}}$,

(i) -S-C_{1-3}-alkyl,

$\mathbf{R^{11.1}}$ denotes -NH_2, , -OH, -O-C_{1-8}-alkyl, and

X independently of one another represent C-$\mathbf{R^6}$ or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

8. Compounds of general formula **I** according to claim 1, wherein $\mathbf{R^1}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, **n** and **X** are defined as in claim 1, 2, 3, 4, 5, 6 or 7 and

$\mathbf{R^2}$ denotes H or CH_3,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

9. Compounds of general formula **I** according to claim 1, wherein $\mathbf{R^1}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, **n** and **X** are defined as in claim 1, 2, 3, 4, 5, 6 or 7 and

$\mathbf{R^2}$ denotes H,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

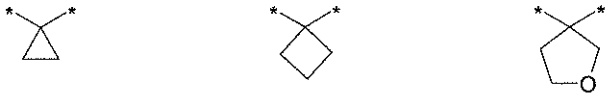
10. Compounds of general formula **I** according to claim 1, wherein $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^7}$, $\mathbf{R^8}$, $\mathbf{R^9}$, $\mathbf{R^{10}}$, $\mathbf{R^{11}}$, **n** and **X** are defined as in claim 1, 2, 3, 4, 5, 6, 7, 8 or 9 and

$\mathbf{R^3}$ and $\mathbf{R^4}$ together with the carbon atom to which they are bonded denote a C_{3-6}-cycloalkylene group wherein a -CH_2- unit may be replaced by an oxygen atom,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

11. Compounds of general formula **I** according to claim 1, wherein R^1, R^2, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as in claim 1, 2, 3, 4, 5, 6, 7, 8 or 9 and

R^3 and R^4 together with the carbon atom to which they are bonded denote a group selected from



the enantiomers, the diastereomers, the mixtures and the salts thereof.

12. Compounds of general formula **I** according to claim 1, wherein R^1, R^2, R^3, R^4, R^6, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or 11 and

R^5 denotes H or CH_3,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

13. Compounds of general formula **I** according to claim 1, wherein R^1, R^2, R^3, R^4, R^5, R^7, R^8, R^9, R^{10}, R^{11}, **n** and **X** are defined as in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 and

R^6 denotes H, F, Cl or methyl,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

14. Compounds of general formula **I** according to claim 1, wherein R^1, R^2, R^3, R^4, R^5, R^6, **n** and **X** are defined as in claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 13 and

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^8 denotes H,

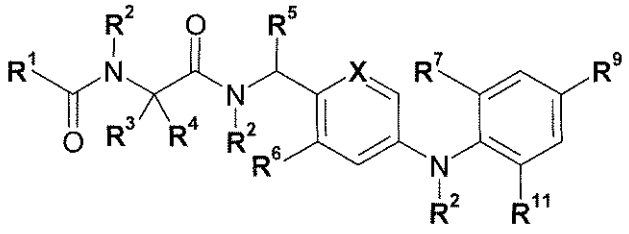
R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

R^{10} denotes H and

R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3 or CHF_2,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

15. Compounds of general formula **Ia**,



, (**Ia**)

wherein

R^1 denotes

(a) a C_{1-6}-alkyl group optionally substituted by a group $R^{1.1}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $R^{1.3}$,

(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $R^{1.4}$, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,

(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $R^{1.4}$, which contains one, two or three N-atoms,

(e) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups $R^{1.4}$, which contains one, two or three N-atoms,

(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $R^{1.4}$, in which a $-CH_2$ unit may be replaced by a -C(O) group,

$R^{1.1}$ denotes -CN, C_{3-6}-cycloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$R^{1.3}$ independently of one another denotes

(a) F, Cl, Br, -OH, $-OCH_3$, C_{1-6}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$\mathbf{R^{1.4}}$ independently of one another denotes

(a) F, Cl, Br, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -NH-C(O)-C_{1-4}-alkyl, C_{1-6}-alkyl, or

(a) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^2}$ denotes H or CH_3,

$\mathbf{R^3}$ and $\mathbf{R^4}$ together with the carbon atom to which they are bonded denote a C_{3-6}-cycloalkylene group wherein a $-CH_2-$ unit may be replaced by an oxygen atom,

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

$\mathbf{R^6}$ denotes H, F, Cl, Br or C_{1-4}-alkyl,

$\mathbf{R^7}$ denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

$\mathbf{R^9}$ denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

$\mathbf{R^{11}}$ denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

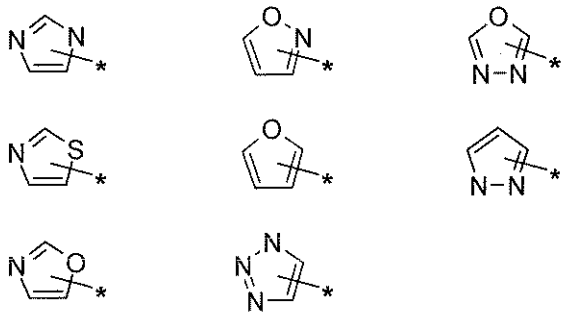
16. Compounds of general formula **Ia** according to claim 14, wherein

$\mathbf{R^1}$ denotes

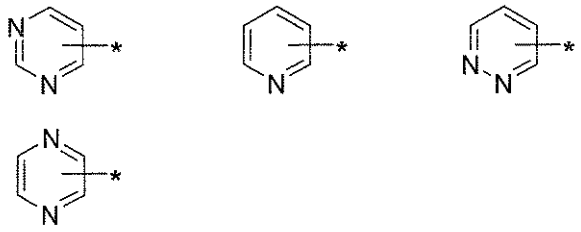
(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R}^{1.3}$,

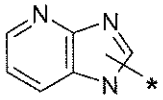
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $\mathbf{R}^{1.4}$, which is selected from among



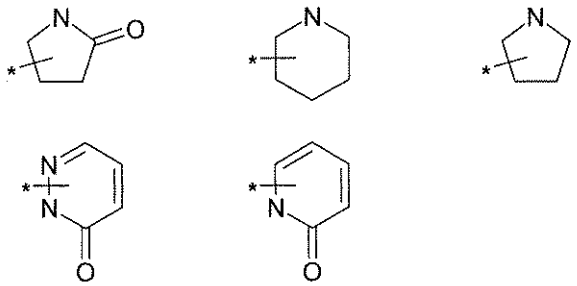
(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R}^{1.4}$, which is selected from among



(e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R}^{1.4}$, which is selected from among



(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R}^{1.4}$, which is selected from among



$R^{1.1}$ denotes -CN, cyclopropyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$R^{1.3}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, C_{1-4}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$R^{1.4}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, $-NH_2$, -NH-C_{1-4}-alkyl, $-N(C_{1-4}\text{-alkyl})_2$, -NH-C(O)-$C_{1-4}$-alkyl, C_{1-6}-alkyl, or

(a) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^2 denotes H or CH_3,

R^3 and R^4 together with the carbon atom to which they are bonded denote a C_{3-6}-cycloalkylene group wherein a $-CH_2$ unit may be replaced by an oxygen atom,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

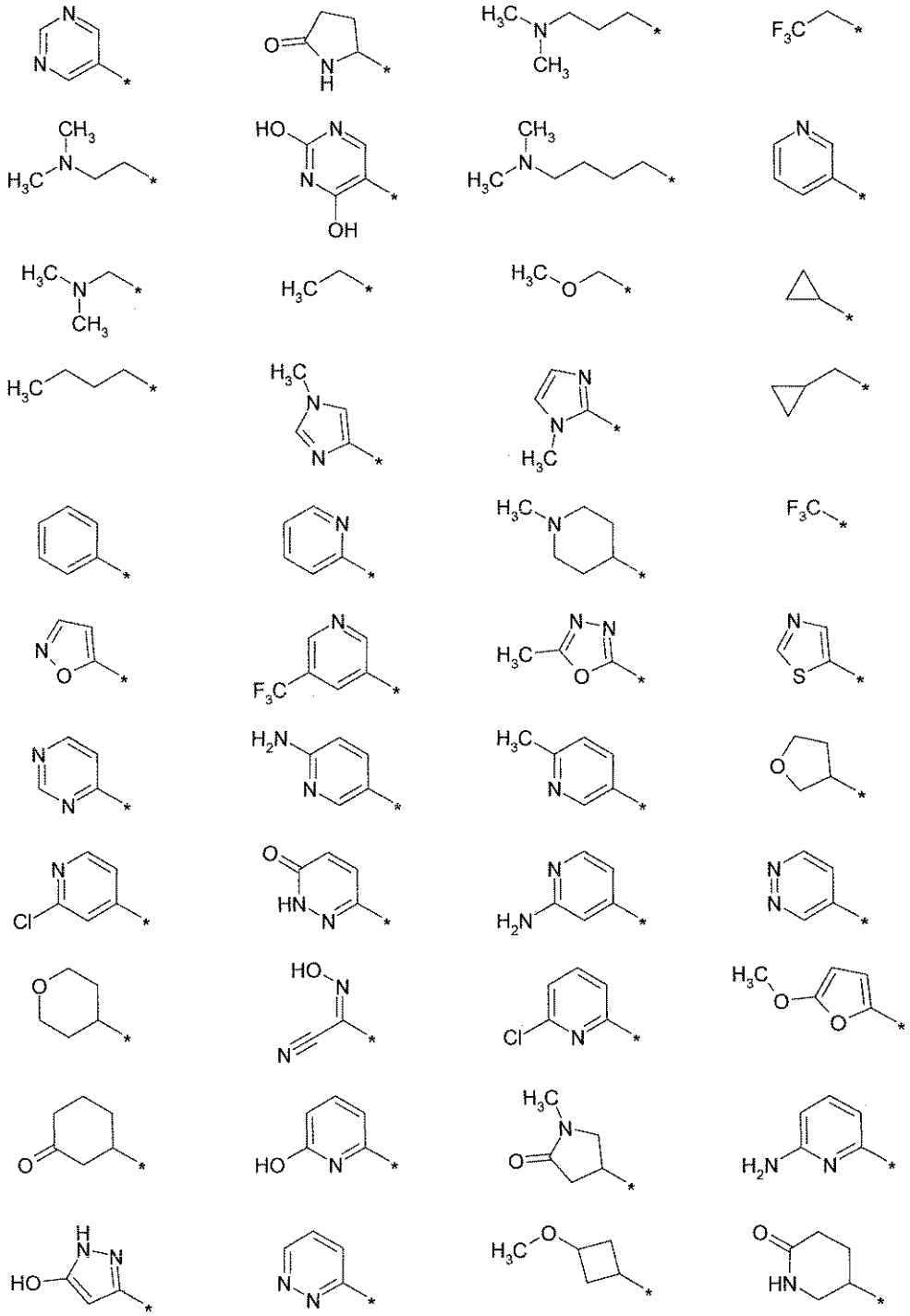
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

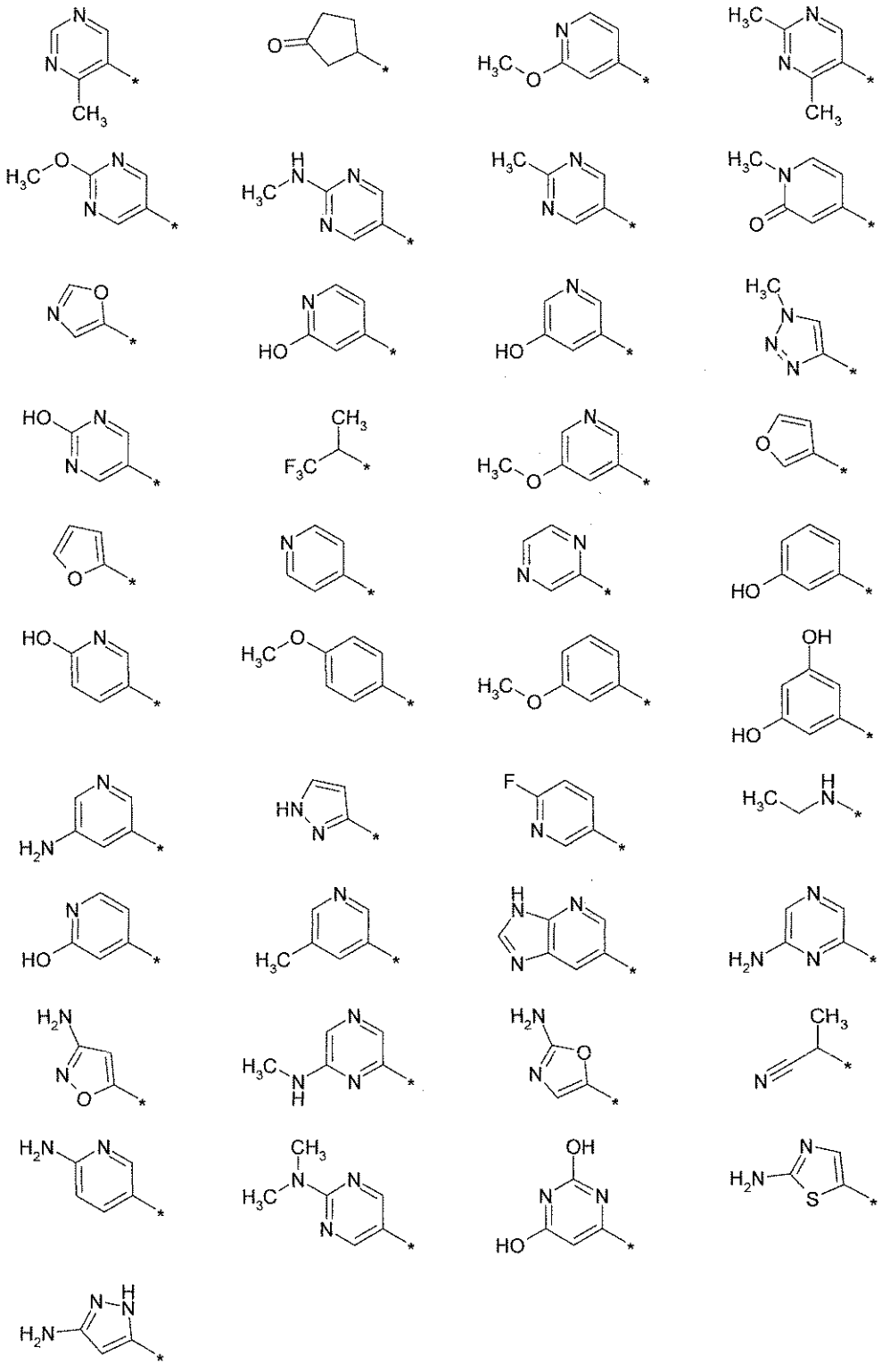
X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

17. Compounds of general formula **Ia** according to claim 14, wherein

R^1 denotes a group selected from





R^2 denotes H or CH_3,

R^3 and R^4 together with the carbon atom to which they are bonded denote a C_{3-6}-cycloalkylene group wherein a $-CH_2$ unit may be replaced by an oxygen atom,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

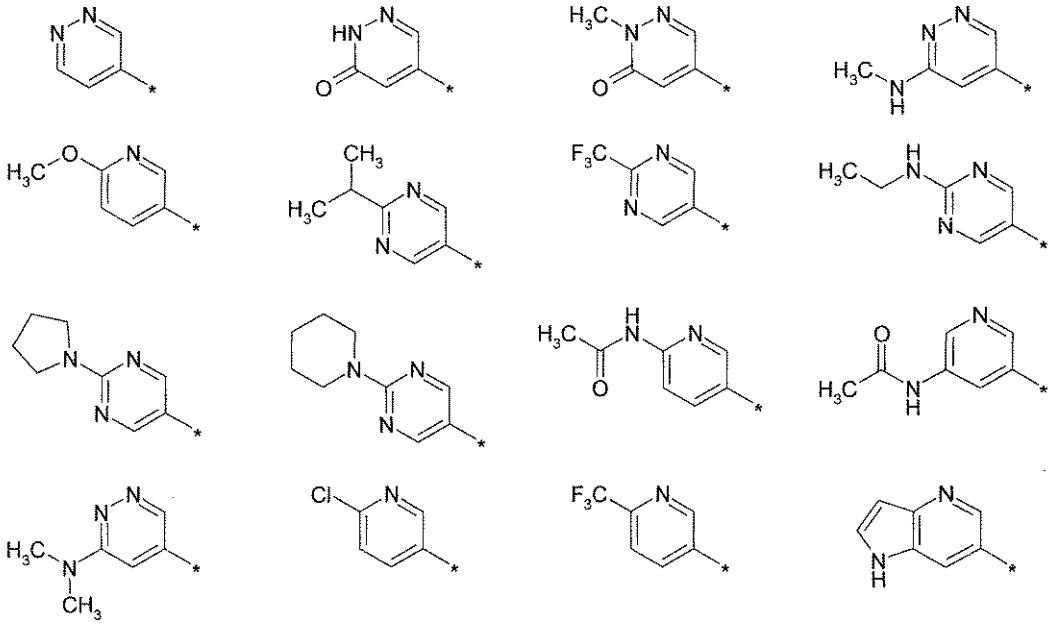
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

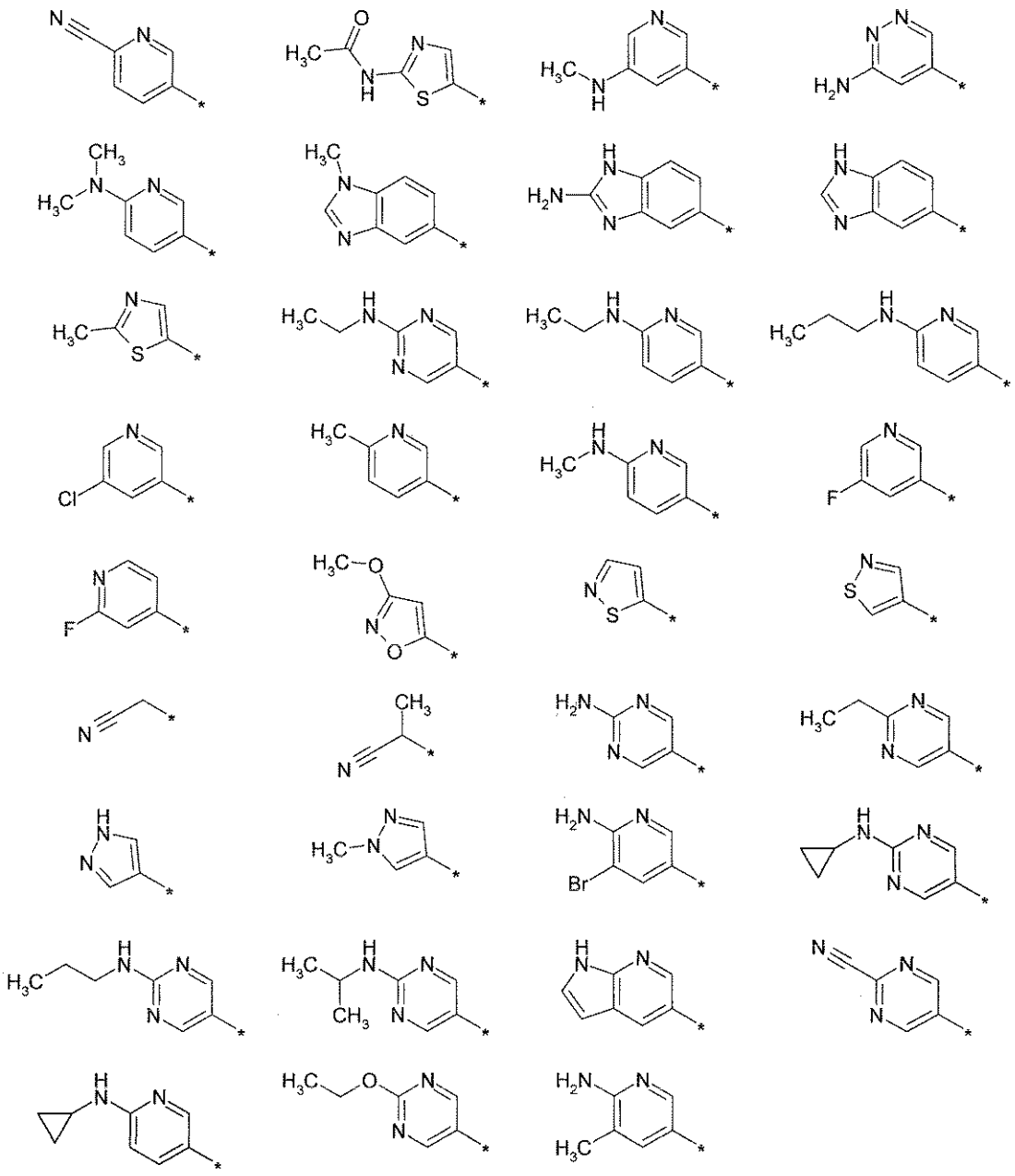
X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

18. Compounds of general formula **Ia** according to claim 15, wherein

R^1 denotes a group selected from





R² denotes H or CH_3,

R³ and **R⁴** together with the carbon atom to which they are attached denote a C_{3-6}-cycloalkylene group wherein a $-CH_2-$ unit may be replaced by an oxygen atom,

R⁵ denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

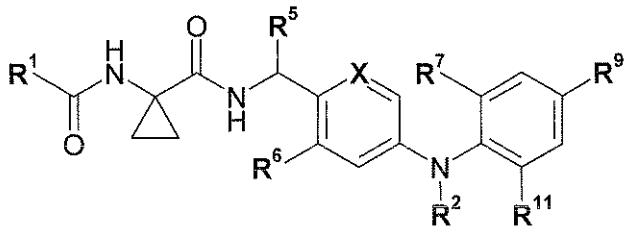
R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

19. Compounds of general formula **Ib**



, (**Ib**)

R^1 denotes

(a) a C_{1-6}-alkyl group optionally substituted by a group $R^{1.1}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $R^{1.3}$,

(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $R^{1.4}$, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,

(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $R^{1.4}$, which contains one, two or three N-atoms,

(e) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups $R^{1.4}$, which contains one, two or three N-atoms,

(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $R^{1.4}$, in which a -CH_2- unit may be replaced by a -C(O)- group,

$R^{1.1}$ denotes -CN, C_{3-6}-cycloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$R^{1.3}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, C_{1-6}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$R^{1.4}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -NH-C(O)-C_{1-4}-alkyl, C_{1-6}-alkyl, or

(a) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^2 denotes H or CH_3,

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

R^6 denotes H, F, Cl, Br or C_{1-4}-alkyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

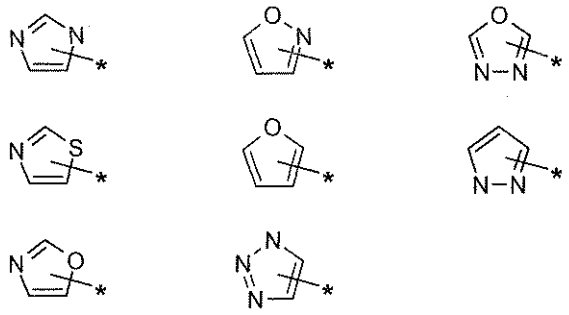
20. Compounds of general formula **Ib** according to claim 17, wherein

R^1 denotes

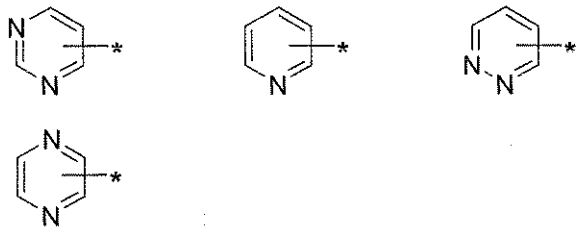
(a) a C_{1-6}-alkyl group optionally substituted by a group **$R^{1.1}$**,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups **$R^{1.3}$**,

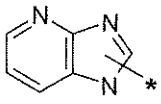
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups **$R^{1.4}$**, which is selected from among



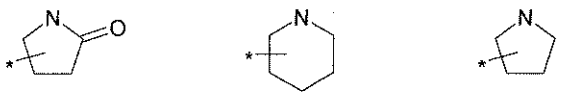
(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups **$R^{1.4}$**, which is selected from among

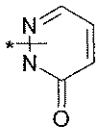
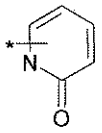


(e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups **$R^{1.4}$**, which is selected from among



(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups **$R^{1.4}$**, which is selected from among



$R^{1.1}$ denotes -CN, cyclopropyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$R^{1.3}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, C_{1-4}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$R^{1.4}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, $-NH_2$, $-NH-C_{1-4}$-alkyl, $-N(C_{1-4}$-alkyl$)_2$, $-NH-C(O)-C_{1-4}$-alkyl, C_{1-6}-alkyl, or

(a) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^2 denotes H or CH_3,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, $-O-C_{1-4}$-alkyl, $-S-C_{1-4}$-alkyl,

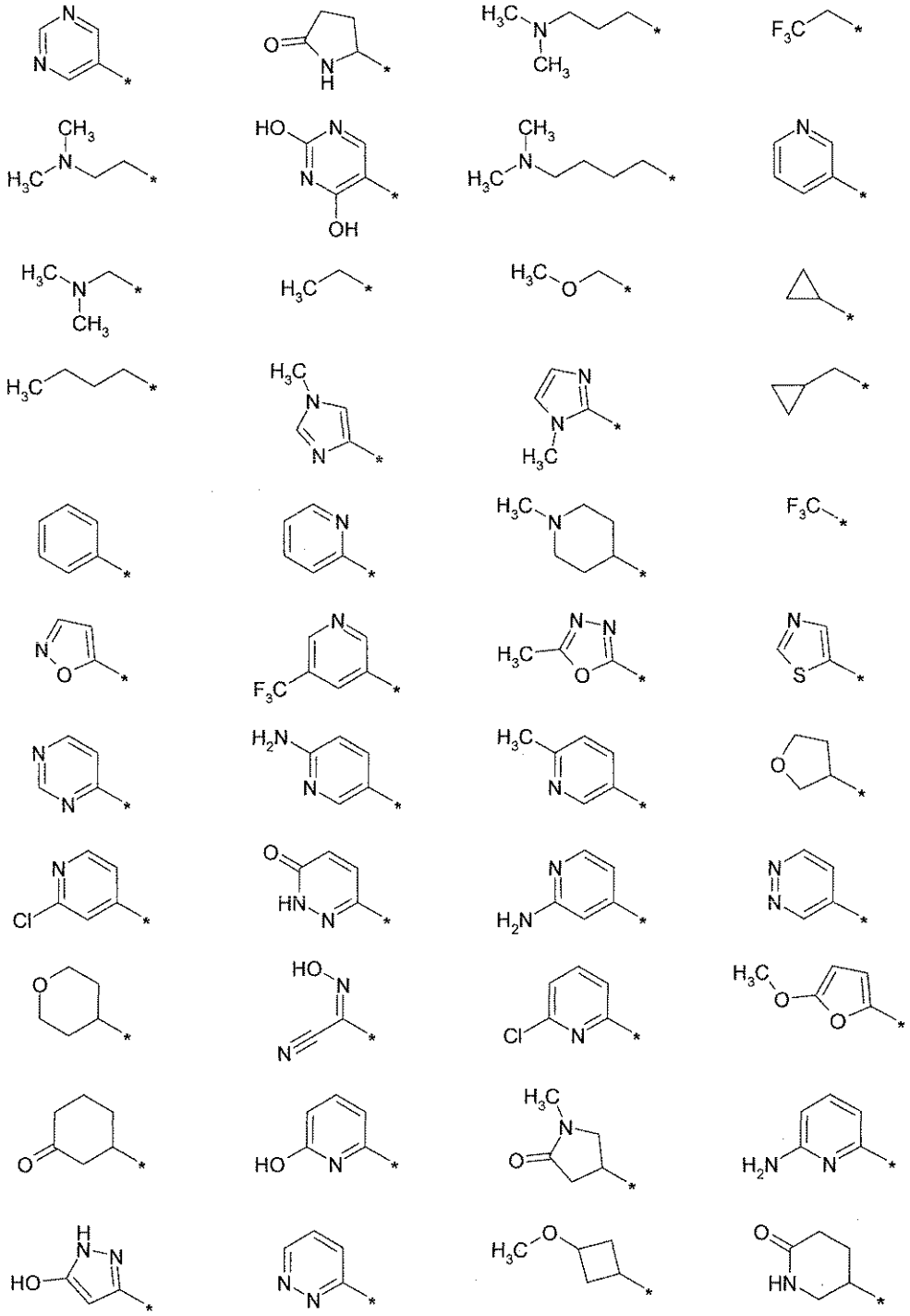
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

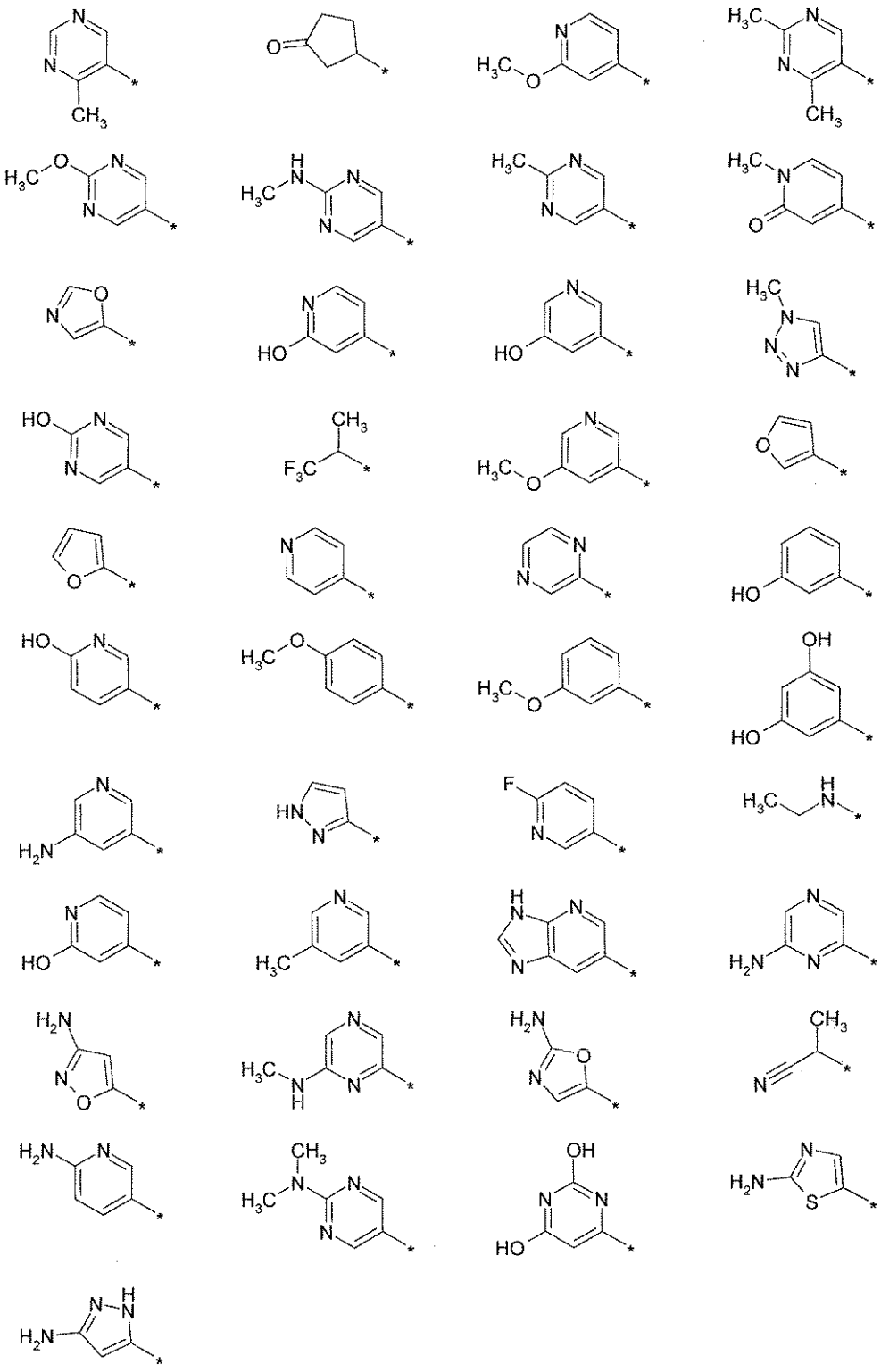
X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

21. Compounds of general formula **Ib** according to claim 17, wherein

R^1 denotes a group selected from





R^2 denotes H or CH_3,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

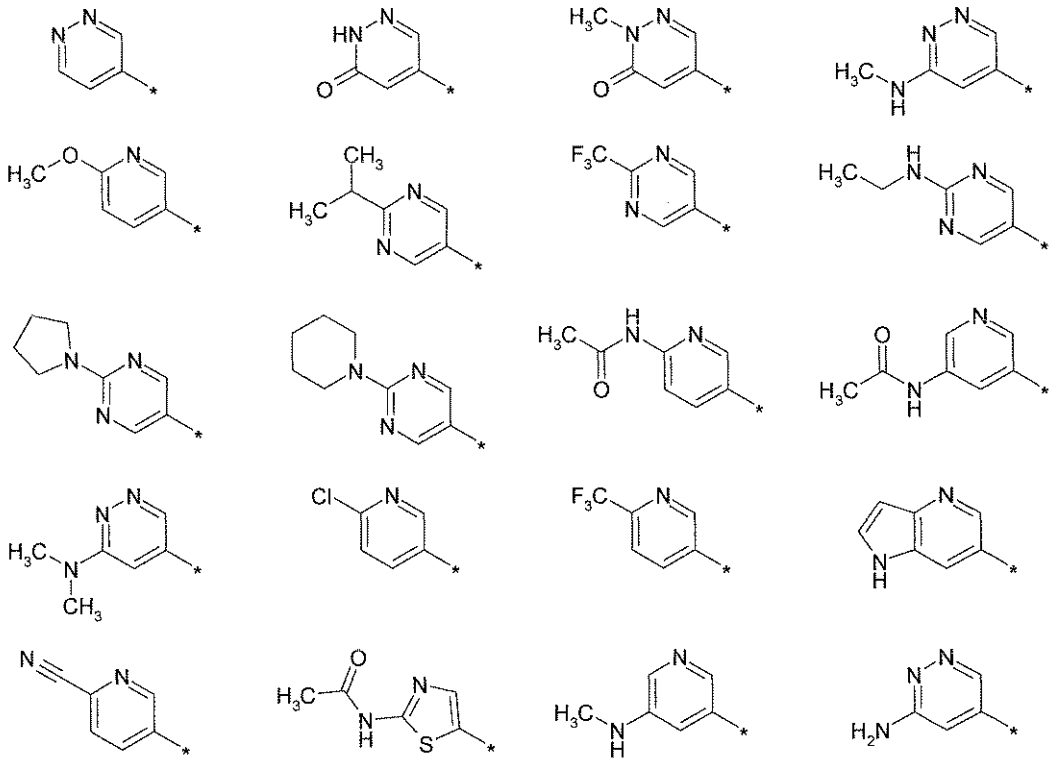
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

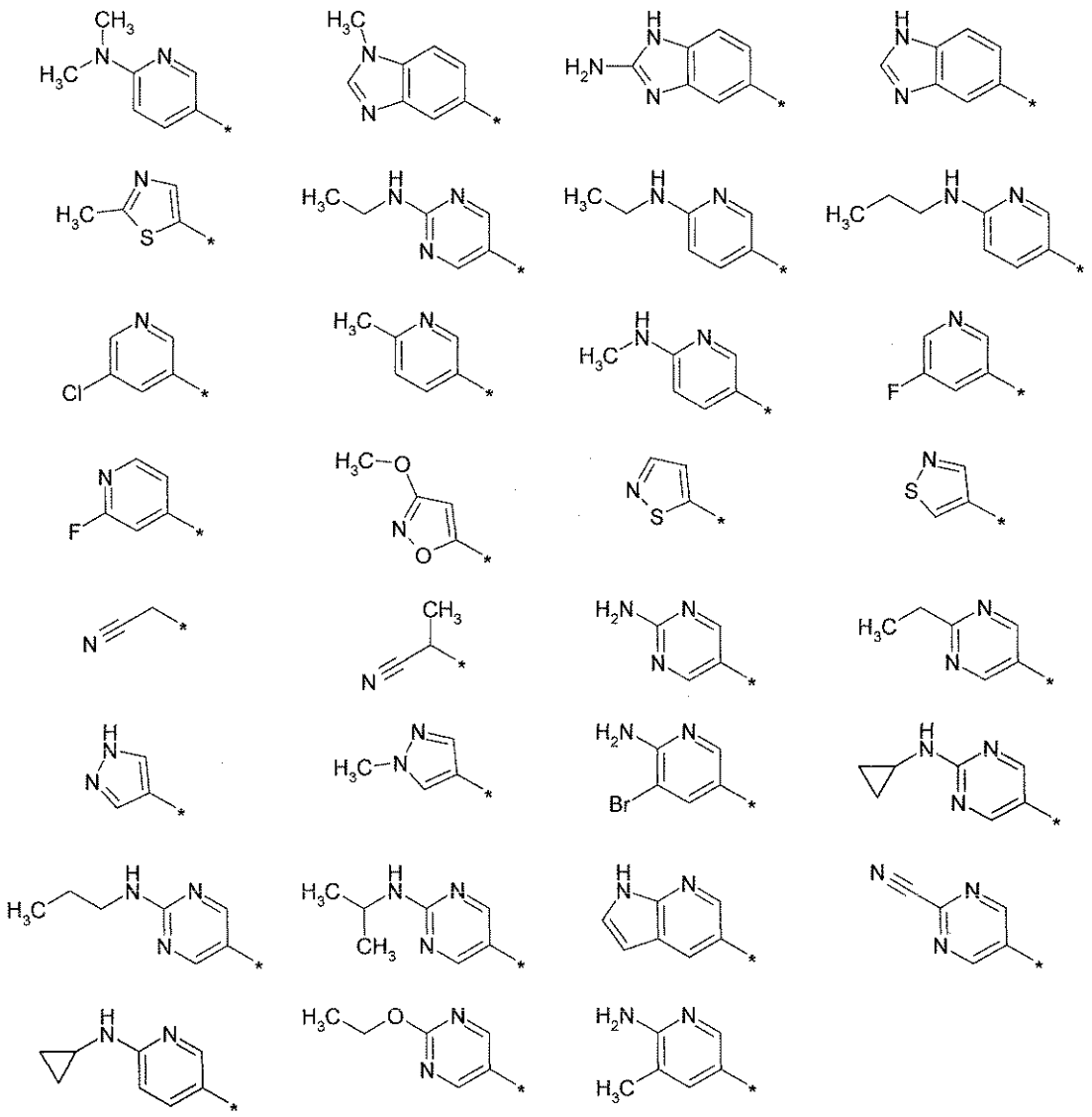
X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

22. Compounds of general formula **Ib** according to claim 19, wherein

R^1 denotes a group selected from





R^2 denotes H,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

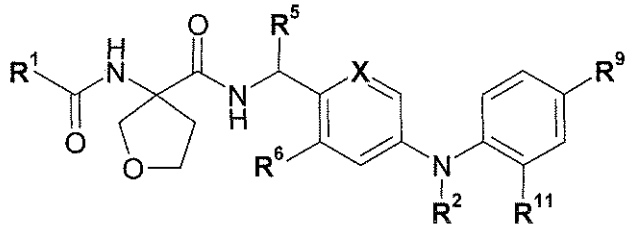
R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

$\mathbf{R^{11}}$ denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

23. Compounds of general formula **Ic**,



, (**Ic**)

wherein

$\mathbf{R^1}$ denotes

(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.3}}$,

(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.4}}$, which contains at least one N, O or S atom and which optionally additionally contains one, two or three further N-atoms,

(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms,

(e) a nine- or ten-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which contains one, two or three N-atoms,

(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, in which a $-CH_2-$ unit may be replaced by a -C(O)- group,

$\mathbf{R^{1.1}}$ denotes -CN, C_{3-6}-cycloalkyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$\mathbf{R^{1.3}}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, C_{1-6}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$\mathbf{R^{1.4}}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -NH-C(O)-C_{1-4}-alkyl, C_{1-6}-alkyl, or

~~(b)~~(a) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

$\mathbf{R^2}$ denotes H or CH_3,

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

$\mathbf{R^6}$ denotes H, F, Cl, Br or C_{1-4}-alkyl,

$\mathbf{R^7}$ denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

$\mathbf{R^9}$ denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

$\mathbf{R^{11}}$ denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

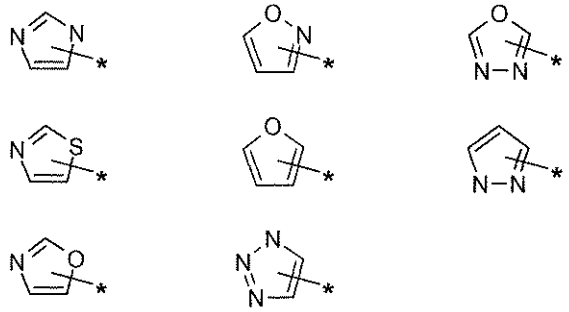
24. Compounds of general formula **Ic** according to claim 20, wherein

$\mathbf{R^1}$ denotes

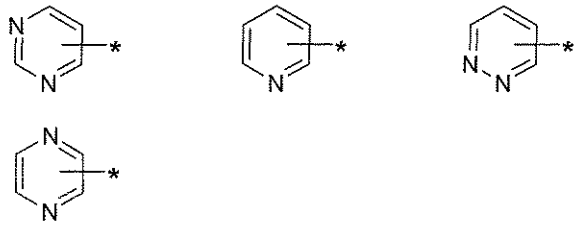
(a) a C_{1-6}-alkyl group optionally substituted by a group $\mathbf{R^{1.1}}$,

(b) a phenyl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.3}}$,

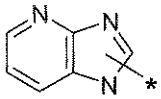
(c) a five-membered heteroaryl group optionally substituted by 1, 2 or 3 groups $\mathbf{R^{1.4}}$, which is selected from among



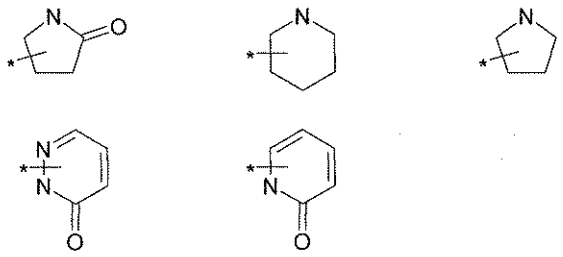
(d) a six-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



(e) a nine-membered heteroaryl group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



(f) a 5- or 6-membered heterocyclic group optionally substituted by 1 or 2 groups $\mathbf{R^{1.4}}$, which is selected from among



$\mathbf{R^{1.1}}$ denotes -CN, cyclopropyl, -OH, $-OCH_3$, $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$,

$\mathbf{R^{1.3}}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, C_{1-4}-alkyl or

(b) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms, and

$R^{1.4}$ denotes independently of one another

(a) F, Cl, Br, -OH, $-OCH_3$, $-OCF_3$, $-NH_2$, -NH-C_{1-4}-alkyl, -N(C_{1-4}-alkyl)$_2$, -NH-C(O)-C_{1-4}-alkyl, C_{1-6}-alkyl, or

(a) a C_{1-3}-alkyl group wherein each methylene group may be substituted by 1 or 2 fluorine atoms and each methyl group may be substituted by 1, 2 or 3 fluorine atoms,

R^2 denotes H or CH_3,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

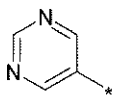
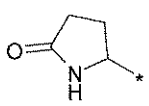
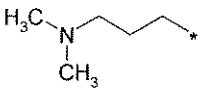
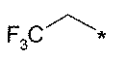
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

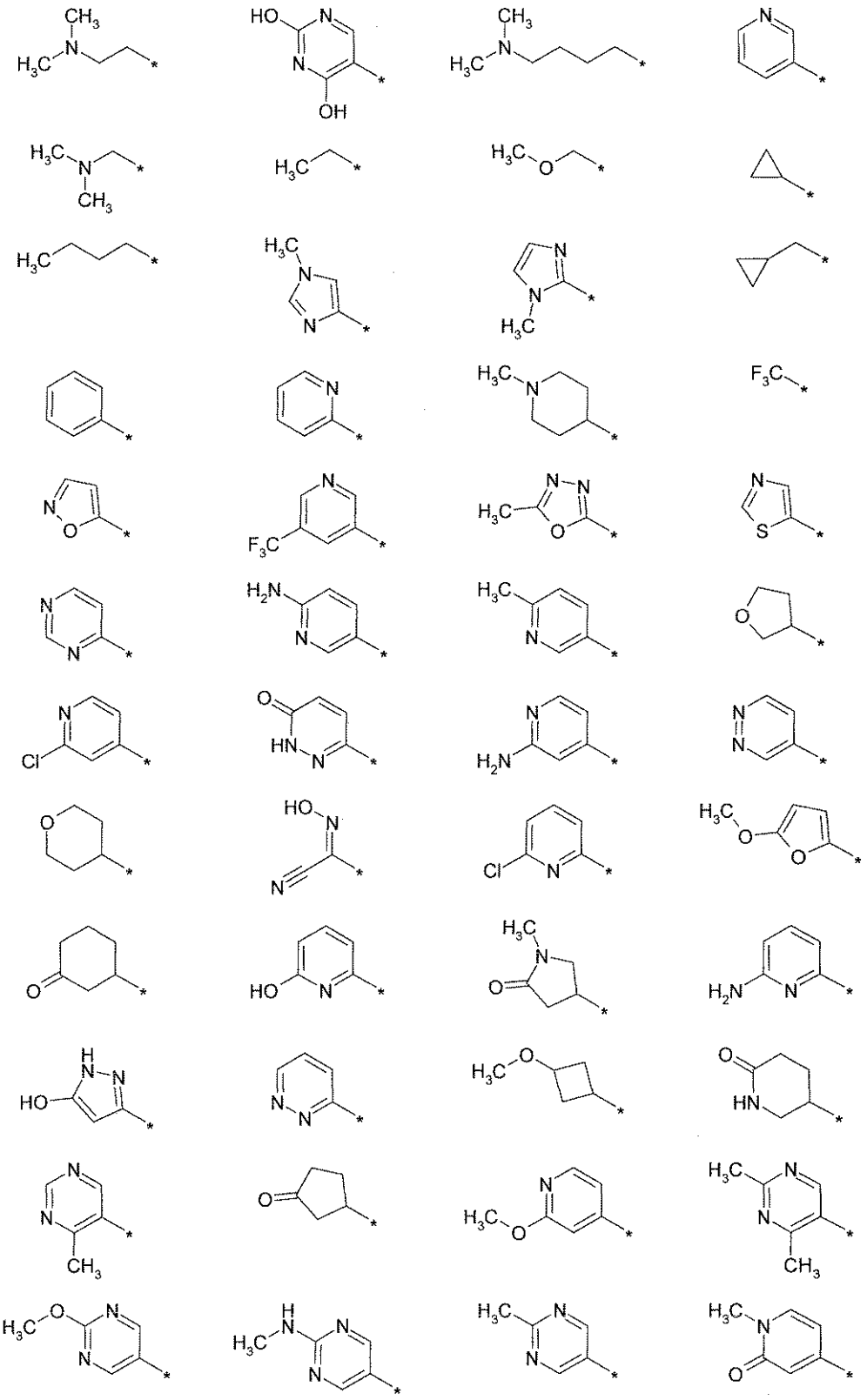
X denotes CH or N,

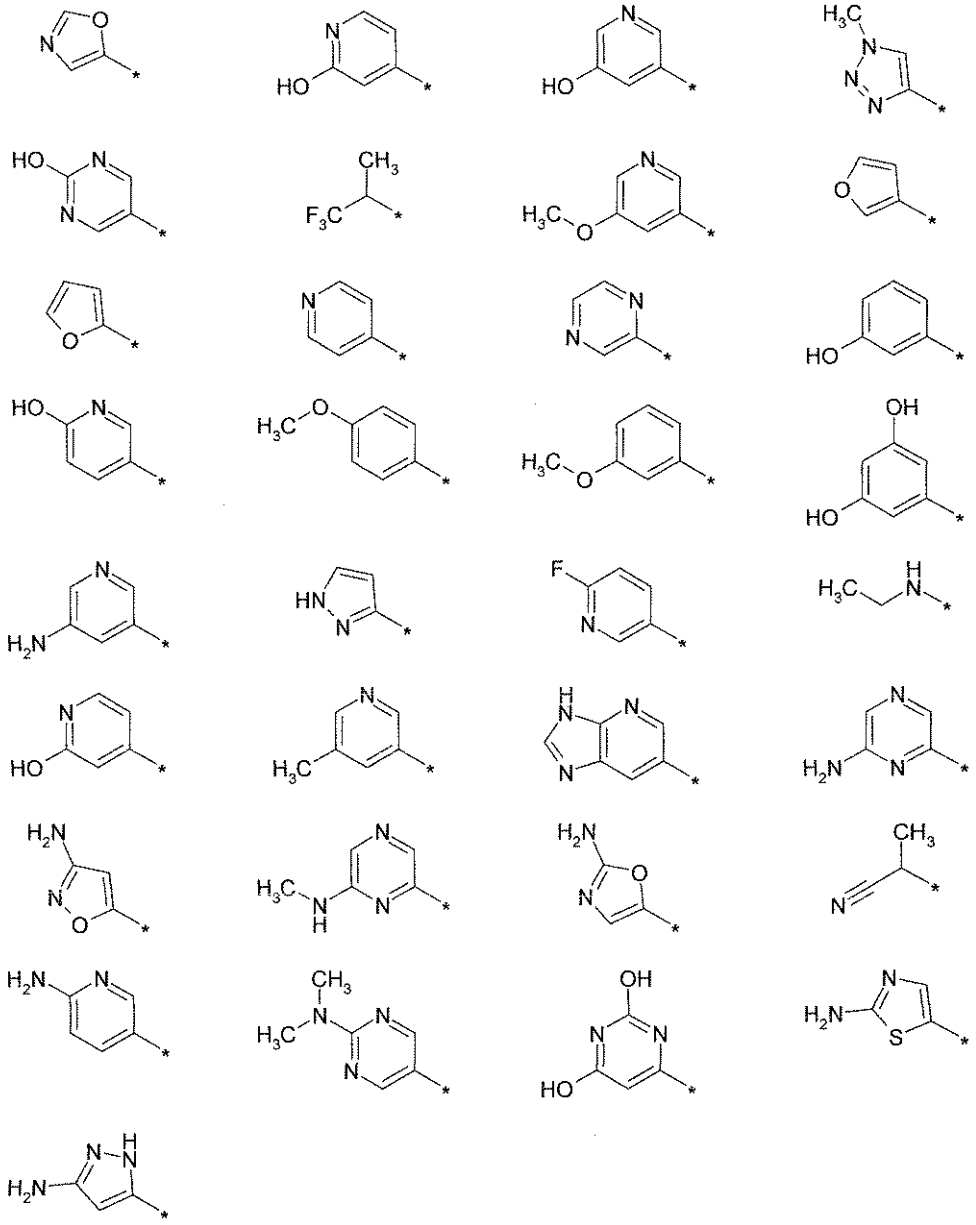
the enantiomers, the diastereomers, the mixtures and the salts thereof.

25. Compounds of general formula **Ic** according to claim 20, wherein

R^1 denotes a group selected from





R^2 denotes H or CH_3,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

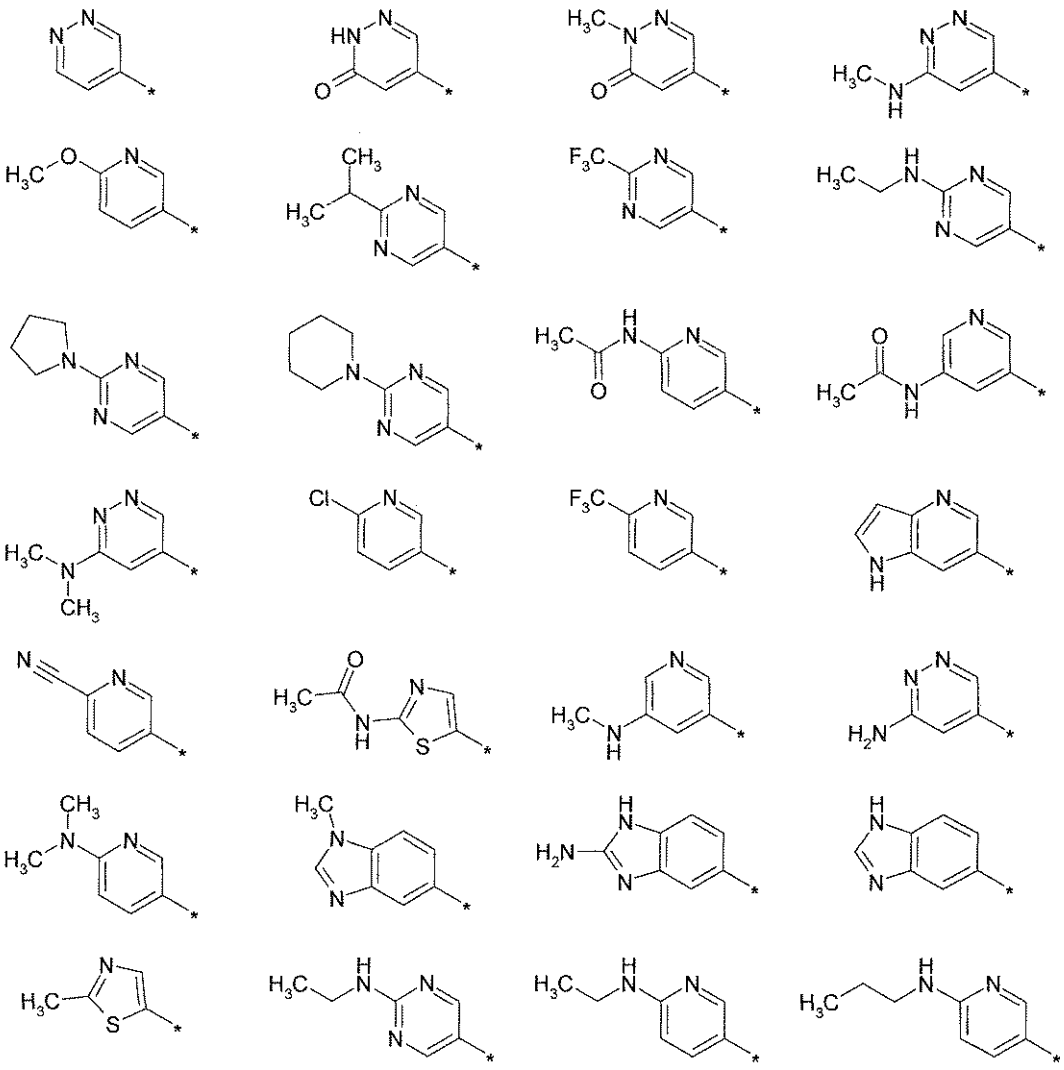
R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

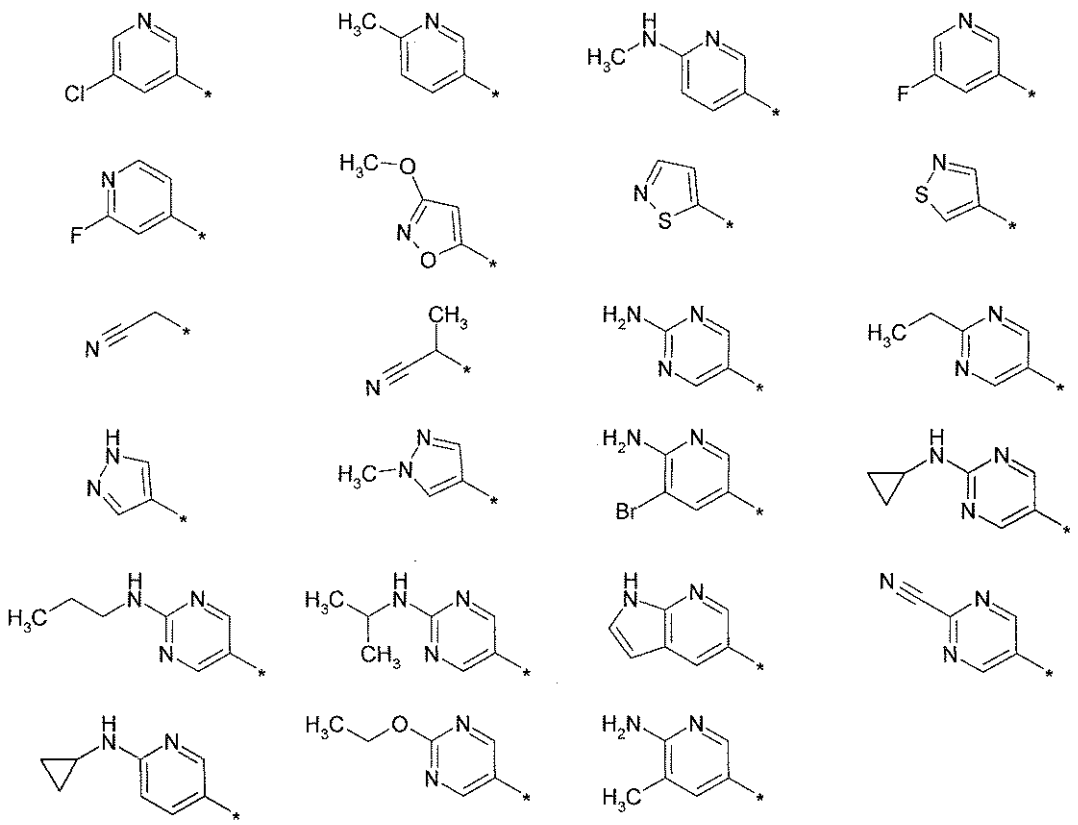
X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof.

26. Compounds of general formula **Ic** according to claim 23, wherein

R^1 denotes a group selected from





R^2 denotes H or CH_3,

R^5 denotes H or CH_3,

R^6 denotes H, F, Cl or methyl,

R^7 denotes H, F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2,

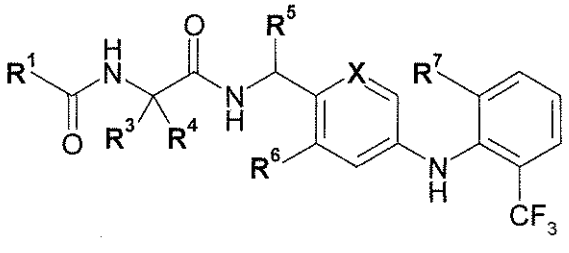
R^9 denotes F, Cl, Br, C_{1-4}-alkyl, -O-C_{1-4}-alkyl, -S-C_{1-4}-alkyl,

R^{11} denotes F, Cl, Br, -CN, C_{1-4}-alkyl, CF_3, CHF_2, and

X denotes CH or N,

the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

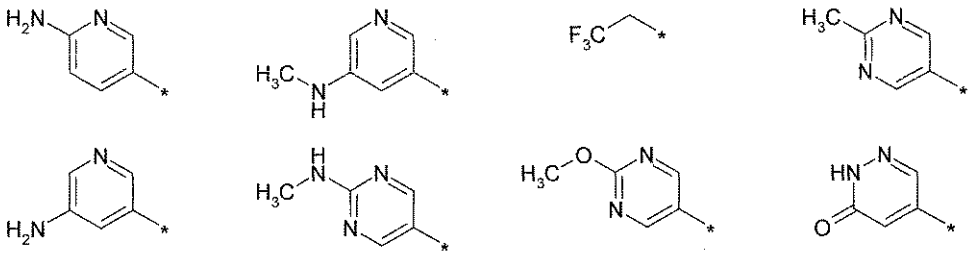
27. Compounds of general formula **Id**,



, (**Id**)

wherein

R^1 denotes a group selected from



R^3 and **R^4** together with the carbon atom to which they are attached denote a C_{3-6}-cycloalkylene group wherein a $-CH_2$ unit may be replaced by an oxygen atom,

R^5 denotes H or CH_3,

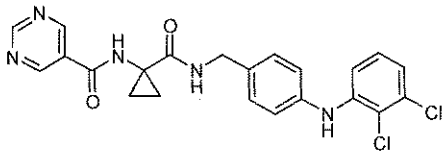
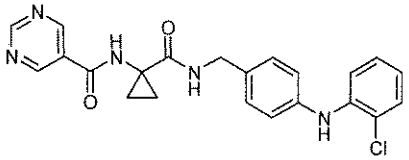
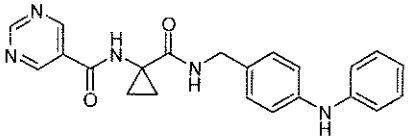
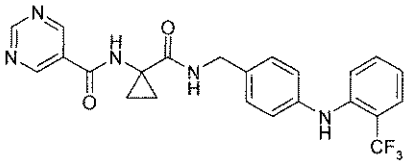
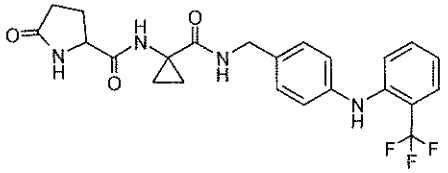
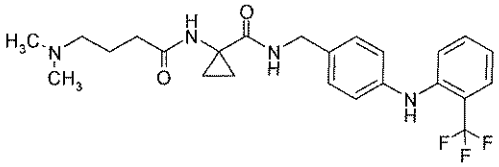
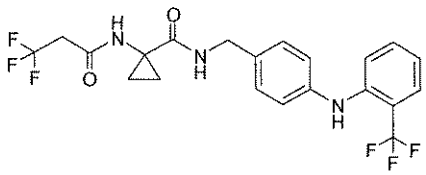
R^6 denotes Cl or CH_3,

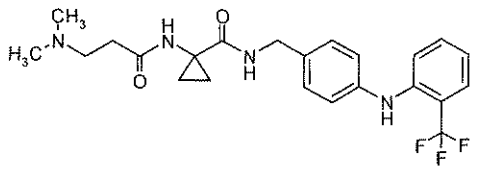
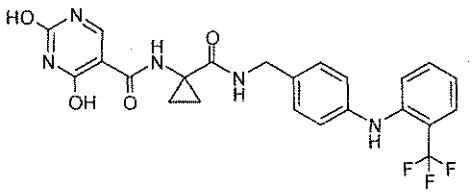
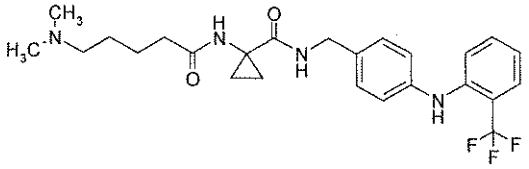
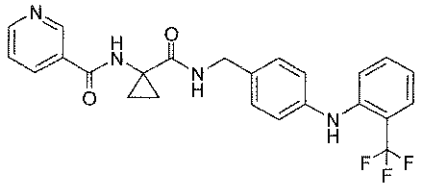
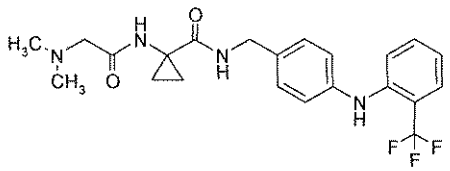
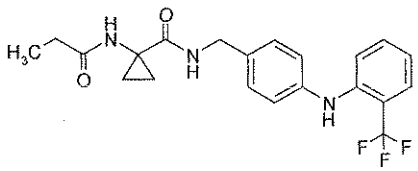
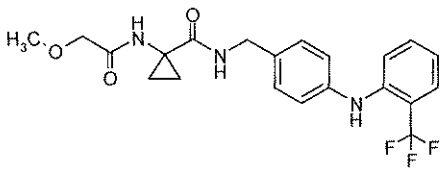
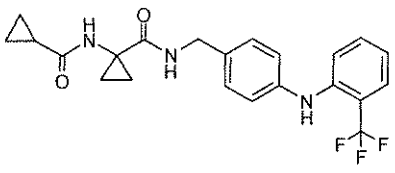
R^7 denotes H or F,

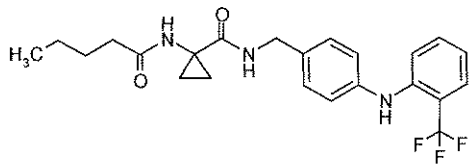
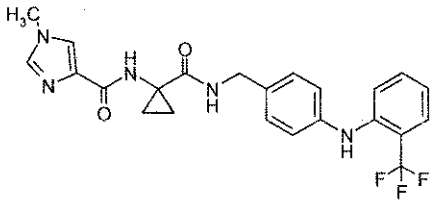
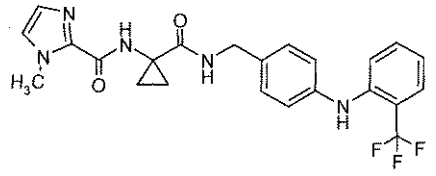
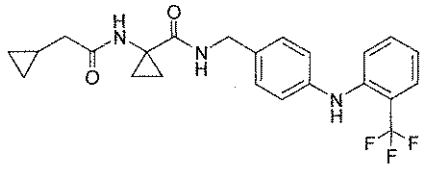
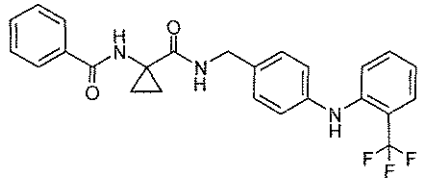
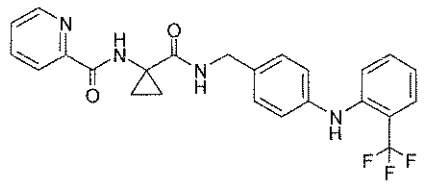
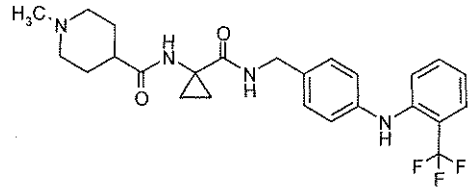
X denotes CH or N,

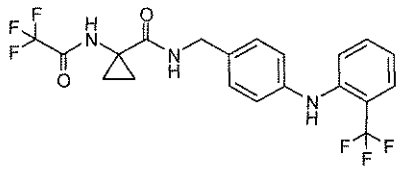
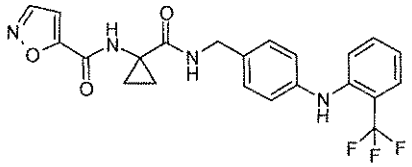
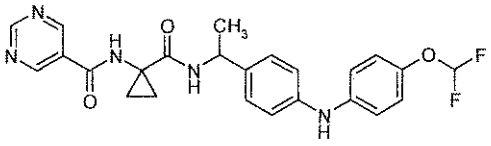
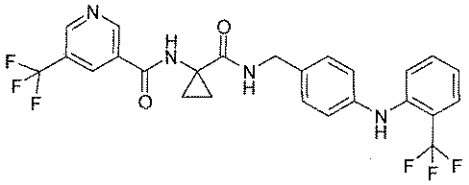
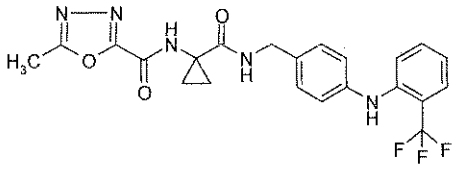
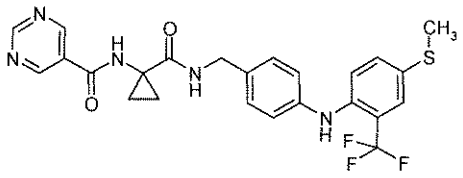
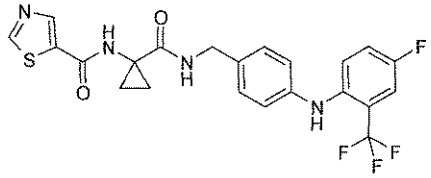
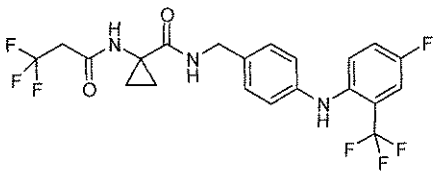
the enantiomers, the diastereomers, the mixtures and the salts thereof, particularly the physiologically acceptable salts thereof with organic or inorganic acids or bases.

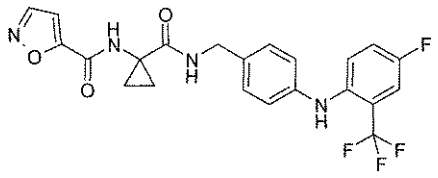
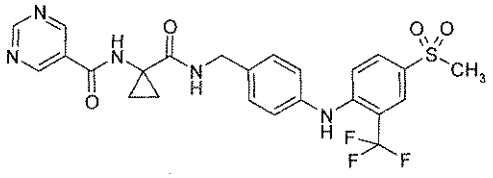
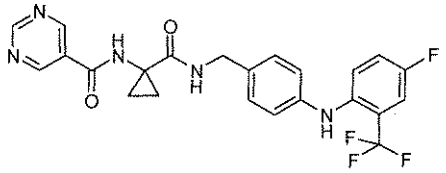
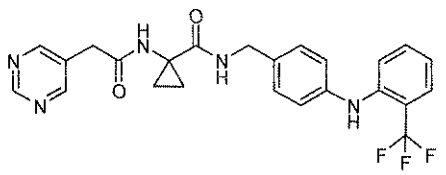
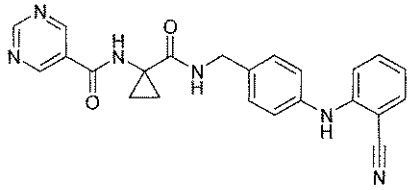
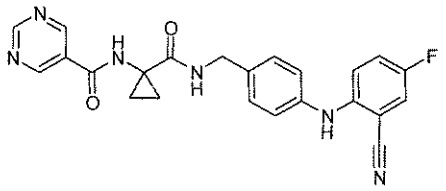
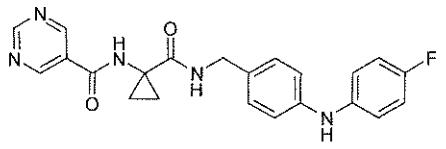
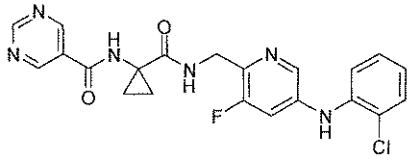
28. The following compounds of general formula I according to claim 1:

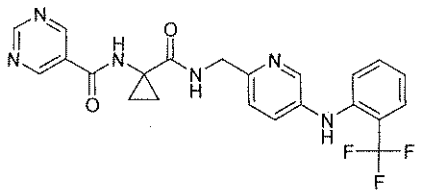
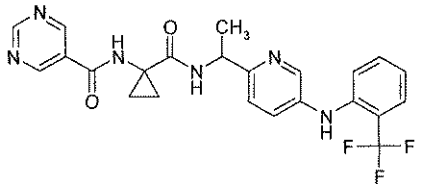
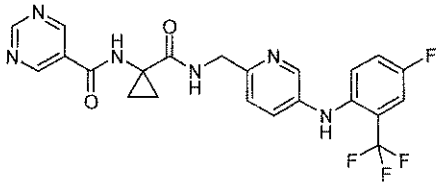
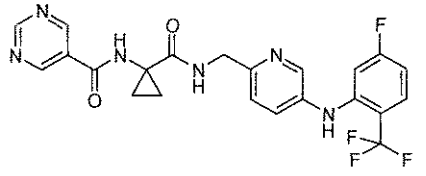
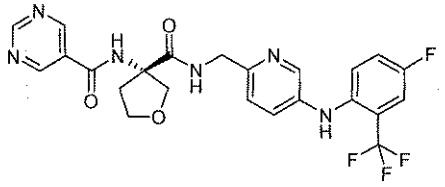
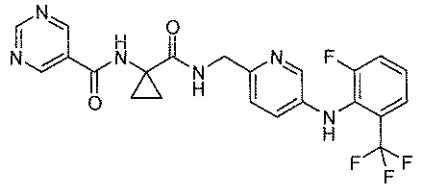
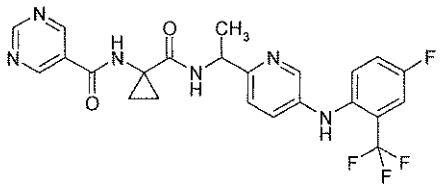
No.	Structure
(1)	
(2)	
(3)	
(4)	
(5)	
(6)	
(7)	

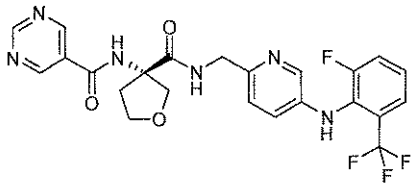
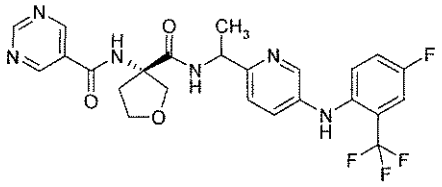
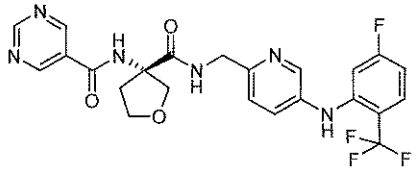
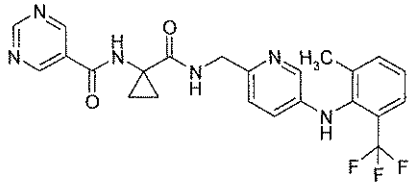
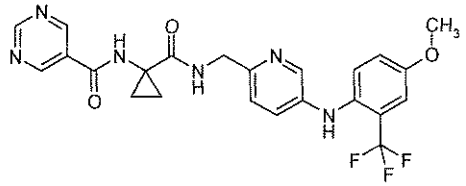
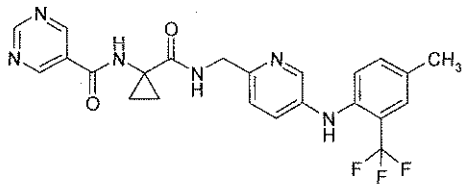
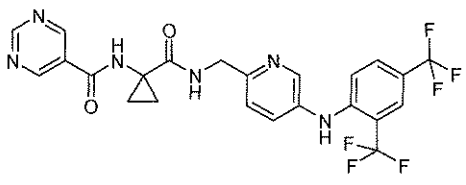
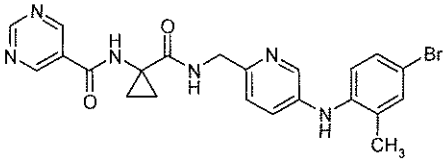
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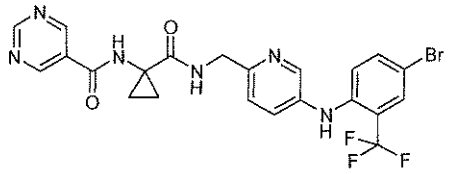
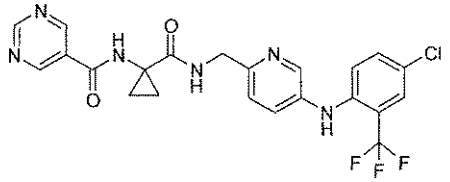
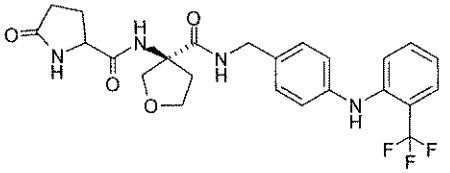
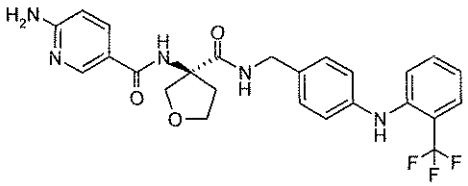
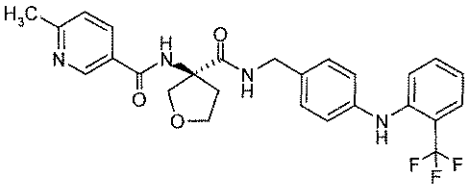
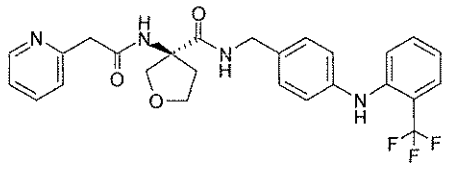
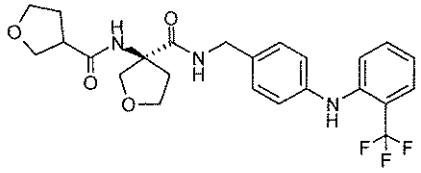
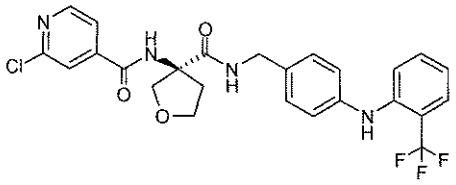
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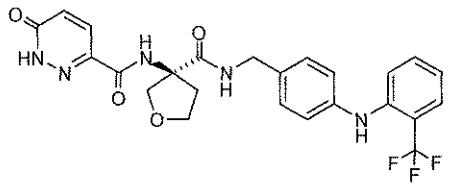
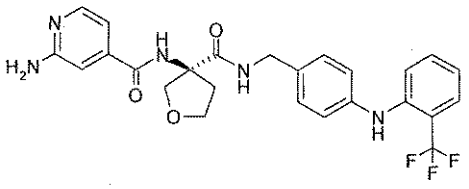
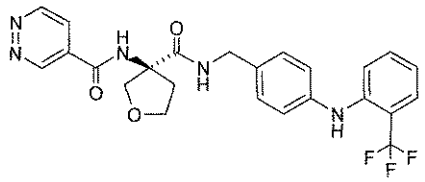
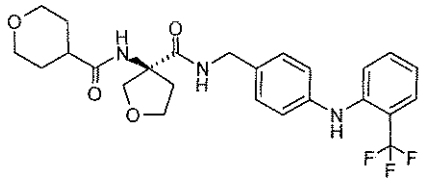
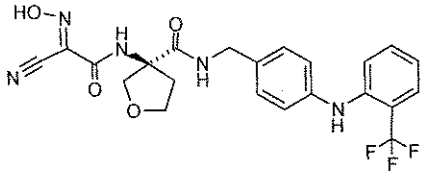
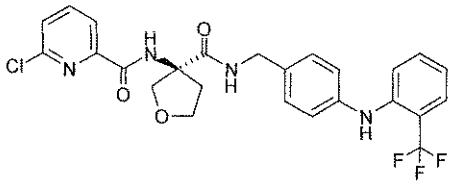
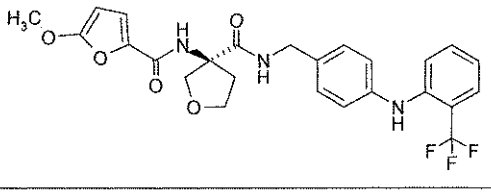
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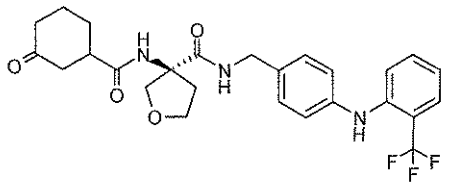
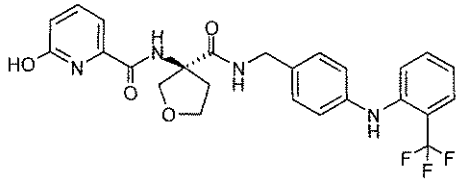
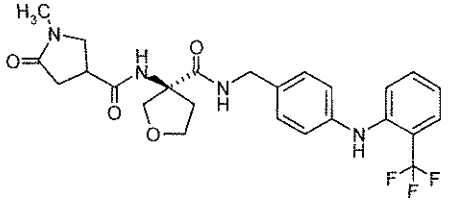
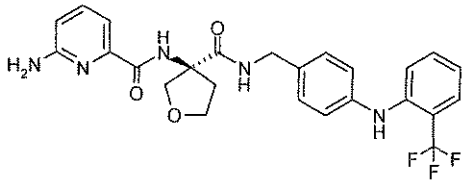
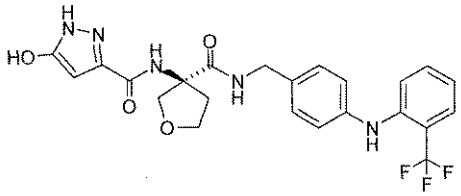
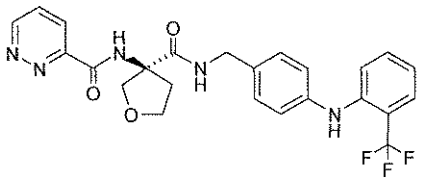
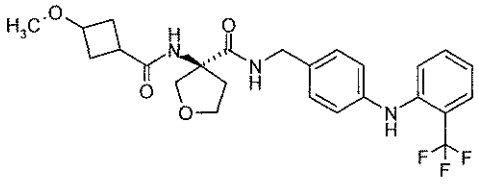
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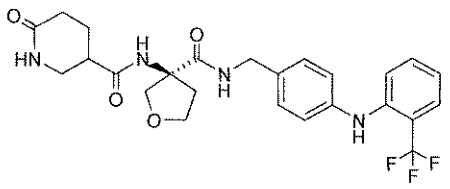
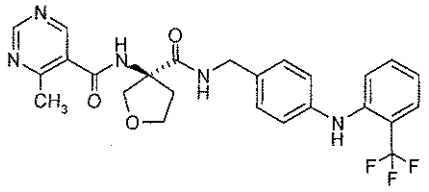
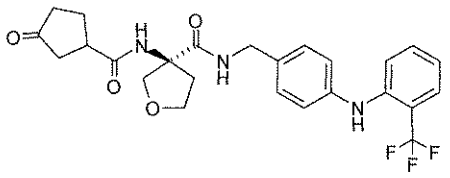
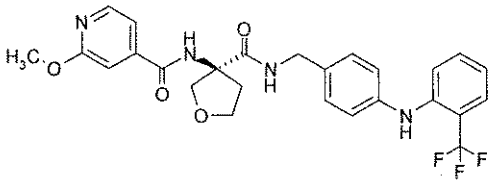
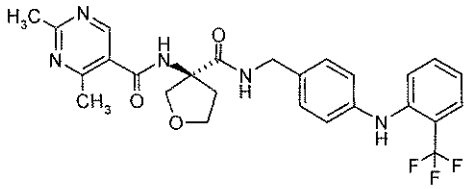
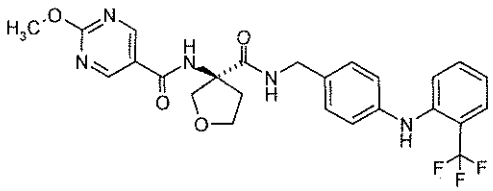
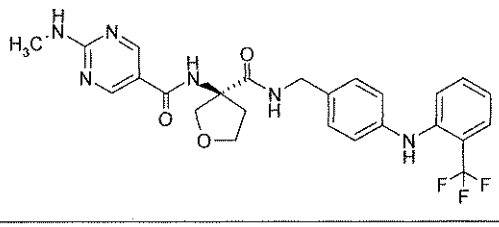
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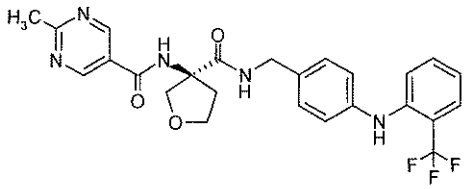
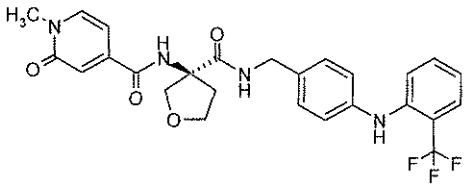
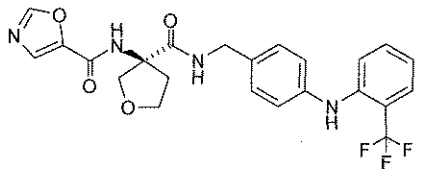
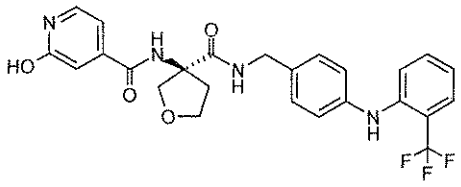
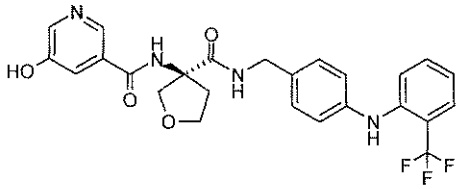
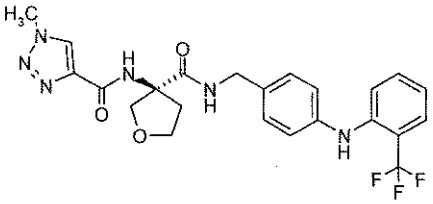
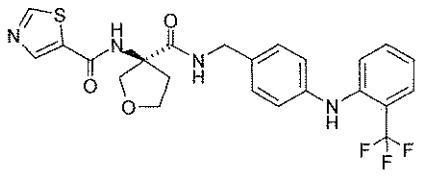
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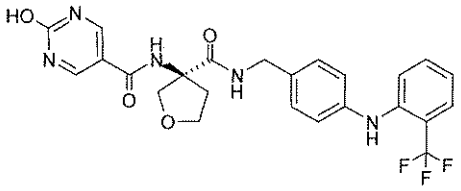
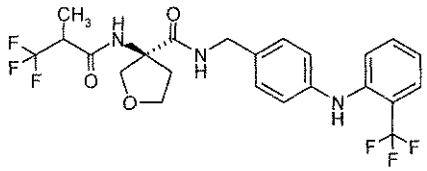
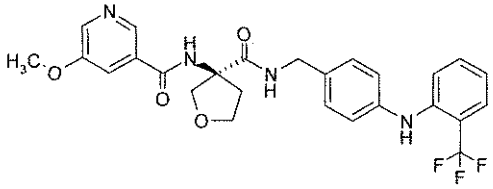
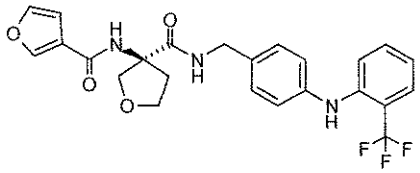
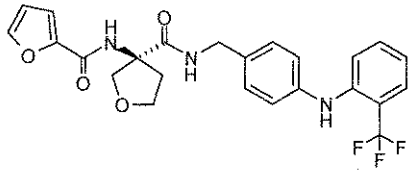
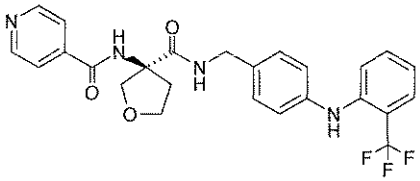
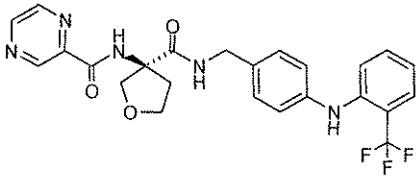
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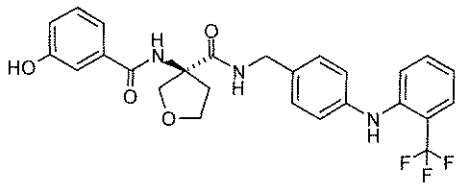
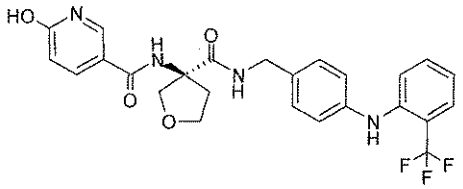
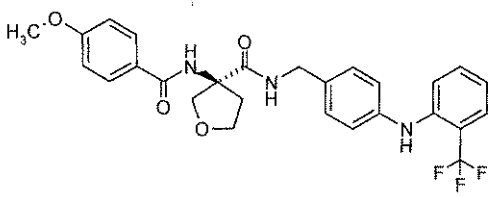
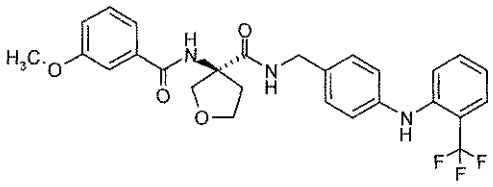
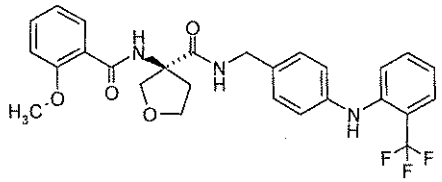
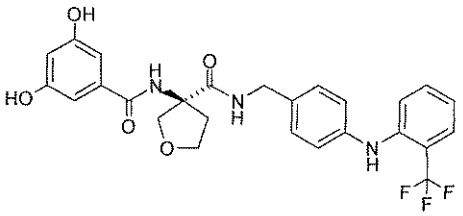
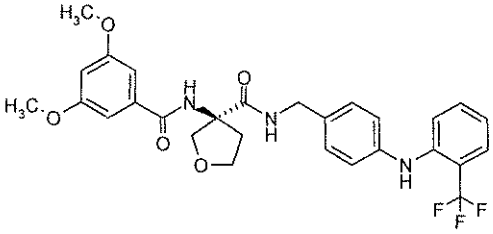
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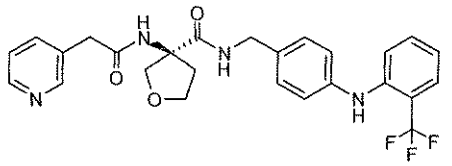
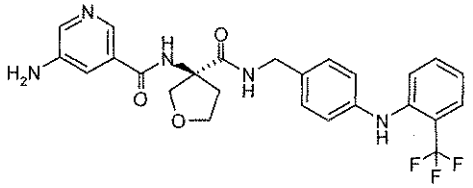
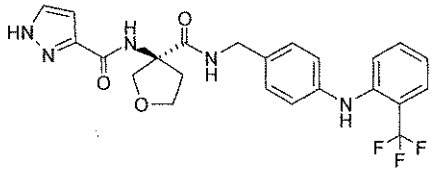
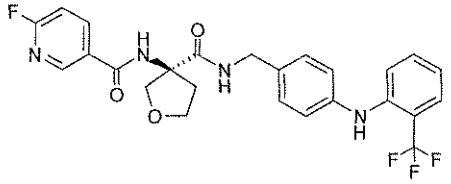
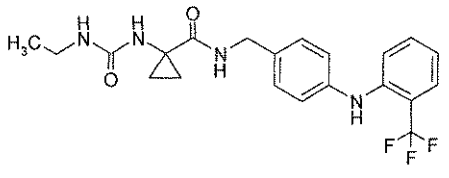
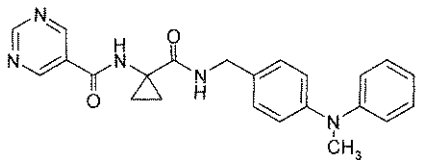
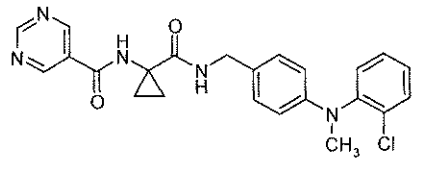
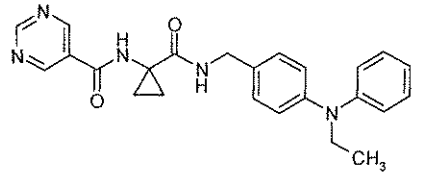
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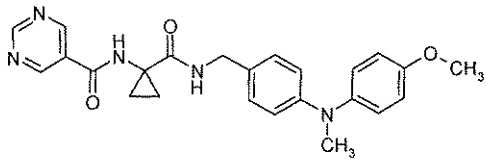
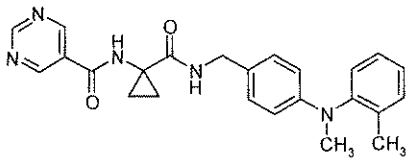
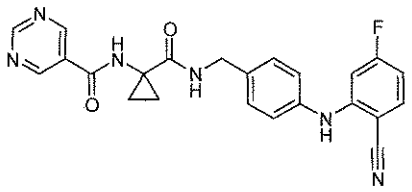
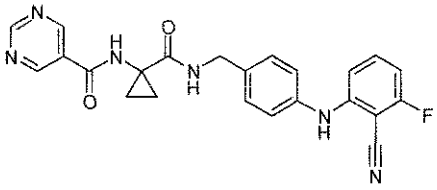
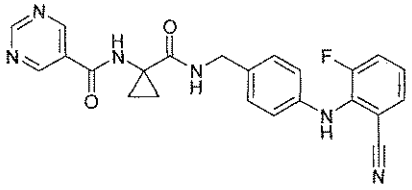
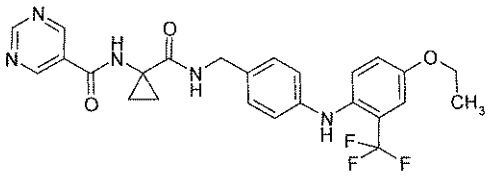
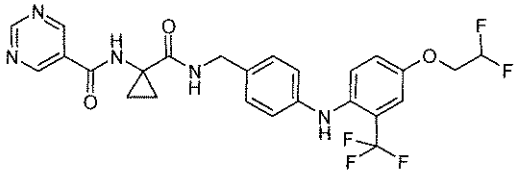
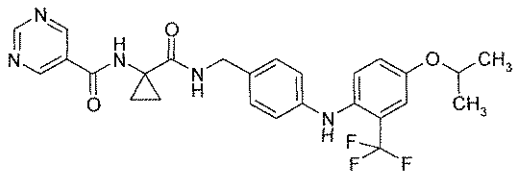
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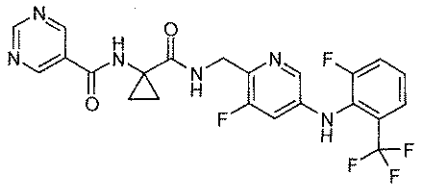
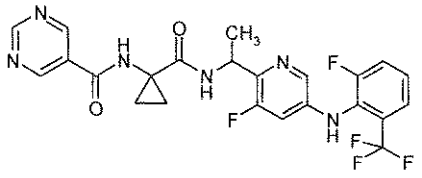
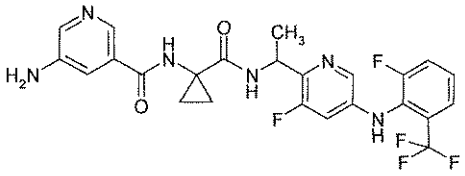
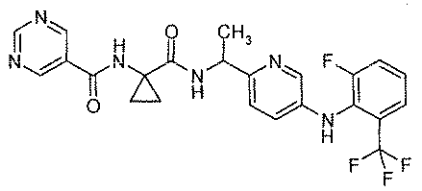
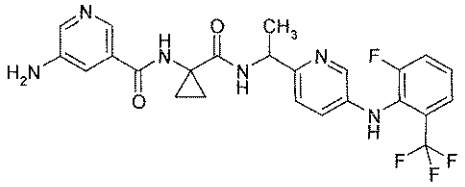
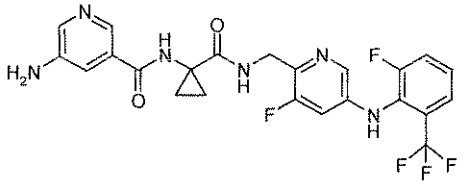
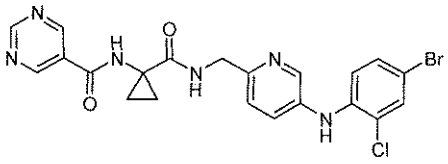
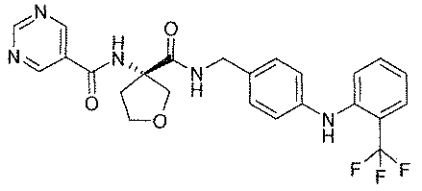
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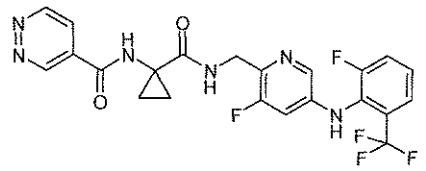
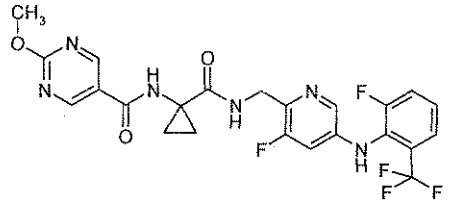
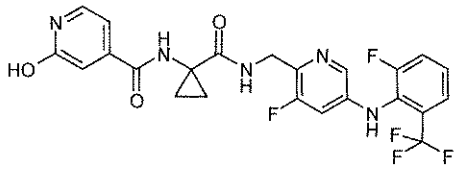
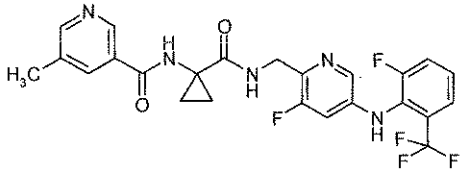
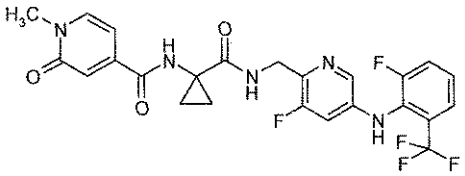
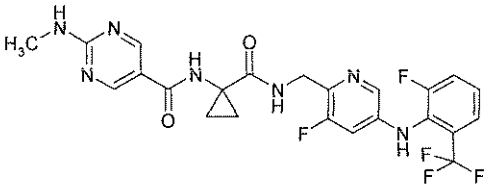
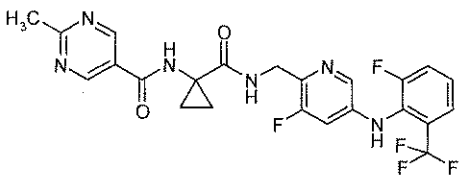
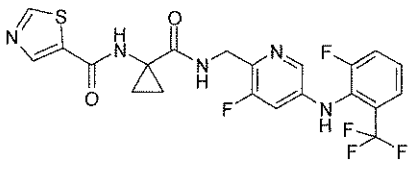
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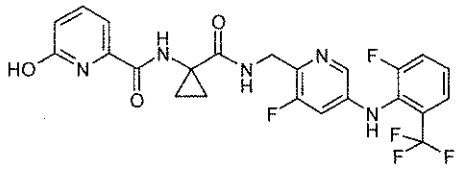
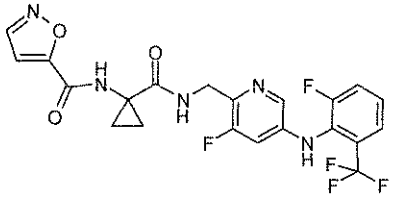
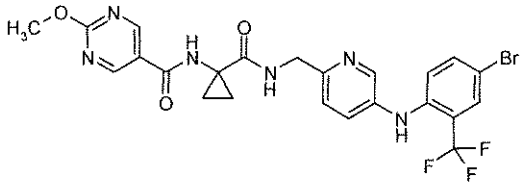
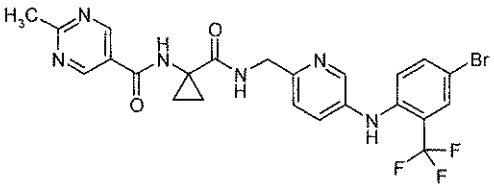
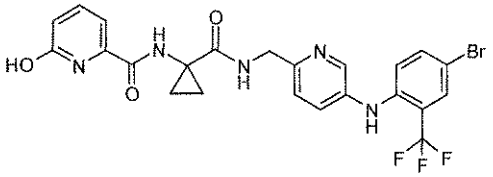
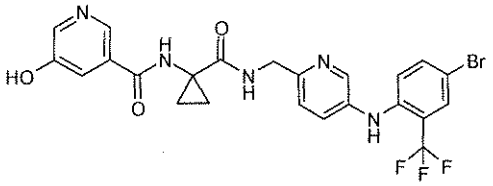
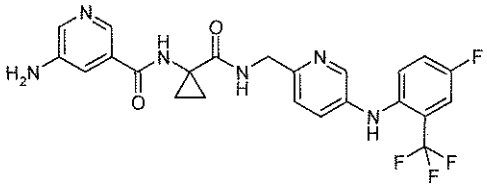
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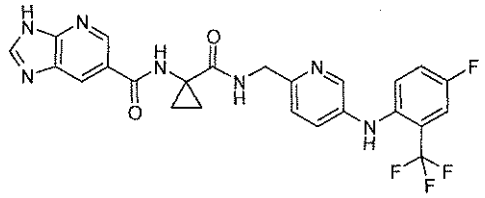
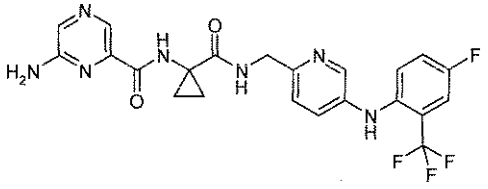
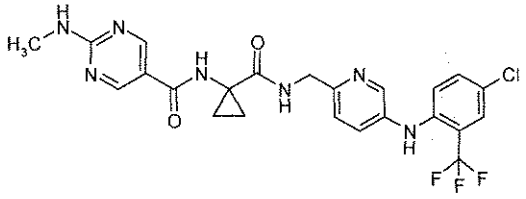
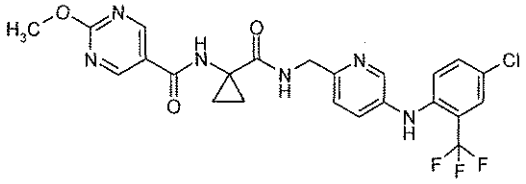
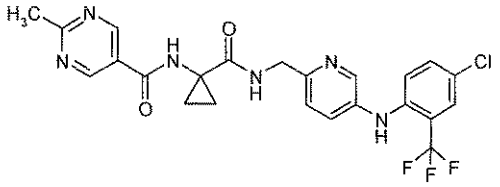
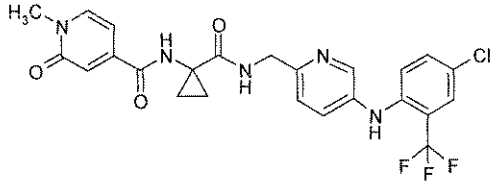
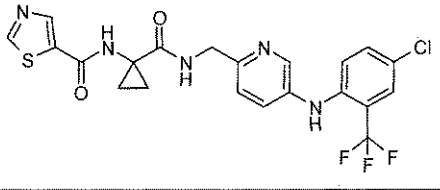
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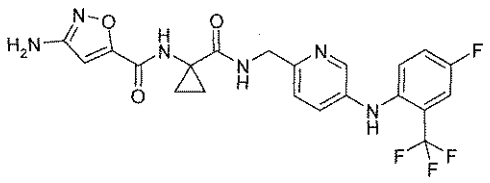
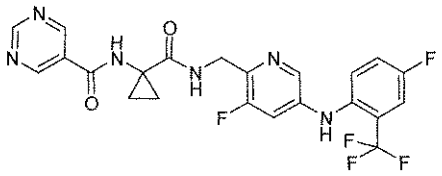
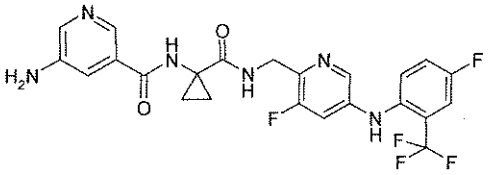
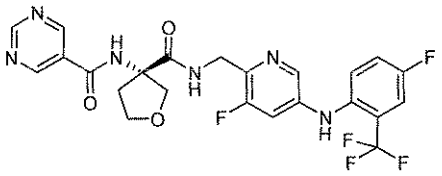
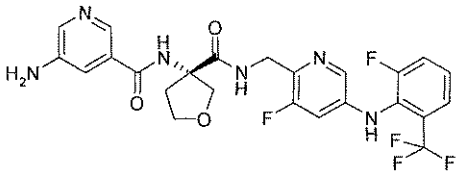
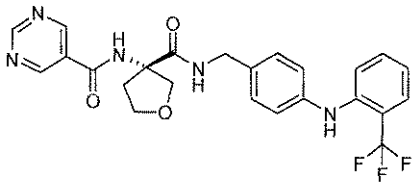
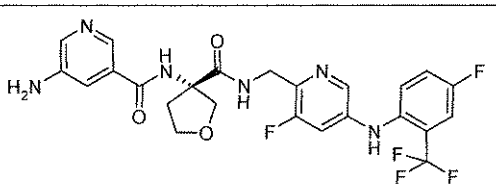
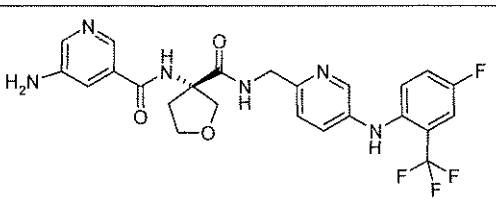
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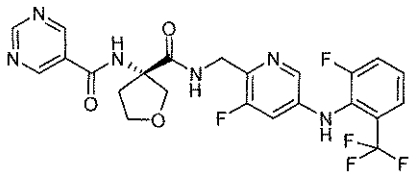
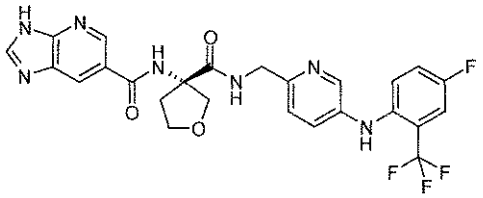
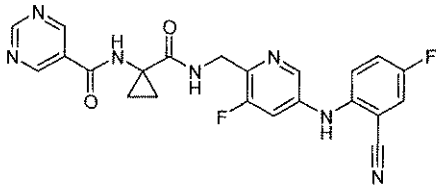
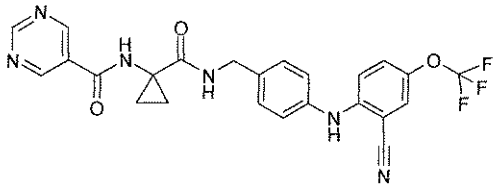
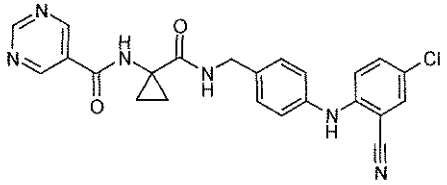
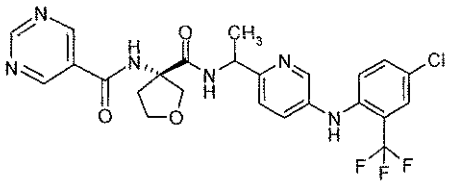
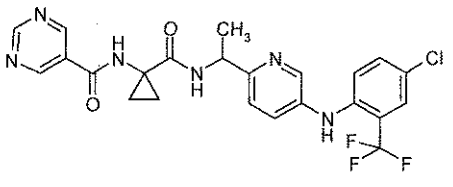
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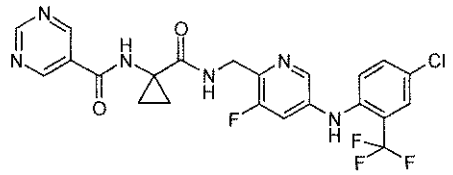
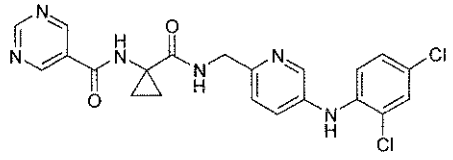
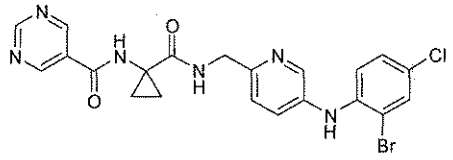
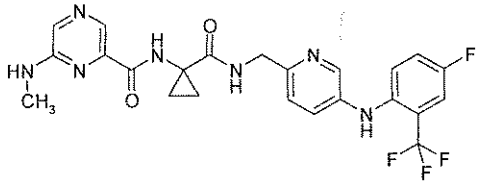
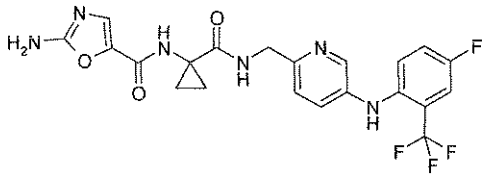
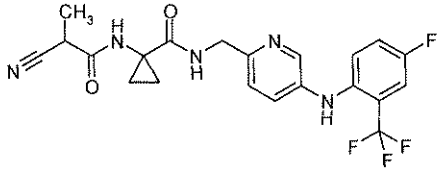
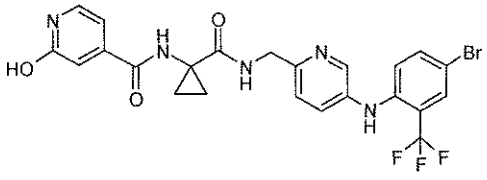
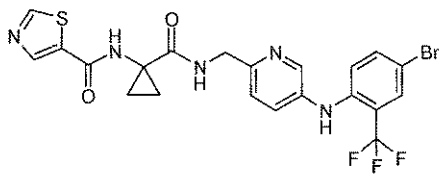
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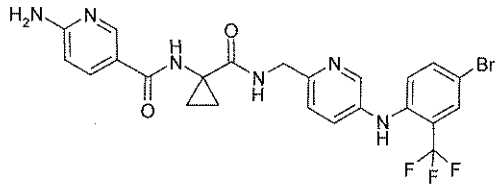
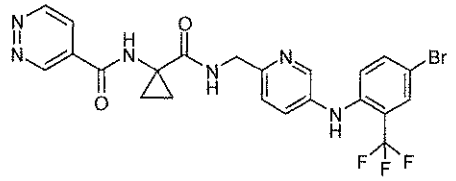
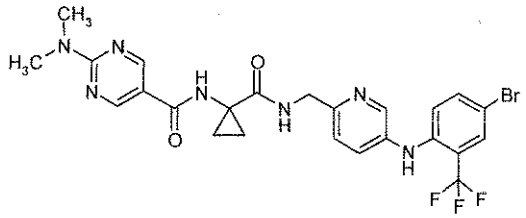
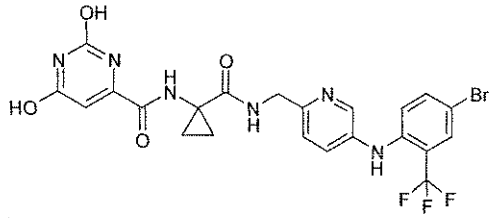
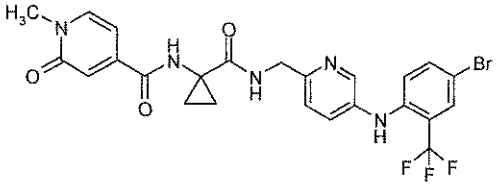
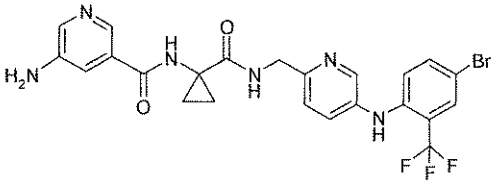
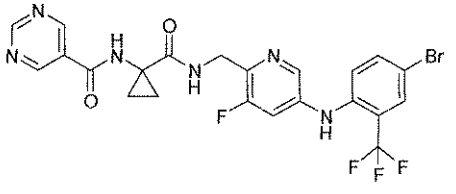
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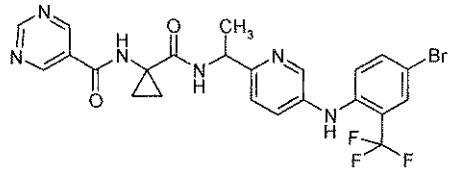
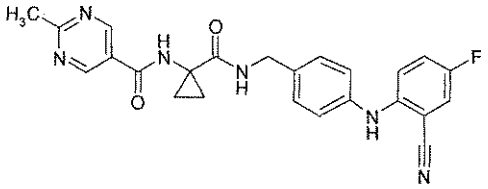
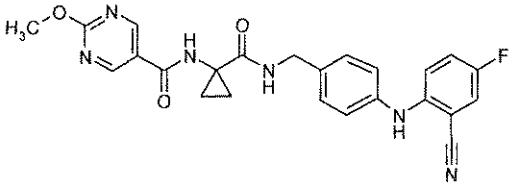
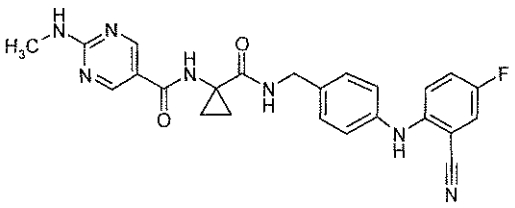
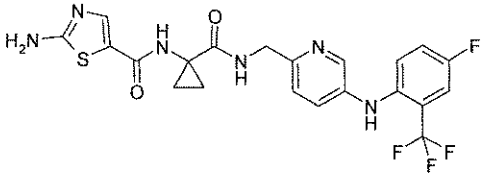
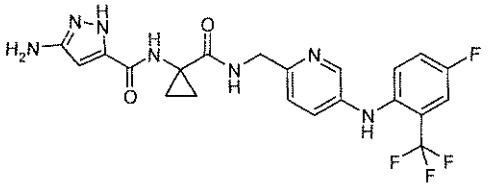
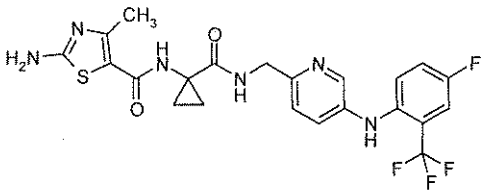
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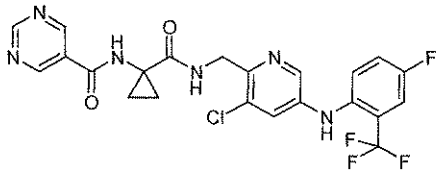
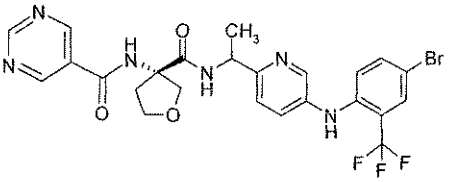
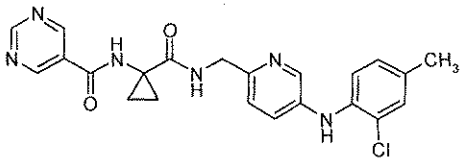
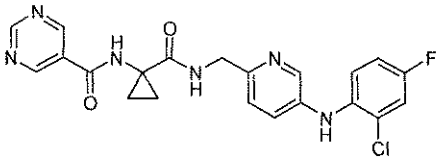
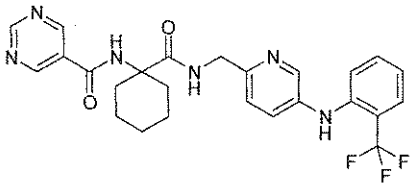
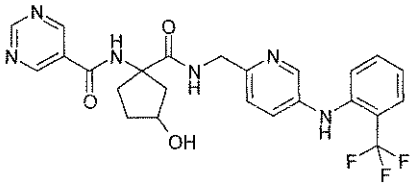
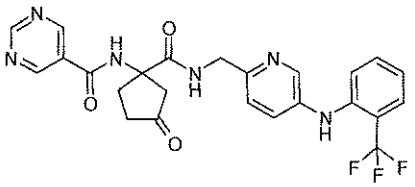
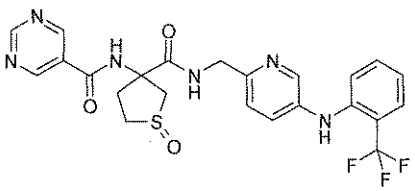
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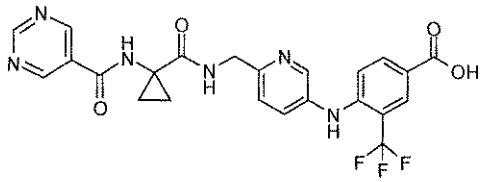
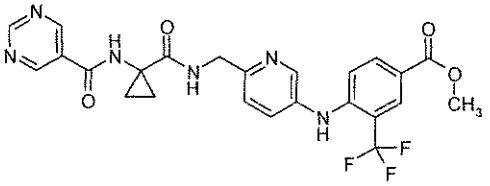
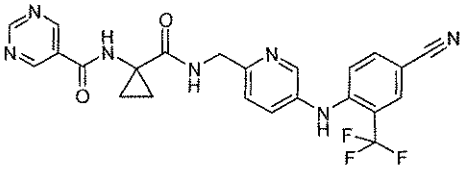
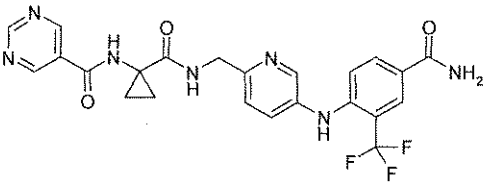
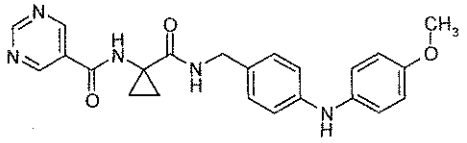
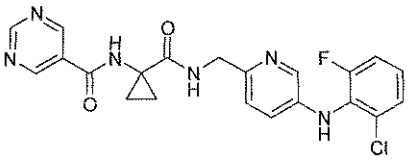
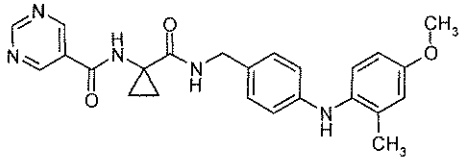
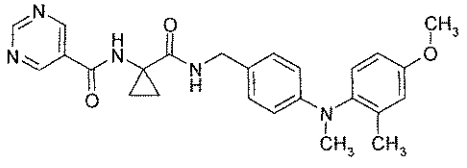
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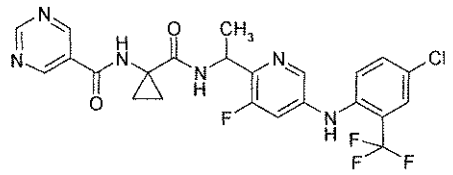
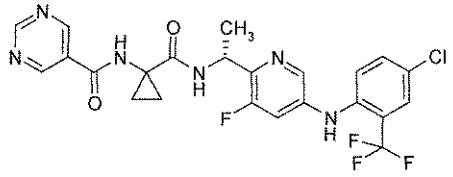
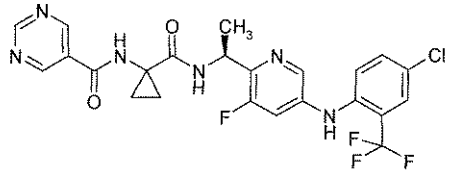
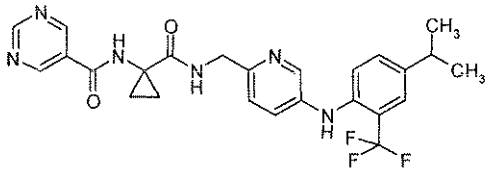
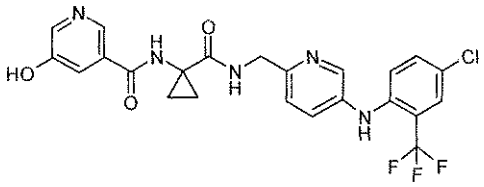
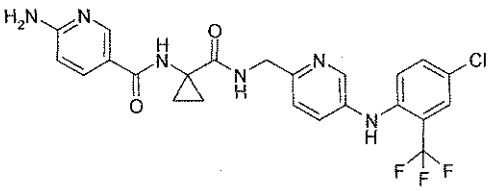
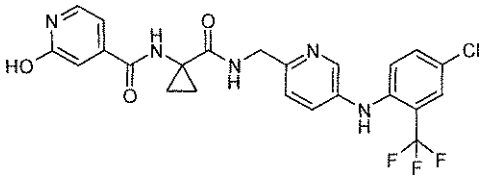
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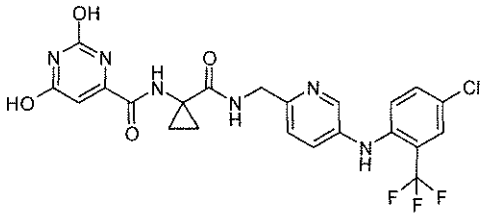
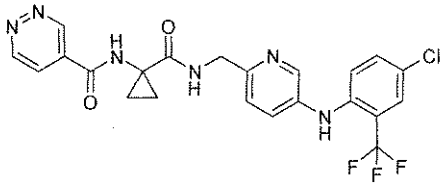
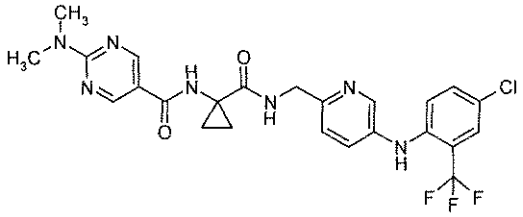
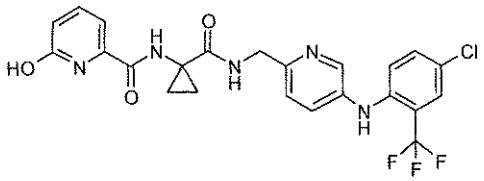
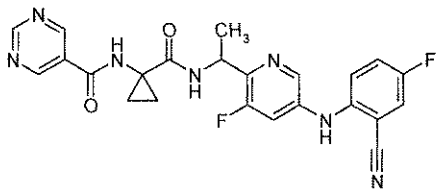
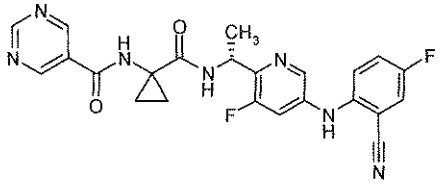
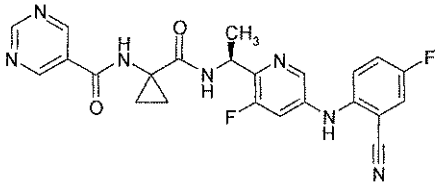
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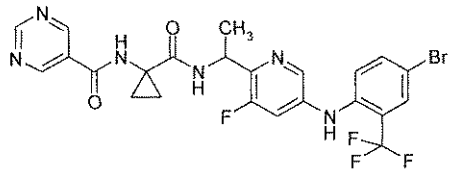
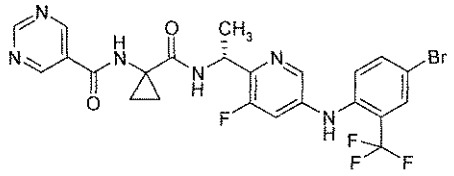
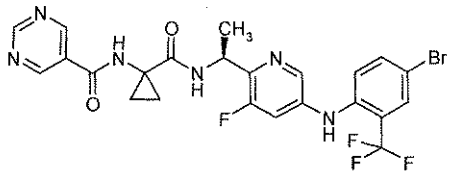
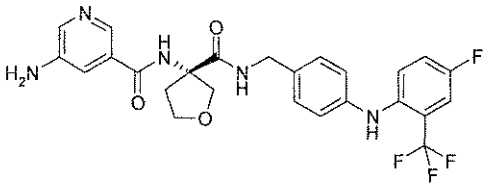
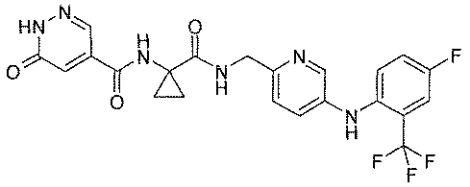
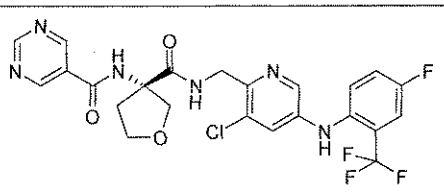
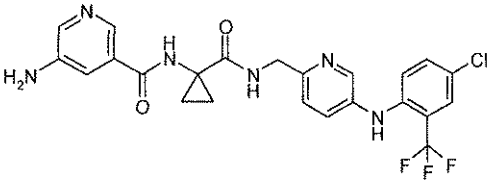
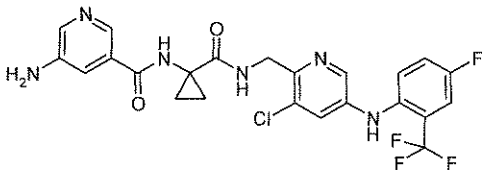
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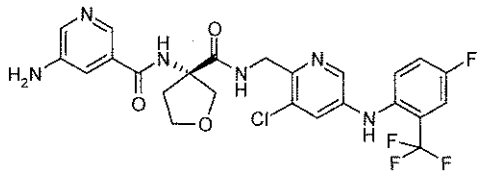
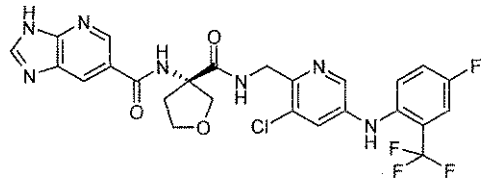
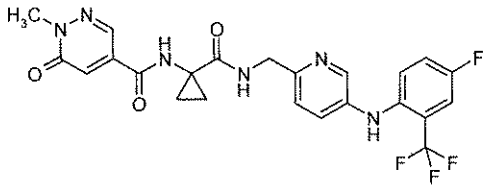
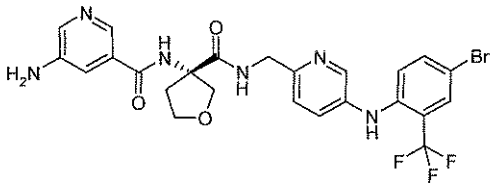
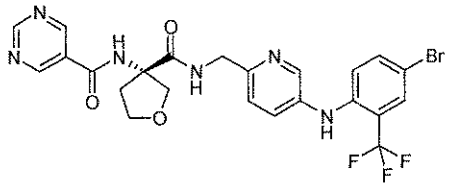
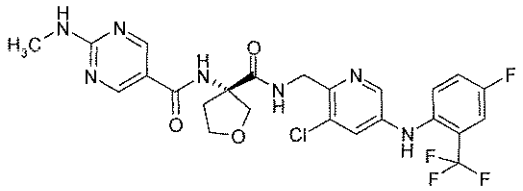
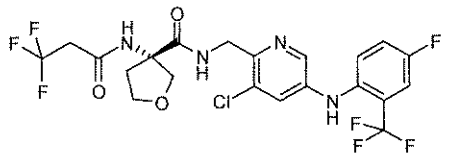
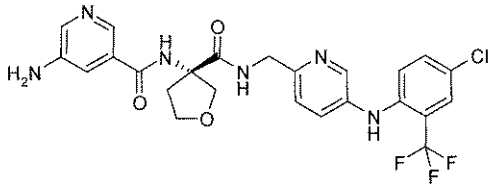
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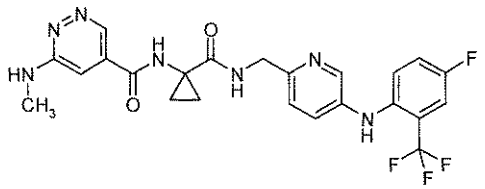
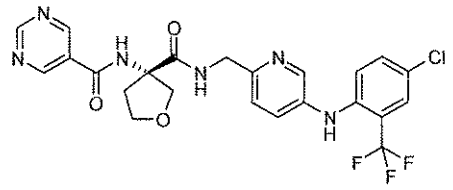
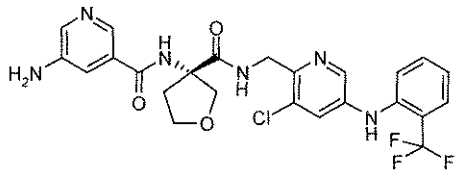
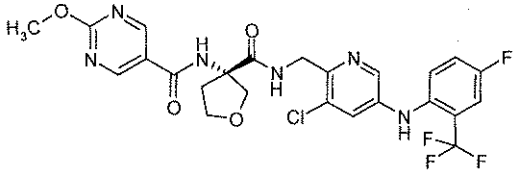
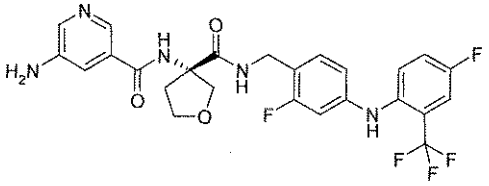
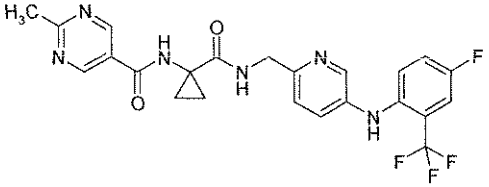
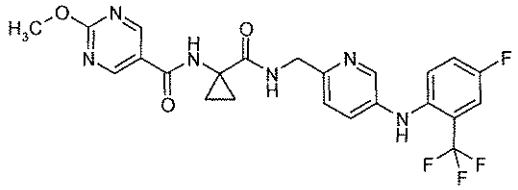
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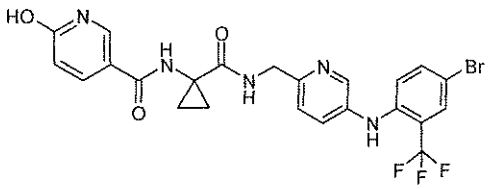
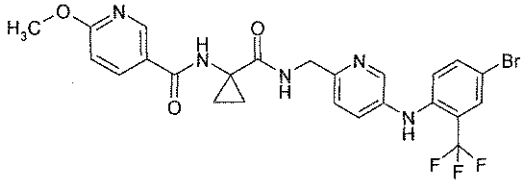
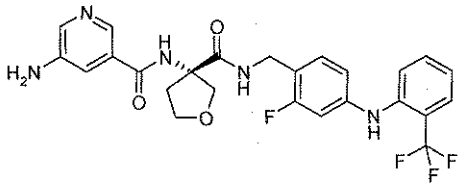
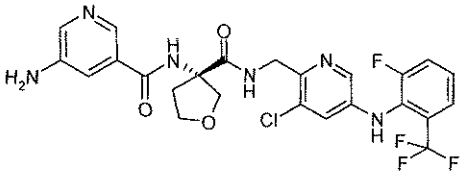
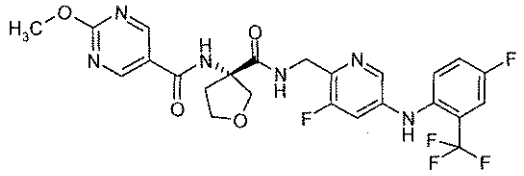
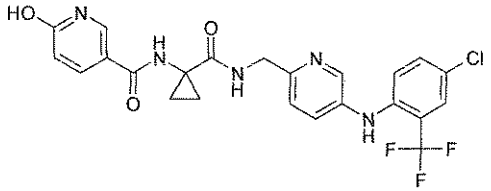
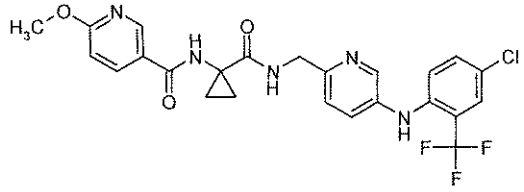
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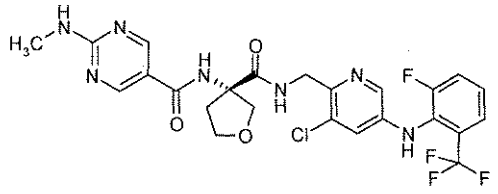
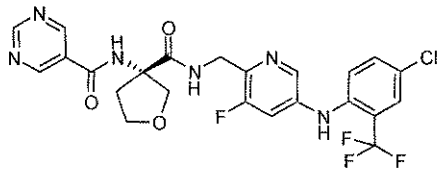
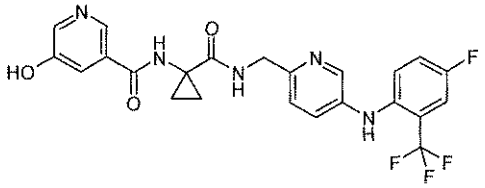
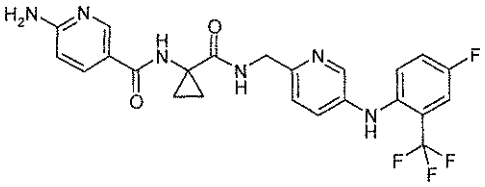
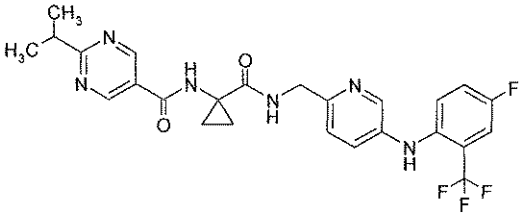
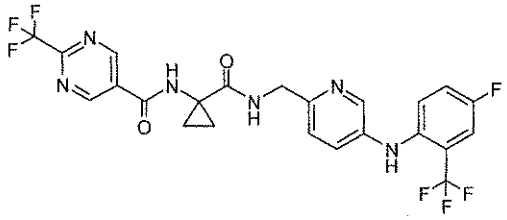
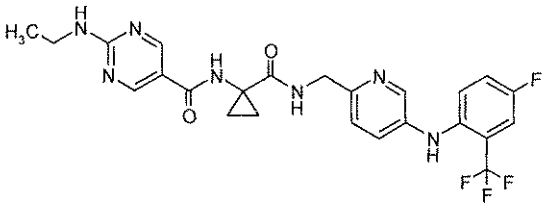
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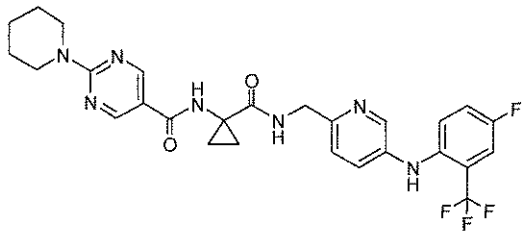
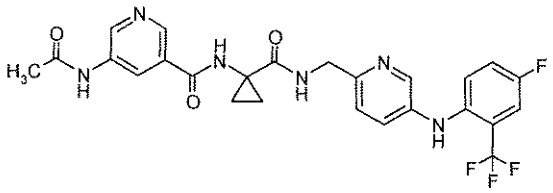
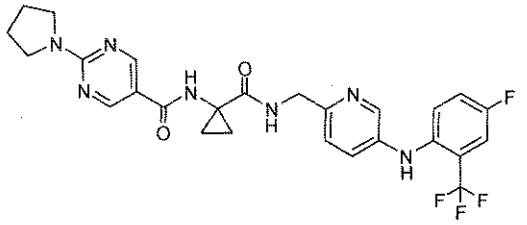
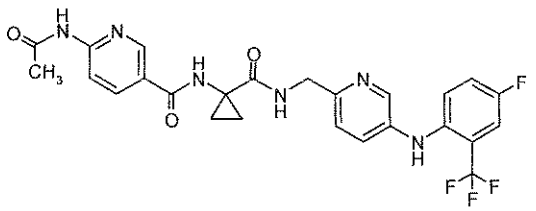
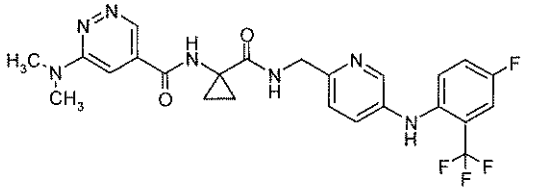
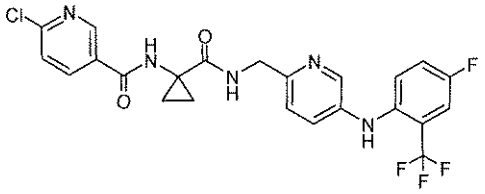
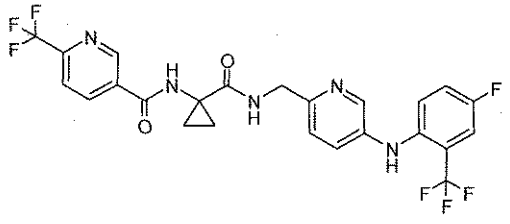
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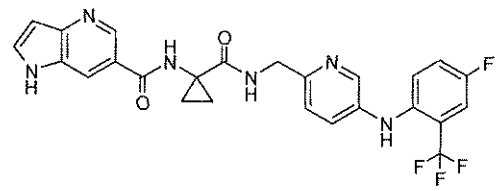
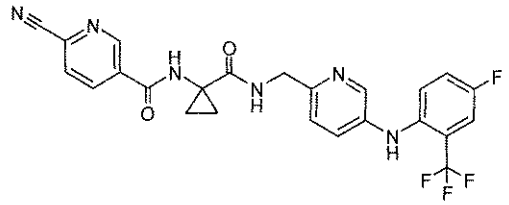
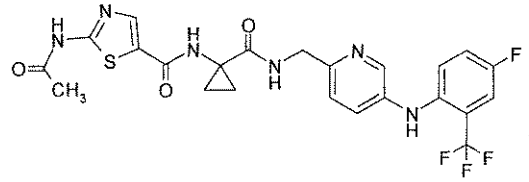
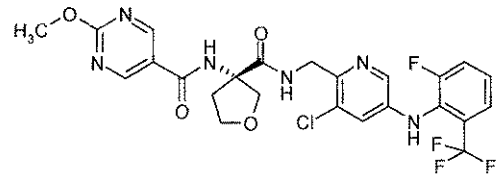
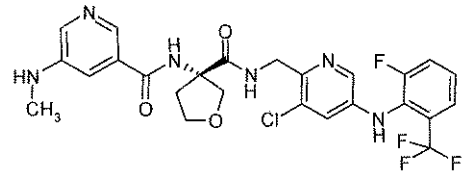
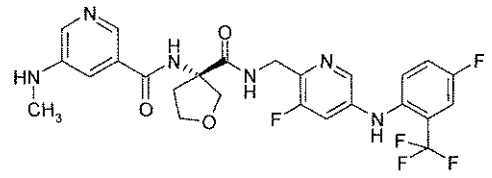
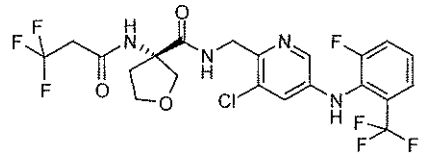
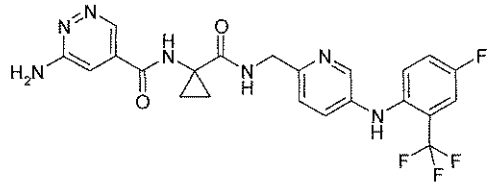
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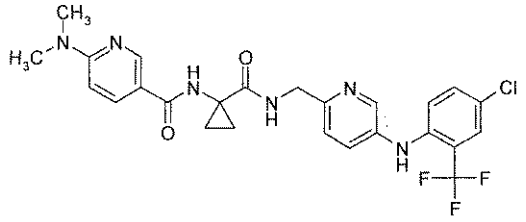
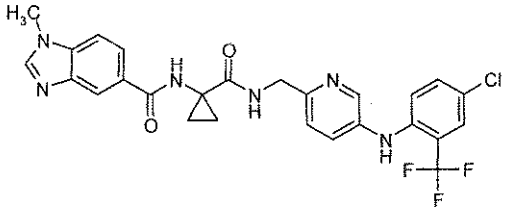
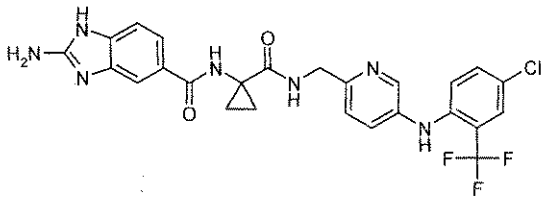
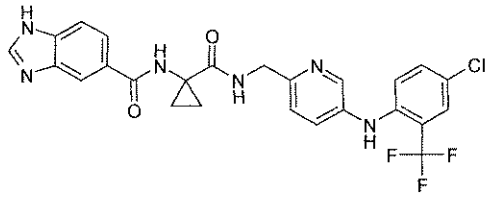
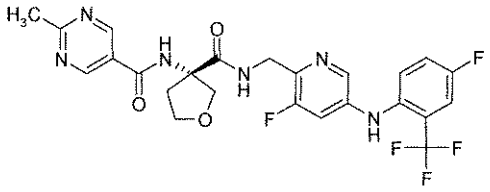
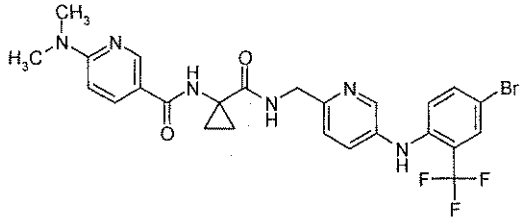
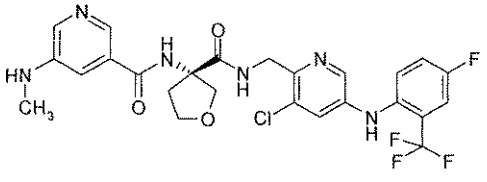
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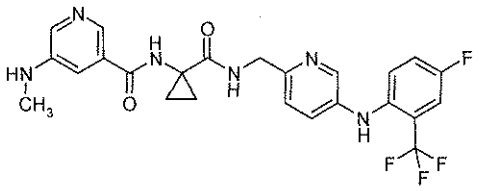
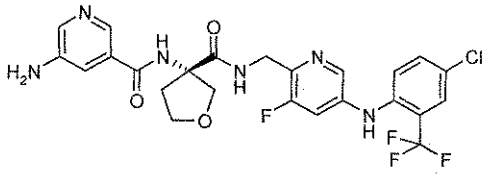
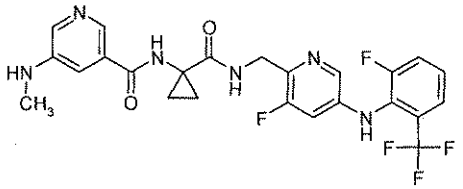
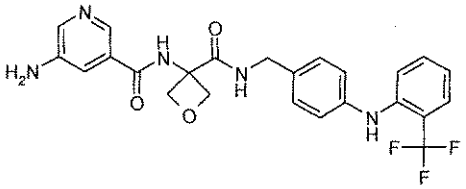
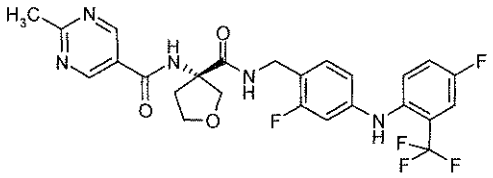
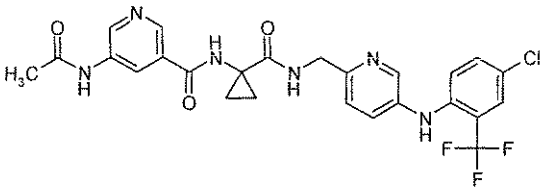
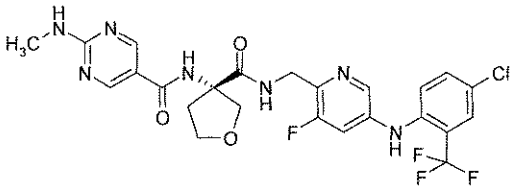
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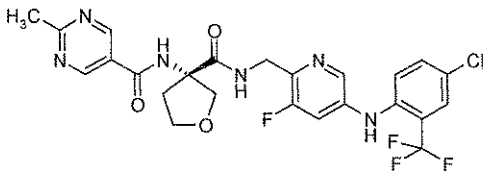
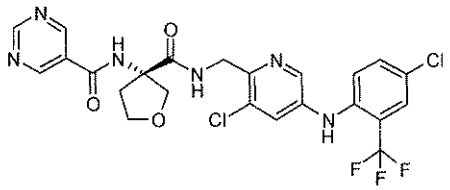
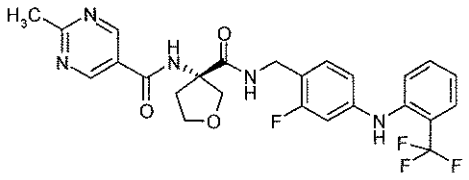
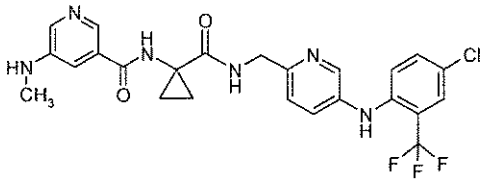
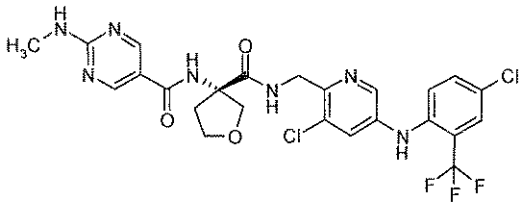
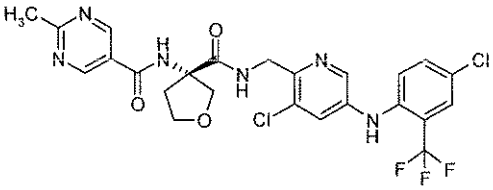
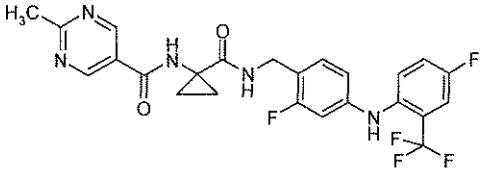
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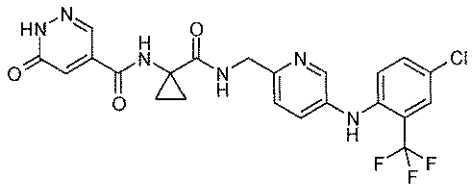
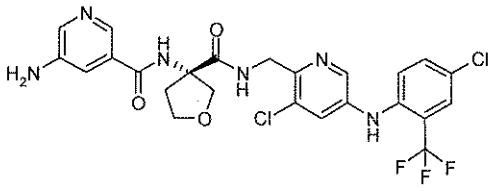
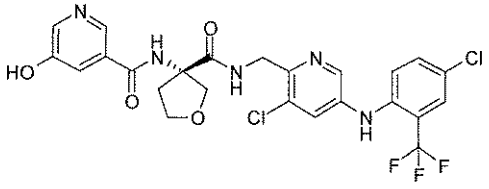
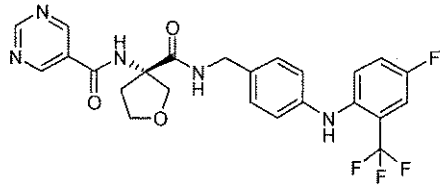
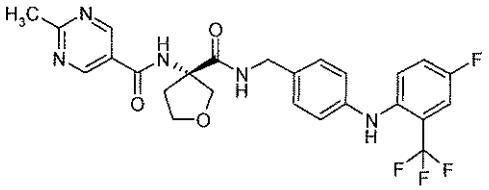
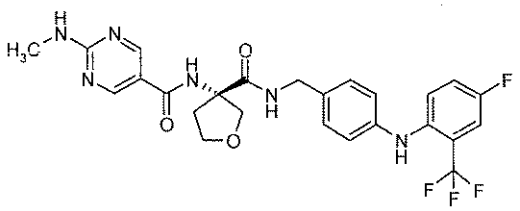
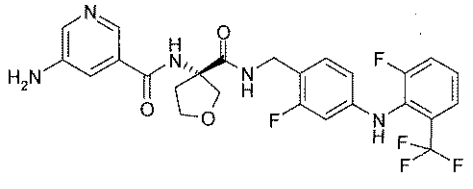
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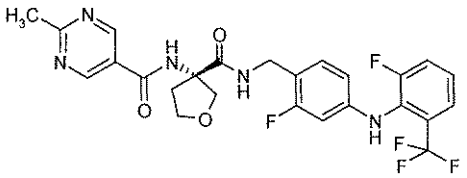
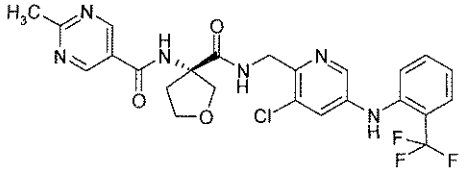
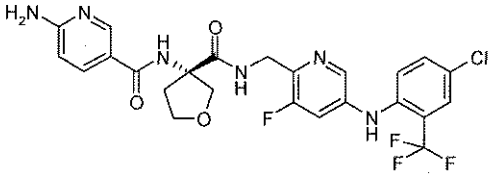
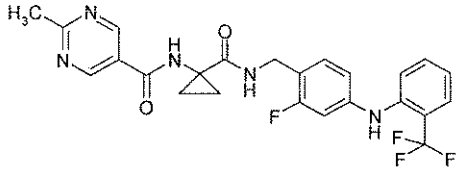
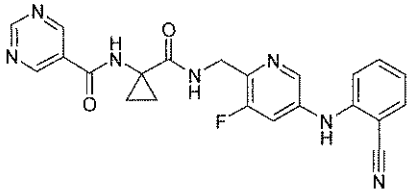
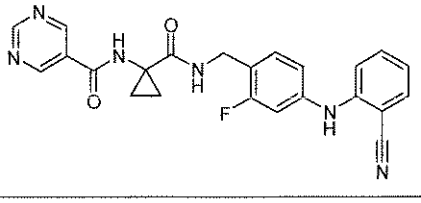
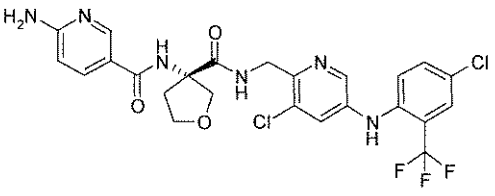
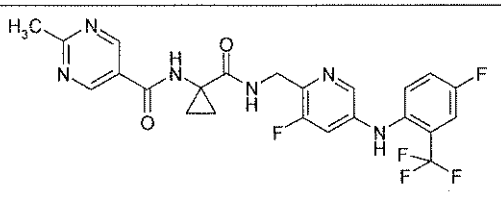
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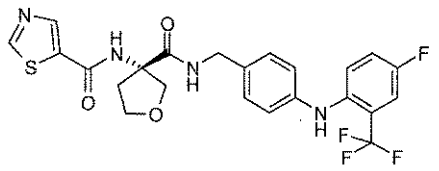
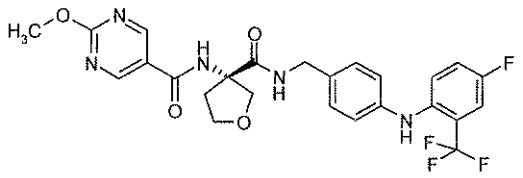
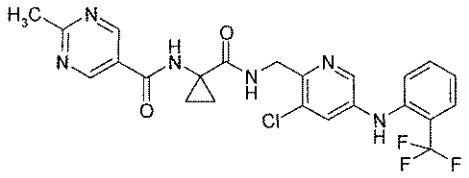
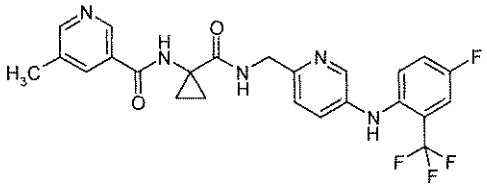
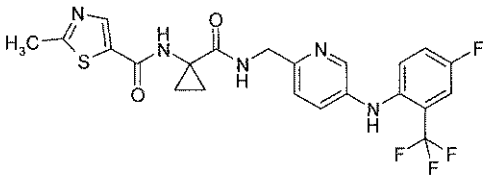
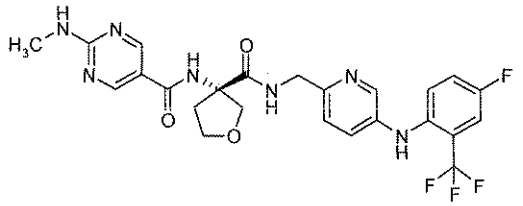
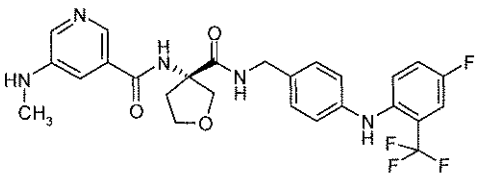
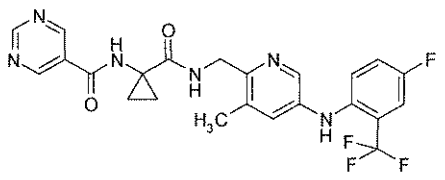
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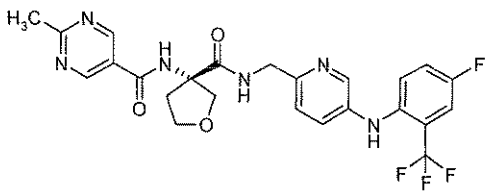
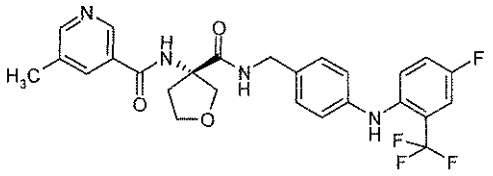
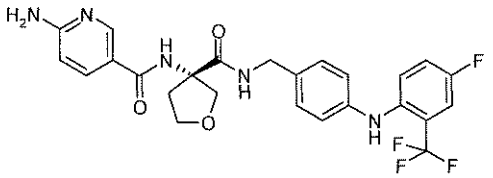
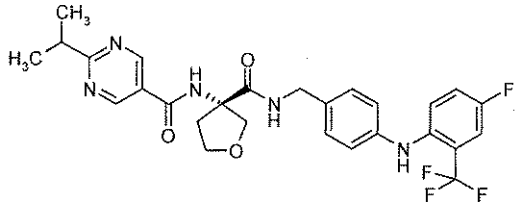
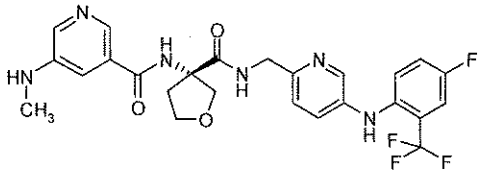
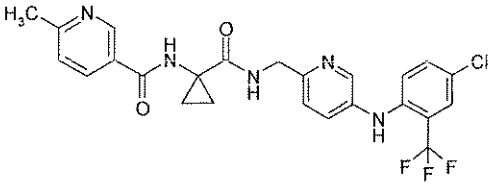
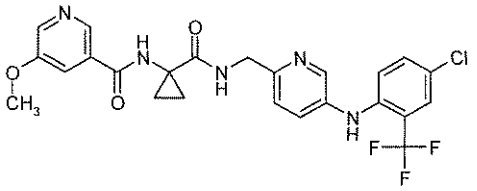
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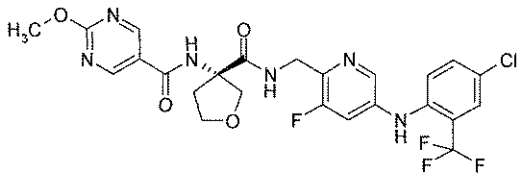
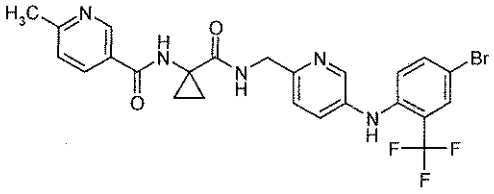
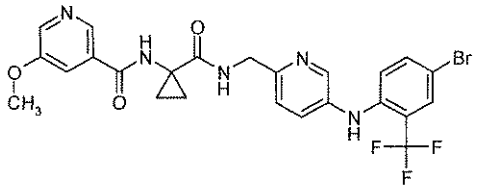
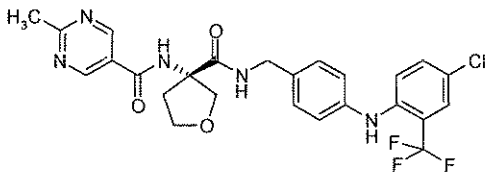
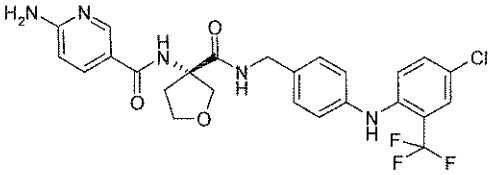
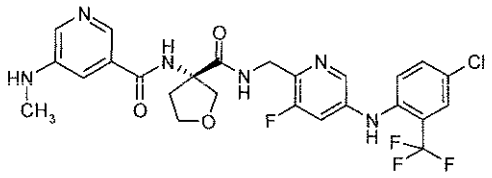
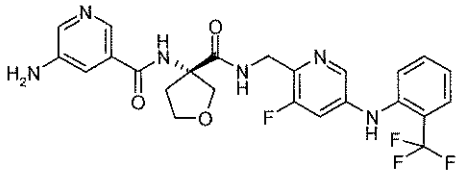
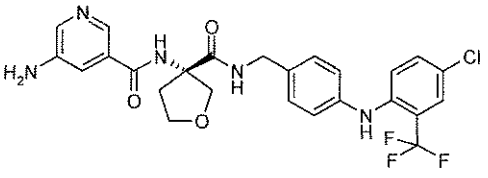
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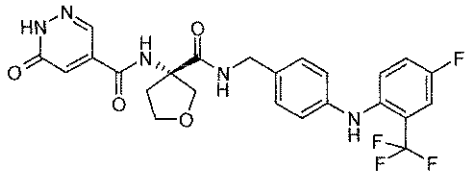
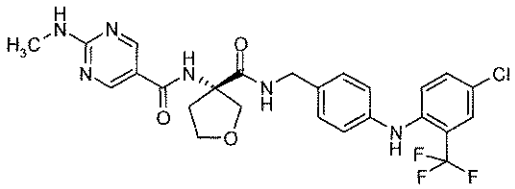
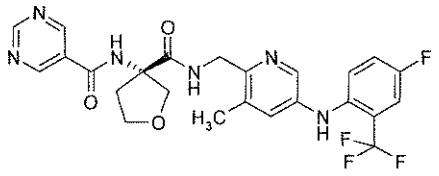
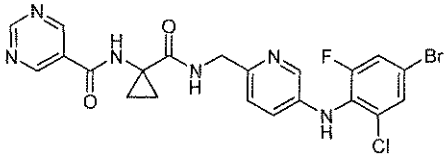
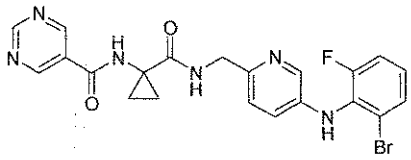
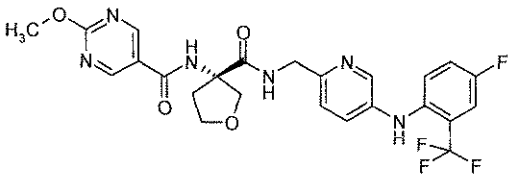
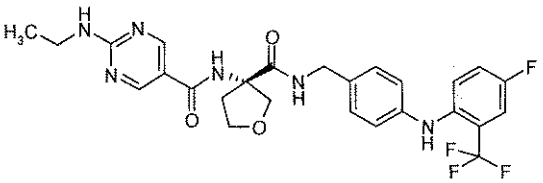
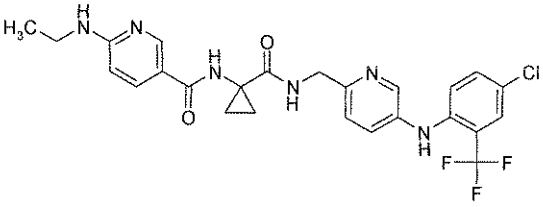
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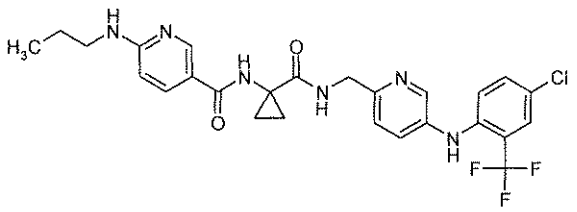
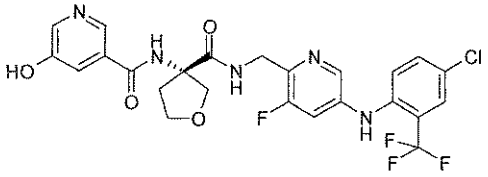
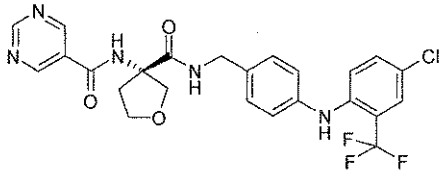
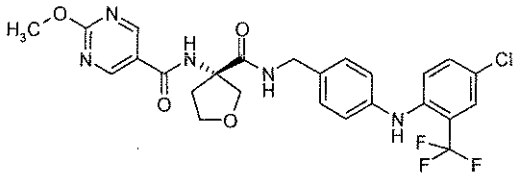
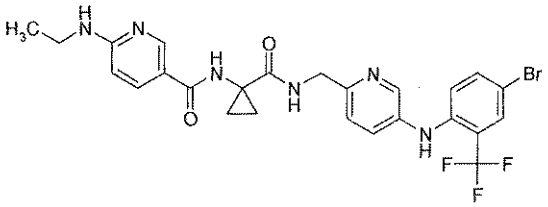
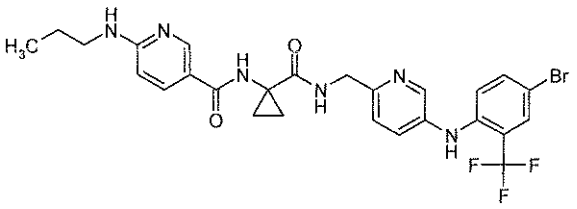
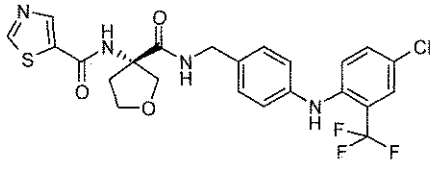
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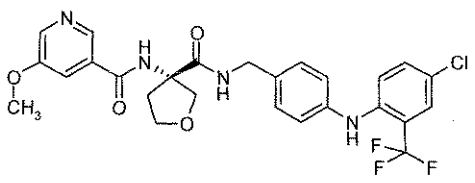
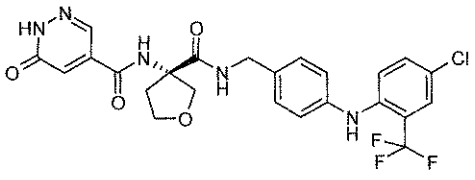
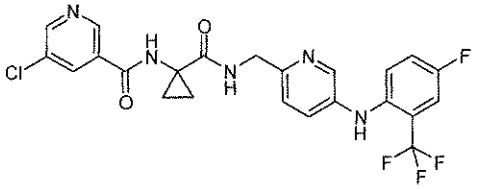
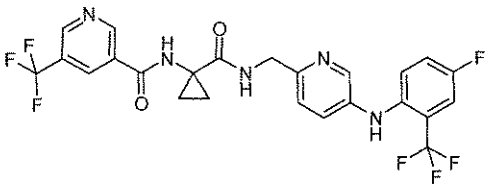
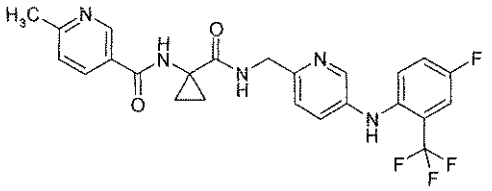
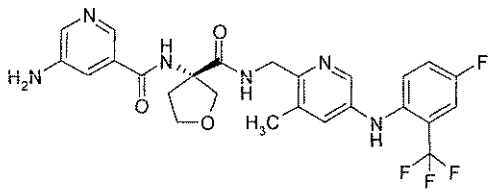
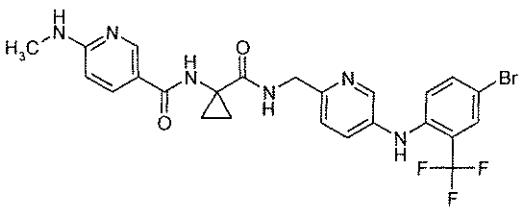
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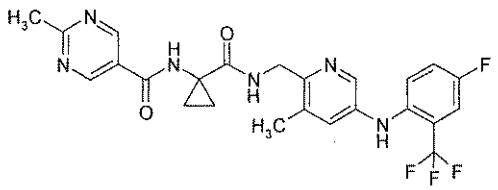
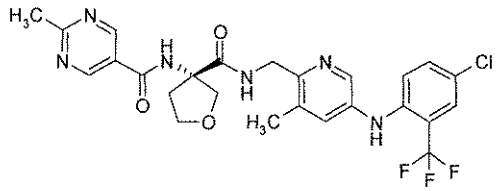
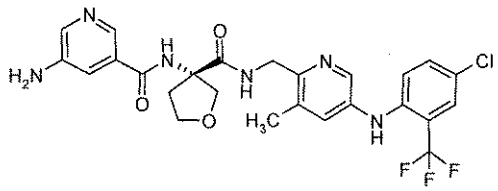
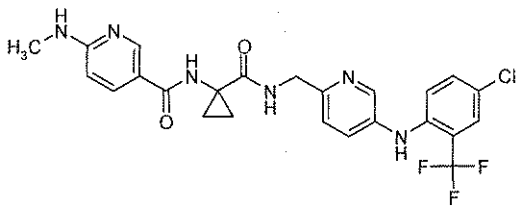
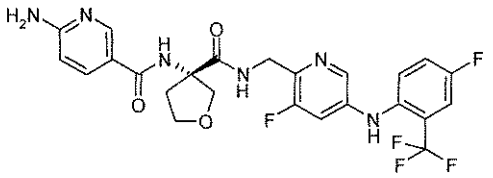
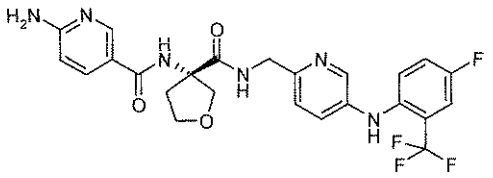
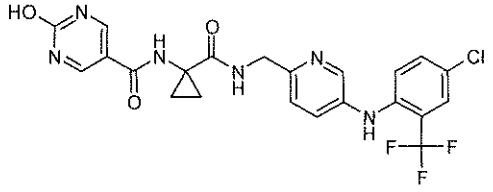
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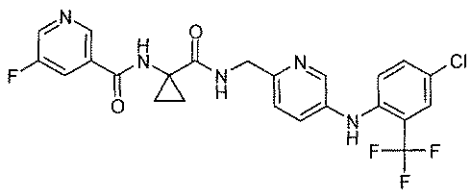
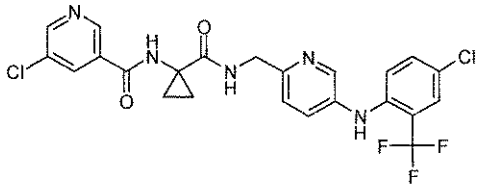
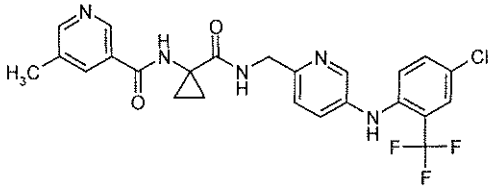
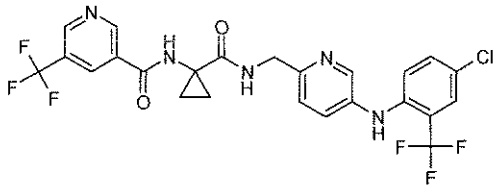
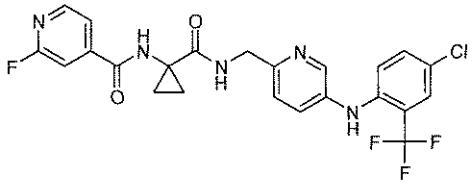
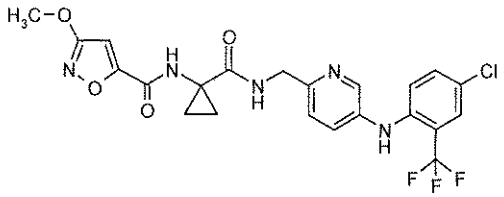
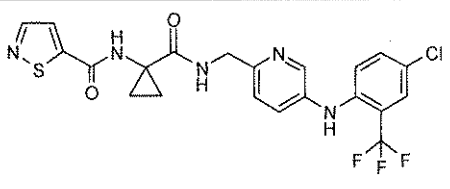
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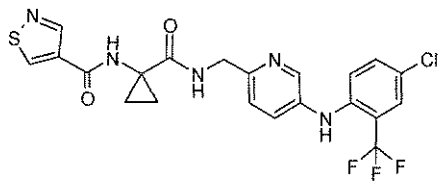
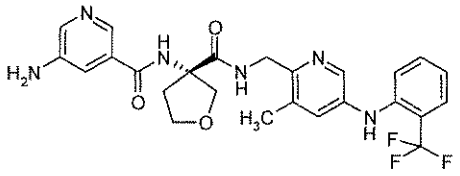
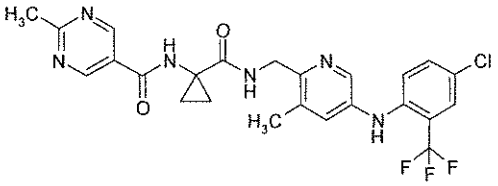
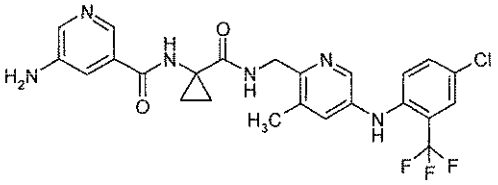
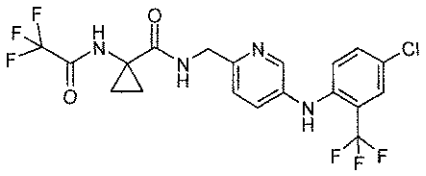
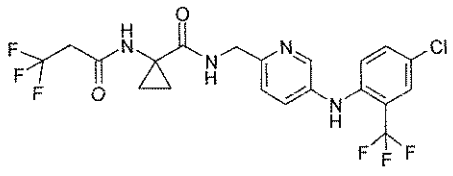
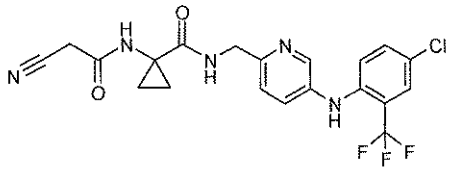
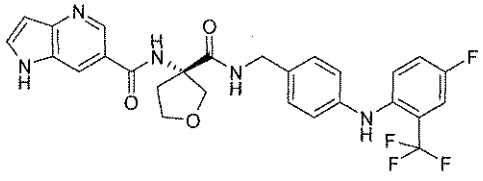
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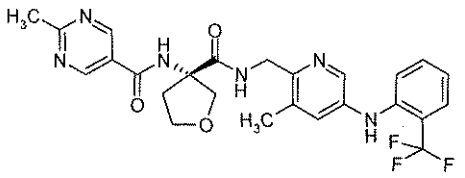
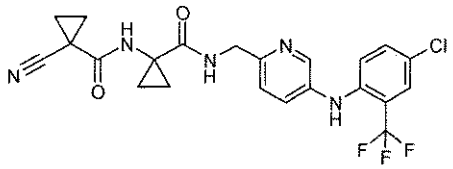
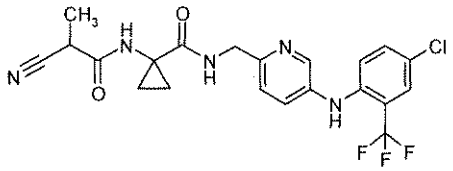
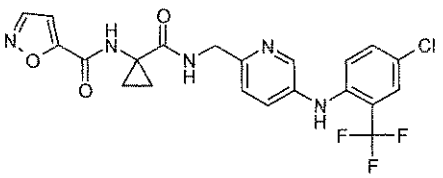
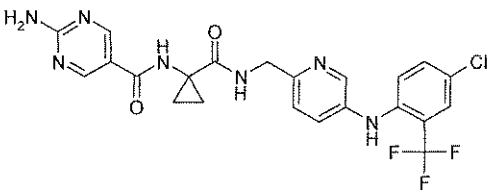
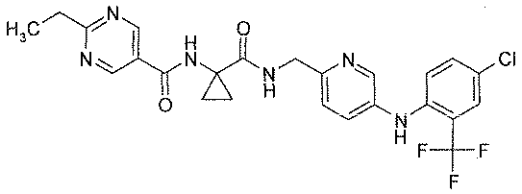
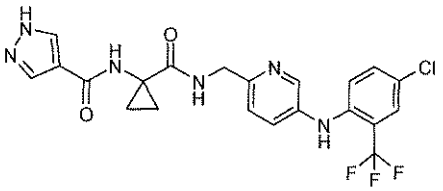
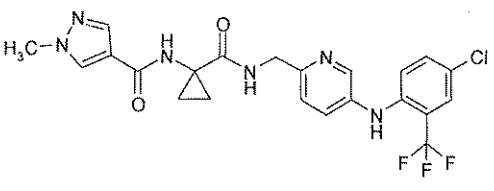
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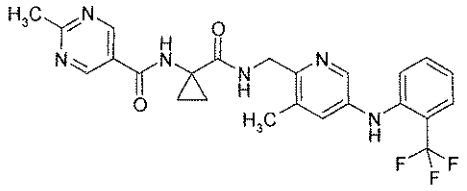
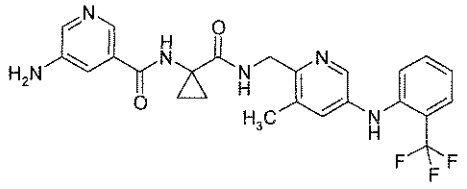
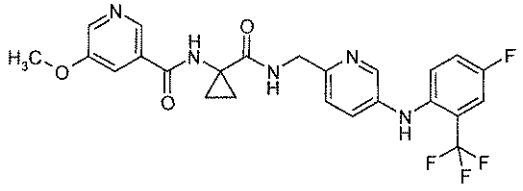
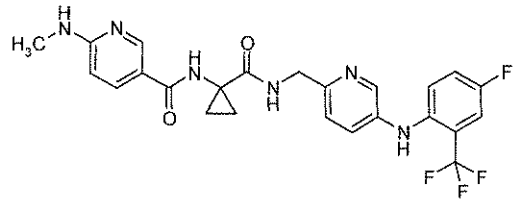
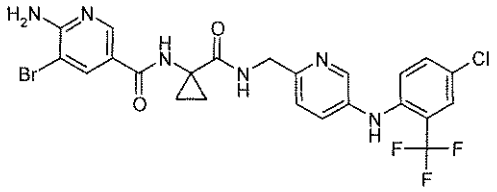
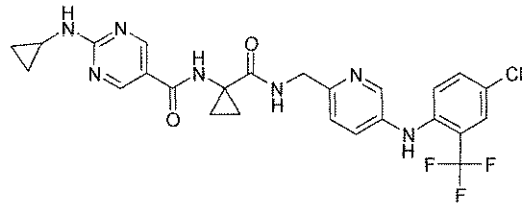
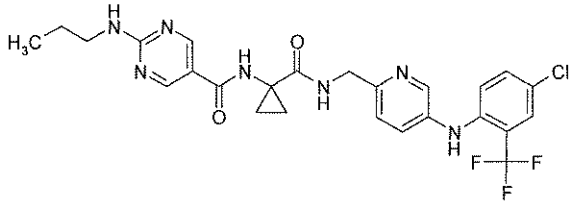
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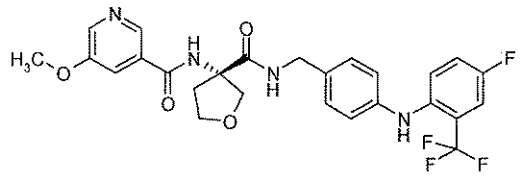
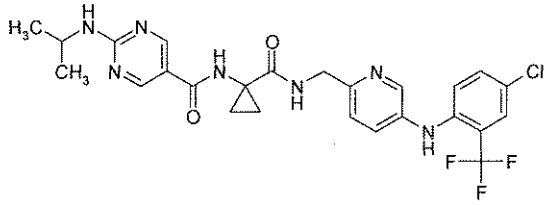
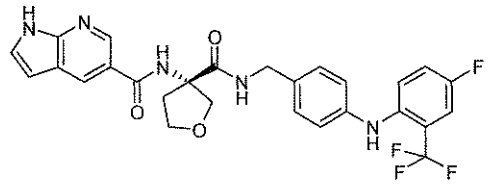
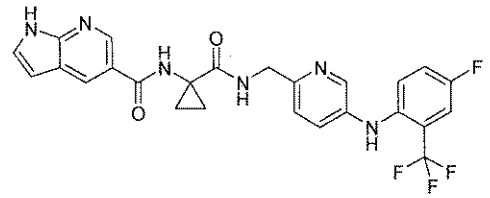
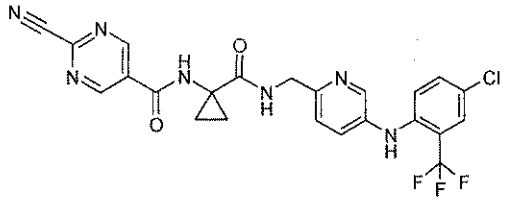
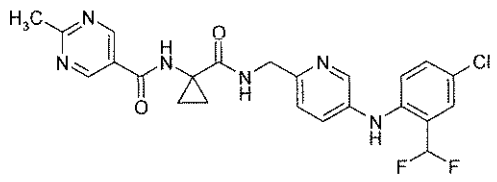
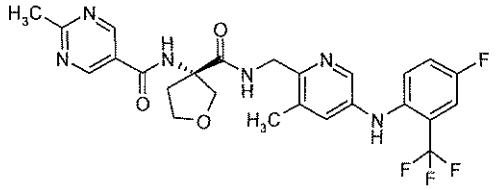
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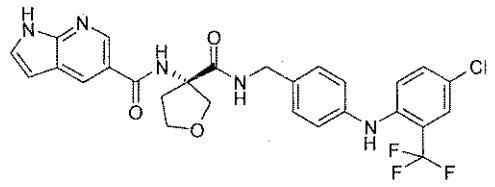
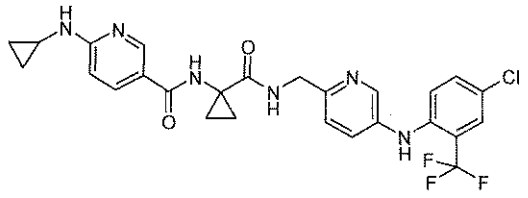
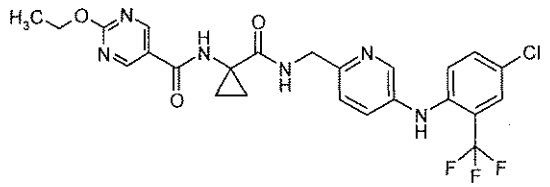
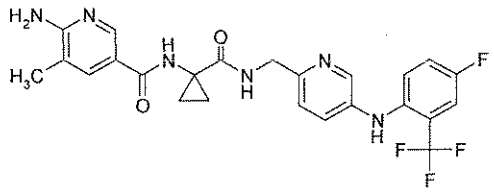
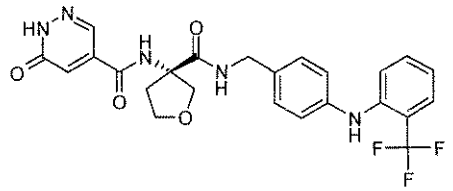
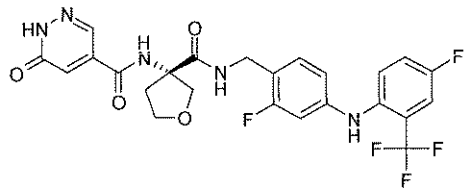
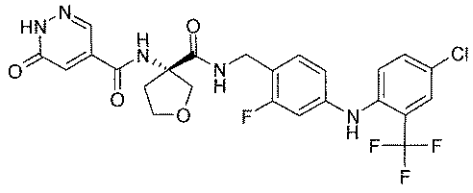
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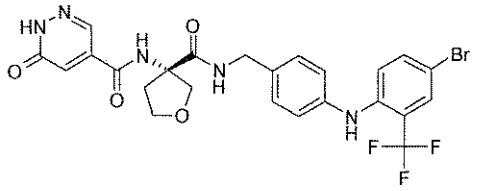
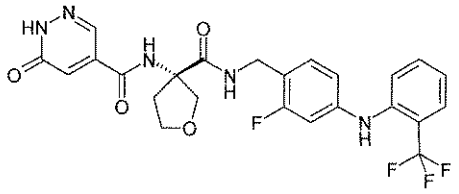
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No.	Structure
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No.	Structure
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No.	Structure
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(396)	

the enantiomers, the diastereomers, the mixtures and the salts thereof.

29. Physiologically acceptable salts of the compounds according to one of claims 1 to 28 with inorganic or organic acids or bases.

30. Medicaments, containing a compound according to at least one of claims 1 to 28 or a physiologically acceptable salt according to claim 29 optionally together with one or more inert carriers and/or diluents.

31. Compound of general formula **I** according to one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29 for use as medicaments.

32. Compound of general formula I according to one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28 or 29 for preparing a medicament for the acute and prophylactic treatment of acute pain, visceral pain, neuropathic pain, inflammatory / pain receptor-mediated pain, tumour pain and headache diseases.

33. Use of a compound according to at least one of claims 1 to 24 for preparing a medicament for the acute and prophylactic treatment of osteoarthritis.

34. Process for preparing a medicament according to claim 30, characterised in that a compound according to at least one of claims 1 to 29 is incorporated by a non-chemical method in one or more inert carriers and/or diluents.

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